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Original Research Article

Clinicopathologic Factors Associated with Prognosis in Patients with Metastatic Squamous Cell Carcinoma of the Anal Canal: A Multicenter Cohort Study

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Abstract

Objectives: Due to its rarity, there is insufficient evidence for managing ASCC patients with distant metastasis. Thus far, the therapeutic strategy for distant metastasis of ASCC is less standardized and requires a more individualized approach. Therefore, it is crucial to obtain information regarding treatment outcomes and prognostic factors following the development of distant metastasis to identify optimal care strategies for better patient outcomes and predict their prognosis.

Methods: In the multi-institute cohort study conducted in Japan, we retrospectively assessed 58 ASCC patients with synchronous distant metastasis and 28 ASCC patients with metachronous distant metastasis.

Results: When comparing the OS between ASCC patients with synchronous distant metastasis and metachronous distant metastasis, there was no statistically significant difference between the two groups. The OS rate at five years was 37.4% for patients with synchronous distant metastasis and 27.6%; for metachronous distant metastasis. In ASCC patients with synchronous distant metastasis, patients with distant metastasis at multiple sites exhibited extremely worse OS than those at single sites (HR: 4.56, 95% CI: 1.16-18.00, $P<0.0001$). In addition, in ASCC patients with metachronous distant metastasis, early recurrence was an independent factor for predicting poor OS in the multivariate analysis (HR: 4.13, 95% CI: 1.22-13.94, $P = 0.022$).

Conclusions: ASCC patients with distant metastasis at multiple sites were a worse prognosis. In addition, early recurrence was identified as an independent prognostic factor for OS among ASCC patients.

Keywords
anal canal cancer, distant metastasis, prognosis

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Introduction

Anal canal cancer (ACC) is a rare malignancy, accounting for 2.8% of all digestive system malignancies with an estimated incidence of around 9760 annually, and the estimated number of ACC deaths is 1.1% of all digestive system ma-

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lignancies in the United States[1]. The incidence rates of ACC have increased from 0.8 to 1.7 cases per 100,000 persons per year from 1975 to 2011 in the United States[2]. Pathologically, most ACC is anal canal squamous cell carcinomas (ASCC), accounting for 85% in the United States[2]. Unlike the United States, ASCC in ACC is less frequent In Japan[3]. Therefore, it is quite challenging to collect sufficient patients to provide solid evidence for predicting prognosis and optimizing patient care in ASCC patients. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) addressed clarifying the characteristics of ASCC in Japan by conducting a retrospective multi-institutional study in which 47 center hospitals in Japan participated.

Currently, the disease stage of the ASCC has been revised in the TNM classification (8th edition). In the TNM classification, the M category (distant metastasis) is the most frequent cause of mortality in patients with ASCC, as is the case with several other cancers[3]. Regarding the incidence of distant metastasis of ASCC, a nationwide analysis using a national cancer database in the United States revealed that 5.7% of ASCC patients had distant metastasis at the time of diagnosis[4]. In addition, 10% to 20% of ASCC patients will later develop distant metastasis after initial therapy with curative intent[5]. Due to its rarity, there is insufficient evidence for managing ASCC patients with distant metastasis. Thus far, the treatment of anal cancer with distant metastases is mainly systemic chemotherapy. However, the therapeutic strategy for distant metastasis of ASCC is less standardized and requires a more individualized approach, whereas Chemoradiotherapy (CRT) has recently been established as the standard initial therapeutic strategy for locally advanced ASCC without distant metastasis[4]. Therefore, it is crucial to obtain information regarding treatment outcomes and prognostic factors following the development of distant metastasis to identify optimal care strategies for better patient outcomes and predict their prognosis.

Several studies have addressed this issue and reported the outcome of ASCC patients with distant metastasis in nationwide research[6,7]. However, the detailed information on patients in previous studies was limited due to the nature of the nationwide study, and there is no study in terms of the factors that influence patients' prognosis of ASCC after the development of metachronous distant metastasis. In addition, whereas synchronous distant metastasis showed a worse prognosis compared with the metachronous disease in other malignancies including colorectal cance, it is obscure in ASCC patients[8]. Clarifying the difference between simultaneous and metachronous distant metastasis regarding the prognosis and clinicopathological factors provide significant information for predicting prognosis and understanding biological differences. The present multi-institutional, retrospective study aimed to investigate the prognosis of ASCC patients with synchronous and metachronous distant metastasis and identified clinicopathological factors that affect the prognosis of ASCC patients with distant metastasis.

Methods

Patients

We included 435 patients with Stage I-IV SCC of anal canal who were enrolled from 1991 to 2015 at 47 participating institutes of the Japanese Society for Cancer of the Colon and Rectum. Of these patients, we assessed 58 Stage IV patients as synchronous distant metastasis and 28 patients with recurrence after curative treatment, excluding local or regional lymph node recurrence as metachronous distant metastasis. This study defines regional lymph nodes as perirectal lymph nodes, internal iliac lymph nodes, external iliac lymph nodes, and inguinal lymph nodes[9]. Figure 1 shows the flow chart of this study. Clinical data were obtained from the database created by collecting patients' information from each institute. The ethical committees of the Japanese Society for Cancer of the Colon and Rectum approved the study protocol. Due to the retrospective study design in this study, a written informed consent from each participating patients was waived.

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 7.0 (GraphPad Software, San Diego, CA) and MedCalc Statistical Software version 16.1 (MedCalc Software, Ostend, Belgium). The outcomes were compared using Pearson's chi-square test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The Kaplan-Meier analysis and log-rank test were performed to estimate and compare the overall survival (OS) rates of patients with ASCC. We assessed the hazard ratio (HR) for the OS using univariate Cox regression analysis. Cox's proportional hazards model was utilized to identify independent prognostic factors determining patient survival. Prognostic information was unavailable for some patients in the OS analysis, so they were analyzed as missing values. All P values were 2-sided, and analysis items with P values less than 0.05 were considered statistically significant.

Results

The pattern of synchronous and metachronous distant metastasis from ASCC

Patients' clinical information of this study was listed on Table 1. The details of chemotherapy, radiation and chemoradiation were listed on Supplementary Table 1. As shown in Figure 2A, ASCC with synchronous distant metastasis included 50 single metastases and eight combinations

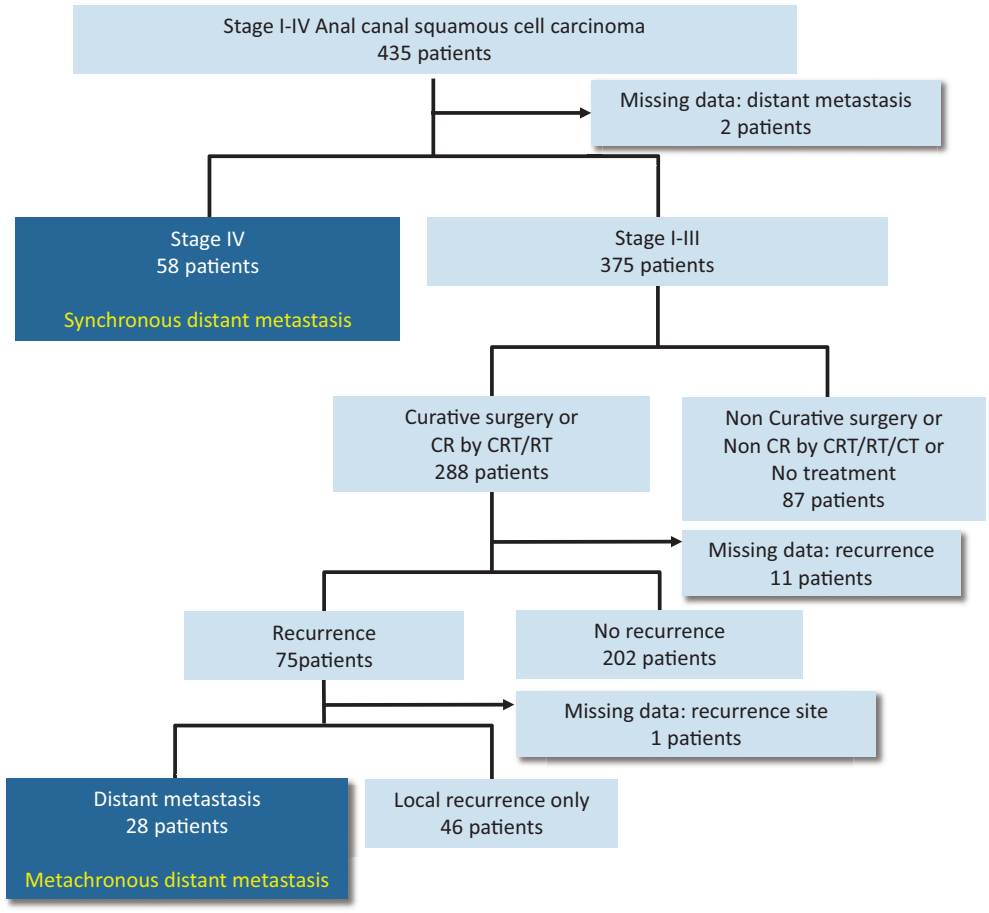

Figure 1. Study flow chart.

of metastases. Among patients with single-organ metastasis, we found that the extra-regional lymph node was the most common site of metastasis (84%), followed by the liver (12%), lung (2%), and bone (2%). For multiple site metastases, the most common site was extra-regional lymph node metastasis (87.5%), followed by bone (75%), lung (62.5%), peritoneum (50%), and liver (37.5%), respectively. Furthermore, as shown in Figure 2B, ASCC with metachronous distant metastasis included 16 single metastases and 12 combinations of metastases. Among patients with single-organ metastasis, we found that the lung was the most common site of metastasis (43.8%), followed by the liver (31.3%), extra-regional lymph node (12.5%), bone (6.3%), and colon (6.3%), respectively. For multiple site metastases, the most common site was the liver (58.3%), followed by local (50%), lung (41.7%), inguinal lymph node (33.3%), bone (16.7%), peritoneum (16.7%), pleura (8.3%), and extra-regional lymph node (8.3%), respectively.

Survival analysis of ASCC patients who had synchronous and metachronous distant metastasis

Figure 2C shows the Kaplan-Meier curves for OS of ASCC patients with synchronous and metachronous distant metastasis. There was no statistically significant difference between the two groups. The OS rate at one year was 74.5% for patients with synchronous distant metastasis and 62.2%; for metachronous distant metastasis, two years (50.4% and 39.0%), and five years (37.4% and 27.6%). In addition, those patients with synchronous distant metastasis had a median survival time of 788 days, compared with a median survival of 481 days in the patients with metachronous distant metastasis.

Next, we explored factors influencing OS in ASCC patients with synchronous distant metastasis. Kaplan-Meier analyses revealed that patients with distant metastasis at multiple sites exhibited extremely worse OS than those at single sites (hazard ratio [HR]: 4.56, 95% confidence interval [CI]: 1.16-18.00, $P< 0.0001$) (Figure 3A). Then, because Extra regional lymph nodes alone accounted for most of the synchronous distant metastasis, we further analyzed OS in ASCC patients with synchronous extra-regional lymph node metastasis alone. When stratifying according to the type of initial treatment modality, chemoradiotherapy was associated with better OS than surgical resection (HR: 3.64, 95% CI: 1.01-13.10, $P= 0.048$). Also, chemotherapy alone or radiotherapy alone tended to have worse OS than chemoradio-

Table 1. Clinicopathologic Characteristics of Anal Canal Cancer Patients with Distant Metastasis.

Variables		Synchronous distant metastasis N=58	Metachronous distant metastasis N=28	*P* value
Gender				
	Male	17	11	0.46
	Female	41	17	
Age				
	< 65	28	13	0.99
	≥ 65	30	15	
Location				
	P	53	25	0.71
	E	5	3	
Initial treatment				
	Surgery	15	11	
	Chemoradiation	29	16	
	Chemotherapy	4	0	
	Radiotherapy	4	1	
	Best supportive care	6	0	
Tumor size				
	< 50mm	23	12	0.27
	≥ 50mm	25	7	
	not available	10	9	
T stage				
	T1-3	30	21	0.022
	T4	24	4	
	not available	4	3	
N stage				
	N0	10	13	0.0032
	N1	48	13	
	not available	0	2	
Preoperative SCC				
	<1.5	12	8	0.40
	1.5≤	36	14	
	not available	10	6	
Preoperative CEA				
	<5	38	22	0.10
	5≤	16	3	
	not available	4	3	

therapy (HR: 2.29, 95% CI: 0.68-7.70, *P*= 0.099) (Figure 3 B).

Furthermore, we analyzed the OS to figure out the prognostic factor in ASCC patients with metachronous distant metastasis. ASCC patients with metachronous distant metastasis were divided into early recurrence and late recurrence by the cutoff value derived from a median time to recurrence (513 days). Kaplan-Meier analyses revealed that patients with early recurrence exhibited significantly worse OS (HR: 4.75, 95% CI: 1.74-12.99, *P* = 0.001) (Figure 3C). Also, patients with positive lymph nodes at the time of primary ASCC treatment showed significantly worse OS (HR: 2.86, 95% CI: 0.99-8.20, *P* = 0.017) (Figure 3D).

Early recurrence was an independent negative predictor of OS in ASCC patients with metachronous distant metastasis

We next performed univariate and multivariate Cox proportional hazards model analyses to explore independent prognostic factors of OS in ASCC patients with metachronous distant metastasis. Univariate analysis revealed that the presence of lymph node metastasis and early recurrence were significantly associated with poor OS (Table 2). Multivariate analysis revealed that early recurrence was an independent factor for predicting poor OS in ASCC patients with metachronous distant metastasis (HR: 4.13, 95% CI: 1.22-13.94, *P* = 0.022) (Table 2). The difference of clinico-

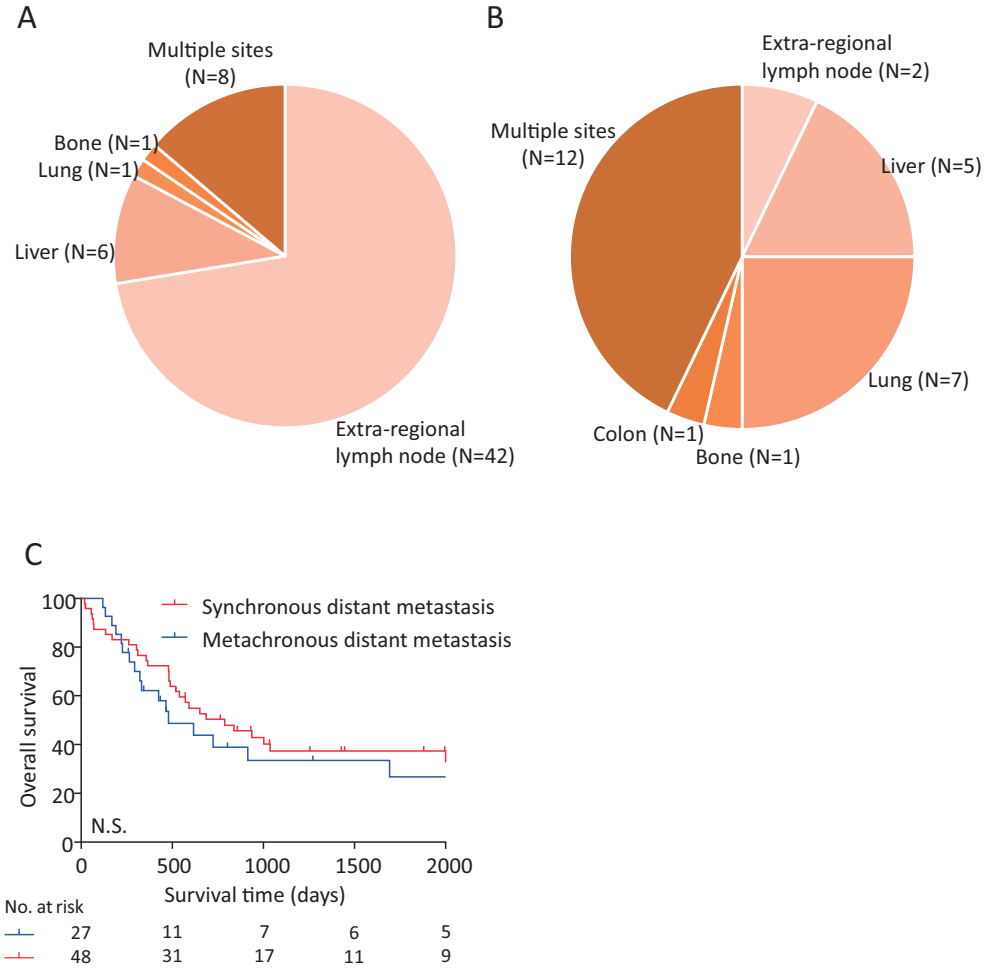

Figure 2. Comparison ASCC patients with synchronous distant metastasis of those with metachronous distant metastasis (A) metastatic site of synchronous distant metastasis, (B) metastatic site of metachronous distant metastasis, (C) Kaplan–Meier curve showing overall survival of ASCC patients with synchronous and metachronous distant metastasis.

pathological factors between early recurrence and late recurrence was listed in Table 3. Lymph node metastasis had a higher prevalence in the early recurrence group.

Discussion

In the current study, we assessed ASCC patients with synchronous and metachronous distant metastasis, a small population of rare malignancy. As a result, our efforts have led to the identification of several intriguing findings. First, in stage IV ASCC patients, patients with distant metastasis in multiple sites are quite worse prognosis compared with those in a single site. Thus far, the M category of the TNM classification for ACC is divided into M0 (without distant metastasis) and M1 (with distant metastasis). Several cancers, including colorectal cancer, have already shown poor prognosis for distant metastases in multiple sites, and the M 1 category is subdivided into M1a (distant metastasis in only one site) and M1b (distant metastasis in multiple sites). From the result of the present study, it could be reasonable to subdivide the M category of ASCC into M1a and M1b, as are the other cancers.

Second, as an initial treatment for stage IV patients who had extra regional lymph nodes alone as sites of distant metastasis, CRT was associated with favorable OS compared with surgery. In addition, CRT tended to be associated with favorable OS compared with chemotherapy or radiotherapy alone. For ASCC patients with distant metastasis, until recently, there was no robust defined standard of care because of the quite infrequency and the lack of phase III clinical trials. From the result of the current study, surgery for ASCC with extra regional lymph nodes alone as sites of distant metastasis was considered to be avoidable. Recently, Abdelazim et al.[6] assessed the treatment outcomes of a large number of patients who underwent CRT for stage IV ASCC and reported that CRT was better OS compared to chemotherapy alone. In addition to the result of our study, CRT has the potential to improve outcomes among ASCC

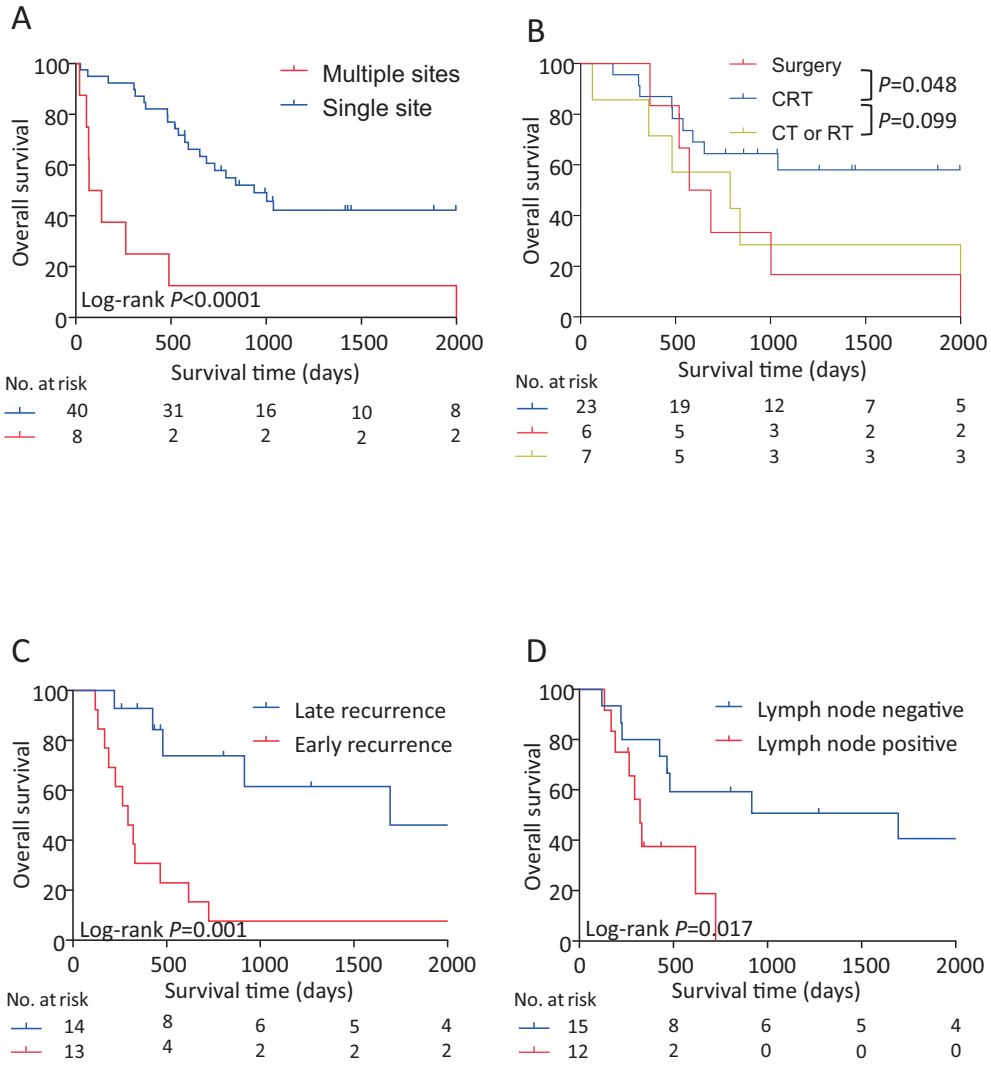

Figure 3. Kaplan–Meier curve showing overall survival (A) according to the number of metastatic sites for ASCC with synchronous distant metastasis, (B) according to the type of treatment for ASCC patients with synchronous extra-regional lymph node metastases, (C) according to the timing of recurrence for ASCC with metachronous distant metastasis, (D) according to the presence of lymph node metastasis for ASCC with metachronous distant metastasis.

Table 2. Univariate and Multivariate Analysis of OS in ASCC Patients with Metachronous Distant Metastasis.

Variables	Univariate			Multivariate		
	HR	95%CI	P Value	HR	95%CI	P Value
Gender (male)	0.54	0.20 to 1.53	0.55			
Age (>69 (median))	1.74	0.66 to 4.61	0.27			
Histological Type (undifferentiated)	1.25	0.40 to 3.90	0.70			
T classification (T3T4)	0.88	0.23 to 3.40	0.85			
Lymphnode metastasis (positive)	3.50	1.19 to 10.30	0.020	1.59	0.48 to 5.29	0.45
CEA level at initial treatment (≥5)	0.84	0.19 to 3.84	0.86			
SCC level at initial treatment (≥1.5)	0.88	0.23 to 3.40	0.85			
Recurrence site (multiple)	0.85	0.32 to 2.26	0.74			
Recurrence from initial treatment (early)	5.12	1.76 to 14.88	0.0027	4.13	1.22 to 13.94	0.022

Table 3. Clinicopathologic Characteristics of Anal Canal Cancer Patients with Metachronous Distant Metastasis.

Variables		metachronous distant metastasis		*P* value
		early recurrence N=14	late recurrence N=14	
Gender				
	Male	6	5	0.99
	Female	8	9	
Age				
	< 65	5	8	0.45
	≥ 65	9	6	
Location				
	P	13	12	0.99
	E	1	2	
Initial treatment				
	Surgery	4	7	0.44
	CRT/RT	10	7	
Tumor size				
	< 50mm	6	6	0.77
	≥ 50mm	3	4	
	not available	5	4	
T stage				
	T1-3	10	11	0.60
	T4	1	3	
	not available	3	0	
N stage				
	N0	4	9	0.047
	N1	10	3	
	not available	0	2	
Preoperative SCC				
	<1.5	5	3	0.67
	1.5≤	7	7	
	not available	2	4	
Preoperative CEA				
	<5	13	9	0.56
	5≤	1	2	
	not available	0	3	
Local recurrence				
	Absent	12	10	0.65
	Present	2	4	

patients with extra regional lymph nodes alone as sites of distant metastasis. As the number of patients is insufficient in this study for any robust conclusions regarding the treatment outcome of CRT, a further large-scale comparative study is warranted.

Third, In the analysis of metachronous distant metastasis, early recurrence was an independent prognostic factor for identifying worse OS in ASCC patients. Early recurrence has already been reported as an adverse prognostic factor in patients with various squamous cell cancer, including head and neck, oral cavity, and esophagus[10-12], whereas not been elucidated in those with ASCC. This is, to our knowledge, the first cohort study to investigate the impact of the recurrence interval on the prognosis of patients with ASCC after curative treatment. In the current study, lymph node metastasis was associated with early recurrence. Thus far, maintenance chemotherapy after CRT is not recommended for overall ASCC patients from the evidence of a randomized controlled trial[13]. Selected ASCC patients, such as those at high risk for early recurrence, might benefit from maintenance chemotherapy to avoid early recurrence.

A significant limitation of the present study was its retrospective nature, which led to missing data and selection bias. Therefore, several relevant clinical information, including treatment for distant metastasis or subsequent treatment after initial therapy, that affects prognosis and treatment se-

lection in ASCC patients with distant metastasis were unavailable. In addition, the number of patients in the present study was still small even though patients were collected from 47 center hospitals in Japan. In addition to that ACC itself is a rare malignancy, one of the possible reasons that the number of patients was limited would be due to the fact that most of the ACCs in Japan are adenocarcinomas, with a less frequency of ASCCs, accounting for only 24.0%[3]. There are regional differences in terms of the histology of ACC, with most of the patients in Western countries having ASCC which accounting for 80%. Although the number of patients is small in the current study, it could be considered valuable to clarify the prognostic factors of the ASCC patients with distant metastasis in Japan, whose frequency differs from that in the United States. Furthermore, during this study period, there has been a significant change in ASCC treatment in Japan. Chemoradiotherapy for ASCC was not the standard treatment until 2004 in Japan[14]. In this study period, initial treatment for all stage IV patients was surgery in the first half, whereas 13.5% of stage IV patients in the second half. This chronological difference in treatment strategies also might affect the prognosis of the current study. Since metastatic ASCC is a small population of rare cancer, especially in Japan, it might be inevitable to take a long period to collect an adequate sample size. A nationwide study and a well-planned large, prospective, multicenter study in the future should validate our results.

In conclusion, in the present multi-institute cohort study conducted in Japan, ASCC patients with distant metastasis at multiple sites were a worse prognosis. In addition, early recurrence was identified as an independent prognostic factor for OS among ASCC patients.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

TM was involved in study concept and design, acquisition of data, analysis, and interpretation of data, drafting of the manuscript. KY, KS, and YA were involved in the acquisition of data, analysis, and interpretation of data and critical revision of the manuscript for important intellectual content. HI was involved in study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision. All authors approved the final draft of the manuscript.

Approval by Institutional Review Board (IRB)

This work was approved by the IRB of Saitama Medical Center, Saitama Medical University (approval code: 1841-III).

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Supplementary Files

Supplementary Table 1.

Please find supplementary file(s);
http://dx.doi.org/10.23922/jarc.2023-064