Survival Predictors of Metastatic Adrenocortical Carcinoma: a SEER-based Retrospective Study

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Abstract

Background: Metastatic adrenocortical carcinomas (MAC) have a poor prognosis. Advanced adrenocortical carcinoma often metastasizes to lung and liver. Prognostic factors of MAC have been rarely reported. This study aims to identify the association between specific metastasis and overall survival (OS) in MAC and determine the survival predictors for MAC patients.

Methods: MAC patients' data was obtained from Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2016. Survival differences were analyzed by Kaplan–Meier analysis and log-rank tests. Cox proportional hazard model was used to identify the prognostic factors associated with overall survival.

Results: A total of 152 MAC patients were selected, among whom 77 patients (50.7%) were diagnosed with one metastatic site, 75 (49.3%) diagnosed with more than one distant metastasis. For the whole MAC cohort, multivariable analysis showed that year of diagnosis between 2013 and 2016, without liver metastasis, surgery and chemotherapy were significantly favorable predictors of OS. For patients with one metastatic site, lung metastases had a better survival outcome than liver metastases(p=0.037). Besides, compared with patients who didn't received surgery, patients underwent surgery were correlated with longer OS (p=0.004). For patients with more than one site of distant metastases, married status, surgery, and chemotherapy predicted a better OS. Radiotherapy did not improve overall survival outcomes in the three cohort.

Conclusion: Liver metastasis has a poor prognosis. Year of diagnosis, metastatic sites, surgery and chemotherapy were significant prognostic factors for OS in MAC patients. For patients with single metastasis, surgery was a favorable prognostic factor, while married patients, surgery and chemotherapy predicted a better survival outcome in patients with more than one metastasis. Based on the collective findings, surgery can be regarded as the preferred treatment option for all MAC patients. Besides, chemotherapy is also a good choice for patients with multiple metastases.

Background

Primary adrenocortical carcinomas are rare and aggressive tumors, with an estimated yearly incidence of 0.7–2 cases per million inhabitants[1, 2]. The occurrence rate, although still low, has increased steadily, owing to the improvement of functional and radiographic examination. However, the survival rates of these rare cancers have not improved significantly which, to a great extent, attributes to the poor survival outcomes in advanced disease, the 5-year survival rate less than 20% in most series[3, 4]. To date, the majority of previous studies have discussed prognosis for localized or the whole adrenocortical carcinoma patients[5-9]. And It's widely accepted that tumor staging is the most important prognostic factor. Besides, the occurrence of metastasis often means the worst prognosis[10]. But there are few studies on prognostic factors of MAC. According to the published literature, adrenocortical carcinoma often metastasizes to liver, lung, bone and distant lymph nodes[11, 12]. By far, hardly there are studies on

the metastatic pattern and the influence of different metastatic sites on prognosis. Here, we have performed a retrospective research on patients identified from the SEER database in order to determine the prognostic factors of MAC. Besides, we also have analyzed the distant metastatic pattern, and further discussed the influence of different metastatic sites on patients' survival.

Methods

Patients and data collection

We searched all patients diagnosed with MAC registered in the SEER database between 2010 and 2016, because patients' metastatic sites, including lung, liver, bone, brain, and distant lymph nodes, have been detailed since 2010. Data were extracted from SEER*Stat (version 8.3.8) (https://seer.cancer.gov/data/) (National Cancer Institute, Bethesda, MD, USA). These public data are open access and don't need Institutional Review Board approval.

Patients enrolled in the study were older than 18 years old pathologically diagnosed with stage IV adrenocortical carcinoma. Variables collected included: year of diagnosis, age at diagnosis, gender, race, marital status, tumor laterality, tumor grade, tumor size, TNM stage, sites of distant metastases, and treatments (surgery, chemotherapy and radiotherapy). Patients whose metastatic sites, treatment, or survival time were unknown were excluded. The primary endpoint was OS.

Statistical analysis

Demographic and clinical characteristics were analyzed by descriptive statistics. Survival time and 95% confidence interval (CI) were analyzed with Kaplan-Meier analysis and log-rank test was used to identify the difference, or independent prognostic factors were determined by univariate Cox proportional hazard models. Factors significantly correlated with OS were further assessed in the multivariate Cox proportional hazard model. A two-side p value < 0.05 was considered statistically significant. Statistical analyses were conducted by SPSS version 24.0 (IBM Inc., Chicago, IL, USA), and survival curves were drew by GraphPad Prism version 8.0 (GraphPad Prism Software Inc., San Diego, CA, USA).

Results

Patient characteristics

A total of 152 patients were selected from the SEER database according to the above criteria. Patients' demographic and clinical information was detailed in table 1. Most of the patients were diagnosed between 2013 and 2016. Patients, diagnosed with MAC at the median age of 56 years, were divided into two groups, which were younger than or equal to 55 years and older than 55 years. In all, 74 patients (48.7%) were ≤ 55 years and 78 (51.3%) were 55 years. In addition, the disease had a slight predominance in women (Female:92, 60.5% vs Male:60, 39.5%), consistent with previous reports[4, 13, 14]. 122 patients (80.3%) of white race accounted for the majority, and more patients were married than

unmarried (53.3% vs 44.1%). Regarding the literality, tumors occurred more common on the left (55.9%) than on the right (40.1%), which was contrary to the previous report that there were slightly more on the right than on the left[3]. In terms of tumor histology, the number of patients identified as grade I + II, grade III and grade IV were 6 (3.9%), 15(9.9%) and 4 (2.6%), respectively. For more than half of patients (127, 83.6%), their tumors' grade was unknown. In total, there were 54 (35.5%) patients with tumor size ≤ 10 cm, 83 (54.6%) patients with tumor size > 10 cm, and 15 patients with tumor size unknown. According to the AJCC 7th edition, the number of MAC patients with T4 (35.5%) was the highest, followed by T2 (23.0%), T3 (16.5%), and T1 (3.3%). There were more patients with N0 (67.8%) than patients with N1(22.3%).

Table 1
Characteristics of 152 MAC patients identified from SEER database between 2010 and 2016

Characteristic	No (%)
Patients	**152**
Year of diagnosis	
2010–2012	60(39.5)
2013–2016	92(60.5)
Gender	
Male	60(39.5)
Female	92(60.5)
Age at diagnosis(years)	
≤55	74(48.7)
>55	78(51.3)
mean	53.7
Median	56
Race	
White	122(80.3)
Black	15(9.8)
Others	12(7.9)
Unknown	3(2.0)
Marital status	
Married	81(53.3)
unmarried	67(44.1)
unknown	4(2.6)
Laterality	
Left	85(55.9)
Right	61(40.1)
Unknown	6(4.0)
Grade	

Characteristic	No (%)
I + II	6(3.9)
III	15(9.9)
IV	4(2.6)
Unknown	127(83.6)
Size	
≤10 cm	54(35.5)
>10 cm	83(54.6)
Unknown	15(9.9)
T stage	
T1	5(3.3)
T2	35(23.0)
T3	25(16.5)
T4	54(35.5)
Unknown	33(21.7)
N stage	
N0	103(67.8)
N1	34(22.3)
Unknown	15(9.9)
Metastatic sites at diagnosis	
Lung	
Yes	100(65.8)
No	52(34.2)
Liver	
Yes	91(59.9)
No	61(40.1)
Bone	
Yes	31(20.4)
No	121(79.6)

Characteristic	No (%)
Distant lymph node	
Yes	34(22.4)
No	118(77.6)
Brain	
Yes	1(0.7)
No	151(99.3)
Number of metastatic sites	
1	77(50.7)
≥ 2	75(49.3)
Treatment	
Surgery	
Yes	59(38.8)
No	93(61.2)
Chemotherapy	
Yes	101(66.4)
No/Unknown	51(33.6)
Radiotherapy	
Yes	12(7.9)
No	140(92.1)
Vital status	
Alive	41(27.0)
Dead	111(73.0)
1-year OS rate	29.0%
5-year OS rate	1.3%

With regard to the metastatic sites, 100 patients (65.8%) were diagnosed with metastases in lung, 91 (59.9%) in liver, 34 (22.4%) in distant lymph node, and 31 (20.4%) in bone. Except that, only one patient was diagnosed with brain metastases. In line with previous findings, liver and lung were considered as the most common metastatic sites[4, 15, 16]. There were quantitative differences from previous reports

that the incidence of bone metastases was higher in our study[4, 13]. Moreover, we also summarized the metastatic patterns of single or multiple organs (Table 2). There were 77 patients (50.7%) with only one metastatic site, while more than one metastatic site was found in 75 patients (49.3%), lung and liver all accounting for a thumping majority for whether single or multiple metastases.

Table 2
Patterns of distant metastases for the 152 MAC patients

Sites of distant metastases	**N (%)**
One site of distant metastasis	**77(50.7)**
Lung	40(26.3)
Liver	26(17.1)
Bone	6(4.0)
Distant lymph node	4(2.6)
Brain	1(0.7)
Two sites of distant metastasis	**49(32.2)**
Liver + lung	29(19.1)
Bone + liver	8(5.3)
Liver + Distant lymph node	4(2.6)
Lung + Distant lymph node	4(2.6)
Bone + Lung	2(1.3)
Bone + Distant lymph node	2(1.3)
Three sites of distant metastasis	**22(14.5)**
Liver + lung + Distant lymph node	13(8.5)
Bone + liver + lung	6(4.0)
Bone + lung + Distant lymph node	2(1.3)
Bone + liver + Distant lymph node	1(0.7)
Four sites of distant metastasis	**4(2.6)**
Liver + lung + bone + Distant lymph node	4(2.6)

In general, 59 patients (38.8%) underwent surgery, among whom 32 patients (21.0%) received chemotherapy, 11 patients (7.2%) received chemotherapy and radiotherapy and 1 patient (0.7%) received

radiotherapy; the remaining 15 patients (9.9%) didn't receive chemotherapy and radiotherapy or whether they had received chemotherapy was unknown. The specific surgical information of the patients was shown in Table 3, and it's unknown of the other 10 patients what kind of surgery they received. Besides, 58 patients (38.2%) only received chemotherapy, while 35 patients (23.0%) neither underwent surgery or radiotherapy nor accepted chemotherapy. A total of 111 (73.0%) deaths were recorded, and the 1- and 5-year OS rates for all the MAC patients were 29.0 and 1.3%, respectively.

Table 3
surgery information for the 49 patients

Primary site of surgery	Distant metastatic Site of surgery	
	Yes(N)	No(N)
Partial surgical removal	2	2
Total surgical removal	10	18
Debulking	0	2
Radical surgery [a]	6	9

a. Partial or total removal of the primary site with a resection in continuity (partial or total removal) with other organs.

Univariate and multivariate analysis of variables associated with OS in MAC patients

The median survival time for MAC patients was 7.0 ± 0.9 months (95% CI, 5.176 ~ 8.824). Then we used log-rank test for univariate analysis(Table 4), and the results showed that multiple factors,including diagnosed at the year between 2010 and 2012, unmarried, liver metastasis and patients with more than one metastatic site, were significantly associated with poor OS. On the contrary, surgery, chemotherapy and radiotherapy all could bring a survival benefit to patients. The other variables: patients' age, gender, race, tumor size, grade and laterality, T stage, N stage and other metastatic sites except liver, didn't show statistically association with survival.

Table 4
Median survival data (months) and Kaplan–Meier method performs univariate analysis of variables in MAC patients

Variable	OS		
	Estimate ± SE	95%CI	log-rank P-value
Year of diagnosis			
2010–2012	6.0 ± 1.0	4.112 ~ 7.888	0.045
2013–2016	8.0 ± 1.9	4.213 ~ 11.787	
Age at diagnosis (years)			
≤ 55	9.0 ± 2.5	4.058 ~ 13.942	0.128
>55	6.0 ± 1.2	3.607 ~ 8.393	
Gender			
Female	6.0 ± 1.2	3.693 ~ 8.307	0.840
Male	7.0 ± 1.7	3.666 ~ 10.335	
Race			
White	7.0 ± 1.0	5.137 ~ 8.863	0.690
Black	10.0 ± 3.9	2.371 ~ 17.629	
Other	15.0 ± 6.0	3.215 ~ 26.785	
Marital status			
Married	8.0 ± 1.3	5.429 ~ 10.571	0.022
unmarried	5.0 ± 1.1	2.762 ~ 7.238	
Grade			
I + II	39.0 ± 31.0	0 ~ 99.760	0.161
III + IV	6.0 ± 1.0	4.111 ~ 7.889	
Laterality			
Left	7.0 ± 1.2	4.713 ~ 9.287	0.903
Right	8.0 ± 1.5	5.142 ~ 10.858	
Size (cm)			
≤ 10	6.0 ± 1.1	3.852 ~ 8.148	0.315
> 10	8.0 ± 1.9	4.286 ~ 11.714	

Variable	OS		
	Estimate ± SE	95%CI	log-rank P-value
T stage			
T1-T2	7.0 ± 2.9	1.413 ~ 12.587	0.808
T3-T4	8.0 ± 1.6	4.940 ~ 11.060	
N stage			
N1	3.0 ± 0.7	1.637 ~ 4.363	0.122
N0	8.0 ± 1.4	5.724 ~ 10.726	
Metastatic sites at diagnosis			
Lung			
Yes	6.0 ± 1.9	2.210 ~ 9.790	0.901
No	7.0 ± 0.9	5.152 ~ 8.848	
Liver			
Yes	6.0 ± 0.8	4.392 ~ 7.608	< 0.001
No	17.0 ± 5.4	6.483 ~ 27.517	
Bone			
Yes	7.0 ± 1.2	4.665 ~ 9.335	0.731
No	6.0 ± 1.3	3.363 ~ 8.637	
Distant lymph node			
Yes	2.0 ± 0.8	0.488 ~ 3.512	0.169
No	8.0 ± 1.3	5.490 ~ 10.510	
No. of metastatic sites			
1	10.0 ± 2.8	4.486 ~ 15.514	0.005
≥ 2	5.0 ± 1.0	3.024 ~ 6.976	
Treatment			
Surgery treatment			
Yes	18.0 ± 2.7	12.752 ~ 23.248	< 0.001
No	4.0 ± 0.9	2.225 ~ 5.775	
Chemotherapy			

Variable	OS		
	Estimate ± SE	95%CI	log-rank P-value
Yes	10.0 ± 2.2	5.781 ~ 14.219	< 0.001
No	3.0 ± 0.7	1.623 ~ 4.377	
Radiation therapy			
Yes	36.0 ± 18.0	3.864 ~ 8.136	0.017
No	6.0 ± 1.1	0.740 ~ 71.260	
Overall	7.0 ± 0.9	5.176 ~ 8.824	

Multivariate cox analysis was performed to further assess the potential factors which proved to be significant above. As shown in Table 5, year of diagnosis between 2013 and 2016, without liver metastasis, surgery and chemotherapy significantly predicted a better survival outcome. However, marital status, the number of distant metastatic organs and radiotherapy were not significantly bound up with the survival prognosis.

Table 5
Cox proportional hazards model performs multivariate analysis for OS in MAC patients

Variable	OS	
	HR (95%CI)	P value
Year of diagnosis		
2010–2012	Reference	0.015
2013–2016	0.619(0.420 ~ 0.912)	
Marital status		
unmarried	Reference	0.091
Married	0.715(0.484 ~ 1.055)	
Liver metastasis		
No	Reference	0.014
Yes	1.818(1.130 ~ 2.926)	
No. of metastatic sites		
1	Reference	0.881
≥ 2	1.307(0.646 ~ 1.663)	
Treatment		
Surgery treatment		
No	Reference	< 0.001
Yes	0.421(0.266 ~ 0.667)	
Radiation therapy		
No	Reference	0.421
Yes	0.674(0.257 ~ 1.764)	
Chemotherapy		
No	Reference	< 0.001
Yes	0.481(0.320 ~ 0.723)	

Prognostic factors for patients with one or more metastatic sites

Furthermore, we conducted a separate prognostic analysis of patients with one or more distant metastases. The median survival time for MAC patients with one and more metastatic sites was 10.0 ± 2.8 and 5.0 ± 1.0 months, respectively (p = 0.005;Table 4 and Fig. 1A). Patients' demographic and clinical information was listed in Table 6. Here, we focused on the patients with only liver or lung metastases, due to the insufficient numbers of patients with only bone, brain or distant lymph node metastases. For patients with one metastatic site (n = 66), the univariate Cox analysis turned out that the metastatic site and surgery were significantly associated with overall survival (Table 7). Multivariate Cox proportional hazard model analysis further proved the results that Compared with liver metastases, lung metastases had a better survival outcome (HR, 0.535; 95% CI, 0.297 ~ 0.964; p = 0.037), and the median survival time was 8 and 20 months for patients with liver and lung metastases, respectively (p = 0.023; Fig. 1B). Besides, compared with patients who didn't received surgery, patients who underwent surgery were correlated with longer overall survival (HR, 0.372; 95% CI, 0.189 ~ 0.732; p = 0.004). For patients with more than one metastatic site (n = 75), marital status, treatments including surgery and chemotherapy were independent prognostic factors resulting from univariate Cox analysis (Table 7). Moreover, we included these variables in a multivariate Cox analysis and the results revealed that surgery and chemotherapy predicted better overall survival (Table 8). Then survival analysis was performed, and the results were showed in Fig. 2. For patients with distant metastases, whether one or more sites, surgery was significantly associated with improved survival months (1 site: surgery vs no-surgery: 21.0 vs 6.0 for median OS, Fig. 2A; >1 site: surgery vs no-surgery: 13.0 vs 4.0 for median OS, Fig. 2B) (all $p < 0.05$). However, the survival outcome of chemotherapy for the two groups showed different results. That is, the median OS for patients with more than one organ metastases were improved from 2 months to 9 months after receiving chemotherapy (Fig. 2C), while for patients with single organ metastasis, chemotherapy did not provide a statistically significant survival benefit. In addition, as the only statistically significant demographic variable, the median survival time of married patients was longer than that of unmarried patients from 4 months to 8 months (Fig. 2D).

Table 6
Characteristics of patients with one or more metastases

Characteristic	One metastatic site	More than one metastatic site
	No (%)	No (%)
Patients	**66**	**75**
Year of diagnosis		
2010–2012	27(40.9)	31(41.3)
2013–2016	39(59.1)	44(58.7)
Gender		
Male	19(28.8)	36(48)
Female	47(71.2)	39(52)
Age at diagnosis(years)		
≤55	32(48.5)	38(50.7)
>55	34(51.5)	37(49.3)
Race		
White	55(83.3)	59(78.7)
Black	6(9.1)	9(12)
Others	5(7.6)	4(5.3)
Unknown	0	3(4)
Marital status		
Married	37(56.1)	38(50.7)
unmarried	26(39.4)	36(48)
unknown	3(4.5)	1(1.3)
Laterality		
Left	35(53.0)	45(60)
Right	29(44.0)	26(34.7)
Unknown	2(3.0)	4(5.3)
Grade		
I + II	2(3.0)	3(4.0)
III + IV	5(7.6)	11(14.7)

Characteristic	One metastatic site	More than one metastatic site
	No (%)	No (%)
Unknown	59(89.4)	61(81.3)
Size		
≤10 cm	22(33.3)	24(32)
>10 cm	42(63.7)	38(50.7)
Unknown	2(3.0)	13(17.3)
T stage		
T1	2(3.0)	2(2.7)
T2	14(21.2)	19(25.3)
T3	13(19.7)	8(10.7)
T4	26(39.4)	26(34.7)
Unknown	11(16.7)	20(26.7)
N stage		
N0	51(77.3)	46(61.3)
N1	9(13.6)	22(29.3)
Unknown	6(9.1)	7(9.4)
Metastatic sites at diagnosis		
Liver	26(39.4)	-
Lung	40(60.6)	-
Treatment		
Surgery		
Yes	34(51.5)	20(26.7)
No	32(48.5)	55(73.3)
Chemotherapy		
Yes	45(68.2)	48(64)
No/Unknown	21(31.8)	27(36)
Radiotherapy		
Yes	4(6.1)	6(8)

Characteristic	One metastatic site	More than one metastatic site
	No (%)	No (%)
No	62(93.9)	69(92)
Vital status		
Alive	20(30.3)	15(20)
Dead	46(69.7)	60(80)
1-year OS rate	36.4%	21.3%
5-year OS rate	3%	0%

Table 7
Univariate Cox regression analysis of prognostic factors in MAC patients with one or more metastases.

Variable	One site of distant metastases		More than one metastasis	
	HR (95%CI)	P value	HR (95%CI)	P value
Year of diagnosis				
2010–2012	Reference		Reference	
2013–2016	0.757(0.423 ~ 1.354)	0.348	0.776(0.465 ~ 1,293)	0.330
Age at diagnosis (years)				
≤ 55	Reference		Reference	
>55	1.295(0.719 ~ 2.331)	0.389	1.349(0.806 ~ 2.256)	0.254
Gender				
Female	Reference		Reference	
Male	0.761(0.398 ~ 1.457)	0.410	0.867(0.519 ~ 1.451)	0.588
Race				
White	Reference		Reference	
Black	0.449(0.108 ~ 1.864)	0.270	1.420(0.601 ~ 3.356)	0.424
Other	0.823(0.292 ~ 2.319)	0.712	0.603(0.145 ~ 2.504)	0.486
Marital status				
unmarried	Reference		Reference	
Married	0.737(0.397 ~ 1.368)	0.333	0.522(0.308 ~ 0.884)	0.016
Grade				
I + II	Reference		Reference	
III + IV	2.356(0.222 ~ 24.989)	0.477	5.347(0.664 ~ 43.044)	0.115
Laterality				
Left	Reference		Reference	
Right	1.462(0.801 ~ 2.667)	0.216	0.740(0.414 ~ 1.324)	0.310
Size (cm)				
≤ 10	Reference		Reference	
> 10	0.713(0.367 ~ 1.385)	0.318	0.788(0.445 ~ 1.395)	0.414

Variable	One site of distant metastases		More than one metastasis	
	HR (95%CI)	P value	HR (95%CI)	P value
T stage				
T1-T2	Reference		Reference	
T3-T4	1.104(0.520 ~ 2.344)	0.797	0.821(0.442 ~ 1.527)	0.534
N stage				
N0	Reference		Reference	
N1	2.149(0.942 ~ 4.904)	0.069	1.001(0.551 ~ 1.820)	0.997
Metastatic sites				
Liver	Reference		-	
Lung	0.504(0.280 ~ 0.909)	0.023	-	-
Treatment				
Surgery treatment				
No	Reference		Reference	
Yes	0.365(0.198 ~ 0.675)	0.001	0.425(0.224 ~ 0.805)	0.009
Radiation therapy				
No	Reference		Reference	
Yes	0.740(0.229 ~ 2.393)	0.615	0.280(0.068 ~ 1.148)	0.077
Chemotherapy				
No	Reference		Reference	
Yes	0.633(0.343 ~ 1.166)	0.142	0.333(0.195 ~ 0.571)	< 0.001

Table 8
Multivariate Cox regression analysis of prognostic factors for MAC patients with one or more metastases.

Variable	One site of distant metastasis		More than one metastasis	
	HR (95%CI)	P value	HR (95%CI)	P value
Marital status				
unmarried	-		Reference	
Married	-	-	0.573(0.334 ~ 0.985)	0.044
Metastatic sites				
Liver	Reference		-	
Lung	0.535(0.297 ~ 0.964)	0.037	-	-
Treatment				
Surgery treatment				
No	Reference		Reference	
Yes	0.384(0.209 ~ 0.705)	0.002	0.372(0.189 ~ 0.732)	0.004
Chemotherapy				
No	-		Reference	
Yes	-	-	0.363(0.209 ~ 0.632)	< 0.001

Discussion

Stage IV adrenocortical carcinoma is associated with poor prognosis[17]. Identification of the risk factors and the metastatic patterns for this disease can help instruct personalized treatment and potentially ameliorate their outcomes. However, there is limited information about the pattern of spread and treatment on prognosis. Furthermore, few studies have reported on the prognosis of these stage IV cancers correlated with the metastatic sites. Considering the shortage of the published research, we analyzed the patterns of cancer spread at diagnosis and prognostic factors in MAC patients with not only the whole cohort but also one or more metastases cohort.

In this study, for all MAC patients, year of diagnosis between 2013 and 2016 was the only demographic predictor for better survival, which may benefit from advances in treatment. Our results were in agreement with prior studies manifesting that age, gender, tumor size, laterality, metastatic sites including bone and lung, did not affect OS[18]. Furthermore, in our study, patients' race, marital status, tumor grade, T stage and N stage showed rarely correlation with survival outcome. Significantly, the death risk in patients with liver metastasis is higher than that in patients without liver metastasis. In addition, it should be noted that

there are some differences from our findings that some previous studies showed patients' age and tumor grade were prognostic factors for advanced adrenocortical carcinoma[4, 8, 19]. Some researchers also argued that clinical symptom, Weiss score, Ki67 and the mitotic rate can predict different survival outcomes[4, 18].

Up to now, only a few researchers have concentrated on the association between the number of metastatic sites and MAC patients' survival. Different from previous studies[4, 18], in our research, and compared to patients with more than one metastatic site, we found a slight benefit in OS of patients with one metastasis, which did not reach statistical significance in a multivariate Cox analysis yet. Erdoganet et al.[16] determined that tumor burden had no relevant impact on the prognosis of advanced adrenocortical carcinoma, which was consistent with the study by den Winkel et al.[20] who argued that the number of metastases and lymph node involvement did not significantly influence survival in a small cohort of 24 patients. On the contrary, Ettaiebet et al.[9] analyzed 117 MAC patients, among whom 84 patients had synchronous metastases and 33 developed metachronous metastases, and came to a conclusion that in the synchronous metastases group, more than one metastasis was found to be associated with reduced overall survival. Due to the rarity of the disease, most recommendations for adrenocortical carcinoma are derived from retrospective studies, and whether the number of metastatic organs is an independent prognostic factor of MAC patients is contentious.

Advanced adrenocortical carcinoma most frequently metastasizes to lung and liver, and the variables except marital status, metastatic sites and therapy didn't seem to have a statistically significant relationship with the survival outcome, whether in patients with single or multiple metastases. Especially, it was the first study to incorporate marital status in the analysis, and the results showed that for patients with more than one metastatic organ, marital status was an independent prognostic factor for survival. Through univariate and multivariate analysis of patients with only liver or lung metastasis, we found that patients with lung metastasis had a lower risk of death. The potential mechanism needs to be explored and our results demand further confirmation.

For early adrenocortical carcinoma patients, surgical treatment is the only radical treatment[10]. Many studies have revealed that patients with MAC should undergo operation if they have potentially resectable disease and can withstand an operation, and the majority of the resections for distant metastases were for pulmonary lesions (55%), liver lesions (28%), or bone lesions (11%), R0 resection of the primary tumor is an independent prognostic factor of OS[16, 21, 22]. Similarly, in our study, for the whole MAC population, whether they had single or multiple metastatic organs, surgical treatment can bring survival benefits and reduce the death risk.

As for the chemotherapy, the landmark study about MAC was published in 2012, Fassnacht et al.[23] found that it was an improved progression-free survival that there was for patients who accepted mitotane and etoposide, doxorubicin, and cisplatin, compared with patients who accepted mitotane and streptozocin. Before that, Terzolo et al.[24] conducted a vital retrospective analysis involving 177 patients with adrenocortical carcinoma who had undergone radical surgery, and proved that compared with

patients who did not receive adjuvant therapy, those received adjuvant mitotane had a better overall survival. At present, it is believed that patients with inoperable or metastatic diseases may benefit from systemic treatment, including multiple cytotoxic drugs, which are usually used in combination with mitotane[17]. In general, the treatment outcome of MAC is still poor, and researchers have developed many trials on targeted therapy and immunotherapy to seek a way out[25–29]. In our study, the chemotherapy regimen used by patients was unknown, and for the whole population and patients with more than one metastatic site, chemotherapy are independent prognostic factors, but for patients with only one metastatic site, chemotherapy may reduce the death risk, which doesn't reach the statistically significance.

In our research, radiotherapy does not benefit patients regardless of the number of metastatic sites. Jiawei Zhu et al. [30] conducted a cohort study in which 12 patients underwent postoperative adjuvant radiotherapy (ART) and were matched one to one to patients with only surgical resection, and the result showed there was no significant difference between ART group and control group. However, their systematic review comparing ART after resection and resection only in ACC demonstrated a significant improvement in OS with ART. Srougi et al.[31]performed a meta-analysis, which included four retrospective series, revealing that there were no benefits in disease recurrence control or overall survival for patients who underwent this adjuvant radiotherapy therapy. At present, the effect of radiotherapy in adrenocortical carcinoma is still controversial[32–35]. Prospective studies are needed to further explore the role of radiotherapy in the future.

Considering that this is a retrospective study, there are a few limitations. Firstly, this research may be influenced by potential bias with missing or incorrect data. And it was unavailable for whether there are multiple metastases within a single organ. Besides, we are unable to get information about less common locations of metastasis for adrenocortical carcinoma. Secondly, the SEER database cannot provide information on patient ECOG performance status, hormonal evaluation, detailed surgical and chemoradiotherapy plan or other factors that may influence prognosis. Thirdly, due to the limitation of sample size, we did not perform subgroup analysis on other variables. Lastly, imbalance ratios of variables may lead to results bias. Considering these limitations, prospective researches should be performed to circumstantiate our results.

Conclusions

In this study, we found that year of diagnosis, metastatic sites, surgery and chemotherapy were significantly prognostic factors for OS in MAC patients. Compared with liver metastases, patients with lung metastases had a better OS. However, the number of distant metastatic organs didn't affect patients' survival outcome. But for MAC patients with single metastasis, surgery was a good prognostic factor, while for patients with more than one metastasis, married status, surgery and chemotherapy were correlated with better OS. Based on the collective findings, surgery can be regarded as the preferred treatment option for all MAC patients. Besides, chemotherapy is also a good choice for patients with multiple metastases.

Abbreviations

MAC: Metastatic adrenocortical carcinomas; OS: overall survival; SEER: Surveillance, Epidemiology, and End Results; CI: confidence interval; HR: hazard ratio; ART: adjuvant radiotherapy.

Declarations

Ethics approval and consent to participate

These public data are open access and don't need Institutional Review Board approval.

Consent for publication

Not applicable.

Availability of data and materials

The SEER database is publicly available. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Data acquisition: NY, QW; Methodology: FC, HO, YZ; Writing original draft and editing: NY; Project administration: YZ. All authors read and approved the final manuscript.

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Figures

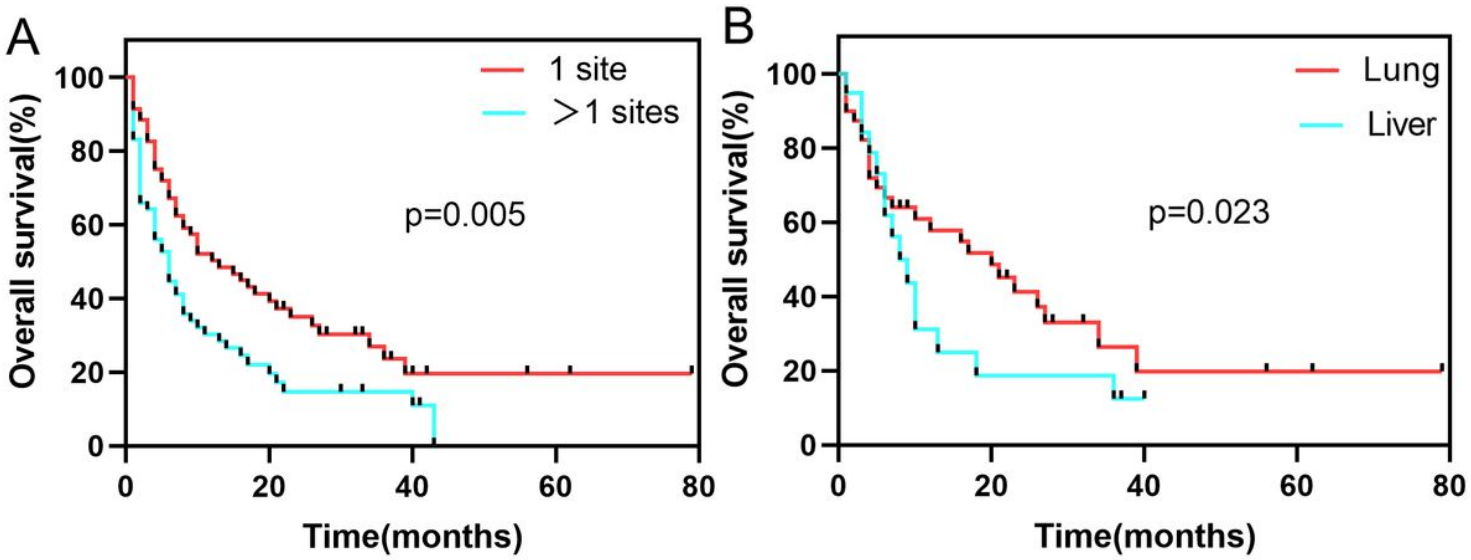

Figure 1

Kaplan-Meier survival curves for MAC patients stratified by the number of metastatic sites (A) and only lung or liver metastases (B).

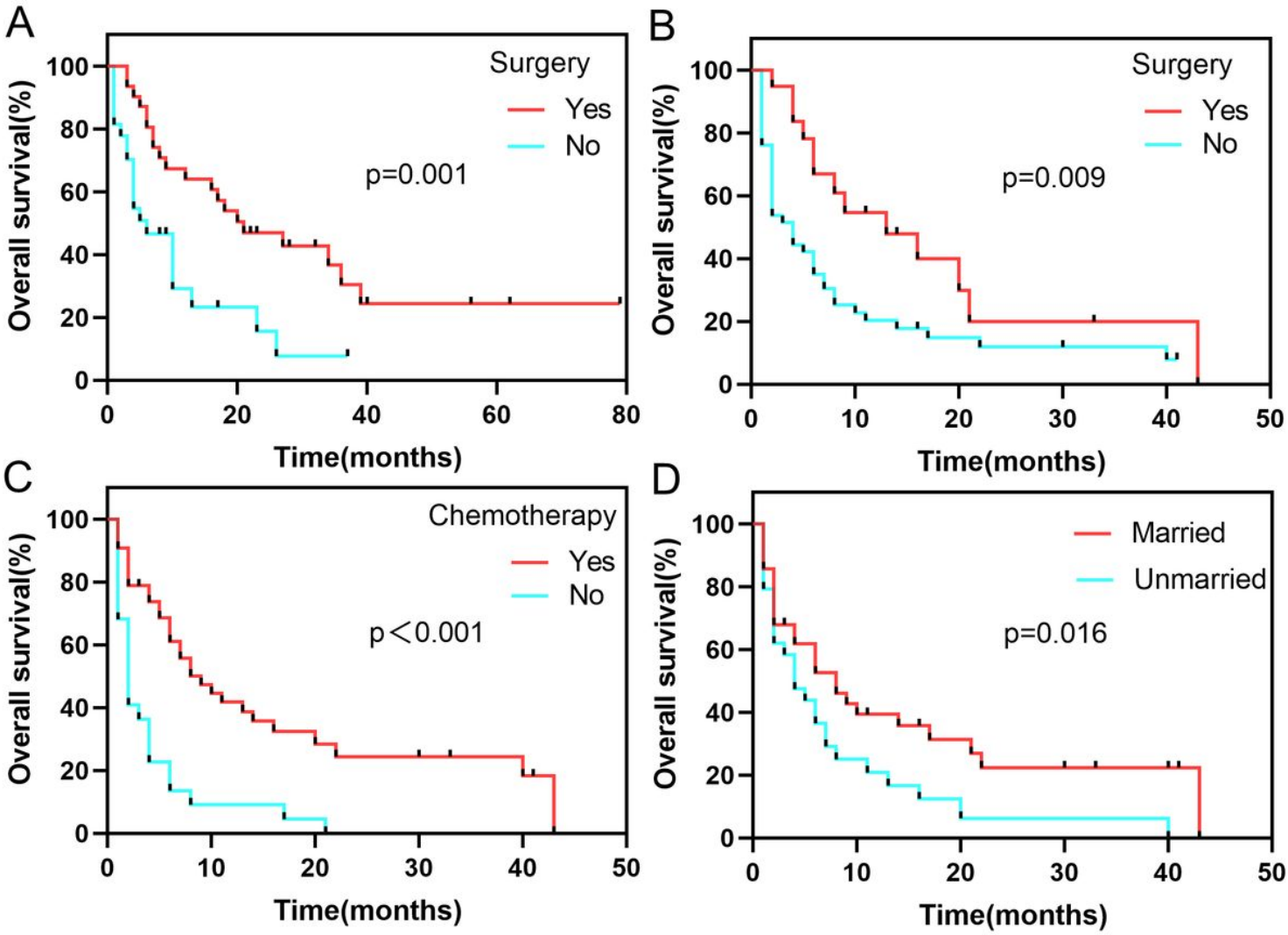

Figure 2

Kaplan-Meier survival curves in patients with one (A) and more (B□C□D) metastatic sites.