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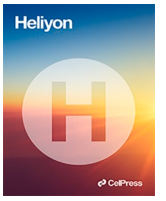

Research article

Metastatic pattern and prognosis in patients with lung adenosquamous carcinoma: A surveillance, epidemiology, and end results-based population study

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ABSTRACT

Background: Lung adenosquamous carcinoma (ASC) is a rare tumor with high invasive and metastatic potential. Few studies have explored metastatic patterns in patients with advanced-stage ASC.

Methods: Patients diagnosed with ASC in the Surveillance, Epidemiology, and End Results database from 2010 to 2015 were selected. Descriptive statistics were obtained to characterize the metastatic sites of the study participants. The Kaplan–Meier method was applied to compare survival curves among patients with different metastatic patterns. Cox regression analysis was performed to evaluate risk factors for metastasis.

Results: A total of 858 eligible patients with ASC were enrolled; the mean age was 71.5 years (standard deviation ± 7.8 years). There was a slightly higher proportion of male patients (54.0 %). A total of 63.2 % of patients harbored single-site metastasis (median OS: 5 months), 23.6 % of patients had two-site metastasis (median OS: 4 months), and approximately 10 % of patients harbored three or more sites metastasis (median OS: 3 months). Bone (56.9 %) was the most frequent site of metastasis (median OS: 4 months), followed by lung metastasis (37.6 %, median OS: 5 months), liver metastasis (22.1 %, median OS: 5 months), and brain metastasis (21.4 %, median OS: 4 months). Chemotherapy decreased the risk of death by 70 % (HR = 0.296, 95 % CI 0.241–0.363), 70 % (HR = 0.302, 95 % CI 0.224–0.406), 78 % (HR = 0.218, 95 % CI 0.151–0.314), and 70 % (HR = 0.302, 95 % CI 0.231–0.396) in patients harboring bone, liver, brain and lung metastases, respectively. The brain increased the risk of death by 50 % (HR = 1.501, 95 % CI 1.209–1.865), 64 % (HR = 1.644, 95 % CI 1.126–2.402), and 128 % (HR = 2.284, 95 % CI 1.653–3.157) in patients harboring bone, liver and lung metastases, respectively.

Conclusion: Patients with advanced-stage ASC have unfavorable outcomes. Early detection and aggressive treatment can improve patients outcomes.

1. Introduction

In recent years, lung cancer has been the leading cause of death globally [1]. Non-small cell lung carcinoma accounts for approximately 85 % of all lung cancers, including lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), large cell

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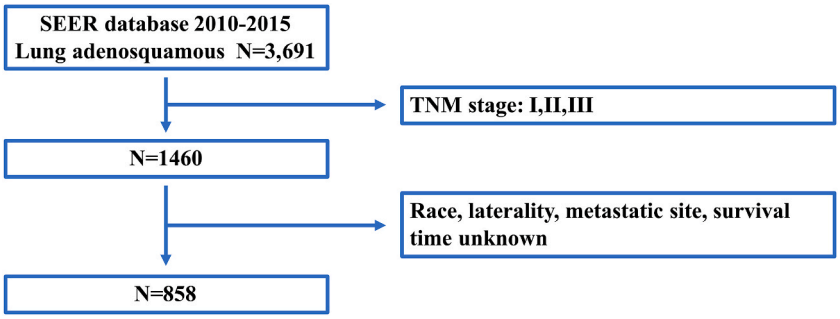

Fig. 1. Flow chart for selecting lung adenosquamous patients from the SEER database.

carcinoma, and other rare tumors, including adenosquamous carcinoma (ASC). According to the 2015 WHO pathological classification, ASC comprises both the squamous and adenocarcinoma histological subtypes (defined as > 10 % of each subtype) [2]. It is estimated that ASC accounts for 0.4–4% of all lung cancer cases [3]. ASC is a highly aggressive disease, with a 5-year cumulative overall survival rate of less than 20 % after surgery [4]. According to previous studies, patients with ASC have a worse prognosis than those with LUAD or LUSC [5,6].

Distant metastasis is the most important biological feature of malignant tumors and is a major life-threatening complication in cancer patients. Similar to other malignancies, patients with ASC are predisposed to metastasis. Due to tumor heterogeneity, there are significant differences in metastatic patterns among different types of tumors, even within the same tumor type [7]. Distant metastasis indicates a lower survival rate and poor prognosis. Therefore, exploring the pattern of metastasis is important for the management of ASC. Because of its low incidence rate, the pattern of metastasis of this tumor is not well understood. An Italian single-center study showed that the brain was the most common site of ASC metastasis after surgery [6]. However, single-center studies have a risk of patient selection bias. Thus, large-scale multicenter studies are urgently needed.

The Surveillance, Epidemiology, and End Results (SEER) database is supported by the National Cancer Institute (NCI) and is recognized as an efficient database for exploring rare cancers. In this study, we selected patients with ASC in the SEER database who were diagnosed between 2010 and 2015 and described the metastatic patterns of patients with ASC. We studied the survival of patients with different metastatic patterns of ASC. Furthermore, we identified the risk factors for metastasis in ASC patients.

2. Methods

2.1. Data source and patient selection

The SEER database covers cancer incidence and mortality data from 18 population-based registries that capture approximately 30 % of the population of the USA [8]. We extracted data from ASC patients diagnosed between 2010 and 2015 from the SEER 18 incidence database (released in April 2019, based on the November 2018 submission). In this database, the International Classification of Diseases, 3rd edition (ICD-*O*-3) code 8560 corresponds to ASC. A flow chart of the study process is shown in Fig. 1. No institutional review was conducted because the SEER database is openly accessible. We obtained the data for this study using the 11348-Nov2019 username.

2.2. Variable selection

Clinical information, including race, sex, age at diagnosis, year of diagnosis, primary site, laterality, T stage, N stage, and metastasis site, was collected from the SEER database for each individual. Patients were divided into three groups according to race, as recorded in the SEER database: white, black, and others. Age at diagnosis is presented as the mean (±standard deviation). The primary site was classified into five groups, as described in the SEER database: main bronchus, upper lung lobe, middle lung lobe, lower lung lobe, or overlapped. Both the T and N stages were categorized into four groups based on the AJCC 7th edition staging system (T1, T2, T3, and T4; N0, N1, N2, and N3). The metastatic sites at diagnosis were the bone, liver, brain and lung. Considering that there were more than 20 % missing values in terms of pathological differentiation, we excluded this from the analysis.

2.3. Statistical analysis

The clinical and demographic characteristics of the patients with ASC are shown by descriptive statistics. Survival curves were created using the Kaplan–Meier method, and any differences in the survival curves were compared by the log-rank test. Overall survival (OS) referred to the duration from diagnosis to any original death or last follow-up. Cox regression analyses were performed to calculate the hazard ratios (HRs). All variables were included in the multivariable analysis.

All the data were obtained using the SEER*Stat software, version 8.3.4 (https://seer.cancer.gov/seerstat/). Statistical analyses were performed using the R language. Statistical significance was defined as a two-sided P-value <0.05.

Table 1
Clinical features of patients with advanced-stage lung adenosquamous carcinoma in SEER database.

Variables	Number
Age	71.5 ± 7.8
Sex	
Male	464 (54.0 %)
Female	394 (45.9 %)
Organ specific metastatic site (N = 858,100 %)	
Bone	489 (56.9 %)
Brain	184 (21.4 %)
Liver	276 (32.1 %)
Lung	323 (37.6 %)
Single-site metastasis (N = 542, 63.2 %)	
Bone	227 (41.9 %)
Brain	37 (6.8 %)
Liver	128 (23.6 %)
Lung	150 (37.6)
Two-site metastasis (N = 226, 26.3 %)	
Bone and brain	59 (26.1 %)
Bone and liver	55 (24.3 %)
Bone and lung	62 (27.4 %)
Brain and liver	5 (2.2 %)
Brian and lung	17 (7.5 %)
Liver and lung	28 (12.4 %)
Three or more sites metastasis (N = 90, 10.5 %)	
Bone and brain and liver	24 (26.7 %)
Bone and brain and lung	30 (33.3 %)
Bone and liver and lung	24 (26.7 %)
Brain and liver and lung	4 (4.4 %)
Bone and brain and liver and lung	8 (8.9 %)

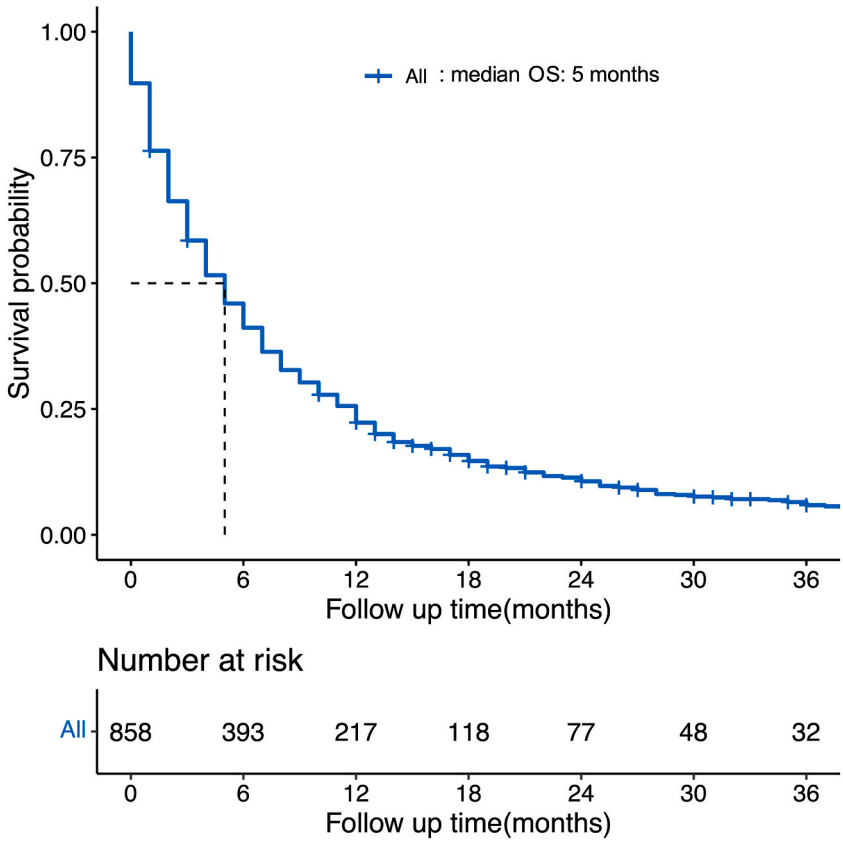

Fig. 2. The K–M curves of patients with advanced-stage lung adenosquamous.

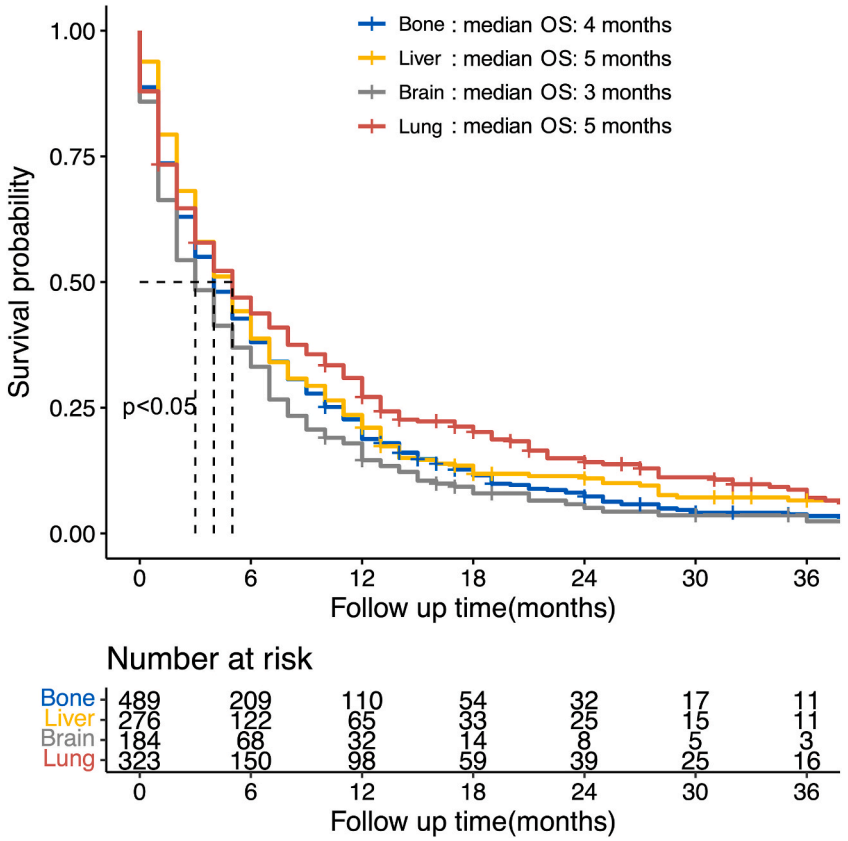

Fig. 3. The K–M curves of patients with advanced-stage lung adenosquamous harbored bone, brain, liver or lung metastases.

3. Results

3.1. Patients' characteristics

From the SEER database, we identified 858 patients with ASC had distant metastasis. As shown in Table 1, the mean age was 71.5 years (standard deviation [SD] ± 7.8 years). There was a slightly higher proportion of male patients (54.0 %). Among the 858 patients with ASC (median OS: 5 months; Fig. 2), bone (489/858, 56.9 %) was the most frequent site of metastasis (median OS: 4 months; Fig. 3), followed by 37.6 % had lung metastasis (median OS: 5 months; Fig. 3), 22.1 % had liver metastasis (median OS: 5 months; Fig. 3), and 21.4 % had brain metastasis (median OS: 4 months; Fig. 3). More detailed metastatic patterns are displayed in Table 1.

A total of 542 (63.2 %) patients harbored single-site metastasis (median OS: 5 months; Fig. 4). Of those, 227 (41.9 %) harbored single-bone metastases (median OS: 5 months; Fig. 5), 150 (37.6 %) harbored single-lung metastases (median OS: 6 months; Fig. 5), 128 (23.6 %) harbored single-liver metastases (median OS: 5 months; Fig. 5) and 37 (6.8 %) harbored solitary brain metastases. A total of 226 (23.6 %) patients harbored two-site metastasis (median OS: 4 months; Fig. 4). Of those, 59 (26.1 %) harbored bone and brain metastases (median OS: 4 months; Fig. 6), 55 (24.3 %) harbored bone and liver metastases (median OS: 4 months; Fig. 6), 62 (27.4 %) harbored bone and lung metastases (median OS: 5 months; Fig. 6), and 28 (12.4 %) harbored liver and lung metastases. Moreover, approximately 10 % of patients harbored metastases at three or more sites (median OS: 3 months; Fig. 4).

3.2. Cox regression analyses for risk factors for different metastatic patterns in patients with ASC

In patients with bone metastases, as shown in Fig. 7a, multivariate Cox regression analysis revealed that race, sex, liver metastases, brain metastases, and chemotherapy were related to OS ($P < 0.05$). In detail, the mortality risk in females (HR 0.818, 95 % CI 0.674–0.993) and patients who received chemotherapy (HR 0.296, 95 % CI 0.241–0.363) subgroup was lower, while patients who harbored liver metastasis (HR 1.419, 95 % CI 1.128–1.786) or brain metastases (HR 1.501, 95 % CI 1.209–1.865) had a poorer survival rate.

In patients with liver metastases, as shown in Fig. 7b, multivariate Cox regression analysis revealed that sex, age, laterality, bone metastasis, brain metastasis, and chemotherapy were related to OS ($P < 0.05$). In detail, the mortality risk in females (HR 0.722, 95 % CI 0.554–0.941) and patients who received chemotherapy (HR 0.302, 95 % CI 0.224–0.406) was lower, while patients with right-sided

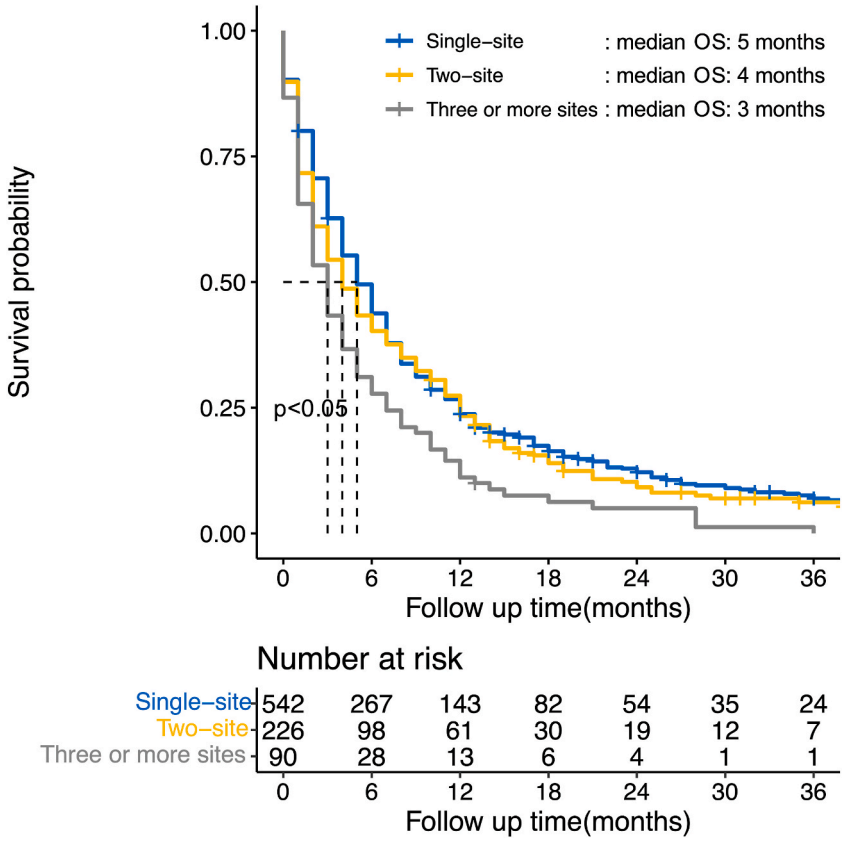

Fig. 4. The K−M curves of patients with advanced-stage lung adenosquamous harboring single-site, two-site, and three or more sites metastases.

primary tumors (HR 1.485, 95 % CI 1.128–1.957), harbored bone metastases (HR 1.563, 95 % CI 1.174–2.082) or brain metastases (HR 1.644, 95 % CI 1.126–2.402) had a poorer survival rate.

In patients with brain metastases, as shown in Fig. 7c, multivariate Cox regression analysis revealed that lung metastasis, and chemotherapy were related to OS ($P < 0.05$). In detail, the mortality risk in patients who received chemotherapy (HR 0.218, 95%CI 0.151–0.314) was lower, while patients harbored lung metastases (HR 1.990, 95%CI 1.333–2.971) had a poorer survival rate.

In patients with lung metastases, as shown in Fig. 7d, multivariate Cox regression analysis revealed that race, primary site, N stage, brain metastasis, and chemotherapy were related to OS ($P < 0.05$). In details, the mortality risk in patients who received chemotherapy (HR 0.302, 95 % CI 0.231–0.396) was lower, while patients who had advanced N stage disease (N2: HR 1.695, 95 % CI 1.194–2.407; N3: HR 1.589, 95 % CI 1.082–2.334) and who harbored brain metastases (HR 2.284, 95 % CI 1.653–3.157) had a poorer survival rate.

4. Discussion

In this study, the data of patients with advanced-stage ASC were retrieved from the SEER database to investigate the metastatic patterns and risk factors related to prognosis in various metastatic patterns. On the one hand, we found that in the whole cohort, patients harbored mainly single-organ metastases, of which bone was the most common metastatic site. The median overall survival time was poor for all metastatic patterns (ranging from 3 months to 6 months). On the other hand, the prognostic factors of ASC differed among the bone, liver, brain, and lung metastasis subgroups. Among these factors, chemotherapy is an important factor for improving the prognosis; however, brain metastasis is an important factor for a worse prognosis in ASC patients.

To the best of our knowledge, this is the first study exploring the metastatic pattern in ASC patients. In this study, we describe the clinical features of patients with ASC at initial diagnosis. Bone was the most common metastatic site for ASC at initial diagnosis. More than half of patients have bone metastasis. This is consistent with previous studies [9,10]. Wang et al. reported that the incidence of bone metastases in advanced-stage LUAD and LUSC patients was 55.8 % and 56.5 %, respectively [9]. There are multiple mechanisms of tumor cell metastasis to bone. The intrinsic properties of tumor cells, the changes caused by tumor cells or their products in the bone microenvironment, and the bone microenvironment itself are all related to the preferential colonization and growth of cancer cells in bone [11]. Although cancer-related single-brain metastases are relatively uncommon in ASC patients, patients with ASC were in connection with a significant higher mortality rate once brain metastases occurred. As previous studies reported, the natural average survival time in lung cancer patients with brain is only 1–2 months [12]. The mechanism of tumor brain metastasis is still unclear. One single-center study reported that the brain was the most common metastatic site during the follow-up period [6]. The differences in

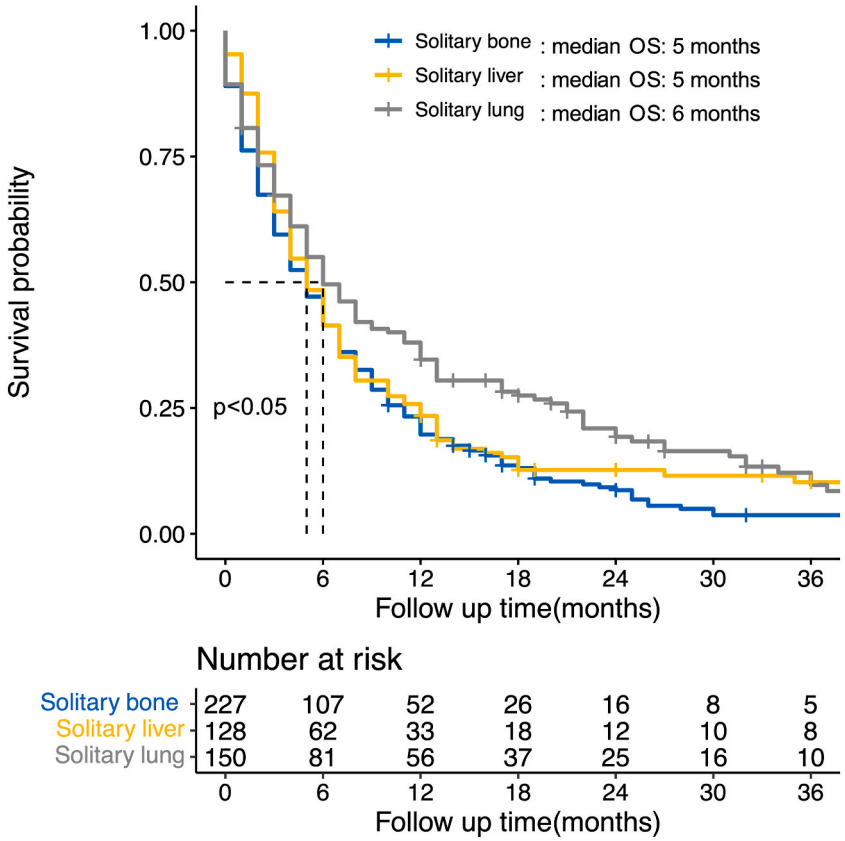

Fig. 5. The K–M curves of patients with advanced-stage lung adenosquamous harboring single-bone, single-liver, and single-lung metastases.

metastatic patterns between newly diagnosed patients and postoperative patients are important for disease monitoring and for post-treatment follow-up.

The risk factors associated with survival in in patients with multiple modes of metastasis were further explored. Among patients with bone or liver metastases, females had better prognoses. Tian Xu et al. reported that in non-small cell lung cancer (NSCLC) patients with liver metastases, compared with males, females had a 10 % lower risk of mortality [13]. Moreover, in NSCLC patients with bone metastases, females had a 24 % lower risk of mortality [14]. Several factors have been reported to explain the better prognosis in females. Male patients were more likely than female patients to be diagnosed with stage 3–4 disease [15]. In terms of treatment, a meta-analysis revealed that women with advanced lung cancer derived a statistically significantly greater benefit from the addition of chemotherapy to anti-PD-1/PD-L1 therapy than men did [16]. Although adverse reactions are common after chemotherapy in clinic scenarios, chemotherapy could improve the outcome of ASC patients with different metastatic patterns drastically. Similar results have been reported in ASC in other sites, such as stomach [17], gallbladder [18], and pancreas [19]. In clinical practice, patients may fail to receive chemotherapy because of economic burdens or worry about chemotherapy-related side effects, or clinicians may believe that patients may not be able to tolerate chemotherapy after evaluation, and so on. This study confirmed the benefits of chemotherapy for patients from large sample data, and clinicians need to dynamically evaluate the physical function of patients, so as to perform chemotherapy as much as possible. Although the treatment of cancer has progressed rapidly, there is a lack of large sample studies to determine the specific treatment plan for rare tumors, such as ASC. This study provides evidence that patients with ASC with different metastasis patterns might benefit from chemotherapy. Chemotherapy for brain tumors usually lacks of effectiveness because most chemotherapeutic drugs have difficultly penetrating the blood-brain barrier, however, blood-brain barrier permeability is highly increased during lung cancer brain metastasis [20].This might explain why ASC patients with brain metastasis could benefit from chemotherapy.

Although the present study found that chemotherapy might improve advanced-stage ASC patients' outcomes, a broader therapeutic arsenal beyond chemotherapy is currently available, such as palliative resection, radiotherapy, targeted therapy, anti-vascular therapy, and immunotherapy. Lung cancer survival has improved significantly, due to treatment advances in the last decade (e.g., targeted therapy and immunotherapy [21]. Sara Manglaviti et al. reported that the median OS in advanced-stage ASC received immunotherapy was 8.8 months [22]. In another study, Chao Li et al. using a real-world data of 46 ASC patients found that the median OS was 24.7 months and not reached in single immunotherapy group and immunochemotherapy group, respectively [23]. In fact, the prognosis of patients at the same stage receiving the same treatment varies greatly in Chao Li 's study. Lung cancer therapy has entered into the era of precision medicine, find more potential targets and immune checkpoints, or finer pathological classification to determine the

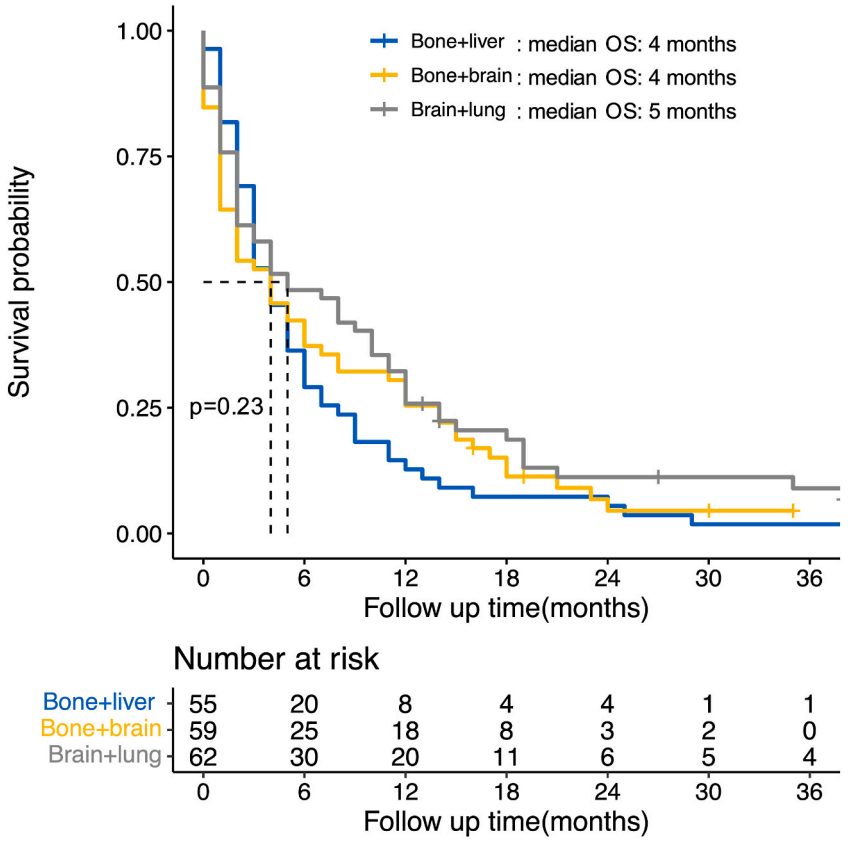

Fig. 6. The K–M curves of patients with advanced-stage lung adenosquamous harboring bone + brain, bone + liver, and bone + lung metastases.

treatment advantage population are the future research direction.

This study has several strengths and limitations. No previous multicenter investigations of the metastatic pattern of ASC patients have been reported. The multicenter nature of our study ensured the reliability of our findings. However, this was a retrospective study and was subject to inherent limitations related to retrospective analyses. Rare sites of metastasis, such as the peritoneum [24] and penis [25], have been reported in previous studies. In addition, data from the SEER database were limited. Other risk factors for metastasis, such as tobacco use [26], a positive bone sialoprotein test [27], and the proportion of adenomatous or squamous components [28], were difficult to obtain.

5. Conclusion

In conclusion, our study illustrated the metastatic patterns of relatively rare malignances by analyzing the SEER database. Patients with advanced-stage ASC have a poor prognosis. There is a difference in the incidence and outcome of various metastatic patterns. Patients harboring single-site metastasis had the best prognosis. Moreover, active treatment is necessary.

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Ethical approval

Written informed consent for participation was not required for this work in accordance with the national legislation and the institutional requirements.

Data availability statement

Data derived from a source in the public domain (https://seer.cancer.gov). The data that support the findings of this study are available from the corresponding author upon reasonable request (11348-Nov2019).

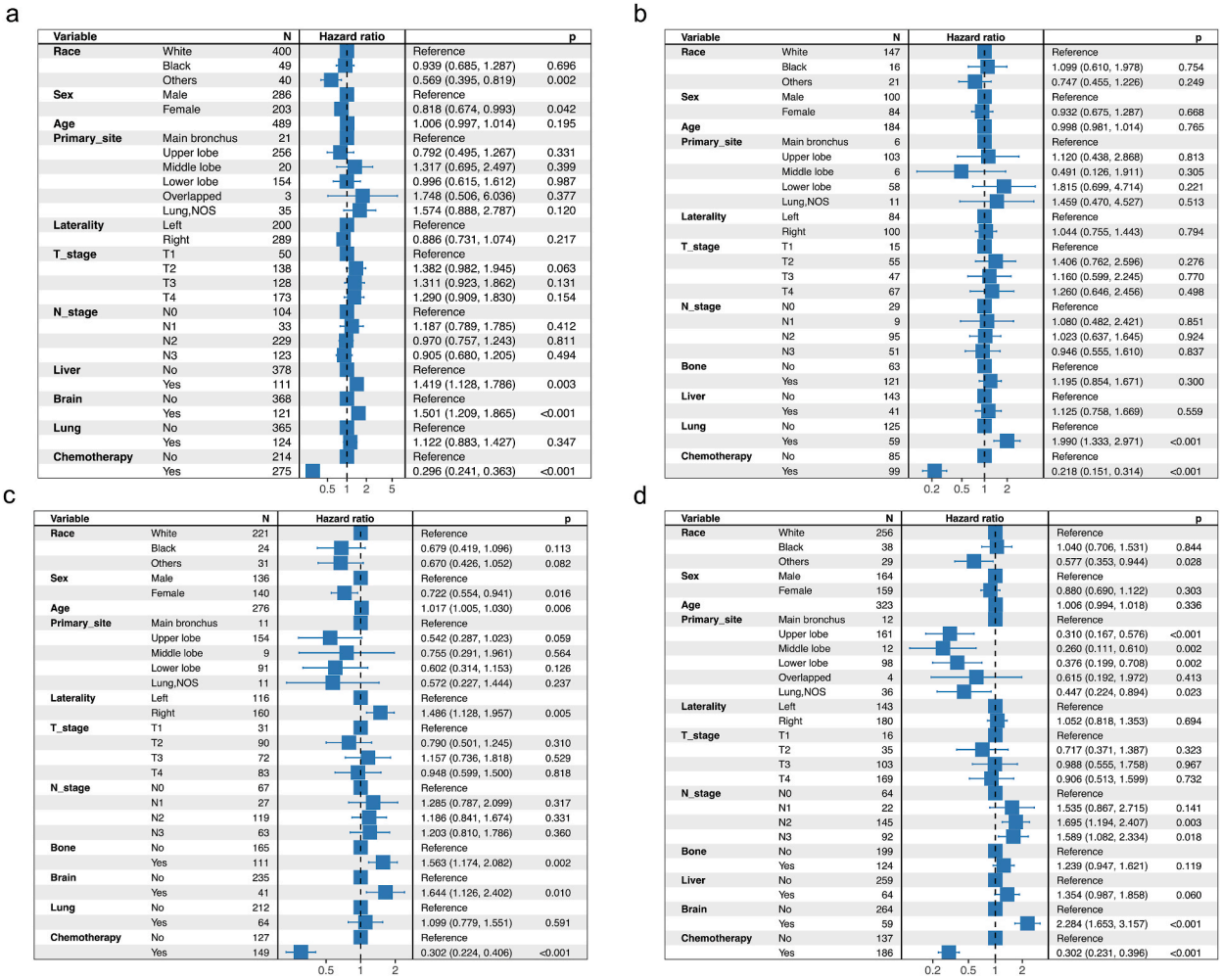

Fig. 7. Cox regression analysis for risk factors in patients with advanced-stage lung adenosquamous harboring bone (a), brain (b), liver (c) or lung (d) metastases.

CRediT authorship contribution statement

Jun Xie: Writing – original draft, Methodology, Conceptualization. **Chong Li:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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