


Increased proportion of the squamous cell carcinoma component is associated with worse survival in resected gastric adenosquamous carcinoma

A STROBE compliant cohort study

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Abstract

For the diagnosis of gastric adenosquamous carcinoma (ASC), discrepancies regarding a rational diagnostic proportion of the squamous cell carcinoma (SCC) component exist among different organizations. Our study aimed to evaluate the impact of the SCC component on the survival of gastric cancer patients and identify the optimal cutoff value for the SCC component necessary for diagnosing gastric ASC.

Cases of gastric cancer with an SCC component were obtained from our center and from case reports and series extracted from Medline. Univariate and multivariate analyses were conducted to compare the overall survival between groups and examine the prognostic value of various clinical parameters.

We identified 45 qualified cases in published literature and 13 in our center. Forty-two of them were males and 16 females (M: F = 2.6:1). Thirty of them were Asian patients and the rest were mainly from the United States and Europe. The mean age was 61.1 years (median 64 years, range 32–84 years). The average tumor size was 6.9 cm (median 6.0 cm, range 2.0–16.0 cm). The most common location of the cancer was the lower third (39.7%). Although a statistical difference was not achieved, the Kaplan–Meier curve demonstrated that as the proportion of the SCC component in the primary lesion increased, the patients' survival risk increased ($P = .489$), and the presence of the SCC component in metastatic lymph nodes also increased the risk of survival ($P = .259$); both of these findings indicated a negative impact of the SCC component on survival. Furthermore, we identified the optimal cutoff for the SCC component as 35% ($\chi^2 = 6.544$, $P = .011$), which was subsequently validated in a Cox regression model as an independent prognostic factor ($P = .026$).

An increased proportion of the SCC component is associated with worse survival in gastric cancer patients with an SCC component. The optimal cutoff for the proportion of the SCC component necessary for the diagnosis of gastric ASC is 35%.

Abbreviations: AC = adenocarcinoma, ASC = adenosquamous carcinoma, CI = confidence interval, HR = hazard ratio, JGCA = Japanese Gastric Cancer Association, LVI = lymphovascular invasion, OS = overall survival, SCC = squamous cell carcinoma, WHO = World Health Organization.

Keywords: adenosquamous carcinoma, component, diagnosis, gastric cancer, survival

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]; The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Primary gastric adenosquamous carcinoma (ASC) is a rare form of gastric cancer associated with dismal survival^[1–8] and is characterized by variable combinations of 2 malignant components, namely, adenocarcinoma (AC) and squamous cell carcinoma (SCC) components. ASC accounts for less than 1% of gastric carcinomas.^[4,6] According to the classification of tumors of the digestive system introduced by the World Health Organization (WHO), without a clear indication of the diagnostic threshold of the SCC component, ASC is defined as a malignant epithelial tumor with significant components of both glandular and squamous differentiation.^[9] However, the Japanese Gastric Cancer Association (JGCA) suggests that the SCC component exceeds 25% of the primary tumor.^[10] This discrepancy in diagnostic criteria also exists in ASC of other organs, such as the esophagus^[11,12] and pancreas.^[13] This divergence comes mainly from the unsure definition of rational thresholds.

Significantly, in the Johns Hopkins study of pancreatic ASC, although the presence of any SCC component was associated with a poorer prognosis than AC, the proportion of the SCC component with a cutoff of 30% according to the WHO classification was not associated with survival,^[14] thus leading to the opposition to the diagnostic standard by some authors.^[13–15] In our perspective, a plausible threshold should maximize the distinction between high-risk and low-risk patient groups.

However, the role of the SCC component in the survival of patients with gastric cancer is not well defined and exploration of a reasonable diagnostic threshold of the SCC component for diagnosing ASC is important. Few studies have yet been conducted to address this issue.

We have therefore conducted this retrospective study aiming to assess the impact of the SCC component on survival in resected gastric cancer patients and determine the optimal cutoff for the proportion of the SCC component necessary for the diagnosis of gastric ASC.

2. Materials and methods

2.1. Patient selection and data preparation

This study was approved by the Ethics Committee of West China Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all participants from our hospital who were included in our study.

Cases of gastric cancer with an SCC component were collected from our hospital and also from the literature. We screened patients who underwent surgery in our hospital from 2008 to 2020, and a literature search of Medline was conducted for articles^[1,5,8,16–20] published from 1986 through 2020. We conducted a computerized search in Medline through internet in March 2020. Because of the rarity of this carcinoma, language limit was not set in the literature search. Terms of “adenosquamous AND stomach,” “adenosquamous AND gastric,” “carcinoma with squamous component AND stomach,” “carcinoma with squamous component AND gastric” were used independently. A combination of these search results was performed by inputting citations into the “clipboard” function of PubMed. Original articles were retrieved and reviewed,

and additional cases were then identified through the review process.

Patients diagnosed on the basis of histology with gastric AC cancer with the squamous component were enrolled in the present study. Inclusion criteria were shown as follows: age at the diagnosis ≥ 18 years; the diagnosis must be confirmed by the tumor tissue sample from surgery but not by autopsy or death certificate; only 1 malignant primary tumor was diagnosed. We excluded patients who had incomplete survival data.

Data including sex, age, tumor site, tumor size, Borrmann classification, differentiation grade, lymphovascular invasion (LVI), tumor depth, nodal status, metastatic status, the proportion of the SCC component, nodal contents, adjuvant therapy, and survival data were collected. All cases were restaged based on the 8th edition classification system released by the American Joint Committee on Cancer.

Overall survival (OS) was applied as the primary outcome of our study, and defined as the time from diagnosis to the last follow-up or death. The cutoff date for follow-up was March 31, 2020. The follow-up time was censored if any primary end point occurred or if the patient was unavailable for follow-up.

2.2. Statistical analysis

The cutoff values for the proportion of the SCC component were analyzed using the X-tile program (<http://www.tissuearray.org/rimmlab/>), which identified the cutoff for the categorical proportion of the SCC component for survival using the minimum *P* values from log-rank χ^2 statistics.^[21] The relationship between various variables and survival was evaluated using the Kaplan–Meier method. Differences between survival curves were tested for statistical significance using the log-rank test. Significant prognostic predictors for patients identified by univariate analysis were further assessed by multivariate analysis using the Cox proportional hazards regression model. Missing attribute values were treated as special values. Data were processed using SPSS 23.0 (SPSS Inc., Chicago, IL). An α value of .05 was used as the examination standard.

3. Results

3.1. Patient selection and baseline characteristics

We identified a total of 301 articles in PubMed, including 146 articles by searching “adenosquamous AND stomach,” 34 by “adenosquamous AND gastric,” 74 by “carcinoma with squamous component AND stomach,” and 47 by “carcinoma with squamous component AND gastric,” respectively. Among all these articles identified by computerized search in PubMed as of March 2020, 4 articles that met criteria were included in this study. They provided information of 60 patients. Additional 6 qualified reports, each presented 1 patient, and were collected by manually reviewing those articles. Thus, with 22 additional patients in our center, a total of 88 patients were qualified. However, 58 patients were included in this study eventually because 30 cases were excluded due to lack of information on proportion of the squamous component or survival time (Fig. 1).

Patient clinicopathological features are summarized in Table 1. There were 42 male (72.4%) and 16 female (27.6%) patients. The median age was 64 years (range 32–84 years). The most common location of the cancer was the lower third (39.7%), followed by upper third (34.5%) and middle third (17.2%) of the stomach. The median tumor size was 6.0 cm (range 2–16 cm).

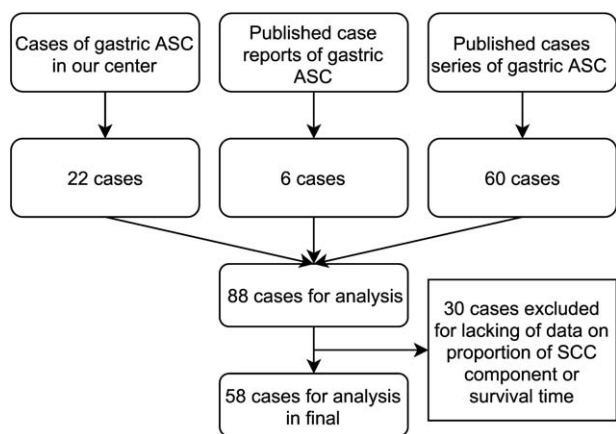


Figure 1. Flowchart of patient selection. ASC = adenosquamous carcinoma; SCC = squamous cell carcinoma.

Type II of the Borrmann classification was most frequently observed (37.9%). Most of the tumors were poorly differentiated (27.6%), followed by tumors that were moderately differentiated (8.6%) and well-differentiated (1.7%). Half of the cases (58.6%) were staged as T4. Most of the patients (46.6%) suffered from lymph node metastases. In terms of the components of the metastatic lymph nodes, a pure AC component was found in 10.3% of cases, both AC and SCC components were found in 24.1% of cases, and a pure SCC component was not found in any of the cases.

3.2. Identification of the cutoff for the minimum proportion of the SCC component

All 58 cases were included in the survival analysis. The median survival time was 14 months, and the median follow-up time was 60 months (range 1–118 months).

To assess the influence of different proportions of the SCC component on OS, we analyzed the individual results using different proportions of the SCC component ranging from 15% to 85%. Proportions less than 15% and greater than 85% were not analyzed to guarantee sufficient statistical power. The 5-year OS was calculated for patients with gastric cancer that had a certain percentage of the SCC component (P) or more and less than P (Table 2). It showed that when P ranged from 15% to 85%, the 5-year OS of patients with P or more than P decreased gradually; however, in patients with gastric cancer who had a proportion of the AC component (calculated by “1-P”) that ranged from 15% to 70%, the 5-year OS increased (range, 15.6–37.5%), although not consistently. Furthermore, the survival hazard plot (Fig. 2A) demonstrated that with the increase in the proportion of the SCC component in the primary lesion, the risk of death gradually increased ($P = .489$). In addition, we observed that the presence of the SCC component in metastatic lymph nodes indicated a higher risk of death ($P = .259$) (Fig. 2B), although a statistical difference was not achieved. X-tile plots were constructed, and the maximum χ^2 log-rank value of 6.544 ($P = .011$) was produced, applying 35% as the optimal cutoff value to divide the cohort into high-risk and low-risk subsets in terms of OS (Fig. 3). We compared the baseline characteristics of the 2 subgroups of patients and no significant differences were found (see Table, <http://links.lww.com/MD/E781> Supplemental

Table 1
Characteristics of patients of gastric cancer patients with the squamous cell carcinoma component.

Characteristics	Total (N = 58)	
Sex		
Female	16	27.6%
Male	42	72.4%
Age, y		
<60	23	39.7%
≥60	35	60.3%
Site		
U	20	34.5%
M	10	17.2%
L	23	39.7%
Others*	5	8.6%
Size, cm		
<5	11	19.0%
≥5	47	81.0%
Borrmann classification		
I	1	1.7%
II	22	37.9%
III	14	24.1%
IV	4	6.9%
Unknown	17	29.3%
Grade		
Well differentiated	1	1.7%
Moderately differentiated	5	8.6%
Poorly differentiated	16	27.6%
Unknown	36	62.1%
LVI		
Negative	11	19.0%
Positive	39	67.2%
Unknown	8	13.8%
TNM stage		
I	1	1.7%
II	5	8.6%
III	21	36.2%
IV	7	12.1%
Unknown	24	41.4%
T stage		
T1	2	3.4%
T2	4	6.9%
T3	17	29.3%
T4	34	58.6%
N stage		
N0	6	10.3%
N1	8	13.8%
N2	4	6.9%
N3	15	25.9%
Unknown	25	43.1%
Surgical procedures		
D1 radical surgery	28	48.3%
D2 radical surgery	25	43.1%
Palliative gastrectomy	5	8.6%
Regional nodes dissected		
<16	8	13.8%
≥16	25	43.1%
Unknown	25	43.1%
Proportion of SCC component		
<35%	15	25.9%
≥35%	43	74.1%
Lymph nodes' contents		
Pure AC	6	10.3%
AC and SCC	14	24.1%
Unknown	38	65.5%
Chemotherapy		
No/Unknown	41	70.7%
Yes	17	29.3%

AC=adenocarcinoma, L=lower third of the stomach, LVI=lymphovascular invasion, M=middle third of the stomach, SCC=squamous cell carcinoma, U=upper third of the stomach.

*Others include two-thirds or more of the stomach and anastomotic site.

Table 2
Univariate analysis of the influence of different proportions of the squamous cell carcinoma component on survival in gastric cancer patients.

P	N	5-y OS rate	Log-rank χ^2	P
<15%/≥15%	4/54	0%/17.2%	0.005	1.000
<25%/≥25%	6/52	16.7%/15.0%	0.281	.584
<28%/≥28%	10/48	29.6%/11.6%	1.699	.193
<30%/≥30%	11/47	37.5%/8.3%	3.493	.061
<32%/≥32%	14/44	35.6%/7.9%	6.257	.012
<35%/≥35%	15/43	35.6%/7.9%	6.544	.011
<37%/≥37%	20/38	25.9%/7.8%	1.988	.157
<38%/≥38%	21/37	24.5%/7.5%	1.666	.192
<40%/≥40%	22/36	23.3%/7.5%	1.070	.294
<45%/≥45%	27/31	22.5%/6.5%	1.272	.254
<48%/≥48%	28/30	22.5%/6.5%	1.272	.254
<50%/≥50%	30/28	22.5%/6.4%	1.211	.273
<51%/≥51%	33/25	20.9%/6.0%	2.097	.147
<54%/≥54%	34/24	20.3%/5.5%	1.520	.221
<55%/≥55%	35/23	23.6%/0%	3.536	.061
<60%/≥60%	36/22	24.0%/0%	4.156	.040
<62%/≥62%	37/21	24.8%/0%	5.713	.017
<63%/≥63%	38/20	24.1%/0%	5.134	.024
<64%/≥64%	39/19	23.4%/0%	3.822	.051
<65%/≥65%	40/18	22.7%/0%	3.432	.065
<68%/≥68%	43/15	21.6%/0%	2.357	.121
<70%/≥70%	45/13	20.5%/0%	1.220	.273
<72%/≥72%	46/12	20.0%/0%	0.860	.343
<75%/≥75%	47/11	19.6%/0%	0.428	.527
<80%/≥80%	50/8	17.5%/0%	0.598	.439
<85%/≥85%	54/4	15.6%/0%	0.080	.752

OS=overall survival, P=proportion of SCC component, SCC=squamous cell carcinoma.

Content, which illustrates the characteristics of the 2 subgroups of patients).

3.3. Prognostic value of the proportion of the SCC component

The proportion of the SCC component ($P=.011$), advanced TNM stage ($P=.008$), and not receiving chemotherapy ($P=.020$) were significant risk factors for poor survival according to the univariate analysis (Table 3). In the multivariate analysis, the TNM stage and proportion of the SCC component (with an optimal cutoff of 35%) were independently and significantly associated with OS, and a higher proportion ($\geq 35\%$) of the SCC component demonstrated a negative effect on survival [hazard ratio (HR) 2.565; 95% confidence interval (95% CI) 1.119–5.877, $P=.026$] (Table 3).

4. Discussion

Although numerous discussions have occurred in previous articles,^[5,7,8,19,22,23] the pathogenesis of the SCC component in gastric cancer remains obscure since the first report of this scarce disease in 1905 by Rolleston and Trevor.^[24] The most convincing hypothesis regarding the pathogenesis of the SCC component is squamous metaplasia of a preexisting AC, which is widely accepted by most authors.^[19,23,25,26] The main evidence supporting this includes the following: the presence of almost identical expression patterns of RB, p16, and p53 proteins, not only in the AC and SCC components of the primary tumor, but in the metastatic lesions as well^[25]; the observation of a close transitional picture of a glandular to squamous element^[19] and the demonstration of individual cells containing both tonofibrils and mucous vacuoles^[27]; and positive expression of CK7 and CEA in the SCC component.^[6,8] Another non-negligible

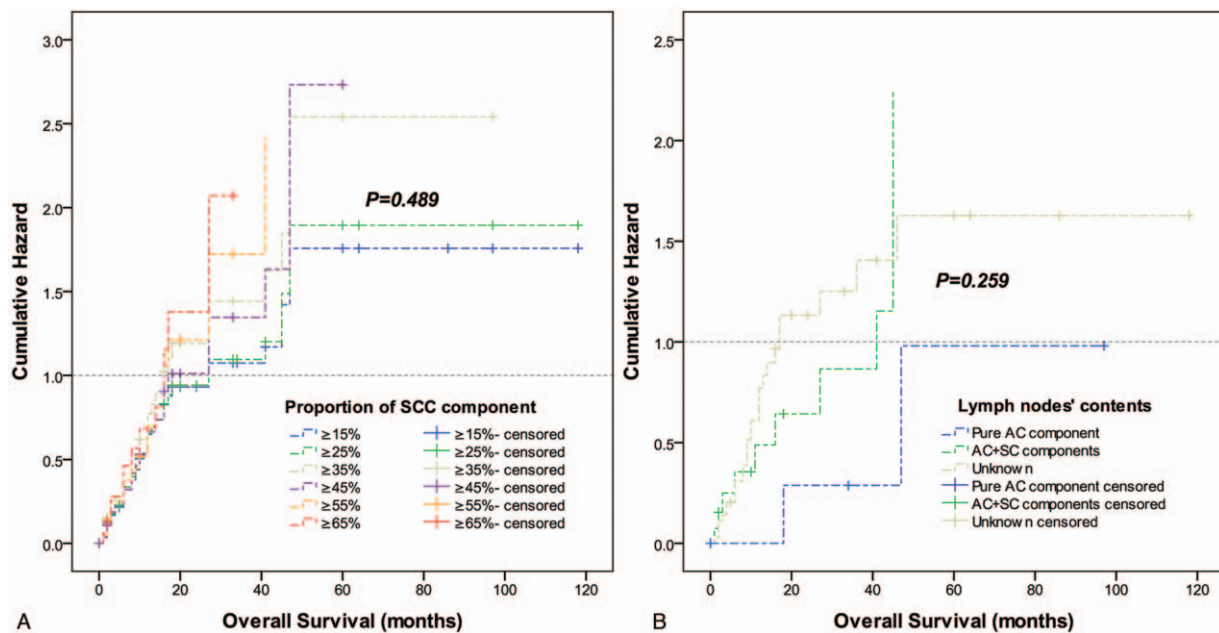


Figure 2. Log-rank tests of overall survival comparing patients with different proportions of the SCC component ($\chi^2=4.435$, $P=.489$) (A) and comparison of patients with different contents in the metastatic lymph nodes ($\chi^2=2.703$, $P=.259$) (B). AC = adenocarcinoma; SCC = squamous cell carcinoma.

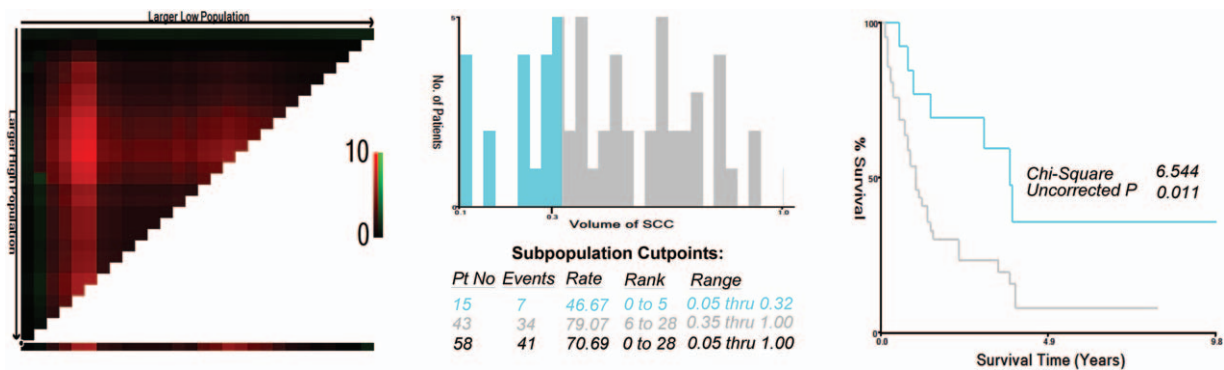


Figure 3. X-tile analysis of survival data in our study. The optimal cutoff value for the SCC component is shown as 35% ($\chi^2=6.544$, $P=.011$). SCC = squamous cell carcinoma.

hypothesis is stem cell differentiation toward both cellular lines, which is also supported by several scholars.^[17,24,28] Moreover, other possible theories including cancerization of ectopic squamous epithelium, cancerization of metaplastic non-neoplastic squamous cells, and concurrent occurrence of AC and SCC cannot be ruled out.

The role of the SCC component in the survival of patients with gastric cancer is not well construed. Usually, the SCC component is associated with less favorable survival than the conventional gastric AC component,^[2-6,8,17,29,30] which, theoretically, proves that the SCC component is more malignant than the AC component. However, it appears that the AC component plays a leading role, even when it is not superior to the SCC component in quantity.^[5,20,31,32] The AC component is predominantly found in hematogenous and hepatic metastases^[4,6,32]; however, the SCC component is not. Mori et al^[19] performed a clinicopathologic analysis of 28 cases and reported that the variations in distribution and quantity of each component had no effect on the survival of patients diagnosed with gastric cancer with the SCC component. However, these conclusions are too empirical and lack statistical validation. With a relatively large sample size, however, our findings revealed that the SCC component had an influence on survival. Our data demonstrated that with the increase in the proportion of the SCC component (range, 15–85%), the 5-year survival rate gradually decreased (range, 17.2% to 0%), which was not the case with the AC component. Moreover, the hazard plot showed that with the increase in the proportion of the SCC component in the primary lesion, the risk of death gradually increased, although no significant difference was revealed due to an inadequate number of cases. Most importantly, excluding the influence of confounding factors, such as the differentiation grade, LVI, and chemotherapy, the multivariate analysis suggested that the proportion of the SCC component (cutoff value of 35%) was independently related to the prognosis. Regardless of the primary organ, an earlier study used human cholangiocellular carcinoma cells in animal models to demonstrate that the SCC component grew more aggressively than the AC component.^[33] Moreover, several studies reported significantly shorter doubling times of the SCC component than the AC component in lung cancer.^[34,35]

The existence of the AC or SCC component in the metastatic lymph nodes remains controversial in the literature.^[5,8] Some studies showed only the AC^[36] or SCC component,^[20,25,27] and others demonstrated both components. Mori et al^[19] demon-

strated that histologically, both components could be found in almost all (9 cases) of the metastatic areas examined, and the quantitative ratio of the AC to SCC component in the metastatic lesions roughly paralleled that of the primary lesions. Our study suggested no association between the proportion of the SCC component in primary lesions and the presence of the SCC or AC component in the metastatic lymph nodes. Therefore, it appears that it is difficult to predict which type of component will be present in metastatic sites. Some authors^[5,37] believe that the ratio of the AC to SCC component in metastatic lymph nodes might influence the prognosis of gastric ASC. Despite insufficient information about the metastatic lymph nodes, the presence of the SCC component in metastatic lymph nodes seemed to be related to worse survival in our study. However, owing to the rarity of this disease, the number of cases is too small to statistically support this claim.

Currently, surgical resection represents the only potentially curative treatment choice for gastric cancer with the SCC component, and the benefit of chemotherapy and radiotherapy as adjuvant treatments remains unclear.^[6-8] In our present study, chemotherapy did not prove to be a prognostic factor in the multivariate analysis. Interestingly, our ongoing population-based study (174 cases) (Li HS, Zhang MY, in preparation) also suggested that adjuvant chemotherapy did not improve survival for resected gastric cancer patients with an SCC component, which is consistent with the results of a study by Li et al (85 cases).^[29] Several possible reasons include the following: the high malignancy of this disease and insensitivity to chemotherapy; not enough statistical power due to the limited sample; the statistical effect of chemotherapy for survival is overshadowed by surgery; and the resistance of cytotoxic drugs caused by the multipotential stem cells.^[38]

Considering the significant differences in clinicopathological characteristics,^[2-6] molecular characteristics,^[19,25,31] treatment patterns,^[2,3] and prognosis,^[2-5,32] a clear and reasonable boundary between gastric ASC and AC is warranted. Different diagnostic criteria increase the heterogeneity between studies, making research on gastric ASC more difficult and contributing to more confusion about the appropriate treatments for ASC patients. Considering the limited data in the literature and from our institution, our study managed to provide a reasonable cutoff value for the proportion of the SCC component necessary for the diagnosis of gastric ASC, which may provide an additional reference for pathologists and clinicians. Our cutoff seemed more stringent than the 25% suggested by the JGCA, but the results of

Table 3**Univariate and multivariate analyses for evaluating the influence of proportion of the squamous cell carcinoma component in gastric cancer patients.**

Characteristics	MST, mo	Univariate analysis		Multivariate analysis	
		Log-rank χ^2	P	HR (95% CI)	P
Sex		1.468	.226		
Male	13				
Female	36				
Age, y		0.018	.893		
<60	16				
≥60	12				
Site		3.318	.345		
U	27				
M	14				
L	10				
Others*	36				
Size, cm		2.430	.119		
<5	41				
≥5	12				
Bormann classification		1.756	.416		
I+II	16				
III+V	12				
Unknown	17				
Grade		5.174	.056		
Well and moderately differentiated	NA				
Poorly differentiated	27				
Unknown	12				
LVI		0.085	.770		
Negative	18				
Positive	12				
Unknown	27				
TNM stage		7.014	.008	1.427 (1.083–1.881)	.011
I+II	36				
III	41				
IV	16				
Unknown	10				
Proportion of SCC component		6.544	.011	2.565 (1.119–5.877)	.026
<35%	45				
≥35%	12				
Lymph nodes' contents		2.703	.259		
Pure AC	47				
AC and SCC component	27				
Unknown	12				
Chemotherapy		5.446	.020		
No/Unknown	10				
Yes	45				

AC=adenocarcinoma, CI=confidence interval, HR=hazard ratio, L=lower third of the stomach, LVI=lymphovascular invasion, M=middle third of the stomach, MST=median survival time, NA=not applicable, SCC=squamous cell carcinoma, U=upper third of the stomach.

* Others include two-thirds or more of the stomach and anastomotic site.

the present study showed that 25% is not an ideal dividing line for ASC. Last but not least, although accurate evaluation of the percentages is sometimes too subjective to be reliably reproduced based on the amount of tumor sectioned, the specific area selected, and the method used to determine the tumor proportions, we believe, by using more objective, uniformed, quality-controlled evaluation standards, the final result has clinical value. Certainly, exploration and verification of a more effective diagnostic standard requires further research.

Several limitations must be considered when interpreting the results of the present analysis. First, as this is not a prospective, controlled, single-site study, there are inconsistencies in the data collection. Second, because the sample size was not large enough, the results of our present study should be explained cautiously. Third,

the completeness of the data is limited due to data acquisition factors. We expect that our results will shed light on the study of ASC in the future, and ongoing research will continue to be conducted in our own hospital to learn more about this rare disease.

5. Conclusion

Our study showed that the increased proportion of the SCC component was associated with worse survival in resected gastric cancer patients with an SCC component. The biological behavior may be controlled by the SCC component. A reasonable cutoff value for the proportion of the SCC component necessary for the diagnosis of gastric ASC is 35%, which may provide an additional reference for pathologists and clinicians.

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