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ORIGINAL ARTICLE

Prognostic Impact of Different Histological Types on Gastric Adenocarcinoma: a Surveillance, Epidemiology, and End Results Database Analysis

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Abstract The clinicopathological characteristics and prognosis of gastric mucinous adenocarcinoma (MAC) and signet ring cell carcinoma (SRC) are still controversial. We designed our study to evaluate the clinicopathologic features and prognosis of MAC, SRC and ordinary gastric adenocarcinoma (OGAC) by analyzing the Surveillance, Epidemiology, and End Results (SEER)-registered database. The 5-year overall survival (OS) of patients with SRC was significantly lower than that of patients with MAC ($P = 0.001$) and OGAC ($P < 0.001$), and there was no significant difference in 5-year OS between MAC and OGAC ($P = 0.804$). Furthermore, there were no significant differences of 5-years OS among these three groups at stage I, II and III (all $P > 0.05$) and no significant difference between MAC and OGAC at stage IV ($P = 0.110$). Patients in SRC group had significantly worse survival than those in MAC and OGAC at stage IV (both $P = 0.008$), with 5-year OS of 3.3%, 5.8%, and 5.8%, respectively. However, the histological type was not found to be an independent prognostic factor of gastric cancer according to the multivariate analysis with Cox regression.

Keywords Gastric carcinoma · Mucinous adenocarcinoma · Signet ring cell carcinoma · Survival · SEER

Introduction

Gastric cancer is one of the most common causes of cancer-related mortality in the world [1, 2]. According to the World Health Organization (WHO) international histological classification of tumors, mucinous adenocarcinoma (MAC) is defined as gastric adenocarcinoma with a substantial amount of extracellular mucin (≥50% of tumor volume) within tumors and signet ring cell carcinoma (SRC) as tumor with only intracellular mucin pools [3]. Both the two types of gastric carcinoma have been differently classified as diffuse type, infiltrative type and undifferentiated type by their potential to infiltrate the stomach wall and poor prognosis [4–7]. In spite of the clinicopathologic characteristics and prognosis of gastric MAC and SRC have been investigated in a few of studies, the results are still inconsistent. Some studies have indicated that patients with MAC have a poor prognosis [8–10], whereas others have shown no significant differences in prognosis between MAC and ordinary gastric carcinoma [11–13]. With respect to gastric SRC, there are fewer studies and the conclusions are more inconsistent. Patients with gastric SRC have presented different outcomes in various studies. Most of the studies have reported the prognosis of SRC was better than non-signet ring cell carcinoma (NSRC), particularly in early gastric carcinoma [14–19], while few researches have shown opposite or no difference [20, 21].

Given the small numbers of patients and the conflicting results of previous studies, we designed our study to evaluate the clinicopathologic characteristics and prognosis of MAC, SRC and ordinary gastric adenocarcinoma (OGAC) by

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analyzing the Surveillance, Epidemiology, and End Results (SEER)-registered database.

Materials and Methods

Patient Selection in the SEER Database

The SEER, a population-based reporting system, was surveyed for the retrospective collection of data used in the analysis. The SEER program collects and publishes cancer incidence and survival data from 18 population-based cancer registries, covering approximately 28% of the population in the United States. The SEER data contain no identifiers and are publicly available for studies of cancer-based epidemiology and survival analysis.

Cases of gastric carcinoma (C16.0–16.9) diagnosed from 2004 to 2010 were extracted from the SEER database (SEER*Stat 8.2.1) according to the Site Recode classifications. Histological type were limited to adenocarcinoma (ICD-03, 8140/3, 8144/3, 8211/3, 8221/3, 8255/3, 8260/3, 8261/3, 8262/3, 8263/3, 8310/3, 8323/3), mucinous adenocarcinoma (ICD-03, 8480/3, 8481/3), and signet ring cell carcinoma (ICD-03, 8490/3). We selected this range because American Joint Committee on Cancer (AJCC) TMN stage was available since 2004 and patients diagnosed after 2010 were excluded to ensure an adequate follow-up time. Other exclusion criteria were as follows: patients with unknown TNM stage and unknown survival months.

This study was based on the publicly available data from the SEER database and we had got the permission to access these research data (Reference number: 10,963-Nov 2014).

Statistical Analysis

Age, sex, race, histological grade, histotype, AJCC TNM stage and overall survival (OS) were extracted from SEER database. OS was calculated from the date of diagnosis to the date of death for any cause. The intergroup comparison of clinicopathologic variables were performed with the chi-square test. Survival was analysed using the Kaplan-Meier method. The association between each of the potential prognostic factors and differences between the curves were analyzed by log-rank test. Multivariate analysis was performed using the Cox regression model. The statistical test was two sided and $P < 0.05$ was considered statistically significant. PASW Statistics 13 (SPSS Inc., Chicago, USA) was used for the statistical analysis.

Results

Patient Characteristics

We identified 19,295 eligible patients with gastric cancer in SEER database during the 7-year study period (between 2004 and 2010), which included 538 patients in mucinous adenocarcinoma, 4118 patients in signet ring cell carcinoma, 14,339 patients in ordinary gastric adenocarcinoma. There were 12,253 (63.5%) males and 7042 (36.5%) females. The median age was 58. Patient demographics and pathological features are summarized in Table 1.

Clinic-Pathological Characteristics of MAC, SRC and OGAC

In terms of clinicopathological characteristics among patients with the three histological types, there were significant differences in race, AJCC stage, LN metastasis and Depth of invasion. There were no significant differences between MAC and OGAC with respect to age ($P = 0.617$), gender ($P = 0.370$) and pathological grade ($P = 0.128$). The SRC appeared to be relatively frequent in young patients and women ($P < 0.001$). There was more poor differentiation (III) and undifferentiation (IV) in pathological grade in SRC compared to MAC and OGAC ($P < 0.001$). In contrast to OGAC tumors, SRC and MAC presented at a relatively advanced stage with deeper invasion and more lymph node involvement, especially the former ($P < 0.001$). (Table 1)

Survival Differences among Histotype Groups

The 5-year overall survival (OS) was 25.4% in MAC, 21.1% in SRC, 28.0% in OGAC, which had significant difference in univariate log-rank test ($P < 0.001$). The 5-year overall survival of patients with SRC was significantly lower than that of patients with OGAC ($P < 0.001$) and MAC ($P = 0.001$), and there was no significant difference in 5-year OS between MAC and OGAC ($P = 0.804$) (Fig. 1). Furthermore, the survival analyses were stratified by each stage in different histotype groups (Stage I-IV, Fig. 2, 3, 4 and 5). It demonstrated that there were no significant differences of 5-years OS among these three groups at stage I, and II (all $P > 0.05$). Patients in SRC group had worse prognosis than those in MAC ($P = 0.277$) and OGAC ($P = 0.098$) group at stage III, although the differences were not statistically significant. However, patients in SRC group had significantly worse survival than those in MAC and OGAC at stage IV (both $P = 0.008$), with 5-year OS of 3.3%, 5.8%, and 5.8%, respectively (Table 2). There was no significant difference between MAC and OGAC at stage III ($P = 0.769$) and IV ($P = 0.110$). Besides, univariate analysis showed that older age, white and

Table 1 Patient characteristics from SEER Datebase by histological type

Variable	Total	Histological Type		*P* value		
	n = 19,295	MAC	SRC	OGAC	MAC vs SRC	MAC vs OGAC	SRC vs OGAC
Age (year), n(%)					<0.001	0.617	<0.001
≤ 60	6223	155(28.8)	2078(47.0)	3990 (27.8)			
> 60	13,072	383(71.2)	2340(53.0)	10,349 (72.2)			
Gender, n(%)							
Male	12,253	350(65.1)	2309(52.3)	9594 (66.9)	<0.001	0.370	<0.001
Female	7042	188(34.9)	2109(47.7)	4745 (33.1)			
Race, n(%)							
White	13,345	390(72.5)	3048(69.0)	9907 (69.1)	0.001	0.003	0.358
Black	2599	84(15.6)	571(12.9)	1944 (13.6)			
Others	3351	64(11.9)	799(18.1)	2488 (17.3)			
Pathological grade, n (%)					<0.001	0.128	<0.001
Grade I	794	33(6.1)	12(0.3)	749 (5.2)			
Grade II	4901	180(33.5)	98(2.2)	4623 (32.2)			
Grade III	11,166	252(46.8)	3515(79.5)	7399 (51.6)			
Grade IV	358	3(0.6)	149(3.4)	206 (1.5)			
Unknown	2076	70(13.0)	644(14.6)	1362 (9.5)			
Stage, n (%)					<0.001	<0.001	<0.001
I	6543	144(26.8)	1164(26.3)	5235 (36.5)			
II	3139	112(20.8)	598(13.5)	2429 (16.9)			
III	3185	118(21.9)	835(18.9)	2232 (15.6)			
IV	6428	164(30.5)	1821(41.3)	4443 (31.0)			
LN metastasis, n(%)					<0.001	<0.001	<0.001
N0	8991	209(38.8)	1905(43.1)	6877(48.0)			
N1	7344	233(43.3)	1528(34.6)	5583(38.9)			
N2	2123	70(13.1)	654(14.8)	1399(9.8)			
N3	837	26(4.8)	331(7.5)	480(3.3)			
Depth of invasion, n (%)					<0.001	<0.001	<0.001
T1	5826	86(16.0)	1099(24.9)	4641(32.4)			
T2	6898	239(44.4)	1442(32.6)	5217(36.4)			
T3	3523	129(24.0)	1012(22.9)	2382(16.6)			
T4	3048	84(15.6)	865(19.6)	2099(14.6)			

LN lymph node, *MAC* mucinous adenocarcinoma, *SRC* signet ring cell carcinoma, *OGAC* ordinary gastric adenocarcinoma

black race, higher tumor grade, higher AJCC stage and signet-ring cancer ($P < 0.001$) were identified as significant risk factors for poor survival (Table 3). When multivariate analysis with Cox regression was performed, age, race, histological grade, AJCC stage were also the independent prognostic factors with the exception of histological type ($P = 0.131$). (Table 3)

Discussion

To our knowledge, this is the first large population-based study to evaluate the prognostic impact of different histological types on gastric adenocarcinoma by analyzing the SEER-registered database. Mucinous adenocarcinoma (MAC) and signet ring cell carcinoma (SRC) are the histological subtypes of gastric cancers with mucin-producing feature, which are quite different in morphology, ultrastructure, cell-functional differentiation and protein expression, indicating different mechanisms of tumorigenesis [22]. MAC is a rare histopathological type of gastric cancer, comprising about 3% to 10% of gastric carcinomas as reported in previous studies [12, 23–25]. The incidence of SRC has been reported to vary from 3.4% to 39% in different countries [26–28]. In the present study, MAC made up 2.8% of all cases and SRC was identified in 22.9% of all patients.

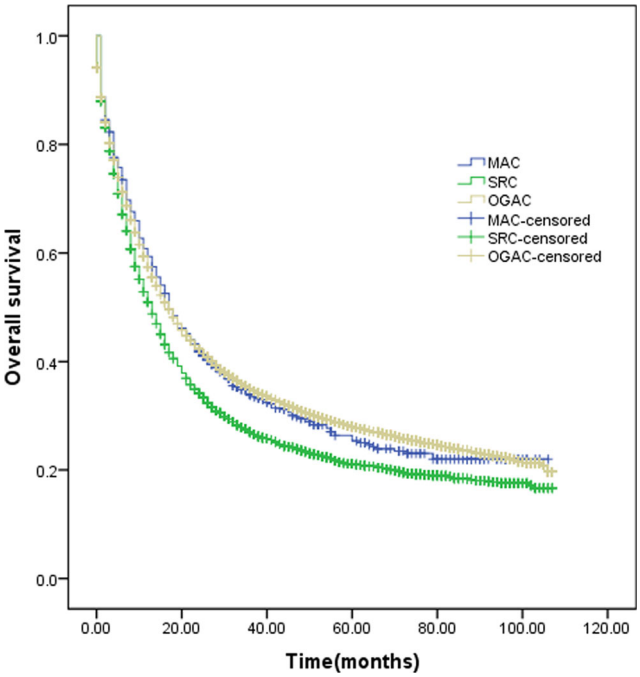

Fig. 1 Survival curves in patients with gastric cancer according to three subgroups

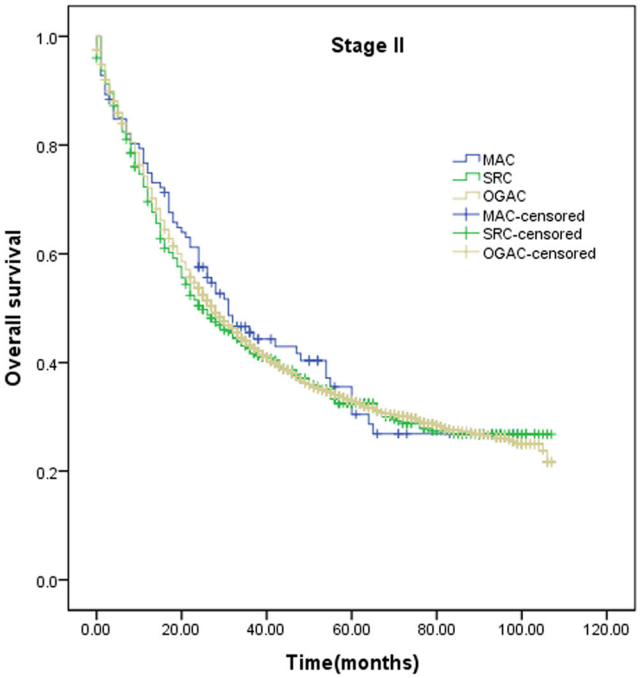

Fig. 3 Survival curves in patients with gastric cancer according to three histological types at stage II

Although clinicopathological characteristics and prognosis of MAC and SRC have been studied, the results of those studies were still controversial. Taro Isobe et al. investigated the clinicopathological characteristics and prognosis of patients with mucinous gastric carcinoma (MGC) [12]. They found prognosis of MGC patients was worse compared to that of non-mucinous gastric carcinoma (NMGC) patients, as the former group consisted of more advanced-stage cases, but the prognosis of MGC and NMGC patients with similar disease stages was not significantly different, which is similar to that of a series of previous studies [11, 13]. In contrast, Ryu SY et al. found patients with early MGC had a better prognosis than those with early NMGC, although mucinous histology itself appeared not to be an independent prognostic factor [29].

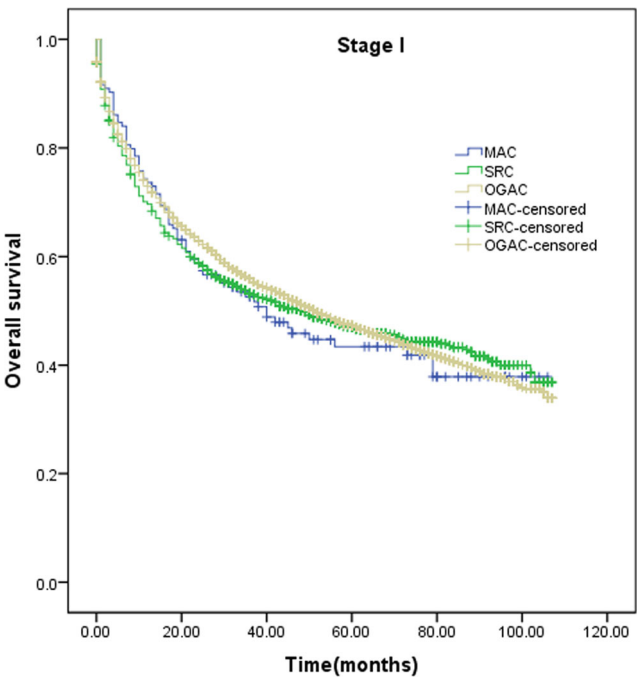

Fig. 2 Survival curves in patients with gastric cancer according to three histological types at stage I

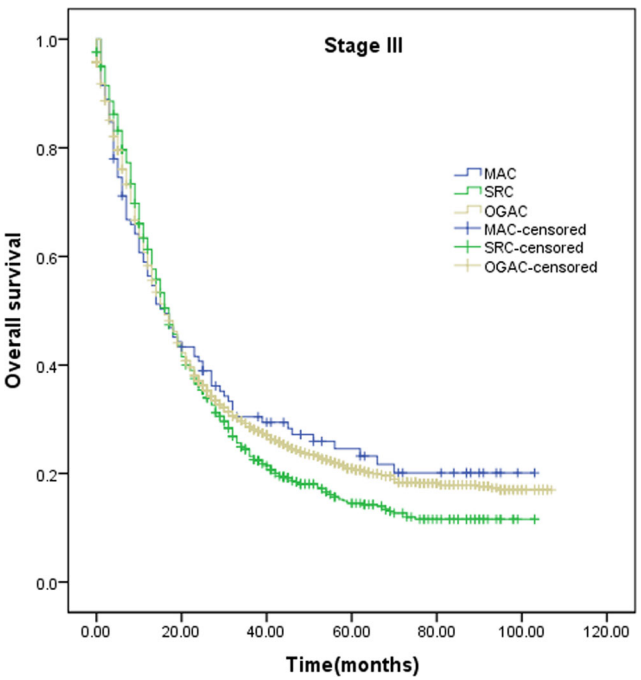

Fig. 4 Survival curves in patients with gastric cancer according to three histological types at stage III

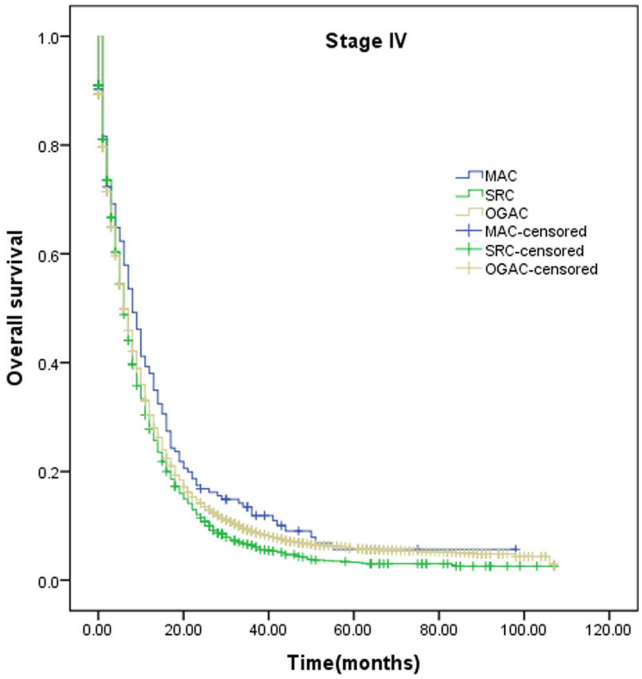

Fig. 5 Survival curves in patients with gastric cancer according to three histological types at stage IV

Table 3 Univariate and multivariate survival analyses of gastric cancer patients according to various clinicopathological variables

Variable	n	5-year OS (%)	Univariate P	Multivariate P
Age (year)			<0.001	<0.001
≤ 60	6223	29.8		
> 60	13,072	24.7		
Gender			0.276	0.114
Male	12,253	26.4		
Female	7042	26.3		
Race			<0.001	<0.001
White	13,345	24.6		
Black	2599	22.7		
Other	3351	36.4		
Pathological grade			<0.001	<0.001
Grade I	794	47.2		
Grade II	4901	33.3		
Grade III	11,166	23.1		
Grade IV	358	20.7		
Stage			<0.001	<0.001
I	6543	47.1		
II	3139	32.8		
III	3185	19.4		
IV	6428	5.1		
Histological Type			<0.001	0.131
Mucinous	538	25.4		
Signet ring cell	4418	21.1		
Adenocarcinoma	14,339	28.0		

In our study, we found patients with MAC had more T3/4 invasion to the gastric wall, more positive lymph node metastasis and more III/IV stage compared to the OGAC. However, there was no significant difference in 5-year OS between MAC and OGAC at each same stage. Thus, our results indicated that the primary factor leading to the poor prognosis of MAC was the more frequent incidence of advanced stage disease at diagnosis, rather than the aggressive biological behavior of MAC.

The SRC appeared to be relatively frequent in young patients and women [23]. Our study confirmed this features, with 47.7% of female patients in SRC, 34.9% of female patients in MAC and 33.1% of female patients in OGAC. Meanwhile, there were significantly more patients under 60 years old in SRC than both MAC and OGAC, with the percent of 47%, 28.8% and 27.8%, respectively. The reason of this characteristic remains unclear and there is a theory that histology may be influenced by sex hormones [30, 31]. Generally, the prominent characteristics of SRC classified as diffuse, infiltrative and undifferentiated type were its potential to diffusely infiltrate the gastric wall and its poor prognosis. Although the biological behavior of SRC has been considered to be different from other histological types, prognoses of patients with SRC were inconsistently reported. Number of studies have reported that SRC had better survival than other histological types [14–16]. In contrast, others reported no significant differences or a poor prognosis [20, 21]. Noteworthily, several studies showed that

Table 2 Comparison of 5-year overall survival by disease stage

Stage	5-year overall survival (%)			*P* value		
	MAC	SRC	OGAC	MAC vs SRC	MAC vs OGAC	SRC vs OGAC
All	25.4	21.1	28.0	0.001	0.804	<0.001
I	43.4	46.9	47.3	0.827	0.569	0.486
II	35.5	32.5	33.0	0.524	0.647	0.626
III	24.6	14.6	20.9	0.277	0.769	0.098
IV	5.8	3.3	5.8	0.008	0.110	0.008

MAC mucinous adenocarcinoma, *SRC* signet ring cell carcinoma, *OGAC* ordinary gastric adenocarcinoma

the survival of patients with early SRC carcinoma was significantly better than that of patients with other types of early gastric carcinoma [15, 32, 33]. Some researchers recommended less invasive surgeries such as endoscopic resection for an improved quality of life for the patients with early SRC carcinoma in view of the lower rate of lymph node metastasis and favorable prognosis [15, 33]. However, some others had the opposite opinion. Lee JH et al. found the rate of lymph node metastasis was similar for tumors with SRC and differentiated histological findings and patients with early gastric cancer with SRC are probably best treated by gastrectomy with lymph node dissection [34]. Li C et al. found advanced gastric SRC had a worse prognosis than NSRC because of deeper tumor invasion and more lymph node and peritoneal metastasis. They recommended curative surgical operation with extended lymph node dissection for patients with advanced gastric SRC [35]. Kwon KJ et al. reported survival in early gastric cancer patients exhibited no difference between histological types. Among advanced gastric cancer patients, SRC patients had a worse prognosis than other cell types [36]. Similarly, Kim JP et al. also found a worse prognosis for patients with advanced SRC carcinoma and no significant differences in survival rates of early SRC and NSRC carcinoma [28]. However, Kim DY and colleagues found there was no significant difference between patients with signet ring cell and non-signet ring cell carcinoma with both early and advanced gastric carcinoma [37]. In the present study, we found SRC tumors were more frequently poorly differentiated and undifferentiated pathological grade as well as advanced stage with deeper invasion and more lymph node involvement. The overall 5-year survival of patients with SRC was significantly lower than that of patients with OGAC or MAC. Upon further analysis, patients in SRC group had no different prognosis with other histological types at I, II stages and worse 5-year OS than those in MAC group and OGAC group at advanced III and IV stage, specifically the latter, similar to the results reported by Kwon KJ and Kim JP. Furthermore, multivariate analysis showed the histological type was not an independent prognostic factor. These findings suggested that the poor prognosis for SRC was not associated with the histology, but rather with the advanced tumor stage. The results indicated that early detection and invasive treatment regardless of histological type in early gastric carcinoma should be recommended. Since patients with advanced SRC had worse prognosis, the more aggressive therapy should be recommended for this population as well. Nevertheless, the origin and progression of MAC and SRC remain poorly understood and need further research.

Although this is a large population-based study, it has several potential limitations. First, the SEER registry does not collect several important tumor characteristics such as lymphatic invasion, vascular invasion and metastatic detail. Thus, our analyses could not adjust for these potential confounding factors. Second, our study is the lack of detailed data on the cancer therapy (use of chemotherapy, curability of surgery), resulting in a potentially significant confounder in the current study. Finally, the current analysis of the nonrandomized patient population could not exclude the possibility of selection bias. However, our study has its convincing power for its larger population based study.

In conclusion, the prognosis of patients with SRC was significantly worse than those with MAC and OGAC, particularly at advanced stage. There was no significant difference of prognosis between MAC and OGAC. However, because histological type was not found to be an independent prognostic factor according to the multivariate analysis, treatment strategy would be focused on the stage of gastric adenocarcinoma at diagnosis, age, race, and pathological grade but not histological types.

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Statement of Author Contributions KTL and JFW conceived of and designed the study. KTL, JFW and YPB performed the analyses. YPB and XC prepared all tables. KTL and MZL wrote the main manuscript. All authors reviewed the manuscript.

Compliance with Ethical Standards

Disclosure The authors declare that they have no competing interests.

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