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ORIGINAL ARTICLE

Retrospective Study

A new scoring system to evaluate adjuvant chemotherapy for patients with T2N0M0 gastric cancer after D2 gastrectomy

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Abstract

BACKGROUND

At present, there is insufficient medical evidence to determine whether adjuvant chemotherapy is necessary for T2N0M0 gastric cancer.

AIM

To obtain a risk score to assess the need for adjuvant chemotherapy in patients with T2N0M0 gastric cancer.

METHODS

We identified 325 patients with pathological T2N0M0 stage primary gastric cancer at the National Cancer Center between 2011 and 2018. Univariate and multivariate Cox regression analyses were performed to predict factors affecting prognosis. Vascular invasion, tumor site, and body mass index were assessed, and a scoring system was established. We compared the survival outcomes and benefits of adjuvant chemotherapy between the different subgroups.

RESULTS

Five-year survival rates of the score 0, 1, 2, and 3 groups were 92%, 95%, 80%, and 50%, respectively ($P < 0.001$). In the score 2-3 group, five-year survival rates for patients in the adjuvant chemotherapy group and postoperative observation group were 95% and 61%, respectively ($P = 0.021$).

CONCLUSION

For patients with T2N0M0 stage gastric cancer and two or more risk factors, adjuvant chemotherapy after D2 gastrectomy may have a survival benefit.

Key Words: Gastric cancer; Risk score; T2N0M0; Adjuvant chemotherapy; D2

gastrectomy; Survival

Core Tip: It is controversial whether adjuvant chemotherapy is necessary for stage T2N0M0 gastric cancer. In our study, we assessed the risk score of patients with pathologic T2N0M0 gastric cancer after D2 gastrectomy, based on clinicopathological factors, and identified a high-risk subgroup that could benefit from adjuvant chemotherapy. For patients with T2N0M0 stage gastric cancer with two or more risk factors, adjuvant chemotherapy after D2 gastrectomy may have a survival benefit.

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INTRODUCTION

Gastric cancer is one of the most common malignancies worldwide[1-3]. D2 gastrectomy combined with postoperative adjuvant chemotherapy is the main treatment modality for advanced gastric cancer[4-8]. According to the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines for gastric cancer, T2 was defined as tumor invasion of the muscularis propria[9]. It is controversial whether adjuvant chemotherapy is necessary for stage T2N0M0 gastric cancer[10-16]. Previous studies have suggested that patients with stage I gastric cancer cannot benefit from adjuvant chemotherapy[17]. However, there are some risk factors for recurrence of T2N0M0 gastric cancer, such as lymphatic and/or blood vessel invasion, tumor diameter, perineural invasion, proximal tumor location, and poor differentiation[14,18]. Postoperative adjuvant chemotherapy may inhibit the recurrence in these patients. To further clarify the indications for the use of postoperative adjuvant chemotherapy in T2N0M0 gastric cancer, we reviewed 325 patients with T2N0M0 gastric cancer admitted to the National Cancer Center between 2011 and 2018. In this study, we assessed the risk score of patients with pathologic T2N0M0 gastric cancer after D2 gastrectomy based on clinicopathological factors and identified a high-risk subgroup that could benefit from postoperative adjuvant chemotherapy.

MATERIALS AND METHODS

Patient selection

We identified 402 patients with pathological T2N0M0 stage primary gastric carcinoma and gastroesophageal junction carcinoma (as defined by the AJCC guidelines, 8th edition) who were admitted to the Department of Pancreatic and Gastric Surgery, National Cancer Center, from 2011 to 2018. Three hundred and twenty-five patients were included in our study, all of whom underwent D2 gastrectomy. A total of 63 patients received post-operative adjuvant chemotherapy. The major chemotherapy regimens included platinum + 5-FU; paclitaxel + platinum + 5-FU; and others. Adjuvant chemotherapy is usually performed for 4-6 cycles. Exclusion criteria included loss to follow-up, lack of adenocarcinoma, neoadjuvant chemotherapy, adjuvant radiotherapy, Siewert I type/Siewert II type gastroesophageal junction carcinoma invading the dentate line, and postoperative survival time < 1 mo. Patients were followed-up by telephone. The follow-up was completed on April 30, 2020. The median follow-up time was 65.4 mo.

Statistical analyses

Univariate and multivariate Cox regression analyses were performed to screen for prognostic variables. Variables with a P value < 0.05 and < 0.25 in the univariate and multivariable Cox regression analyses were included in the study. Three variables were included in total: Vascular invasion, tumor site, and body mass index (BMI). The tumor site was classified as cardiac or non-cardiac. Cardiac cancer refers to Siewert type II gastroesophageal junction carcinoma that does not invade the dentate line and Siewert type III gastroesophageal junction carcinoma. BMI of < 18.5 or > 23.9, positive result of vascular invasion, and cardiac cancer were defined as risk factors. Each risk factor was assigned one point, and a total of four groups were obtained, which were defined as scores 0, 1, 2, and 3, respectively. We found that patients with a score ≥ 2 had a poor prognosis, and chemotherapy significantly improved

Table 1 Clinicopathologic variables of 325 T2N0M0 gastric cancer patients

Variable	Overall	Adjuvant chemotherapy group	Postoperative observation group	*P* value
	325	63	262	
Age (yr) *n* (%)				0.609
< 40	20 (6.2)	3 (4.8)	17 (6.5)	
≥ 40	305 (93.8)	60 (95.2)	245 (93.5)	
Sex, *n* (%)				0.878
Male	250 (76.9)	48 (76.2)	202 (77.1)	
Female	75 (23.1)	15 (23.8)	60 (22.9)	
Smoking history, *n* (%)				0.363
Yes	169 (52.0)	36 (57.1)	133 (50.8)	
No	156 (48.0)	27 (42.9)	129 (49.2)	
Family history of gastric cancer, *n* (%)				0.852
Yes	24 (7.4)	5 (7.9)	19 (7.3)	
No	301 (92.6)	58 (92.1)	243 (92.7)	
BMI, *n* (%)				0.150
< 18.5 or > 23.9	176 (54.2)	29 (46.0)	147 (56.1)	
18.5-23.9	149 (45.8)	34 (54.0)	115 (43.9)	
Postoperative hospital stay, *n* (%)				0.747
≤ 14 d	285 (87.7)	56 (88.9)	229 (87.4)	
> 14 d	40 (12.3)	7 (11.1)	33 (12.6)	
Tumor site, *n* (%)				0.004
Cardia cancer	105 (32.3)	30 (47.6)	75 (28.6)	
Non-cardia gastric cancer	220 (67.7)	33 (52.4)	187 (71.4)	
The degree of differentiation, *n* (%)				0.571
Poorly differentiated	121 (37.2)	24 (38.1)	97 (37.0)	
Moderately differentiated	178 (54.8)	36 (57.1)	142 (54.2)	
Highly differentiated	26 (8.0)	3 (4.8)	23 (8.8)	
Vascular invasion, *n* (%)				0.014
Yes	54 (16.6)	17 (27.0)	37 (14.1)	
No	271 (83.4)	46 (73.0)	225 (85.9)	

BMI: Body mass index.

prognosis. According to the study results, scores of 2-3 were defined as the high-risk group. The Kaplan-Meier method was used to calculate the 5-year survival rate and compare the overall survival (OS) between the different score groups.

Statistical analysis was performed using the R software 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) and the SPSS 22.0 software (SPSS Inc., Chicago, IL, United States). Each test was bilateral, and statistical significance was set at $P < 0.05$.

RESULTS

Clinicopathological characteristics, univariate and multivariable cox regression analyses

A total of 325 patients were recruited for this study. Table 1 summarizes the clinicopathological characteristics of the patients enrolled in this study. Univariate Cox regression analysis demonstrated that the tumor site ($P = 0.022$, Table 2), vascular invasion ($P < 0.001$, Table 2), and BMI ($P = 0.036$, Table 2) were

Table 2 Univariate Cox Proportional Hazards Modeling for overall survival

Clinicopathological features	HR (95%CI)	*P* value
Sex		
Male	Reference	
Female	0.278 (0.066-1.172)	$P = 0.081$
Smoking history		
Yes	Reference	
No	0.605 (0.276-1.323)	$P = 0.208$
Family history of gastric cancer		
Yes	Reference	
No	0.550 (0.075-4.057)	$P = 0.558$
BMI		
18.5-23.9	Reference	
> 23.9 or < 18.5	2.509 (1.060-5.937)	$P = 0.036$
Postoperative hospital stay		
≤ 14 d	Reference	
> 14 d	0.990 (0.298-3.292)	$P = 0.987$
Tumor site		
Cardia cancer	Reference	
Non-cardia gastric cancer	0.411 (0.192-0.878)	$P = 0.022$
The degree of differentiation		
Poorly differentiated	Reference	
Moderately differentiated	1.330 (0.574-3.082)	$P = 0.507$
Highly differentiated	0.857 (0.182-4.043)	$P = 0.846$
Vascular invasion		
Yes	Reference	
No	0.097 (0.044-0.212)	$P < 0.001$

BMI: Body mass index; HR: Hazard ratio; 95%CI: 95% confidence interval.

significant risk factors for OS. Multivariate Cox regression analysis demonstrated that vascular invasion was an independent risk factor for OS ($P < 0.001$, Table 3).

Vascular invasion, tumor site, and BMI were assessed in the study, and a scoring system was established.

Survival results of different groups

Figure 1A summarizes the survival curves of patients with scores of 0, 1, 2, and 3. There were significant differences among all groups except for the score 0 and 1 groups (score 0 group *vs* score 1 group, $P = 0.537$; score 0 group *vs* score 2 group, $P = 0.049$; score 0 group *vs* score 3 group, $P < 0.001$; score 1 group *vs* score 2 group, $P = 0.003$; score 1 group *vs* score 3 group, $P < 0.001$; score 2 group *vs* score 3 group, $P = 0.008$). For all patients, 5-year survival rates of the adjuvant chemotherapy and postoperative observation groups were 96% and 90%, respectively ($P = 0.676$, Table 4). Five-year survival rates of the score 0, 1, 2, and 3 groups were 92%, 95%, 80%, and 50%, respectively ($P < 0.001$, Table 4). In the score 0 and score 1 groups, there were no differences in the 5-year survival rates between the postoperative observation and adjuvant chemotherapy groups. In the score 2-3 group, 5-year survival rates for patients in the adjuvant chemotherapy group and postoperative observation group were 95% and 61%, respectively ($P = 0.021$, Table 4).

Figure 1B-D summarizes the survival curves of patients with scores of 0, 1, and score 2-3 T2N0M0 gastric cancer in the adjuvant chemotherapy and postoperative observation groups. Table 5 summarizes the distribution of the different risk factors in each risk score group.

Table 3 Multivariable Cox Proportional Hazards Modeling for overall survival

Clinicopathological features	HR (95%CI)	*P* value
Sex		
Male	Reference	
Female	0.390 (0.076-1.988)	*P* = 0.257
Smoking history		
Yes	Reference	
No	0.725 (0.308-1.710)	*P* = 0.463
Family history of gastric cancer		
Yes	Reference	
No	0.495 (0.058-4.224)	*P* = 0.521
BMI		
18.5-23.9	Reference	
> 23.9 or < 18.5	1.848 (0.760-4.490)	*P* = 0.175
Postoperative hospital stay		
≤ 14 d	Reference	
> 14 d	1.198 (0.350-4.100)	*P* = 0.960
Tumor site		
Cardia cancer	Reference	
Non-cardia gastric cancer	0.620 (0.277-1.390)	*P* = 0.246
The degree of differentiation		
Poorly differentiated	Reference	
Moderately differentiated	0.517 (0.206-1.300)	*P* = 0.161
Highly differentiated	0.390 (0.077-1.960)	*P* = 0.305
Vascular invasion		
Yes	Reference	
No	0.106 (0.045-0.246)	*P* < 0.001

HR: Hazard ratio; 95%CI: 95% confidence interval.

DISCUSSION

Our study found that adjuvant chemotherapy is necessary for the treatment of T2N0M0 gastric cancer patients with two or more risk factors. The risk factors included vascular invasion, BMI, and tumor site. Based on these results, we obtained a simple risk score to assess the need for adjuvant chemotherapy in patients with T2N0M0 gastric cancer. Patients with a score 2-3 were assigned to the high-risk group.Previous studies have shown that adjuvant chemotherapy can prolong OS in advanced gastric cancer and reduce recurrence[19]. However, evidence of the survival benefits of adjuvant chemotherapy for early gastric cancer is lacking. Although there is no lymph node metastasis in T2N0M0 gastric cancer, some patients still experience recurrence[10-16]. Therefore, it is important to identify patients with stage T2N0M0 gastric cancer who are at high risk of recurrence and may require adjuvant chemotherapy. Univariate Cox regression analysis demonstrated that tumor site (P = 0.022, Table 2), vascular invasion (P < 0.001, Table 2), and BMI (P = 0.036, Table 2) were significant risk factors for OS in patients with T2N0M0 disease. Multivariate Cox regression analysis showed that vascular invasion was an independent prognostic indicator in patients with T2N0M0 disease[14]. Tumor site has been reported to be a prognostic risk factor for stage IB gastric cancer[11]. The 5-year OS rate of patients with stage IB gastric cancer whose tumors are located in the upper third of the stomach is only 81.8%, which is lower than that of patients with stage II disease receiving S-1 adjuvant chemotherapy[5]. Another study that followed 532 patients reported poorer long-term survival in patients with proximal gastric cancer than in those with distal gastric cancer[20]. Proximal gastric cancer has a higher proportion of undifferentiated tumors, and tumors located in this region can metastasize to almost all lymph nodes, except in the

Table 4 Five-year survival rates of different groups

	Group	*n*	5-year survival rate	Log rank test
All patients				$P = 0.676$
	Adjuvant chemotherapy	63	96%	
	Postoperative observation	262	90%	
Risk score				$P < 0.001$
	Score 0 group	98	92%	
	Score 1 group	152	95%	
	Score 2 group	69	80%	
	Score 3 group	6	50%	
Score 0 group				$P = 0.825$
	Adjuvant chemotherapy	13	92%	
	Postoperative observation	85	92%	
Score 1 group				$P = 0.308$
	Adjuvant chemotherapy	22	92%	
	Postoperative observation	130	96%	
Score 2-3 group				$P = 0.021$
	Adjuvant chemotherapy	28	95%	
	Postoperative observation	47	61%	

Table 5 Distribution of three different risk factors in each score group

	BMI < 18.5 or > 23.9	Vascular invasion	Cardia cancer
All	149	54	105
Score 0 group	0	0	0
Score 1 group	92	15	45
Score 2 group	51	33	54
Score 3 group	6	6	6

BMI: Body mass index.

five groups[11]. These factors may account for the lower survival rates of patients with proximal gastric cancer. Several studies have shown that BMI affects the prognosis of patients with gastric cancer[21-26]. Low BMI was associated with malnutrition, whereas high BMI was associated with a higher risk of surgery and a higher rate of postoperative complications. A high BMI also increases the risk of stomach cancer[27]. The degree of tumor differentiation was not included in the study, possibly because poorly differentiated tumors do not show significant aggressiveness in the early stages of tumor development.

Based on these findings, we developed a scoring system to assess the need for the use of adjuvant chemotherapy in patients with T2N0M0 gastric cancer. Patients with no or only one risk factor had good prognosis after D2 gastrectomy and did not require adjuvant chemotherapy. Patients in the score 2-3 group had a significantly worse prognosis and could benefit from adjuvant chemotherapy. Our study may help to provide targeted treatment for patients with stage T2N0M0 gastric cancer.This study had some limitations. This was a single-center retrospective study with a lower level of evidence than that of a prospective study. We did not classify the patients into subgroups based on the number of lymph nodes removed. The number of lymph node dissections has a significant effect on OS. For patients with stage T1-2 node-negative gastric cancer, the 5-year survival rate increased by 7.6% for every 10 Lymph nodes examined[28]. No recurrence-free survival or recurrence pattern was observed. We did not discuss the genetic characteristics of patients with gastric cancer included in the study. Genetic characteristics of patients with gastric cancer may influence the efficacy of adjuvant chemotherapy.

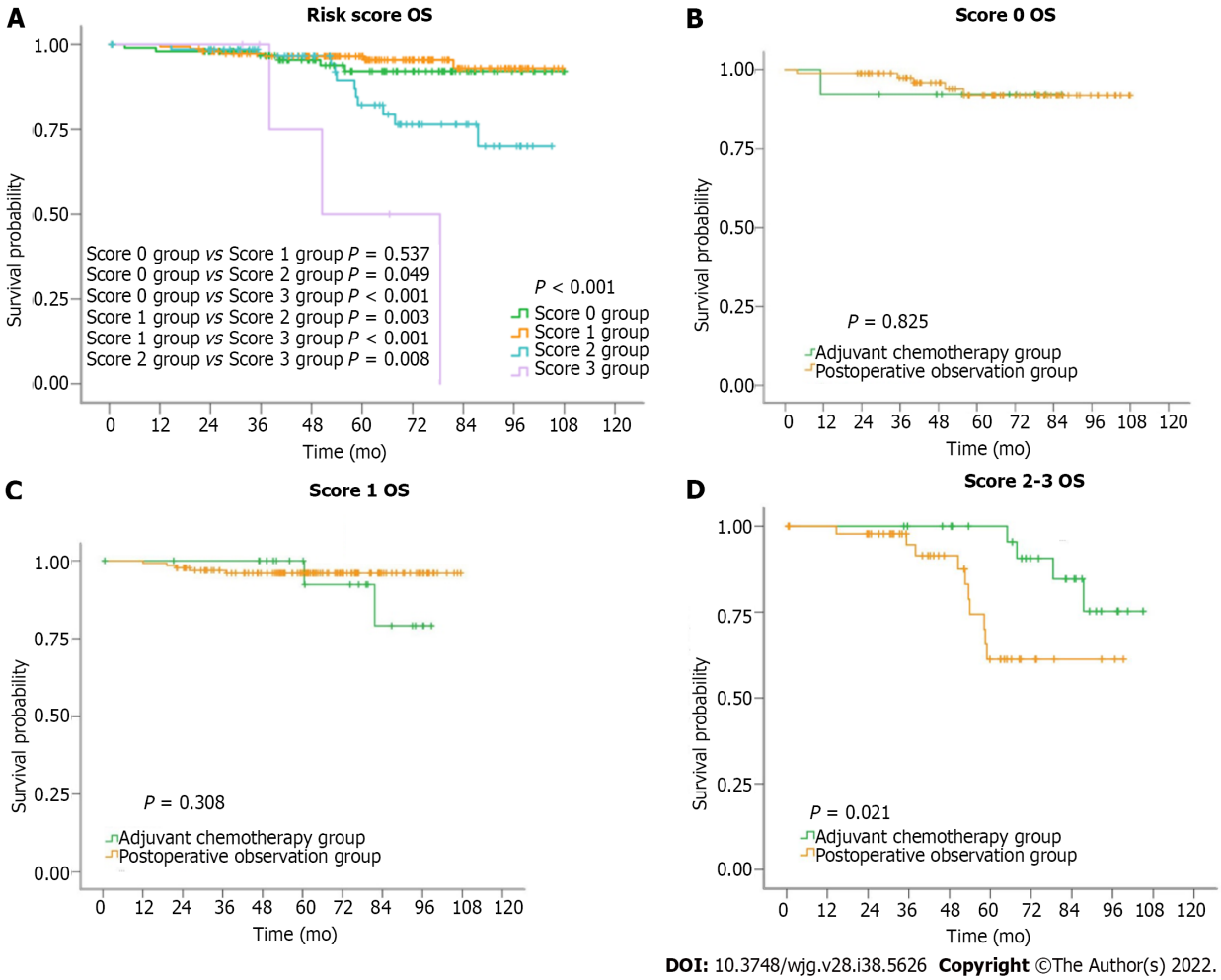

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Figure 1 Survival curves. A: The survival curves of score 0 group, score 1 group, score 2 group and score 3 group patients; B: The survival curves of score 0 T2N0M0 gastric cancer patients in adjuvant chemotherapy group and postoperative observation group; C: The survival curves of score 1 T2N0M0 gastric cancer patients in adjuvant chemotherapy group and postoperative observation group; D: The survival curves of score 2-3 T2N0M0 gastric cancer patients in adjuvant chemotherapy group and postoperative observation group. OS: Overall survival.

CONCLUSION

For patients with T2N0M0 stage gastric cancer and two or more risk factors, adjuvant chemotherapy after D2 gastrectomy may have a survival benefit. Individualized treatment should be adopted according to examination and pathological results in patients with T2N0M0 gastric cancer.

ARTICLE HIGHLIGHTS

Research background

It is controversial whether adjuvant chemotherapy is necessary for stage T2N0M0 gastric cancer.

Research motivation

To further clarify the indications for the use of postoperative adjuvant chemotherapy in patients with T2N0M0 gastric cancer.

Research objectives

To obtain a risk score to assess the need for adjuvant chemotherapy in patients with T2N0M0 gastric cancer.

Research methods

Univariate and multivariate Cox regression analyses were performed to predict factors affecting prognosis. Vascular invasion, tumor site, and BMI were assessed, and a scoring system was established.

We compared the survival outcomes and benefits of adjuvant chemotherapy between the different subgroups.

Research results

Five-year survival rates of the score 0, 1, 2, and 3 groups were 92%, 95%, 80%, and 50%, respectively ($P < 0.001$). In the score 2-3 group, five-year survival rates for patients in the adjuvant chemotherapy group and postoperative observation group were 95% and 61%, respectively ($P = 0.021$).

Research conclusions

For patients with T2N0M0 stage gastric cancer and two or more risk factors, adjuvant chemotherapy after D2 gastrectomy may have a survival benefit.

Research perspectives

Individualized treatment should be adopted according to examination and pathological results in patients with T2N0M0 gastric cancer.

FOOTNOTES

Author contributions: Xu Q and Kang WZ contributed equally to this work; Tian YT and Xu Q designed the research; Kang WZ, Xiong JP, and Shao XX analyzed the data and wrote the paper; Li WK and Hu HT collected the patient's clinical data.

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