Int J Clin Exp Med 2016;9(11):22217-22221
www.ijcem.com /ISSN:1940-5901/IJCEM0030103

Original Article

Effect of splenectomy on the survival of patients underwent radical surgery for gastric cardia cancer

Fujian Ji[1], Jian Zhang[2], Dacheng Wen[3], Xuedong Fang[1], Hongyong Jin[1], Wenlei Zhang[4]

[1]Department of Gastrointestinal Colorectal and Anal Surgery, China-Japan Union Hospital of Jilin University, Changchun 130033, China; Departments of [2]Hepatobiliary Surgery, [3]Gastrointestinal Surgery, The Second Hospital of Jilin University, Changchun 130041, China; [4]Department of Interventional Therapy, First Hospital of Jilin university, No. 71 of Xinmin Street, Chaoyang District, Changchun 130021, Jilin Province, China

Received April 8, 2016; Accepted September 13, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Aims: In gastric cardia cancer, the spleen is usually removed when the tumor is resected. This allows thorough lymph node dissection in the splenic hilus. However, the effect of splenectomy on patient survival is controversial. This study gives insight into the effect of splenectomy in radical surgery for gastric cardia cancer. Methodology: We reviewed the records of 348 patients who underwent radical resection for gastric cardia cancer. Of these 348 patients, 105 underwent splenectomy and 243 had splenic preservation. The clinicopathologic features of 105 patients underwent gastrectomy combined with resection of the spleen (splenectomy group) and 243 patients underwent gastrectomy (spleen-preservation group) were compared. Results: Gastric cardia cancer with splenectomy was characterized by serosal invasion, and positive lymph node metastasis. For age, sex, and tumor size, there was no significant difference between the patients with splenectomy and spleen-preservation. The 5-year survival of splenectomy group was 20.8% as compared with 30.5% for spleen-preservation group. With respect to patients with splenectomy, multivariate analysis showed that lymph node metastasis was significant factors affecting survival. Conclusions: Compared with spleen-preservation group, patients who underwent gastrectomy combined with splenectomy have a greater chance of serosal invasion, and positive lymph node metastasis and a significantly poor prognosis.

Keywords: Gastric cardia cancer, prognosis, splenectomy, survival

Introduction

In China, gastric carcinoma ranks second among all causes of death from cancer. Despite the incidence of gastric cancer has decreased over the past several decades, gastric cardia cancer has increased over the same period [1-3]. Surgery remains the treatment of choice and when it results in complete tumor removal, namely R0 resection, can be associated with long-term survival or even cure [4]. Splenectomy is the most commonly performed simultaneous operation with radical resection of gastric cardia cancer, and its purpose is to remove metastatic lymph nodes when there is invasion of the splenic hilus or splenic artery [5]. Preservation of the spleen is feasible with extende d lymph node dissection in the splenic hilus, and it might improve survival after radical surgery for gastric cardia cancer.

Some reports state that the average survival of patients with who underwent gastrectomy combined with splenectomy is poor [6-8], whereas others have refuted the difference [9, 11]. Thus, the long-term effect of splenectomy on survival is still controversial.

In this study, we retrospectively analyzed the records of patients who underwent gastrectomy combined with splenectomy and described the most recently available details of clinicopathological features and prognosis of patients who underwent gastrectomy combined with splenectomy.

Patients and methodology

Patients

We analysed data from 348 patients with histologically proven gastric cardia cancer under-

Table 1. Clinicopathological features of 348 patients who underwent radical resection for gastric cardia cancer

Variables	Resection of the spleen (n=105; %)	Preservation of the spleen (n=243; %)	*t or* χ^2 value (*P* value)
Age (mean, years)	57.9±10.5	58.5±11.1	0.825 (0.458)
Sex			
Male	67 (63.8)	144 (59.3)	
Female	38 (36.2)	99 (40.7)	0.636 (0.425)
Tumor size (mean, cm)	6.7±3.4	6.2±2.9	1.125 (0.159)
Depth on invasion			
T1	5 (4.8)	25 (10.3)	
T2	11 (10.5)	58 (23.9)	
T3	58 (55.2)	107 (44.0)	
T4	31 (29.5)	53 (21.8)	5.236 (0.005)
Lymph node metastasis			
N0	8 (7.6)	55 (22.6)	
N1	22 (21.0)	72 (29.6)	
N2	45 (42.9)	69 (28.4)	
N3	30 (28.6)	47 (19.3)	6.532 (<0.001)

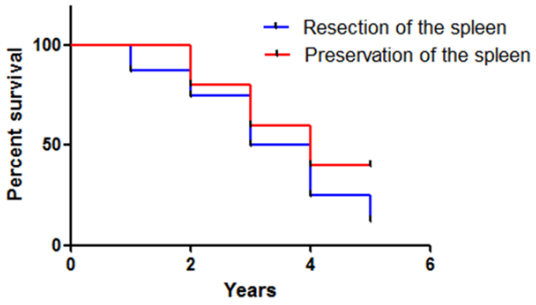

Figure 1. The K-M survival curve between resection of the spleen and preservation of the spleen group.

went radical surgery in our institution between September 2003 and December 2010. Of these, 105 patients (30.2%) underwent gastrectomy combined with resection of the spleen, and 243 patients (69.8%) underwent only gastrectomy.

We examined 5 factors based on patient and tumor findings: age, sex, tumor size, depth on invasion, and lymph node metastasis. This information was obtained from the hospital records. These findings were assessed according to the Japanese General Rules for Gastric Cancer Study in Surgery and Pathology [12]. The American Joint Committee on Cancer tumor-node-metastasis staging system was used for pathologic staging [13]. Curative resection (R0) was determined as there being no tumor left macroscopically or microscopically after the operation. Informed consent had been obtained, and the Ethics Committee of Jilin University approved this study.

Follow-up of patients was carried out until death or the cut-off date (October 31, 2013). Generally, patients return every 3 months for the first year, every 6 months for the next 2 years, and after 3 years every 12 months for life. Only patients who died of breast cancer were regarded as tumor-related death cases. For all patients, at the time of the last follow-up, 17 patients (4.9%) had been lost to follow-up. The median follow-up period was 54 months (range: 1-105 months). For 105 patients underwent gastrectomy combined with resection of the spleen, five patients (4.8%) had been lost to follow-up. The median follow-up period was 37 months (range: 1-84 months).

Statistical analysis

Statistical comparisons for significance were performed with the chi-square test for discrete variables and Student's t-test for continuous variables. Cumulative survival rates were determined with the Kaplan-Meier method, and the difference between groups was assessed by using the log-rank test. Covariates that remained significant through the univariate analysis were selected for multivariate analysis. Cox regression was used for multivariate analysis, with backward stepwise elimination model. Significance of differences was assumed at *P* values of less than 0.05. All data analysis was performed using the SPSS for Windows, Version 13.0 software package.

Results

In our study, the patients consisted of 211 men and 137 women. The mean age was 58.3 years (range 24-78 years). For 105 patients (67 men and 38 women) underwent gastrectomy combined with splenectomy, the mean age was

Table 2. Five-year survival rates between two groups

Age (years)	Number of patients	Five-year survival rate (%)	χ^2 value (*P* value)
Resection of the spleen	105	20.8	
Preservation of the spleen	243	30.5	5.698(0.002)

Table 3. Univariate analysis of 5-year survival rate for patients who underwent gastrectomy combined with splenectomy

Variable	Number of patients	5-year survival rate (%)	*P*-value
Depth on invasion			
T1	5	67.6	
T2	11	50.2	
T3	58	17.9	
T4	31	6.7	<0.001
Lymph node metastasis			
N0	8	68.5	
N1	22	38.9	
N2	45	16.7	
N3	30	0.0	<0.001

57.9 years (range 26-76 years). The clinicopathologic features of 105 patients underwent gastrectomy combined with splenectomy (splenectomy group) and 243 patients underwent gastrectomy (spleen-preservation group) were compared (**Table 1**).

There were significant differences in depth on invasion and lymph node metastasis between the patients with splenectomy and spleen-preservation. Gastric cardia cancer with splenectomy was characterized by serosal invasion (95.2%), and positive lymph node metastasis (92.4%). For depth on invasion, T3 was registered in 55.2% and 44.0% of the patients respectively and T4 was registered in 29.5% and 21.8% of the patients in the two groups respectively. For pN stage, N2 was registered in 42.9% and 28.4% of the patients respectively and N3 was registered in 28.6% and 19.3% of the patients in the two groups respectively. For age, sex, and tumor size, there was no significant difference between the patients with splenectomy and spleen-preservation.

The K-M survival analysis was shown in **Figure 1**. The 5-year survival rates of patients are shown in **Table 2**. The 5-year survival of splenectomy group was 20.8% as compared with 30.5% for spleen-preservation group (P=0.002) (**Table 2**). With respect to patients with splenectomy, the 5-year survival rate was influenced by depth on invasion and lymph node metastasis (**Table 3**). Two factors significant in the univariate analysis were included in the multivariate analysis, which indicated that the length of the survival period was independently influenced by lymph node metastasis (present vs. absent, relative risk 1.912, P<0.001) (**Table 4**). With respect to the overall patients with gastric cardia carcinoma, the Cox proportional hazards model showed that serosal invasion and lymph node metastasis were significant factors affecting survival. Splenectomy was not an independent prognostic factor (**Table 5**).

Discussion

The two main tumor sites of gastric cancer are proximal (cardia) and distal. Despite a decline in distal gastric cancers, proximal tumors have been increasing in incidence since the 1970s. Curative gastrectomy combined with complete removal of regional lymph nodes is a promising approach for the treatment of advanced gastric cancer. The spleen is rarely a target of direct invasion by gastric cancers, but sometimes tumor metastasis is found in the lymph nodes close to the splenic hilus and splenic artery. The role of the preservation or resection of the spleen during gastrectomy has not yet been clarified. The uncertainty regarding resection-over-preservation of the spleen prompted us to conduct this prospective study. In our study, there were significant differences in depth on invasion and lymph node metastasis between the patients with splenectomy and spleen-preservation. Gastric cardia cancer with splenectomy was characterized by serosal invasion (95.2%), and positive lymph node metastasis (92.4%). For age, sex, and tumor size, there was no significant difference between the patients with splenectomy and spleen-preservation.

The frequency of lymph node metastasis to the splenic hilum and splenic artery has been reported as about 10%, and to depend on tumor site and depth of invasion [10]. Tumors

Table 4. Multivariate analysis of Lymph node metastasis for survival in patients who underwent gastrectomy combined with splenectomy using the Cox proportional hazard model

Variables	Risk ratio	95% Confidence interval	*P*-value
Lymph node metastasis (present vs. absent)	1.912	1.718-2.156	<0.001

Table 5. Multivariate analysis of prognostic factors for survival in patients with gastric cardia carcinoma using the Cox proportional hazard model

Variables	Risk ratio	95% Confidence interval	*P*-value
Serosal invasion (present vs. absent)	1.875	1.203-2.694	<0.001
Lymph node metastasis (present vs. absent)	1.965	1.301-2.475	<0.001
splenectomy (present vs. absent)	1.195	0.967-1.548	0.206

located in the upper and middle thirds of the stomach and those infiltrating the serosa (pT3, pT4) have significantly higher invasion rates of these lymph nodes, necessitating splenectomy [14, 15].

The spleen is an important component of the reticuloendothelial system and constitutes 25% of the total lymphoid mass [16]. There was a 12-fold increased risk of septicemia compared with the general population after splenectomy [17]. Okinaga et al. [18] reported that advanced stage gastric cancer patients who underwent gastrectomy combined with splenectomy who were treated with immunotherapy had improved overall survival. The role of the spleen in tumor immunology is still controversial [19]. Therefore the indication for splenectomy is debatable. Kunisaki et al. [20] reported that splenectomy should be limited in those patients with gastric cardia tumors invading the spleen or with metastatic bulky lymph nodes extending to the spleen. Zhang et al. [21] reported that the spleen should be preserved in patients without direct cancer invasion of the spleen.

Several studies have investigated the impact of splenectomy on prognosis. However, the results remain inconsistent. Some investigators have reported that patients who undergo only gastrectomy have a better prognosis [9-11]. However, some reports have stated that the survival of patients who undergo curative gastrectomy with resection of the spleen and extended lymph node dissection for gastric cancer is longer than that of patients who undergo only gastrectomy [6, 8]. In this study, the 5-year survival of splenectomy group was 20.8% as compared with 30.5% for spleen-preservation group (P=0.002). In our study, splenectomy was not an independent prognostic factor.

The depth of wall invasion and lymph node metastasis are confirmed as two important prognostic factor of gastric cardia cancer [22]. In our study, gastric cardia cancer with gastrectomy combined with splnectomy was characterized by serosal invasion (95.2%), and positive lymph node metastasis (92.4%). With respect to the overall patients with gastric cardia carcinoma, the Cox proportional hazards model showed that serosal invasion and lymph node metastasis were significant factors affecting survival.

Conclusions

In summary, compared with spleen-preservation group, patients who underwent gastrectomy combined with splenectomy have a greater chance of serosal invasion, and positive lymph node metastasis and a significantly poor prognosis. For age, sex, and tumor size, there was no significant difference between the patients with splenectomy and spleen-preservation.

Acknowledgements

This work was supported by Department of science and technology of Jilin Province, Item number: 20150101161JC.

Disclosure of conflict of interest

None.

Address correspondence to: Department of Gastrointestinal Colorectal and Anal Surgery, China-Japan Union Hospital of Jilin University, Changchun 130033, China. Tel: +86043184997620; Fax:

+86043184997620; E-mail: hongyongjin48@sina.com; Wenlei Zhang, Department of Interventional Therapy, First Hospital of Jilin University, No. 71 of Xinmin Street, Chaoyang District, Changchun 130021, Jilin Province, China. Tel: +86043184997620; Fax: +86043184997620; E-mail: wenleizhang123@sina.com

References

[1] O'Connell JB, Maggard MA, Liu JH, Etzioni DA and Ko CY. A report card on outcome for surgically treated gastrointestinal cancers: are we improving? J Surg Res 2004; 121: 214-221.

[2] Levi F, Lucchini F, Gonzalez JR, Fernandez E, Negri E and La Vecchia C. Monitoring falls in gastric cancer mortality in Europe. Ann Oncol 2004; 15: 338-345.

[3] Pye JK, Crumplin MK, Charles J, Kerwat R, Foster ME, Biffin A; Hospital clinicians in Wales. Hospital clinicians in Wales. One-year survey of carcinoma of the oesophagus and stomach in Wales. Br J Surg 2001; 88: 278-285.

[4] Roukos DH and Kappas AM. Perspectives in the treatment of gastric cancer. Nat Clin Pract Oncol 2005; 2: 98-107.

[5] Soga J, Ohyama S, Miyashita K, Suzuki T, Nashimoto A, Tanaka O, Sasaki K and Muto T. A statistical evaluation of advancement of gastric cancer surgery with special reference to the significance of lymphadenectomy for cure. World J Surg 1988; 12: 398-405.

[6] Hulscher JB, Van Sandick JW and Offerhaus GJ. Prospective analysis of the diagnostic yield of extended en bloc resection for adenocarcinoma of the oesophagus or gastric cardia. Br J Surg 2001; 88: 715-719.

[7] Wu PC and Posner MC. The role of surgery in the management of esophageal cancer. Lancet Oncol 2003; 4: 481-488.

[8] Sano T, Yamamoto S, Sasako M; Japan Clinical Oncology Group Study. LCOG 0110-MF: Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan Clinical Oncology Group study JCOG 0110-MF. Jpn J Clin Oncol 2002; 32: 363-364.

[9] Griffith JP, Sue-Ling HM, Martin I, Dixon MF, McMahon MJ, Axon AT and Johnston D. Preservation of the spleen improves survival after radical surgery for gastric cancer. Gut 1995; 36: 684-690.

[10] Monig SP, Collet PH, Baldus SE, Schmackpfeffer K, Schröder W, Thiele J, Dienes HP and Hölscher AH. Splenectomy in proximal gastric cancer: frequency of lymph node metastasis to the splenic hilus. J Surg Oncol 2001; 76: 89-92.

[11] Graham AJ, Finley RJ, Clifton JC, Evans KG and Fradet G. Surgical management of adenocarcinoma of the cardia. Am J Surg 1998; 175: 418-421.

[12] Japanese Gastric Cancer Association: Japanese classification of gastric carcinoma, 3rd English edn. Gastric Cancer 2011; 14: 101-112.

[13] In: Edge SB, Byrd DR and Compton CC, editors. AJCC cancer staging manual, 7th edition. New York: Springer; 2010.

[14] Sakaguchi T, Sawada H,Yamada Y, Fujimoto H, Emoto K, Takayama T, Ueno M and Nakajima Y. Indication of splenectomy for gastric carcinoma involving the proximal part of the stomach. Hepatogastroenterology 2001; 48: 603-605.

[15] Han FH, Zhan WH, Li YM, He YL, Peng JS, Ma JP, Wang Z, Chen ZX, Zheng ZQ, Wang JP, Huang YH and Dong WG. Analysis of long-term results of radical gastrectomy combining splenectomy for gastric cancer. Zhonghua Wai Ke Za Zhi 2005; 43: 1114-1117.

[16] Ellison EC and Fabri PJ. Complications of splenectomy. Etiology, prevention, and management. Surg Clin North Am 1983; 63: 1313-1330.

[17] Csendes A, Burdiles P, Rojas J, Braghetto I, Diaz JC and Maluenda F. A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma. Surgery 2002; 131: 401-407.

[18] Okinaga K, Iinuma H, Kitamura Y, Yokohata T, Inaba T and Fukushima R. Effect of immunotherapy and spleen preservation on immunological function in patients with gastric cancer. J Exp Clin Cancer Res 2006; 25: 341.

[19] Okuno K, Tanaka A, Shigeoka H, Hirai N, Kawai I, Kitano Y and Yasutomi M. Suppression of T-cell function in gastric cancer patients after total gastrectomy with splenectomy: implications of splenic autotransplantation. Gastric Cancer 1999; 2: 20-25.

[20] Kunisaki C, Makino H, Suwa H, Sato T, Oshima T, Nagano Y, Fujii S, Akiyama H, Nomura M, Otsuka Y, Ono HA, Kosaka T, Takagawa R, Ichikawa Y and Shimada H. Impact of splenectomy in patients with gastric adenocarcinoma of the cardia. J Gastrointest Surg 2007; 11: 1039-1044.

[21] Zhang CH, Zhan WH, He YL, Chen CQ, Huang MJ and Cai SR. Spleen preservation in radical surgery for gastric cardia cancer. Ann Surg Oncol 2007; 14: 1312-1319.

[22] Zhang M, Li Z, Ma Y, Zhu G, Zhang H and Xue Y. Prognostic predictors of patients with carcinoma of the gastric cardia. Hepatogastroenterology 2012; 59: 930-933.