Clinicopathological difference of gastric cancer between lesser and greater curvature

Guocai Li（ ✉ mrlgc@163.com ）

  xi'an international medical centre   https://orcid.org/0000-0001-5857-4646

Qing-Chuan Zhao

  Xijing Hospital

Hong-Wei Zhang

  Xijing Hospital

Peng Yang

  xi'an

Fang-Ning Pang

  xi'an

Long-Long Xu

  xi'an

Xin-An Wu

  xi'an

Research article

Abstract

Background: Gastric cancer(GC) is heterogeneous disease, recent years has established a molecular classification and described distribution of molecular subtypes in stomach. However, the clinicopathological difference of gastric cancer between lesser and greater curvature is still unknown. In this study, we investigated the clinicopathological difference of gastric cancer between lesser and greater curvature. Methods: Between January 2010 and August 2014, 1249 consecutive patients with GC located at lesser or greater curvature were treated in our surgery department, the data of demographic, pathological type, differentiation, tumor size, TNM stage, tumor markers, operative methods, complications and follow-up data were analyzed by univariant analysis and Kaplan-Meier analysis retrospectively. Results: We found the tumor size in lesser curvature was larger than in greater curvature (4.95±2.57 vs. 4.43±2.62cm, P=0.034); The patients with gastric cancer in lesser curvature had a higher incidence of total gastrectomy, but a lower incidence of distal gastrectomy than it in greater curvature (60.2% vs. 43.2%, and 34.8% vs. 49.2%, P=0.002); The 5-year survival rate of gastric cancer between the curvatures was not statically significant (62.6±0.02% vs.66.1±0.06%, P=0.496); The rate of EGFR expression in lesser curvature was 40.55%, which was significantly higher than that in greater curvature (25.92%，P=0.024), and the 5-year survival rate in patients with EGFR positive was 50.8±0.06%, which was significantly lower than that in patients with EGFR negative (64.8±0.03%，P=0.021). Conclusions: Our results suggest that the clinicopathological difference of gastric cancer is significant between lesser and greater curvature. Emphasizing the difference contribute to improve outcome of treatment.

Background

Gastric cancer (GC) ranks third for morbidity and second for morality worldwide. Although the number of deaths has decreased, there are 1.3 million incident cases of GC and 819000 deaths in 2015(1). The 5-year survival from GC was 25–39% (2), and the median survival is 50, 14 and 3 months for treatment with chemotherapy plus surgery, chemotherapy alone and best supportive care, respectively(3).

GC is a heterogeneous disease. The Cancer Genome Atlas (TCGA) project propose a molecular classification dividing gastric adenocarcinomas into four subtypes: tumours positive for Epstein–Barr virus; microsatellite unstable tumours; genomically stable tumours and tumours with chromosomal instability. (4) A tissue subtype of gastric adenocarcinomas is also constructed by Birkman.(5) Through the molecular and genomic basis of GC, the distribution of molecular subtypes in tumors has obtained. It has reported Epstein-Barr virus positive intestinal-type tumours are more often found in the gastric corpus. And majority of the intestinal-type tumours with TP53 aberrations are located in proximal gastric. These findings are making it feasible to integrate genome-based and phenotype-based diagnostic and therapeutic methods.(6–8)

The molecular subtype and its distribution suggest that clinicopathologic characteristic and prognostic of GC are closely correlate with the tumor location. It has reported that the proportion of cardia/fundus cancer remained stable in recent years, but that of corpus cancer increased, and the proportion of

localized tumor increased, but regional tumor decreased(9). Cristescu demonstrate microsatellite-unstable tumors are hyper-mutated intestinal-subtype tumors occurring in the antrum, and the tumors have the best overall prognosis and the lowest frequency of recurrence. (10)

Lesser curvature near to stomachic angular is the most common location for GC, however, the tumor located in greater curvature is less than 3%.(11) Till now, the clinicopathological difference of gastric cancer between greater and lesser curvature is unclear. Therefore, in this study, we investigated the difference between lesser curvature and larger curvature and aimed to provide powerful evidence for GC treatment.

Results

baseline characteristics.

A total of 1249 cases met the inclusion criteria and were analyzed in this cohort study (Figure. 1), of whom 1124 cases were distributed in lesser curvature of gastric, and other 125 cases were distributed in greater curvature. The comparison of baseline data between the lesser and greater curvature was described in Table 1. There were no significant differences between the lesser and greater curvature regarding preoperative variables, such as age, sex, symptoms, positive sign and blood test. The patients with gastric cancer in lesser curvature had a higher rate of family history of neoplasm than that in greater curvature.(9.4% vs. 4%, P = 0.041). (Table 1)

Table 1

Characteristics of Patients with gastric cancer in Lesser curve and Greater curve

Feature	Gastric cancer		P value
	Lesser curve	Greater curve	
No.	1124	125	
Male/female	872/252	90/35	0.178
Age(Mean ± SD)	56.97±10.98	55.92±12.04	0.312
Symptom			
Abdominal Pain(%)	798(71)	96(76.8)	0.394
Abdominal Distension(%)	453(40.3)	41(32.8)	0.122
Vomit(%)	78(6.9)	9(7.2)	0.854
Dysphagia(%)	117(10.4)	10(8)	0.653
Sour regurgitation (%)	166(14.8)	17(13.6)	0.886
Positive sign(no/yes)	341/769	39/81	0.679
Weight loss(no/yes)	390/477	43/55	0.835
Family history of tumor (%)	106(9.4)	5(4)	0.041
Heart disease(%)	21(1.9)	6(4.8)	0.046
Hypertension(%)	133(11.8)	18(14.4)	0.389
others(%)	130(11.6)	14(11.2)	0.887
Blood Test			
WBC (10e9/L)	5.88 ± 1.99	5.99 ± 2.61	0.555
HGB (g/L)	126.14 ± 27.86	124.85 ± 26.03	0.623
GRA(%)	0.67 ± 0.97	0.60 ± 0.10	0.673
RBC (10e12/L)	4.71 ± 7.90	4.25 ± 0.70	0.519
TP (g/L)	66.44 ± 7.30	66.87 ± 7.08	0.527
ALB (g/L)	42.03 ± 5.30	42.41 ± 5.96	0.456

Student t-test was used to analyze age and blood test, and Chi-square test were used to analyze categorical variables, respectively. SD, standard deviation; L, litre; WBC, white blood cell count; GRA, Granulocyte; RBC, red blood cell count; HGB, hemoglobin; TP, serum protein; ALB, albumin;

The difference of pathological type, histological subtype, Borrman type, tumor differentiation, and TNM stage was not found between lesser and greater curvature. While, the tumor in lesser curvature was larger than greater curvature (4.95 ± 2.57 vs. 4.43 ± 2.62 cm, P = 0.034). (Table 2)

Table 2
Pathological Characteristics of Patients with gastric cancer in Lesser curve and Greater curve

Feature	Gastric cancer		P value
	Lesser curve	Greater curve	
Tumor size(cm)	4.95 ± 2.57	4.43 ± 2.62	0.034
Borrman type			
⬚	37	4	0.817
⬚	211	26	
⬚	307	27	
⬚	105	14	
unkown			
Pathological type			
Ulcer	823	86	0.085
Infiltrate	67	6	
Mucus	41	4	
Signet ring cell	22	2	
Fungating	24	0	
Higher level	12	3	
Other			
Grade of differentiation			
Well	119	19	0.350
Moderate	300	31	
Poor	269	30	
unknown			
T stage			
⬚	42	2	0.170
⬚	133	20	

Chi-square test and The Fisher's exact test were used to analyze categorical variables

Feature	Gastric cancer		P value
	Lesser curve	Greater curve	
⬜	421	36	
⬜	14	1	
Lymph node involvement			
N0	365	49	0.200
N1	221	18	
N2	170	21	
N3	13	0	
Chi-square test and The Fisher's exact test were used to analyze categorical variables			

Comparison of serum markers of gastric cancer

The concentrate of serum markers of cancers, CEA, CA19-9, CA125 and AFP, were not significantly different between lesser curvature and greater curvature. And according to cut-off values, the positive rate of these markers were not significantly different yet. (Table 3)

Table 3
Characteristics of Patients with gastric cancer in Lesser curve and Greater curve

		Gastric cancer		P value
		Lesser curvature	Great curvature	
CEA	(ng/ml)	14.70 ± 118.48	11.47 ± 79.69	0.780
	Total no.	974	110	
	n(%)	165(16.9%)	13(11.8%)	0.370
CA19-9	(U/L)	77.72 ± 473.35	141.89 ± 609.27	0.213
	Total no.	908	100	
	n(%)	165(18.2%)	22(22.0%)	0.438
AFP	(ng/ml)	17.67 ± 167.89	18.51 ± 117.03	0.961
	Total no.	911	99	
	n(%)	66(7.2%)	12(12.1%)	0.225
CA125	(U/L)	15.69 ± 34.40	16.45 ± 36.79	0.832
	Total no.	922	103	
	n(%)	42(4.6%)	4(3.9%)	0.639

The measurement data were described as mean ± SD (standard deviation), and were analyzed by Student t-test; Total no. mean the total specimen detected; n(%) denoted positive specimen and rate. Chi-square test and the Fisher's exact test were used to analyze categorical variables.

Comparison of operative data

The patients with gastric cancer in lesser curvature had a higher incidence of total gastrectomy, but a lower incidence of distal gastrectomy than it in greater curvature(60.2% vs. 43.2%, and 34.8% vs. 49.2%, P = 0.002), Also, the incidence of radical resection in lesser curvature was higher than in greater curvature (96.1% vs. 91.7%, P = 0.002). In addition, the incidence of other organ combined resection was higher in lesser curvature than in greater curvature (17.6% vs. 10.1%, P = 0.012). moreover, the amount of operative bleeding in lesser curvature was larger than greater curvature (272.88 ± 262.27 vs. 218.23 ± 196.37 ml, P = 0.041). but, the operation time was similar between two curvatures. (Table 4)

Table 4
Comparison of operative data

Variables	Lesser curve	Greater curve	P value
	No.	No.	
Operative methods			
laparotomy	723(90.1%)	79(9.1%)	0.892
laparoscopic	374(89.9%)	42(10.1%)	
Gastrectomy methods			
total	662(60.2%)	51(43.2%)	0.002
distal	383(34.8%)	58(49.2%)	
proximal	54(4.9%)	9(7.6%)	
Radical resection			
no	43(3.9%)	10(8.3%)	0.025
yes	1063(96.1%)	111(91.7%)	
Combined resection			
no	1010(89.9%)	103(82.4%)	0.012
yes	114(10.1%)	22(17.6%)	
Operation time(min)	205.62 ± 87.22	211.84 ± 70.63	0.485
Bleeding (ml)	218.23 ± 196.37	272.88 ± 262.27	0.041
Student t-test was used to analyze age, and Chi-square test were used to analyze categorical variables, respectively. SD, standard deviation;			

Postoperative complications

there was no hospital death in this study. The incidence rate of total complications in lesser curvature was not statistically different from that in the lager curvature (6.49% vs. 10.4%, P = 0.102) and anastomotic complications wee similar between curvatures(0.71% vs. 0%, P = 0.344). In addition, there were no differences regarding pulmonary complications, wound rupture, duodenum leak,anastomotic leakage and stricture, and severe bleeding according to the univariate analysis (Table 5).

Table 5
Postoperative complications in patients

Postoperative complication	Lesser curve	Greater curve	P value
Hospital death	0	0	
Death within 30 days	9	2	0.364
Pulmonary complications	25	3	0.755
Wound rupture	9	3	0.110
Severe bleeding	10	1	0.919
Duodenums leakage	2	0	0.637
Anastomosis stricture	5	0	0.455
Anastomosis leakage	3	0	0.563
Any complication (%)	63(5.60%)	9(7.20%)	0.482
Anastomotic complication (%)	8(0.71%)	0(0%)	0.344
The data were showed by no. Chi-square test was used to analyze complication incidence.			

5-year survival rate between gastric cancer in greater and lesser curvature

1108 Cases had complete follow-up data, and average flow-up time was 29.14 ± 17.09 months (ranged from 0.17 to 66.73 months). The difference of 5-year survival rate between greater and lesser curvature were not statically significant by Kaplan-Meier analysis (62.6 ± 0.02% and 66.1 ± 0.06%, P = 0.496). (Fig. 2A and C)

The difference of EGFR expression between greater and lesser curvature

The positive rate of EGFR expression in lesser curvature was 40.55%, which was significantly higher than that in greater curvature (25.92%,P = 0.024). EGFR expression was negatively correlated with 5-year survive, the survival rate in patients with EGFR positive was 50.8 ± 0.06%, which was significantly lower than that in patients with EGFR negative by Kaplan-Meier analysis. (64.8 ± 0.03%,P = 0.021). (Fig. 2B and D). But the difference of HER2, CD44, CD34, S-100 and c-MET expression was not found between the curvatures. (Table 6).

Table 6

Characteristics of Patients with gastric cancer in Lesser curve and Greater curve

		Gastric cancer			P value
		Total	Lesser curve	Greater curve	
HER-2	No.	621	556	65	0.446
	Positive no.(%)		204(36.69%)	19(29.23%)	
EGFR	No.	870	789	81	0.024
	Positive no.(%)		320(40.55%)	21(25.92%)	
CD44	No.	240	225	15	0.110
	Positive no.(%)		106(47.11%)	9(60%)	
CD34	No.	465	414	51	0.261
	Positive no.(%)		209(50.48%)	30(58.82%)	
S-100	No.	465	415	50	0.426
	Positive no.(%)		293(70.77%)	38(76%)	
c-met	No.	216	204	12	0.113
	Positive no.(%)		137(67.15%)	5(41.67%)	
Chi-square test and the Fisher's exact test were used to analyze categorical variables					

Discussion

The aim of the present study was to investigate clinicopathological difference of gastric cancer between lesser and greater curvature. We found tumor size, the extent of gastrectomy, postoperative complication and EGFR expression level were significantly different between lesser curvature and greater curvature.

In this study, we found gastric cancer were more commonly founded in lesser curvature than in larger curvature. The distributed characteristic of our results was also agreed with the prior studies(11). It has reported H. pylori infection is regard as a definite environmental risk factor for the development of GC(19),H. pylori infection cause intestinal metaplasia (IM) and atrophy. In addition, mean atrophy and IM scores are higher in lesser curvature of the corpus than in greater curvature(20), moreover, yellowish-white nodules are observed in Helicobacter pylori-associated gastritis, which are frequently observed on lesser curvature of the corpus mucosa in 20%, greater curvature of the corpus mucosa in 0.9%.(21) In addition, Gastric "crawling-type" adenocarcinoma (CTAC) is a neoplasm histologically comprising irregularly fused glands with low-grade cellular atypia that tends to spread laterally in the mucosa. CTAC was most frequently located in the lesser curvature of the middle-third of the stomach.(22) Combined with the

above studies, our results emphasized the susceptibility of carcinogenesis in lesser curvature of stomach. We found a higher ratio of family history in patients with lesser curvature tumor, this give us sign that gastric cancer in lesser curvature was more frequently correlated with heritage background than in larger curvature.

It has reported that the anatomical location-based classification of lymph node metastasis is an important tool for gastric cancer prognosis,(23) and the incidence of lymph nodular metastasis tended to be higher in cases at the lower location than in those at the middle/upper location.(24) Therefore, some authors hypothesize that primary gastric tumors towards the lesser curvature can be treated by a modified D2 lymphadenectomy, and for tumors towards the greater curvature, a D1(+) lymphadenectomy always including the no. 7 & 9 lymph node stations complex, might be enough.(25) In this study, we didn't find the difference of lymph node metastasis between lesser curvature and large curvature. Our result was consistent with the study demonstrated that metastasis of tumors located in greater curvature was similar to lesser curvature(26), but contrast to the study showed the most frequent metastasis were located in the lower third and lesser curvature of the stomach(27).

We investigated the operative mode of gastrectomy in all patients, and found the patients with gastric cancer in lesser curvature had a higher incidence of total gastrectomy, but a lower incidence of distal gastrectomy than it in greater curvature, the incidence of radical resection in lesser curvature was higher than in greater curvature. In addition, the incidence of other organ combined resection was higher in greater curvature than in lesser curvature. Moreover, the amount of operative bleeding in greater curvature was larger than lesser curvature. These results suggest that tumor in greater curvature was more commonly infiltrate adjacent organs such as pancreas and spleen. The incidence rate of total postoperative complications and anastomotic complications were not different between curvatures in this study. Our results were not consistent with the study by Hirota and Kim who report lesser curvature tumor has significantly higher frequency of postoperative complications than greater curvature(28), such as prolonged abdominal symptoms, food residue, and perforation.(29)

Several studies have reported that the 5-year overall survival rate of gastric cancer were influenced by tumor size, depth of invasion, lymph node metastasis, and chemotherapy, early detection and radical resection are essential to improve the prognosis of patients gastric cancer(30, 31). We found the 5-year survival rate of gastric cancer between greater and lesser curvature was not statically significant. Our results were not consistent with the report showed the worse survival at the greater curvature location than lesser curvature of the gastric cancer.(32)

In our study, we investigated the expression status of several tumor markers which are closely related with clinicopathologic characteristic and prognosis in GC, and are commonly used in the current clinic. But except for EGFR, none of them were found statically different expression between lesser curvature and larger curvature. We found an increasing expression levels of EGFR in lesser curvature than in lager curvature. This result supplemented for the distribution of EGFR in gastric cancer. In addition, enhancement of EGFR in lesser curvature maybe reveal its new prognostic value in gastric cancer. EGFR

is a potential therapeutic target for various cancers including gastric cancer(33). We also found the 5-year survival in EGFR negative group was significantly higher than it in EGFR positive group, therefore, our results provided powerful evidence for the therapeutic value of EGFR in gastric cancer.

Conclusion

Our results suggest there exist clinicopathological difference of gastric cancer between lesser and greater curvature. EGFR expression level were also significantly different between lesser curvature and greater curvature. These findings supplement for the distributing characteristics of gastric cancer and contribute to make reasonable treatment.

Abbreviations

GC
gastric cancer
CEA
Carcinoembryonic antigen
CA
Carbohydrate antigen
AFP
Alpha fetoprotein
EGFR
Epidermal growth factor receptor
HER-2
human epidermal growth factor receptor-2

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Fourth Military Medical University. All patients received verbal and written information regarding the study, and informed consent, obtained from all patients, was written.

Consent for publication

All participants gave written consent for their personal or clinical details along with any identifying images to be published in this study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable requesturrent study are available from the corresponding author on reasonable request

Authors' contributions

GCL⬚conceiving and designing the study, and writing the manuscript⬚HWZ and QCZ: providing critical revisions; PY: analyzing and interpreting the data; FNP, LLX and XAW: collecting the data; All authors approved the final version of the manuscript.

References

1.
Global Burden of Disease. Cancer C, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524–48.
2.
Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015;385(9972):977–1010.
3.
Morgagni P, Solaini L, Framarini M, Vittimberga G, Gardini A, Tringali D, et al. Conversion surgery for gastric cancer: A cohort study from a western center. International journal of surgery (London England). 2018;53:360–5.
4.
Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–9.
5.

Birkman EM, Mansuri N, Kurki S, Algars A, Lintunen M, Ristamaki R, et al. Gastric cancer: immunohistochemical classification of molecular subtypes and their association with clinicopathological characteristics. Virchows Arch. 2017/10/20 ed2018. p. 369–82.

6.

Liu X, Meltzer SJ. Gastric Cancer in the Era of Precision Medicine. Cell Mol Gastroenterol Hepatol. 2017;3(3):348–58.

7.

Kim HJ, Kang SK, Kwon WS, Kim TS, Jeong I, Jeung HC, et al. Forty-nine gastric cancer cell lines with integrative genomic profiling for development of c-MET inhibitor. Int J Cancer. 2018;143(1):151–9.

8.

Hansford S, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, et al. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. JAMA Oncol. 2015;1(1):23–32.

9.

Eom BW, Jung KW, Won YJ, Yang H, Kim YW. Trends in Gastric Cancer Incidence According to the Clinicopathological Characteristics in Korea, 1999–2014. Cancer Res Treat. 2018;50(4):1343–50.

10.

Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015;21(5):449–56.

11.

Sheikh IA, Mirza Z, Ali A, Aliev G, Ashraf GM. A proteomics based approach for the identification of gastric cancer related markers. Curr Pharm Des. 2016;22(7):804–11.

12.

Zhou H, Dong A, Xia H, He G, Cui J. Associations between CA19-9 and CA125 levels and human epidermal growth factor receptor 2 overexpression in patients with gastric cancer. Oncol Lett. 2018;16(1):1079–86.

13.

Laboissiere RS, Buzelin MA, Balabram D, De Brot M, Nunes CB, Rocha RM, et al. Association between HER2 status in gastric cancer and clinicopathological features: a retrospective study using whole-tissue sections. BMC Gastroenterol. 2015;15:157.

14.

He C, Bian XY, Ni XZ, Shen DP, Shen YY, Liu H, et al. Correlation of human epidermal growth factor receptor 2 expression with clinicopathological characteristics and prognosis in gastric cancer. World J Gastroenterol. 2013;19(14):2171–8.

15.

Yuan TM, Liang RY, Hsiao NW, Chuang SM. The S100A4 D10V polymorphism is related to cell migration ability but not drug resistance in gastric cancer cells. Oncol Rep. 2014;32(6):2307–18.

16.

Szczepanik A, Sierzega M, Drabik G, Pituch-Noworolska A, Kolodziejczyk P, Zembala M. CD44(+) cytokeratin-positive tumor cells in blood and bone marrow are associated with poor prognosis of patients with gastric cancer. Gastric Cancer. 2018.

17.

Tenderenda M, Rutkowski P, Jesionek-Kupnicka D, Kubiak R. Expression of CD34 in gastric cancer and its correlation with histology, stage, proliferation activity, p53 expression and apoptotic index. Pathol Oncol Res. 2001;7(2):129–34.

18.

Uda H, Kanda M, Tanaka C, Kobayashi D, Inaoka K, Tanaka Y, et al. Perioperative Serum Carcinoembryonic Antigen Levels Predict Recurrence and Survival of Patients with Pathological T2-4 Gastric Cancer Treated with Curative Gastrectomy. Dig Surg. 2018;35(1):55–63.

19.

You WC, Zhang L, Gail MH, Chang YS, Liu WD, Ma JL, et al. Gastric dysplasia and gastric cancer: Helicobacter pylori, serum vitamin C, and other risk factors. J Natl Cancer Inst. 2000;92(19):1607–12.

20.

Cho SJ, Choi IJ, Kook MC, Yoon H, Park S, Kim CG, et al. Randomised clinical trial: the effects of Helicobacter pylori eradication on glandular atrophy and intestinal metaplasia after subtotal gastrectomy for gastric cancer. Aliment Pharmacol Ther. 2013;38(5):477–89.

21.

Hayashi S, Imamura J, Kimura K, Saeki S, Hishima T. Endoscopic features of lymphoid follicles in Helicobacter pylori-associated chronic gastritis. Dig Endosc. 2015;27(1):53–60.

22.

Okamoto N, Kawachi H, Yoshida T, Kitagaki K, Sekine M, Kojima K, et al. "Crawling-type" adenocarcinoma of the stomach: a distinct entity preceding poorly differentiated adenocarcinoma. Gastric Cancer. 2013;16(2):220–32.

23.

Galizia G, Lieto E, Auricchio A, Cardella F, Mabilia A, Diana A, et al. Comparison of the current AJCC-TNM numeric-based with a new anatomical location-based lymph node staging system for gastric cancer: A western experience. PLoS One. 2017;12(4):e0173619.

24.

Asakawa Y, Ohtaka M, Maekawa S, Fukasawa M, Nakayama Y, Yamaguchi T, et al. Stratifying the risk of lymph node metastasis in undifferentiated-type early gastric cancer. World J Gastroenterol. 2015;21(9):2683–92.

25.

Griniatsos J, Moris D, Spartalis E, Gakiopoulou H, Karavokyros I, Apostolou K, et al. Towards a tailored lymphadenectomy for gastric cancer based on the correlation between the primary tumor location and the first lymphatic drain basin: Preliminary data. J BUON. 2017;22(5):1137–43.

26.

Aoyama J, Kawakubo H, Goto O, Nakahara T, Mayanagi S, Fukuda K, et al. Potential for local resection with sentinel node basin dissection for early gastric cancer based on the distribution of primary sites. Gastric Cancer. 2018.

27.

Lee JH, Lee HJ, Kong SH, Park DJ, Lee HS, Kim WH, et al. Analysis of the lymphatic stream to predict sentinel nodes in gastric cancer patients. Ann Surg Oncol. 2014;21(4):1090–8.

28.

Hirota M, Nakajima K, Miyazaki Y, Takahashi T, Kurokawa Y, Yamasaki M, et al. Clinical outcomes of laparoscopic partial gastrectomy for gastric submucosal tumors. Asian J Endosc Surg. 2015;8(1):24–8.

29.

Kim M, Jeon SW, Cho KB, Park KS, Kim ES, Park CK, et al. Predictive risk factors of perforation in gastric endoscopic submucosal dissection for early gastric cancer: a large, multicenter study. Surg Endosc. 2013;27(4):1372–8.

30.

Zhu YL, Yang L, Sui ZQ, Liu L, Du JF. Clinicopathological features and prognosis of Borrmann type IV gastric cancer. J BUON. 2016;21(6):1471–5.

31.

Kang WM, Meng QB, Yu JC, Ma ZQ, Li ZT. Factors associated with early recurrence after curative surgery for gastric cancer. World J Gastroenterol. 2015;21(19):5934–40.

32.

Kang SH, Kim YH, Roh YH, Kim KW, Choi CJ, Kim MC, et al. Gallstone, cholecystectomy and risk of gastric cancer. Ann Hepatobiliary Pancreat Surg. 2017;21(3):131–7.

33.

Aratani K, Komatsu S, Ichikawa D, Ohashi T, Miyamae M, Okajima W, et al. Overexpression of EGFR as an Independent Prognostic Factor in Adenocarcinoma of the Esophagogastric Junction. Anticancer Res. 2017;37(6):3129–35.

Methods

Patient enrollment.

Between January 2010 and August 2014, 4421 consecutive patients with GC underwent gastrectomy by the First Department of Digestive Surgery of XiJing Hospital, Fourth Military Medical University (Xi'an, China). For this retrospective cohort study, all patient data were evaluated by two researchers and the inclusion criteria were as follows: i) patients were diagnosed as gastric adenocarcinoma according to pathologic characteristics; ii) patients underwent gastrectomy or explorative surgery, the tumors were located at lesser or greater curvatures and were clearly recorded by surgeons; iii) patients had not severe basic disease and were at the level of Ⅰ or Ⅱ according to American Society Anesthesiology Physical Status Classification System.

This study was approved by the Ethics Committee of the Fourth Military Medical University. All patients received verbal and written information regarding the study and provided informed consent prior to surgery.

Demographic and preoperative data.

Demographic data, including sex, age, symptom, positive sign, history of past illness, and preoperative data, including routine hematological, biochemical tests and X-rays, were collected to enable subsequent

analysis of the comparability of the groups. The concentrate of serum markers of cancers, CEA(Carcinoembryonic antigen), carbohydrate antigen (CA)19 – 9,AFP(Alpha fetoprotein) and CA125,were also detected by radioimmune method in our hospital, and putting 5 ng/ml, 7 ng/ml, 27 U/ml and 35 U/ml as cut-off values respectively, we classified the expression level of markers as positive and negative expression.

Perioperative observations

Postoperative data included pathological type, Borrman type, grade of differentiation and tumor size. The histological subtype and pathological stage were determined using the Union for International Cancer Control and TNM classification for gastric cancer. Several tumor markers has been confirmed to be closely related with clinicopathologic characteristic and prognosis of GC, and are commonly used in the current clinic, including EGFR(Epidermal growth factor receptor),HER-2(human epidermal growth factor receptor-2) (12–14),S-100(s-100 calcium-binding protein) (15), CD44(16), CD34(17), c-MET(Receptor tyrosine kinase MET)(18). These markers were stained postoperatively by immunohistochemistry and were judged as positive or negative staining by two pathologists.

Patients were performed radical gastrectomy with D2 lymphadenectomy by the method of laparotomy or laparoscopic. The extent of resection of stomach were determined by tumor size, location, infiltration of organ and pathological type, which included total, proximal and distal gastrectomy. And when tumor infiltration with surrounding organ, an enlarged gastrectomy combined with organ resection were performed, but when tumor metastasis profoundly, the explosive or palliative operation was performed. The anastomoses including esophagogastrostomy, gastroduodenostomy and esophagojejunostomy, were performed with 28 mm diameter circular stapler. Operative bleeding and operation time were counted by anesthesia doctor.

Postoperative complications, including anastomotic complication, wound infection, wound rupture, lung infection, bleeding, reoperation, duodenal leak and intestinal obstruction were evaluated. Anastomotic complication assessment was performed using a water-soluble radiological contrast enema at 6–8 days post- operatively. A clinical leak was defined by extravasation of the contrast medium detected on radiography.

Follow-up Data

All patients were followed for five years from the beginning of operation. And at the end of follow-up, the status of patients were recorded, which included survival, death, and lost follow-up.

Statistical analysis.

Statistical analysis was performed using SPSS 17 software (SPSS Inc., Chicago, IL, USA). Differences among groups consisted of measurement data were analyzed by students' t test; Differences in expression rate among groups were analyzed by Pearson's Chi-squared ($\chi2$) test. The Fisher's exact test

was used to assess the difference of positive rate when the number of total cases was less than 40. P value < 0.05 was considered statistically significant. Survival analysis were used by Kaplan-Meier.
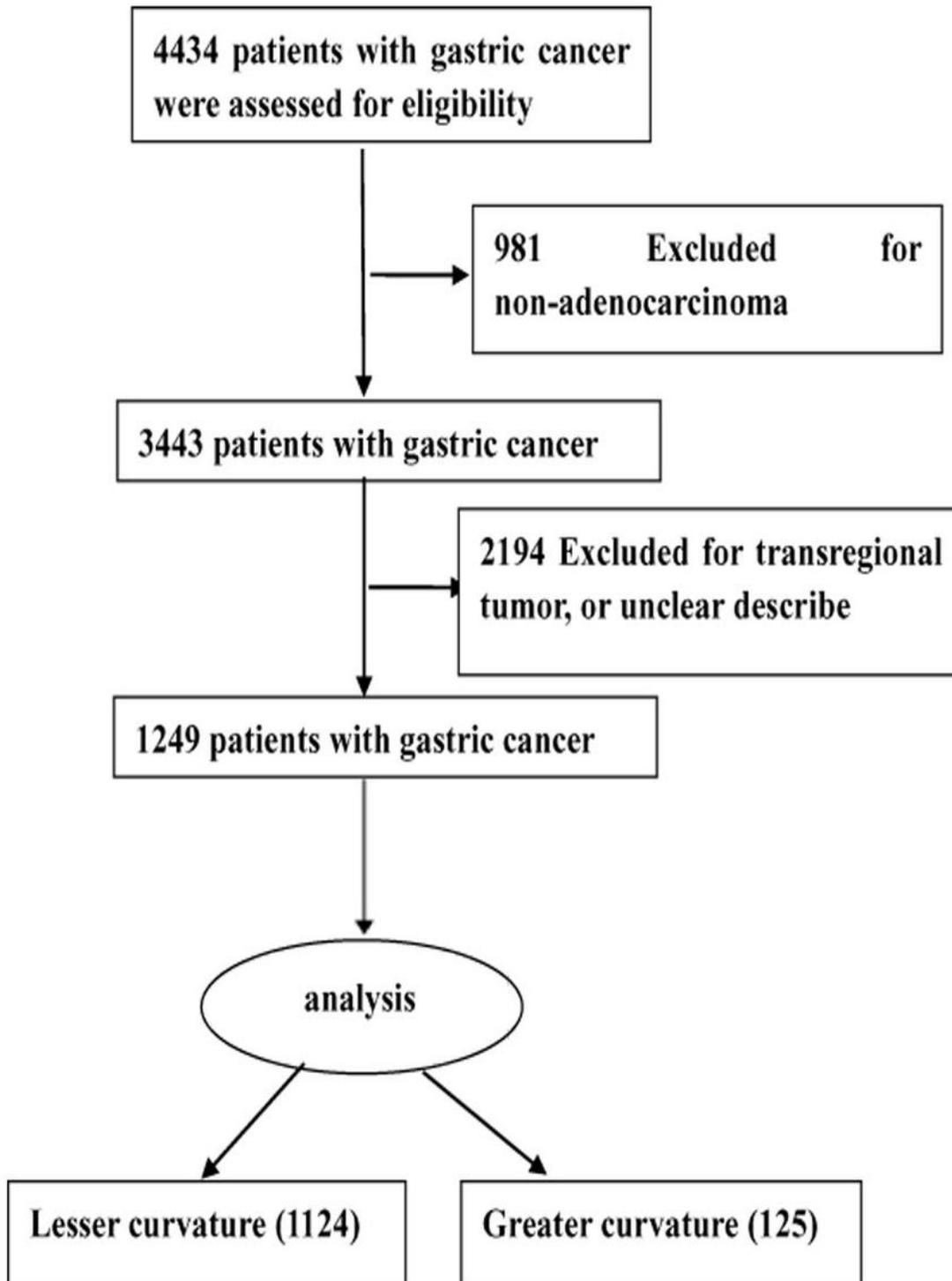
Figures

Figure 1

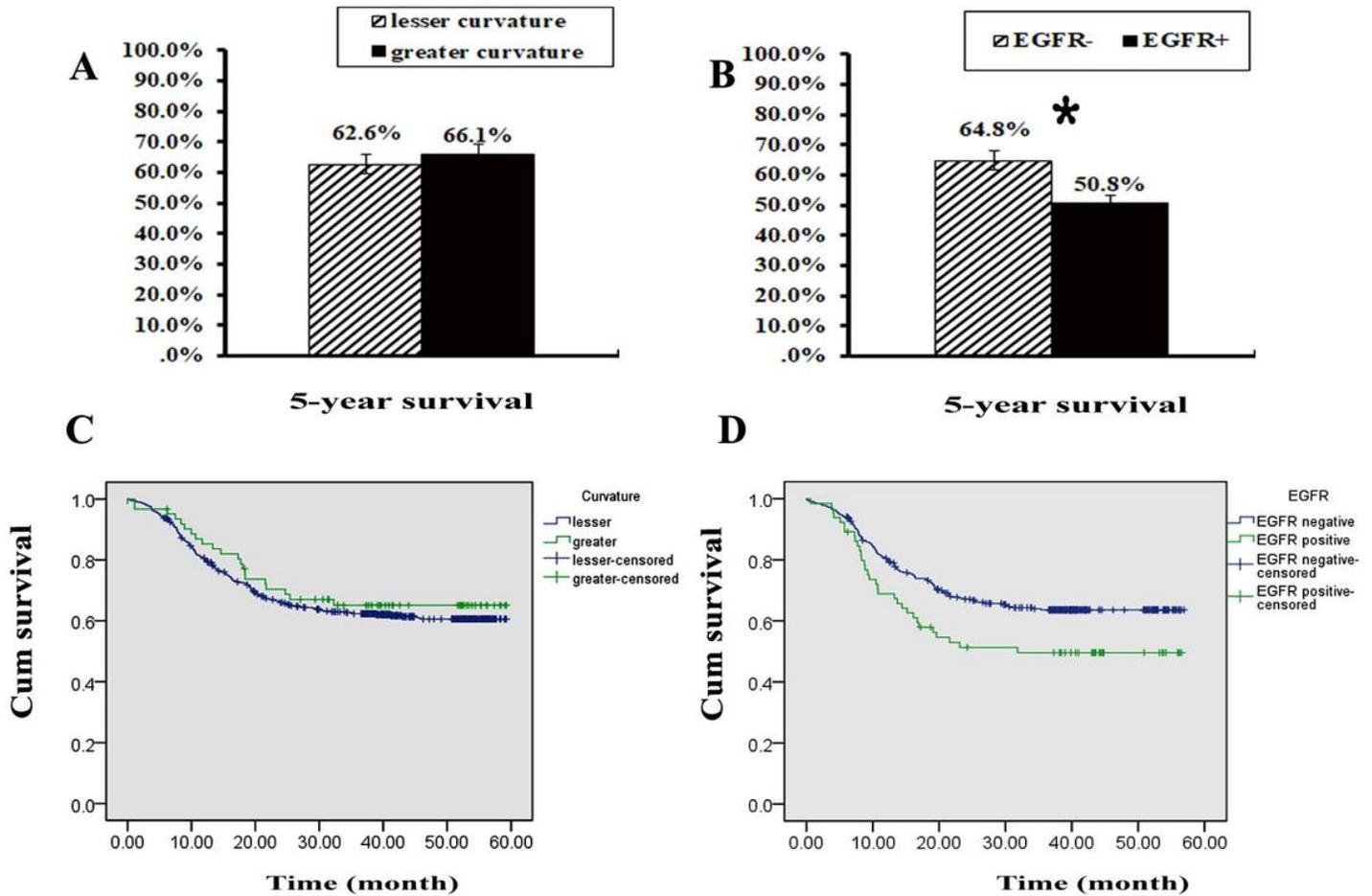flow diagraph of data enrollment.

Figure 2

the survival difference between lesser curvature and larger curvature in patients with gastric cancer. A). the difference of 5-survival rate between lesser curvature and larger curvature. B) the difference of 5-survival rate between EGFR-positive group and EGFR-negative group. * denoted there was a statistically difference between the two groups, P value <0.05. C) 5- year survival curve of patients with gastric cancer located in lesser curvature and larger curvature. D) 5- year survival curve of patients with EGFR-positive or with EGFR-negative.