Clinicopathological difference of gastric cancer between lesser and greater curvature

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Abstract

Background: Gastric cancer (GC) is a 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, Bormann 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                 |                |         |
| Ⅰ                            | 37             | 4       | 0.817 |
| Ⅱ                            | 211            | 26      |
| Ⅲ                            | 307            | 27      |
| Ⅳ                            | 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                      |                |         |
| Ⅰ                            | 42             | 2       | 0.170 |
| Ⅱ                            | 133            | 20      |

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 | Lesser curvature | Great curvature | P value |
|----------------|------------------|-----------------|---------|
| 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 larger curvature (6.49% vs. 10.4%, P = 0.102) and anastomotic complications were 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   |
| Duodenum 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 gives 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, 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. 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. 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, but contrast to the study showed the most frequent metastasis were located in the lower third and lesser curvature of the stomach.

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 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, such as prolonged abdominal symptoms, food residue, and perforation.

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. We found the 5-year survival rate of gastric cancer between greater and lesser curvature was not statistically 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.

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 larger 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 request.

**Competing interests**

All authors of this study declare no competing interests.

**Funding**

There was no funding conflict in this study.

**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.

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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, Bormman 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 (χ²) 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**

![Diagram](image.png)

**Figure 1**
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.