Gastric Stump Cancer: Demanding a More Suitable Definition and TNM Staging System

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Abstract

Background

The incidence of gastric stump cancer (GSC) following resection of gastric cancer has increase. However, the definition between GSC and recurrent gastric cancer (RGC) is still being debated. This study was conducted to compare the clinicopathological characteristics and outcome for this two groups.

Methods

The investigators retrospectively reviewed patients in the Surveillance Epidemiology and End Results (SEER) databases from 1975 to 2016 to identify patients who underwent resection of gastric cancer subsequently experienced metachronous gastric cancer. GSC was defined as cancer occurring in remnant stomach of ≥ 10 years after gastrectomy, while RGC was defined as < 10 years after gastrectomy. T-test, Pearson χ^2 -test and Kaplan-Meier estimator method was used in the present study.

Results

Among the 167,747 gastric cancer patients, 1,006 (0.6%) patients were diagnosed multiple gastric cancer, 93 patients met the GSC criterion, and 282 patients met the RGC criterion. The mean time interval between the initial cancer and second cancer for GSC was 13.34 years and 4.24 years for RGC. Male gender ($P=0.003$), younger age (60.1 years old vs. 65.9 years old, $P<0.001$) developed more frequently in GSC group. The median OS in GSC group was 20.0 months compared with 16.0 months for RGC group ($p=0.302$). Surgery treatment or not, the median OS have statistically significant (in RGC group, 64.0 months vs. 10.0 months, $P=0.001$; 33 months vs. 13 months, $P=0.014$ in GSC group).

Conclusions

In our definition of GSC and RGC, the OS were not statistically significant and gastrectomy may be the appropriate treatment for this two groups. It may demand for a more suitable definition and TNM staging system for GSC.

Background

Gastric stump cancer (GSC) was defined as “cancer occur in the remnant stomach after surgery for benign disease at least five years and those after surgery for gastric cancer at least 10 years.” According to the previous reported, the incidence of GSC range 1.0–3.0 % [1]. Most of previous GSC studies focused on benign disease after gastrectomy. However, gastrectomy for peptic ulcer has been greatly reduced in recent decades since drug therapy. It can expect that the number of patients with GSC after gastrectomy for benign diseases will decrease in the future [2]. On the other hand, partial gastrectomy has been widely accepted for early gastric cancer. And since the early detection and early treatment for gastric cancer, the number of patients with long-term survival after gastrectomy has increased. Therefore, some studies

have reported that the number of patients with GSC after partial gastrectomy for gastric cancer will increase in the future[2-4].

However, to date, only a few studies have described the current status of GSC on the basis of long-term follow up data after surgery for gastric cancer and most of those studies were performed as single institutional and base on small number cases[5-7]. There were not studies clarified whether there are differences in clinicopathological characteristics and prognosis between patients with GSC and patients with RGC. In addition, the definition of GSC and RGC still controversy since the time limit was various. This study aimed to reveal the clinicopathological characteristics, treatment and outcomes between GSC and RGC after gastrectomy for gastric cancer and further discuss whether it is necessary to limit 10 years later for the definition of GSC following resection of gastric cancer.

Methods

Study Population

A retrospective cohort was identified by use of the Surveillance Epidemiology and End Results (SEER) databases, which is a population-based database that assembles data related to cancer patients in the United States. We obtained the study cases in 18 SEER registries from 1975 to 2016 (November 2018 submission) and identified patients who underwent gastrectomy for primary gastric cancer (ICD-O-3 site codes C34.0–C34.9) and subsequently experienced a second gastric cancer. The select gastrectomy codes included “site-specific surgery” codes (20, 30, 40,50,60and 70) for cases before 1998 and “surgery primary site” codes (30-33, 40-42, 50-52, and 60-63) after 1998. The enrolled demographic variables include gender, age and race. The TMN stage were re-stage base on the eight edition AJCC stage. GSC was defined as cancer occur in the remnant stomach after the first primary cancer surgery at least 10 years despite whether the histology is the same or not. RGC was defined as cancer occur in the remnant stomach after the first primary cancer surgery within 10 years. Patients underwent total gastrectomy or nonsurgical were excluded in the study. The patient selection algorithm is described in Fig 1.

Statistical methods.

Statistical analysis was performed by SPSS (version22, IBM Corp). χ^2 -test was performed for categorical variables and Student's t-test was performed for continuous variables. Unadjusted overall survival (OS) and cancer-specific survival (CSS) were analyzed using the Kaplan-Meier estimator method. A two-sided P-value of less than 0.05 was considered statistically significant.

Results

A total 167,747 patients who underwent gastric cancer, 1006 patients (0.6%) were second primary gastric cancer which meet the multiple primary criteria of SEER. Among these 1,006 patients, 93 (9.2%) met the GSC criteria and 282 (28.0%) met the RGC criteria (Fig. 1).

Incidence trend

The incidence trend of RGC and GSC were shown in Figures 2 and 3. We can observe that both the RGC and GSC were increased in the following years. The increase was more obvious after 2007 in both groups.

Patients characteristic

The first primary gastric cancer characteristics of two study patients are described in Table 1. For the group of GSC, 70 (75.3%) were male, while 163 (57.8%) were male in the RGC group ($P=0.003$). The mean age at diagnosis for the first cancer of GSC group (FGSC) was 60.1 years, and those for the first cancer of RGC group (FRGC) were 65.9 years ($P<0.001$). In patients with staging, most patients had stage I/II disease, 95.2% for FGSC and 84.1% for FRGC ($p=0.322$). The most location both of two groups were low gastric, include gastric antrum and pylorus, 44 (47.3%) in FGSC and 133 (47.2%) in FRGC.

The characteristics of second gastric cancer are described in Table 2. The mean age at diagnosis for GSC patients was 73.4 years, and the average latency period was 13.34 years. As for RGC group, the mean age was 70.0 years, and the average interval was 4.24 years ($p=0.25$). In GSC with staging, 39 (70.9%) were stage I/II disease and 10 (13.9%) were stage M1, while 89 (65.4%) were stage I/II and 38 (13.9%) were stage M1 for RGC ($p=0.396$).

On univariate analysis, younger age at diagnosis of primary gastric cancer ($p<0.001$), male gender ($p=0.003$) and difference grade ($p=0.039$) were significantly associated with the GSC (Table 1, Table 2).

Survival analysis

Both the median CSS and median OS between the GSC and RGC were not statistically significant (40.0 months vs. 25.0 months, $p=0.032$ and 20.0 months vs. 16.0 months, $p=0.547$, respectively) (Fig 4). To evaluate the effectiveness of surgery treatment, we compared both RGC and GSC according to CSS and OS. The results showed that surgery treatment or not, the CSS and OS have statistically significant (64.0 months vs. 10.0 months in median OS, $p=0.001$) (Fig. 5). Similarly, in GSC group, the median OS were 33 months by surgery treatment and 13 months in patients not underwent surgery ($p=0.014$) (Fig. 6).

Discussion

The definition of gastric stump cancer remains controversial. It was first described and defined in 1922 as "cancer in the remnant stomach after surgery for benign disease at least 5 years" [8]. Subsequently, studies suggested that cancer appeared in remnant stomach after surgery for gastric cancer at least 10 years also classified as GSC in 1982 [9]. However, the Japanese Gastric Cancer Association suggested that GSC refers to all cancers detected from the remnant stomach after partial gastrectomy, irrespective of the primary disease and interval [10]. In China, it still suggested that the time interval of GSC must at least 10 years after surgery for first gastric cancer [11]. The time interval of GSC was varied in previous

studies[1]. Since the rarely morbidity and long-time follow up, the clinicopathology, treatment and the definition of GSC following resection of gastric cancer lacks of a large sample study.

Previous studies often focus on compare the clinicopathology of GSC between gastric cancer and benign disease or compare the prognosis of GSC and primary gastric cancer (PGC). Most studies have reported that the prognosis between GSC and PGC have no significant difference[6, 12, 13] and revealed that the 5-year survival rates were 41.7 % vs. 45.2 % [1].

With increasing number of partial gastrectomy for gastric cancer and the number of patients with long-term survival after gastrectomy, the number of patients with GSC following resection of gastric cancer has increased[2, 14]. The present study also approved this trend. This raises two practical questions: 1) Should the interval of GSC following the first resection for malignant disease be at least 10 years? 2) How to treatment base on TMN stage after the normal anatomic structure has been destroyed?

In order to answer the first question, we compared the clinicopathology between GSC and RGC, male and younger patients may more likely to develop GSC and there was no statistically significant on others variable. This difference may be explained that younger and early gastric cancer patients may more likely to have long-term survival more than 10 years. On the other hand, the prognosis was not significant difference between GSC and RGC. Thus, we suggest that the definition of GSC should not be limited to 10 years after surgery. However, different to the traditional recurrence of gastric cancer, in the present study, RGC were classified as multiple primary gastric cancer by SEER database, which was defined as the following rules: 1) Tumors diagnosed more than one year apart, and 2) Tumors with ICD-O-3 histology codes that are different at the first (x xxx), second (x xxx) or third (x xxx) number are multiple primaries. 3) These rules are NOT used for tumor(s) described as metastases. Based on the present study outcome and this definition, we suggest the definition of GSC may be based on the following rules: 1) cancer occur in the remnant stomach after surgery for benign disease at least five years and those after surgery for gastric cancer at least 10 years. 2) Or tumors with difference histology between the primary cancer and second cancer after surgery within 10 years. Similarly, many previous study defined GSC as cancer that occurs within 10 years following the initial gastrectomy for gastric cancer and is thought to have developed independently of the initial lesion[2, 15]. With the development of molecular markers, the analysis of molecular genetic characteristics might be expected to improve the specificity of the definition of GSC.

In order to answer the second question, we evaluated the effective of surgery treatment for GSC and RGC. The result showed that surgery still suit for GSC and RGC since the satisfactory prognosis compare to those no underwent surgery. Previous studies considered that although previous gastric resection tends to render surgery for GSC more challenging, due to adhesions and anatomical changes, R0 resection remains as the best treatment for GSC[14-17]. However, due to the anatomical changes for first gastric cancer, the patterns of lymph drainage from lesions in the remnant stomach were also changed. Studies have shown that in most patients with previous cancer, lymph drainage from the remnant stomach was newly developed to the lower mediastinum, to the jejunal mesentery, or to the duodenal side through the

anastomotic line made at the initial surgery. The reason was probably due to the surgical ablation of preexisting lymphatics and lymph nodes in the peri-gastric areas at the initial cancer surgery[15, 18, 19]. This situation reveals that the N stage of TNM staging system based on primary gastric cancer is unsuitable for GSC patients. Base on this conclusion, some studies recommended develop a new and more suitable staging systems for GSC[12, 20]. However, a consensus has not been reach on the new N stage. More studies are needed to explore a suitable N stage and appropriate treatment base the new stage. For the surgery treatment, R0 resection should comprise a total gastrectomy and radical lymph node resection, especially the jejunal mesentery of the anastomosis[14].

Although the present study has revealed some significant clinical information, there were some limitations. The SEER database did not provide information on the type of resection (R0, R1 or R2), lymph node dissected pattern, or pattern of recurrence. Furthermore, for the classification of multiple primary gastric cancer, a second primary versus a recurrence can be complex. There may be some misclassification cases on the study. In addition, the missing variable on the present study may cause bias.

Conclusions

The number of patients of GSC following resection of gastric cancer has increased. The definition of GSC may not be limited to cancer occurrence in the remnant stomach after surgery for benign disease for at least five years, and those after surgery for gastric cancer for at least 10 years. Patients who had tumors with difference histology between the primary cancer and second cancer after surgery within 10 years may classified as GSC. R0 resection may be the first choice for GSC, but lower mediastinum lymph and jejunal mesentery of the anastomosis resection must be taken into consideration due to the high incidence of lymph node metastasis.

Abbreviations

GSC: Gastric stump cancer

RGC: Recurrent gastric cancer

SEER: Surveillance Epidemiology and End Results databases

OS: Overall survival

CSS: Cancer-specific survival

FGSC: First cancer of GSC

FRGC: First cancer of RGC group

Declarations

Ethics approval and consent to participate

For the institutional cohorts, data were extracted from the Surveillance, Epidemiology, and End Results database. This article does not contain any studies with human participants performed by any of the authors. For this type of study, formal consent is not required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available in the SEER*Stat software (version 8.3.6, download from <https://seer.cancer.gov/data/options.html>). A registration form needs to be completed before using the software, and filter criteria need to be added.

Competing interests

All authors have no relevant conflicts of interest to declare.

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Authors' contributions

YLH and CHZ study concept and design and contributed to the development of the manuscript. JNX and GYL approved the proposal with revisions, participated in data analysis and revised subsequent drafts of the paper. XHJ, HJW and LHZ participated in the data analysis and drafted the paper. All authors read and approved the final manuscript.

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Tables

Table 1. The Clinicopathologic Features According to First Surgery

Variables	FGSC	FRGC	χ^2/t	<i>P</i>
Number of patients	93	282		
Gender				
Male	70(75.3)	163(57.8)	9.07	0.003
Female	23(24.7)	119(42.2)		
Age (years)				
Average	60.1	65.9	14.88	< 0.001
Range	10-86	34-92		
Race				
White	57(61.3)	188(66.7)	2.88	0.237
Black	11(11.8)	41(14.5)		
Other	25(26.9)	53(18.8)		
Stage				
I/ II	20(95.2)	143(84.1)	1.85	0.322
III/ IV	1(4.7)	27(15.9)		
NA	72	102		
Depth of tumor invasion				
T1	8(38.1)	48(28.4)	1.89	0.596
T2	8(38.1)	89(52.3)		
T3	5(23.8)	39(22.9)		
T4	0(0)	4(2.4)		
NA	72	102		
Lymph node metastasis				
N0	12(57.1)	98(54.4)	0.06	0.814
N1/ N2/ N3	9(42.9)	82(45.6)		
NA	72	102		
Distant metastasis				
M0	21(100)	177(97.8)		0.642
M1	0(0)	4(2.2)		
NA	72	101		
Location				
Upper gastric	20(21.5)	74(26.2)	0.514	0.773
Middle gastric	12(12.9)	35(12.4)		
Lower gastric	44(47.3)	133(47.2)		
Others	17(18.3)	40(14.2)		
Surgery				
Partial/subtotal gastrectomy	79(84.9)	238(84.4)	0.16	0.899
Near-total gastrectomy	14(15.1)	44(15.6)		

FGSC: The first cancer in gastric stump cancer group. FRGC: The first cancer in recurrent gastric cancer group. NA: unknow

Table 2. The Clinicopathologic Features According to the Second Surgery

Variables	GSC	RGC	χ^2/t	P
Number of patients	93	282		
Age (years)				
Average	73.4	70.0	5.03	0.25
Range	32-97	37-95		
Interval	13.34	4.24	683.8	< 0.001
Stage				
I/ II	39(70.9)	89(65.4)	0.53	0.467
III/ IV	16(29.1)	47(34.6)		
NA	38	148		
Depth of tumor invasion			5.76	0.124
T1	20(40.0)	66(54.1)		
T2	17(34.0)	32(26.2)		
T3	2(4.0)	10(8.2)		
T4	11(22.0)	14(11.5)		
NA	40	160		
Lymph node metastasis				
N0	46(79.3)	119(86.2)	1.47	0.225
N1/ N2	12(20.7)	19(13.8)		
NA	36	144		
Distant metastasis				
M0	52(83.9)	142(78.9)	0.72	0.396
M1	10(16.1)	38(21.1)		
NA	31	102		
Differentiation				
Similar	34(53.1)	117(67.6)	4.25	0.039
Different	30(46.9)	56(32.4)		
NA	29	109		
Location				
Upper gastric	23(24.7)	68(24.1)	0.89	0.638
Middle gastric	8(8.6)	27(9.6)		
Lower gastric	26(28.0)	60(21.3)		
Others	36(38.7)	121(43.0)		
Treatment				
Surgery	30(32.3)	80(28.4)	3.57	0.167
Chemotherapy	15(16.1)	36(12.7)		
S+R	12(12.9)	14(5.0)		
NA	36(38.7)	152 (53.9)		

GSC: Gastric stump cancer. RGC: Recurrent gastric cancer. NA: unknow. S+R☐Surgery+Radiation

Figures

Figure 1

Patient selection algorithm.

Figure 1

Patient selection algorithm.

Figure 2

The incidence trend of RGC.

Figure 2

The incidence trend of RGC.

Figure 3

The incidence trend of GSC.

Figure 3

The incidence trend of GSC.

Figure 4

Comparison of survival between GSC and RGC. (A). Cancer-specific survival (CSS), (B)overall survival (OS).

Figure 4

Comparison of survival between GSC and RGC. (A). Cancer-specific survival (CSS), (B)overall survival (OS).

Figure 5

Comparison of survival according to surgery in RGC patients. (A). Cancer-specific survival(CSS), (B)overall survival (OS).

Figure 5

Comparison of survival according to surgery in RGC patients. (A). Cancer-specific survival(CSS), (B)overall survival (OS).

Figure 6

Comparison of survival according to surgery in GSC patients. (A). Cancer-specific survival(CSS), (B)overall survival (OS).

Figure 6

Comparison of survival according to surgery in GSC patients. (A). Cancer-specific survival(CSS), (B)overall survival (OS).