Original Article

Is there difference between anastomotic site and remnant stump carcinoma in gastric stump cancers?—a single institute analysis of 90 patients

Ramachandra Chowdappa[1], Ajeet Ramamani Tiwari[1], Namrata Ranganath[2], Rekha V. Kumar[3]

[1]Department of Surgical Oncology, [2]Department of Anaesthesia and Pain Relief, [3]Department of Pathology, Kidwai Cancer Institute, Bengaluru, India

Contributions: (I) Conception and design: AR Tiwari; (II) Administrative support: R Chowdappa; (III) Provision of study materials or patients: R Chowdappa, N Ranganath, RV Kumar; (IV) Collection and assembly of data: AR Tiwari, N Ranganath, RV Kumar; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ajeet Ramamani Tiwari. Department of Surgical Oncology, Kidwai Cancer Institute, M.H. Marigowda Road, Near Dairy Circle, Bengaluru 560029, India. Email: drajeetramantiwari@gmail.com.

Background: Little has been reported regarding differences between malignancies that develop at the anastomotic site (ASC) and those that develop at the remnant stump (RSC) in gastric stump carcinomas (GSC). The purpose of our study was to compare clinical, pathological and survival characteristics of ASC patients with those of RSC patients.

Methods: Patients who underwent surgery for GSC between January 2005 and December 2017 were analyzed. Of the total 112 patients, 22 patients were excluded from the study due to extensive loss of data. Ninety patients underwent curative resection and were evaluated based on anatomic site at which they developed malignancy, i.e., ASC and RSC. Clinical, pathological and survival characteristics were assessed.

Results: As per Lauren's classification, diffuse and intestinal variety were significantly associated with ASC (P=0.0001) and RSC (P=0.0001) respectively. RSC was associated with lower pT [pT2, 15/33 (45.5%), P=0.0002]. ASC was significantly associated with higher pN [pN3, 30/57 (52.6%), P=0.0013], stage [stage III, 48/57 (84.2%), P=0.0022], positive mesenteric nodes (P=0.006) and poor 3-year survival (10.5% versus 36.4%, P=0.003).

Conclusions: ASC is substantially different than RSC. ASC is more aggressive disease compared to RSC and has different pathophysiology, higher rates of nodal involvement (both primary and mesenteric), presents with higher stage and has significantly poor 3-year survival.

Keywords: Gastric stump carcinoma (GSC); anastomotic site cancer; remnant stump cancer

Submitted Sep 16, 2018. Accepted for publication Dec 04, 2018.
doi: 10.21037/jgo.2018.12.03
View this article at: http://dx.doi.org/10.21037/jgo.2018.12.03

Introduction

Balfour was the first to elucidate the effects of gastric reconstruction on development of gastric stump carcinoma (GSC) (1). Since then many authors especially those from China and Europe have tried to explain the pathophysiology behind development of GSC through their reviews. However, many have been published in local languages and hence difficult to interpret globally (2-8). Also extensive comparison has been done between GSC caused due to previous benign disease versus those developing after being operated for malignant disease several years back (9). Another group of authors have tried to compare GSC with proximal gastric cancers (10-12). Nonetheless a few of these papers have tried to differentiate between malignancies that develop at the anastomotic site (ASC) from those that develop at the remnant stump (RSC). Little has been

reported regarding differences between these two different entities since Sinning *et al.* (13) in 2006 recognized the pathophysiological differences in the malignancy that developed at ASC from those of RSC.

The purpose of our study was to compare clinical, pathological and survival characteristics of ASC patients with those of RSC patients. In this study which is the only study from Indian subcontinent to the best of our knowledge, we have applied 7th TNM staging system to describe pathological, clinical and survival analysis of patients presenting with GSC with respect to anatomical site of presentation (ASC versus RSC).

Methods

After institutional review board approval (KMIO/MEC/007/25.November 2017) retrospective analysis was done for patients who underwent surgery for GSC between January 2005 and December 2017. Of the total 112 patients, 22 patients were excluded from the study due to extensive loss of data. Ninety patients underwent curative resection and were evaluated based on anatomic site at which they developed malignancy. Patients who presented with metastatic disease were excluded from the study. Eight patients who were found to have metastatic disease during surgery have also been excluded from the analysis due to grossly unavailable data. Anastomotic site and RSC carcinoma were defined based upon the location of bulk of the disease. Mere extension of the disease which occupied major part of body/antro-pylorus into the anastomotic site was not termed as anastomotic disease and vice versa.

Clinical parameters compared were age, gender, previous site of ulcer, type of previous surgery (vagotomy with Billroth II reconstruction with intact antro-pyloric region or distal gastrectomy with Billroth II reconstruction) and interval between previous surgery with development of GSC. Most of the patients while recording history could not remember the type of surgery that was performed previously and was confirmed by endoscopic and intraoperative findings on the data record sheet. No patient received Billroth I reconstruction in our series. Treatment related variables were resection status (R0/R1), type of lymphadenectomy (D1/D2) and splenectomy status during surgery. A number of pathological variable were analyzed such as total number of nodes extracted, number of nodes positive for metastasis, ratio of positive to total nodes extracted (>20 and <20), status of mesenteric nodes, Laurens classification (intestinal type, diffuse type or unspecified), H. Pylori, pT, pN and TNM staging as per 7th edition of AJCC on cancer staging system.

Statistical analysis

Survival assessment was performed using Kaplan Meier analysis. Cox Proportional Hazard Model was used for studying prognostics variables. Log rank test was used to compare the survival curves. Chi square test was used to study the association between quantitative data. Any P value <0.05 was considered as statistically significant.

Results

Clinical parameters (Table 1)

Demographic data is provided in *Table 1*. High incidence of malignancy developed in those who underwent vagotomy with gastrojejunostomy (V + GJ) compared to those who had distal gastrectomy + Billroth II (DG+BII) (90%, P=0.015). ASC was significantly associated with development Lauren's diffuse type cancer (63.2%) compared to RSC (18.2%, P=0.0001). H. Pylori seemed more strongly associated with RSC (72.7%) compared to ASC (15.8%, P=0.001).

Pathology and staging (Tables 1,2)

Detailed pathological assessment and staging results are provided in *Tables 1,2*. However notable ones are mentioned here. Sixty-nine patients (76.6%) had pT3 and above disease. Overall 80% of patients (n=72) had pN2 and above disease, however pN3 nodal metastasis was significantly higher for ASC (P=0.0013). Also nodal ratio of greater than 20 was highly associated with ASC (P=0.0001). Since patients with metastatic disease have been excluded from the study only stages I to III have been analyzed. In a subgroup analysis of stage, RSC patients significantly contributed to stage IIa (P=0.0083) whereas stage IIIb had significantly higher number of patients with ASC (P=0.0203). Close to half number of patients (n=27, 47.4%) with ASC presented with positive mesenteric nodes and was significantly higher compared to RSC (n=6, P=0.006).

Survival analysis (Table 1, Figures 1,2)

The overall survival curves for ASC and RSC are shown in *Figure 1*. Overall median survival was 20 months (range, 16.9–23.09 months). Patients with ASC had poorer median

Table 1 Characteristics of patients with ASC and RSC

Clinical features	Site of malignancy, n (%)		Chi square	P value
	ASC	RSC		
Gender				
Female	6 (10.5)	12 (36.4)	8.72	0.003
Male	51 (89.5)	21 (63.6)		
Previous ulcer (duodenum/gastric)				
Duodenum	39 (68.4)	30 (90.9)	5.908	0.015
Gastric	18 (31.6)	3 (9.1)		
Previous surgery extent of resection (vagotomy + GJ-1/ distal gastrectomy with GJ-2)				
1	39 (68.4)	30 (90.9)	5.908	0.015
2	18 (31.6)	3 (9.1)		
Resection status (R0/R1)				
R0	51 (89.5)	33 (100.0)	3.722	0.054
R1	6 (10.5)	0 (0.0)		
Macroscopy				
Infiltrative	6 (10.5)	6 (18.2)	1.06	0.3032
Proliferative	24 (42.1)	9 (27.3)	1.98	0.1594
Ulcer	27 (47.4)	18 (54.5)	0.431	0.511
Lauren classification				
Diffuse	36 (63.2)	6 (18.2)	16.987	0.0001
Intestinal	15 (26.3)	27 (81.8)	25.868	0.0001
Unclassified	6 (10.5)	0 (0.0)	3.722	0.053
H. pylori				
Yes	9 (15.8)	24 (72.7)	29.177	0.001
No	48 (84.2)	9 (27.3)		
Type of lymphadenectomy (D1/D2)				
D1	18 (31.6)	15 (45.5)	1.733	0.188
D2	39 (68.4)	18 (54.5)		
Splenectomy				
Yes	9 (15.8)	3 (9.1)	0.812	0.368
No	48 (84.2)	30 (90.9)		
LVSI				
Yes	33 (57.9)	9 (27.3)	7.874	0.005
No	24 (42.1)	24 (72.7)		
Initial surgery				
Benign	45 (78.9)	30 (90.9)	2.153	0.142
Malignant	12 (21.1)	3 (9.1)		
3-year survival				
Alive	6 (10.5)	12 (36.4)	8.72	0.003
Dead	51 (89.5)	21 (63.6)		

ASC, anastomotic stump cancer; RSC, remnant stump cancer; GJ, gastrojejunostomy; LVSI, lymphovascular invasion.

survival (18 months; range, 16.4–19.6 months) compared to those with RSC (30 months; range, 25.5–34.5 months, log rank =0.000). Overall 3-year survival and 5-year survival was 20% and 13.3% respectively. Three-year survival was significantly lower (10.5%) for patients with ASC compared to those with RSC (36.4%, P=0.003). Patients with pT4b, stage III, positive mesenteric node and nodal ratio of >20 were associated with worst survival (*Figures 1*,*2*).

Discussion

Before the era of proton pump inhibitors, the most commonly performed surgery for peptic ulcer in India was vagotomy and drainage procedure. However, antrectomy was also performed for patients who presented with bleeding gastric ulcers along with Billroth II reconstruction (14). Both these surgeries had at least two things in common, one that they both were performed mostly for ulcer and secondly both required gastrojejunostomy—a procedure that diverted the jejunal bile into stomach and changed its microenvironment to a great extent. Duodenogastric reflux has been cited as the major cause for GSC by a number of authors. Vagotomy leads to hypochlorydia and increased epithelial proliferation rendering the mucosa more prone to DNA damage and resultant gastric cancer (15).

Sinning *et al.* (13) in their succinct review on GSC have described an altogether different pathogenesis for cancers developing at two different sites- anastomotic site and remnant gastric stump. Diffuse type carcinoma develops in premalignant lesions involving adenoid cystic proliferation at the anastomotic site due to duodenogastric

Table 2 Pathological features of patients with ASC and RSC

Pathological parameters	Site of malignancy, n (%)		Chi square	P value
	ASC	RSC		
pT (depth of penetration)				
T2	6 (10.5)	15 (45.5)	14.253	0.0002
T3	30 (52.6)	12 (36.4)	2.222	0.136
T4a	15 (26.3)	6 (18.2)	0.773	0.379
T4b	6 (10.5)	0 (0.0)	–	0.538
pN subgroup				
N0	3 (5.3)	3 (9.1)	–	0.665
N1	3 (5.3)	9 (27.3)	6.96	0.0083
N2	21 (36.8)	15 (45.5)	0.646	0.421
N3a	27 (47.4)	6 (18.2)	7.667	0.0056
N3b	3 (5.3)	0 (0.0)	–	0.2955
pN				
N0	3 (5.3)	3 (9.1)	–	0.665
N1	3 (5.3)	9 (27.3)	6.96	0.0083
N2	21 (36.8)	15 (45.5)	0.646	0.421
N3	30 (52.6)	6 (18.2)	10.335	0.0013
Stage AJCC 7th				
I	3 (5.3)	3 (9.1)	–	0.665
II	6 (10.5)	12 (36.4)	8.72	0.0031
III	48 (84.2)	18 (54.5)	9.405	0.0022
Stage subgroup AJCC 7th (Fischer exact test)				
Ib	3 (5.3)	3 (9.1)	–	0.665
IIa	3 (5.3)	3 (9.1)	6.96	0.0083
IIb	3 (5.3)	3 (9.1)	–	0.665
IIIa	18 (31.6)	12 (36.4)	0.215	0.6426
IIIb	24 (42.1)	6 (18.2)	5.383	0.0203
IIIc	6 (10.5)	0 (0.0)	–	0.0818
Mesenteric nodal status				
Negative	30 (52.6)	27 (81.8)	7.667	0.006
Positive	27 (47.4)	6 (18.2)		
Nodal ratio				
<20%	18 (31.6)	24 (72.7)	14.218	0.0001
>20%	39 (68.4)	9 (27.3)		

ASC, anastomotic stump cancer; RSC, remnant stump cancer.

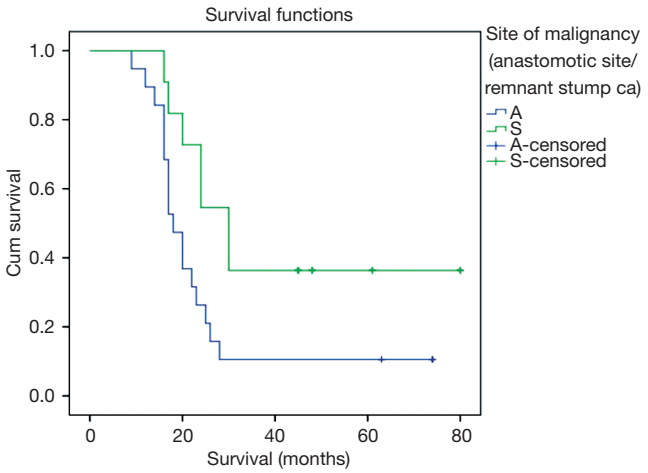

Figure 1 Survival curves of patients following surgery for (ASC: blue; RSC: green). ASC, anastomotic stump cancer; RSC, remnant stump cancer.

reflux. Intestinal type carcinoma develops at the body of gastric stump which is preceded by stump dysplasia that progressively loses its gastric phenotype (13). However, Morgagni *et al.* did not find any such relationship in their study (16).

Not just the pathogenesis and histology but these two differ in multiple clinical parameters including extent of nodal involvement, staging and survival as evident by our analysis. Multiple authors presented their series of GSC where they found that anastomotic site malignancy developed significantly more in patients who were previously operated for benign disease (11,17,18). Even though we failed to find any such correlation, in Cox proportional hazard model prior malignant disease was associated with poor survival (HR =1.797, P=0.049) (*Table 3*).

Păduraru *et al.* stated that H. pylori infection does not seem to be an important risk factor for development of GSC however they themselves noted that this finding may be controversial (15). We found that H. pylori was more significant in development of non-anastomotic site cancer rather than the anastomotic site. Ohira *et al.* demonstrated that H. pylori prevalence was less where duodenogastric reflux was the primary cause for malignancy i.e., anastomotic site which conforms with our finding (19).

Multiple authors have demonstrated that involvement of mesenteric nodes confers poor survival to those with GSC. In our study we found that patients with anastomotic site cancers had much higher prevalence of mesenteric

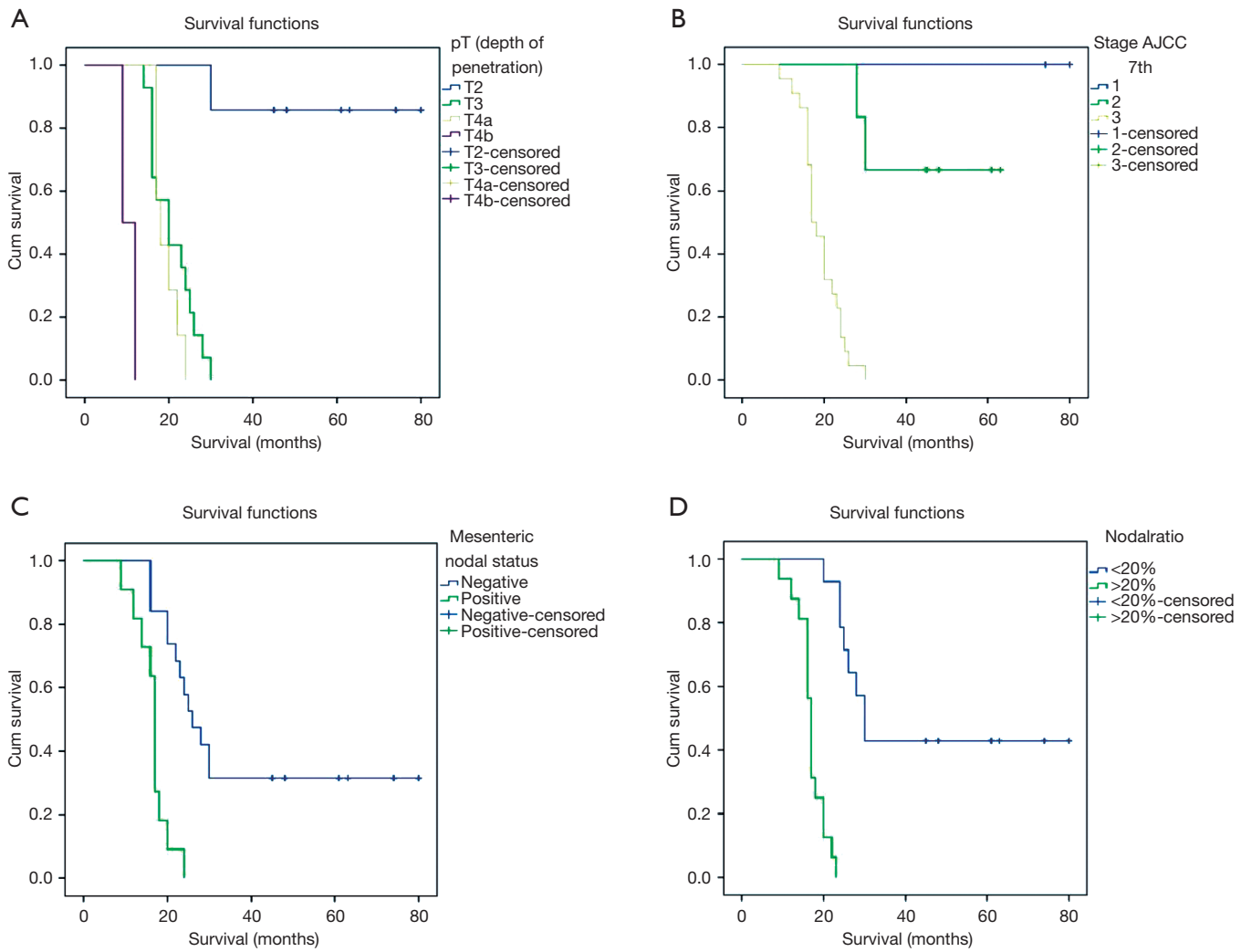

Figure 2 Survival curves of patients following surgical treatment stratified by pathological characteristics. Patients with (A) pT4b, (B) stage III, (C) positive mesenteric node and (D) nodal ratio of >20 were associated with worst survival.

LN metastasis and also that it contributed to poor 3-year survival (18,20). Shimada *et al.* in his review concluded that LN involvement of jejunal mesentery in GSC was between 7% and 46.8% (21). We found an incidence of 36.7% that is well within this range. Moreover, an important aspect we noted was that the incidence was significantly higher in anastomotic group than the non-anastomotic one. Greater than two thirds of patients presented with stage III disease especially those with anastomotic site cancer. Our findings are in line with those of Huang *et al.* (9).

Since more than 85% of our patients succumbed to the disease within 5 years of treatment, we calculated their 3-year survival curves (*Figures 1,2*). Compared to previous authors our median survival time was less (20 versus 30.9 months) (20). However, there was a significant difference between survival of anastomotic site (18 months) and body site malignancy (30 months) that has not been highlighted by most of the authors. Stage wise deterioration of survival too occurred which was worst with anastomotic site cancers (9) (*Figure 2*).

Conclusions

Our study shows that cancer originating at the anastomotic site is substantially different than that at the body site of GSC. ASC is more aggressive disease compared to RSC and has different pathology, higher rates of nodal involvement (both primary and mesenteric), presents with higher stage

Table 3 Cox proportional hazard model for survival

Clinical characteristics	Reference	Factor	HR	95% CI for HR		P value
				Lower	Upper	
Age (years)	>65	≤65	1.422	0.870	2.323	0.160
Gender	Male	Female	0.508	0.251	1.027	0.059
Site of malignancy	RSC	ASC	2.603	1.546	4.383	0.000
Previous Ulcer	Gastric	Duodenal	0.453	0.266	0.774	0.004
Previous surgery	1	2	2.206	1.293	3.765	0.004
Resection status	R0	R1	0.639	0.200	2.040	0.450
Lauren classification	Unclassified	Diffuse	0.553	0.229	1.333	0.187
	Unclassified	Intestinal	0.458	0.190	1.108	0.083
H. pylori	Positive	Negative	2.167	1.309	3.586	0.003
Number of mesenteric node positive	Zero	Others	1.938	1.604	2.342	0.000
pN subgroup	3B	0	0.000	0.000	3.43621E+73	0.790
	3B	1	0.000	0.000	3.07579E+60	0.754
	3B	2	0.000	0.000	2.61188E+49	0.817
	3B	3A	0.095	0.019	0.473	0.004
Type of lymphadenectomy	D2	D1	2.121	1.266	3.554	0.004
Splenectomy	Yes	No	0.323	0.170	0.612	0.001
LVSI	Yes	No	0.367	0.226	0.595	0.000
Etiology for previous surgery	Benign	Malignant	1.797	1.001	3.229	0.049
Mesenteric nodal status	Positive	Negative	0.172	0.098	0.303	0.000
Nodal ratio positive	>20%	<20%	0.025	0.007	0.082	0.000

1, vagotomy + gastrojejunostomy; 2, distal gastrectomy with gastrojejunostomy; HR, hazard ratio; LVSI, lymphovascular invasion; ASC, anastomotic stump cancer; RSC, remnant stump cancer.

and has worst 3-year survival. An early surveillance plan for patients who have undergone Billroth II reconstruction should be in place after 10 years of initial surgery (14). We suggest that early recognition of patients with anastomotic site cancer would help to improve survival by undertaking aggressive management.

Acknowledgements

We would like to thank Dr. Durgesh Sahoo for his assistance with statistical analysis.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study has been approved by Institutional ethics committee for assessment of retrospective data (KMIO/ MEC/007/25.November 2017).

References

1. Balfour DC. Factors influencing the life expectancy of patients operated on for gastric ulcer. Ann Surg 1922;76:405-8.
2. Gao Z, Li Y, Jiang K, et al. Progress and controversy on diagnosis and treatment of gastric stump cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2018;21:588-92.
3. Li Y, Gao Z, Zhao X, et al. Meta-analysis of gastric stump cancer after gastrectomy for gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2018;21:569-77.
4. Wang Y, Li Z, Jin C, et al. Clinicopathological

characteristics and prognostic factor analysis of carcinoma in remnant stomach cancer at Peking University Cancer Hospital. Zhonghua Wei Chang Wai Ke Za Zhi 2018;21:522-8.
5. Chen L. Epidemiological characteristics and inducing factors of gastric stump cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2018;21:498-501.
6. Gao Z, Jiang K, Ye Y, et al. Interpretation on Chinese surgeons' consensus opinion for the definition of gastric stump cancer (version 2018). Zhonghua Wei Chang Wai Ke Za Zhi 2018;21:486-90.
7. Nienhüser H, Blank S, Sisic L, et al. Gastric stump carcinoma: frequency, treatment, complications and prognosis. Chirurg 2017;88:317-27.
8. Vajda D, Nagy E, Molnar G. Gastric stump carcinoma. Fortschr Geb Rontgenstr Nuklearmed 1960;92:653-8.
9. Huang H, Wang W, Chen Z, et al. Prognostic factors and survival in patients with gastric stump cancer. World J Gastroenterol 2015;21:1865-71.
10. Takeno S, Hashimoto T, Maki K, et al. Gastric cancer arising from the remnant stomach after distal gastrectomy: a review. World J Gastroenterol 2014;20:13734-40.
11. Tokunaga M, Sano T, Ohyama S, et al. Clinicopathological characteristics and survival difference between gastric stump carcinoma and primary upper third gastric cancer. J Gastrointest Surg 2013;17:313-8.
12. Rabin I, Kapiev A, Chikman B, et al. Comparative study of the pathological characteristics of gastric stump carcinoma and carcinoma of the upper third of the stomach. Isr Med Assoc J 2011;13:534-6.
13. Sinning C, Schaefer N, Standop J, et al. Gastric stump carcinoma - epidemiology and current concepts in pathogenesis and treatment. Eur J Surg Oncol 2007;33:133-9.
14. Balraj V, Perakath B. Post-gastric surgery: is a closer follow up required? Natl Med J India 2001;14:251-2.
15. Păduraru DN, Nica A, Ion D, et al. Considerations on risk factors correlated to the occurrence of gastric stump cancer. J Med Life 2016;9:130-6.
16. Morgagni P, Gardini A, Marrelli D, et al. Gastric stump carcinoma after distal subtotal gastrectomy for early gastric cancer: experience of 541 patients with long-term follow-up. Am J Surg 2015;209:1063-8.
17. Irino T, Hiki N, Ohashi M, et al. Characteristics of gastric stump cancer: A single hospital retrospective analysis of 262 patients. Surgery 2016;159:1539-47.
18. Di Leo A, Pedrazzani C, Bencivenga M, et al. Gastric stump cancer after distal gastrectomy for benign disease: clinicopathological features and surgical outcomes. Ann Surg Oncol 2014;21:2594-600.
19. Ohira M, Toyokawa T, Sakurai K, et al. Current status in remnant gastric cancer after distal gastrectomy. World J Gastroenterol 2016;22:2424-33.
20. Thorban S, Böttcher K, Etter M, et al. Prognostic factors in gastric stump carcinoma. Ann Surg 2000;231:188-94.
21. Shimada H, Fukagawa T, Haga Y, et al. Does remnant gastric cancer really differ from primary gastric cancer? A systematic review of the literature by the Task Force of Japanese Gastric Cancer Association. Gastric Cancer 2016;19:339-49.

Cite this article as: Chowdappa R, Tiwari AR, Ranganath N, Kumar RV. Is there difference between anastomotic site and remnant stump carcinoma in gastric stump cancers?—a single institute analysis of 90 patients. J Gastrointest Oncol 2019;10(2):307-313. doi: 10.21037/jgo.2018.12.03

