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Gastric stump carcinoma after distal subtotal gastrectomy for early gastric cancer: experience of 541 patients with long-term follow-up

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Gastric stump carcinoma;
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Abstract

BACKGROUND: Gastric stump carcinoma (GSC) has been studied after primary gastrectomy for benign disease but few studies have evaluated its correlation with gastric cancer.

PATIENTS: We assessed 541 patients submitted to subtotal gastrectomy for early gastric cancer at least 15 years ago.

RESULTS: GSC was diagnosed in 16 (2.9%) patients, giving a 4% cumulative risk of GSC 20 years after surgery. Diagnosis was made within 5 years of surgery in 10 patients and after 8 years in 6 cases. GSC occurred in 13/470 (2.8%) patients submitted to Billroth 2 reconstruction, 2/30 (6.7%) patients who underwent Billroth 1, and 1/41 (2.4%) patients after Roux-en-Y reconstruction. Significant risk factors observed for GSC were histologic type and sex. Other synchronous or metachronous extragastric tumors were registered in 56 (11.2%) patients.

CONCLUSIONS: The risk of GSC was low, even 20 years after subtotal gastrectomy for early gastric cancer. Lauren intestinal histotype and male sex were frequently associated with GSC. No correlation was observed between GSC and reconstruction technique or multifocality. Clinically speaking, GSC could be considered a subset of gastric cancer.

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Gastric stump carcinoma (GSC) has recently been re-evaluated as a separate cancer when diagnosed after subtotal gastrectomy performed not only for benign lesions but also for neoplastic disease.[1–3] Numerous studies have been published on patients treated for benign gastric disease, and gastric resection is considered to be a risk factor for GSC even 15 to 20 years

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after surgical treatment, especially when Billroth 2 (B2) reconstruction is performed.[1,4] However, for patients operated on initially for gastric cancer, it is still not clear when GSC should be considered a recurrence or a new carcinoma arising on the stump. Recurrence after early gastric cancer (EGC) varies between 1.4% and 24%[5–7] and generally occurs within 2 years of surgery. It has also been observed up to 5 years after surgery but rarely after that. Few patients who relapse have stump recurrence. Some authors have arbitrarily defined GSC as metachronous cancer arising 5[8] or 10[3] years after the first malignancy, while others also consider metachronous cancer as tumors detected after 1 year if followed up with accurate endoscopy.[9] However, no clear guidelines exist as yet.

The aim of this study was to present our experience of GSC in radically resected EGC patients surgically treated with different types of anastomosis. We also calculated the risk of GSC in our patients operated on at least 15 years ago and confirmed the difficulty in identifying whether gastric stump cancer is a relapse, missed lesion, or new tumor.

Patients and Methods

Six hundred and fifty-seven patients who represent the whole population registered in our database because submitted to surgical resection for EGC between 1976 and 1994 were considered for this study. Surgical treatment was performed in four Italian Surgical Units: Department of General Surgery, Morgagni-Pierantoni Hospital, Forlì; Surgical Oncology Unit of Siena University; Second Surgical Clinic of Padua University; and First Surgical Clinic of Verona University. A total of 541 patients submitted to subtotal gastrectomy were included in this study. The recruitment period did not extend beyond 1994 to obtain long-term patient follow-up.

Patients were classified at the time of the first diagnosis on the basis of sex, age, tumor site, tumor size, macroscopic type,[10] Lauren's histologic type,[11] differentiation, TNM staging,[12] lymphadenectomy, multifocality when detected by pathologist, and reconstruction type. Subsequently, patients with GSC were classified in relation to the time interval after first surgical treatment and the site of the neoplastic lesion on the stump. Anamnestic data on synchronous or metachronous nongastric tumors were retrieved and information on death from recurrence, other tumors, or noncancer causes was collected. Clinicopathologic characteristics were compared with risk factors for both GSC and recurrence. D1 lymph node dissection was performed during the first period of this study (until 1990) and thereafter only in elderly or critical patients. En bloc D2 lymphadenectomy was performed in all other patients, in accordance with Japanese Gastric Cancer Association recommendations.[10] The greater and lesser omentum was removed and surgical reconstruction consisted of gastrojejunal Billroth 1 (B1), B2, or Roux-en-Y anastomosis.

Death from postoperative complications was considered as a variable if it occurred during hospitalization or within 30 days of surgical treatment. Follow-up examinations for the first 5 years comprised clinical evaluation, ultrasound scan, and serum markers every 6 months, and annual endoscopy. Thereafter patients were monitored once a year.

Statistical analysis was carried out using SPSS software (version 8.0, SPSS Inc, Chicago, IL) and all P values were based on 2-sided testing (threshold value = .05). Survival curves and the cumulative risk of recurrence were calculated according to the Kaplan–Meier method.[13]

Results

Five hundred and forty-one patients were submitted to subtotal gastrectomy for lesions sited at the lower or middle gastric third. Full patient characteristics are reported in Table 1. Distal third location, small size, depressed or ulcerated macroscopic type, and well-differentiated intestinal histotype were the most frequently observed characteristics. D1 lymph node dissection was performed in 347 patients with a median of 9.4 lymph nodes removed (range 1 to 21), whereas 194 patients underwent D2 lymphadenectomy with a median of 18.8 nodes removed (range 15 to 55). B2 anastomosis was performed in the majority of patients (470), B1 in 30 patients, and Roux-en-Y in 41 cases. Five patients died for postoperative complications (.9%) and were not considered for follow-up. The median follow-up period was 150 months (range 2 to 356). Two patients were lost to follow-up and thus excluded from the survival analysis.

The cumulative risk of recurrence was calculated according to the Kaplan–Meier method (one minus survival) on 534 patients with EGC treated with subtotal gastrectomy; a risk of 13.5% at 20 years was estimated (Fig. 1). The recurrence pattern is described in Table 2.

Sixteen of the 534 patients (3 %) were diagnosed with GSC at different times after the first treatment (range 1 to 21 years); in 10 cases it occurred within 5 years of surgery, while in 6 it was detected after 8 years (Fig. 2). The cumulative risk of GSC was 2.6% at 10 years, 3.2% at 15 years, and 4% at 20 years (Fig. 3). GSC occurred in 13 of 470 patients submitted to B2 reconstruction (2.8%), in 2 patients after B1 reconstruction (6.7%), and in 1 patient after Roux-en-Y anastomosis (2.4%). The 20-year risk of relapse (in any site) and the risk of GSC were stratified according to several clinical and pathologic variables (Table 1).

Lymph node status ($P < .001$), depth of invasion ($P < .001$), male sex ($P = .016$), and tumor differentiation ($P = .028$) were significantly associated with the risk of relapse. Intestinal histotype ($P = .002$) and male sex ($P = .015$) were significant predictors of GSC. Interestingly, all GSCs occurred in patients previously resected for intestinal-type tumors; only 2 GSC occurred in women (one 24 years after the primary resection).

Multivariate analysis (Cox proportional hazard model) confirmed nodal status, depth of invasion, and male sex as independent predictors of overall risk of recurrence, while Lauren's intestinal histotype was revealed as the only

Table 1 Overall risk of relapse and risk of gastric stump cancer at 20 years calculated on the basis of clinical and pathologic variables

Variable	No. of cases	Overall risk of recurrence at 20 years (%)	*P* value	Risk of gastric stump cancer at 20 years (%)	*P* value
Sex					
Male	319	16.5	.016	6.2	.015
Female	222	8.9		0.8	
Age group (years)					
≤65	264	12.5	.387	4.0	.882
>65	277	13.3		3.3	
Tumor location					
Middle third	108	9.3	.546	4.6	.841
Lower third	405	14.4		4.0	
Unknown	28				
Tumor size (cm)					
≤2	260	10.6	.080	4.5	.613
2–4	120	19.0		3.5	
>4	29	11.1		0	
Unknown	132				
Macroscopic type					
I, IIa, IIb	98	7.2	.172	3.8	.407
IIc, III	350	15.0		4.2	
Unknown	93				
Lauren histotype					
Intestinal	349	11.3	.138	5.1	.002
Diffuse–mixed	162	16.7		0	
Unknown	30				
Differentiation					
G1	213	7.6	.028	4.8	.325
G2	109	11.7		5.3	
G3	200	20.1		2.8	
Unknown	19				
Depth of invasion					
Mucosa	288	7.6	<.001	3.1	.603
Submucosa	253	20.0		5.1	
Lymph node status					
Negative	471	9.8	<.001	4.1	.622
Positive	61	31.7		3.2	
Unknown	9				
Lymphadenectomy					
D1	346	15.1	.617	5	.818
D2	191	10.1		2.3	
Unknown	4				
Multifocality					
Absent	433	13.4	.998	4.9	.165
Present	80	13.0		0	
Unknown	28				
Reconstruction					
B1	30	17.8	.759	7.6	.580
B2	470	13.6		3.8	
Roux-en-Y	41	8.8		2.7	

B1 = Billroth 1; B2 = Billroth 2.

predictor of GSC. None of the patients with multifocal lesions were subsequently diagnosed with GSC.

With regard to the site of lesions in the gastric stump, only 1 was observed at the anastomotic site, 3 were diffuse within the stump, and 7 were located near the cardia; no information was available for 5 patients.

Fourteen patients with GSC were submitted to total gastrectomy, while 2 patients with diffuse stump carcinoma involving other organs and diaphragm were judged unresectable. Of note, all 14 patients had had intestinal histotype tumors; unfortunately, histologic referrals for 2 GSC patients were not available for this study.

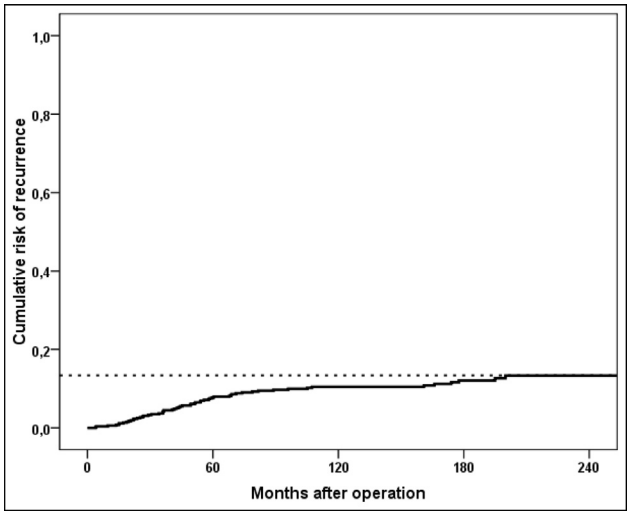


Figure 1 Cumulative risk of recurrence at any site calculated according to Kaplan–Meier method in 539 patients with EGC treated by subtotal gastrectomy. A risk of 13.5% at 20 years was estimated.

An interesting observation concerns the number of extragastric primary cancers observed in this series; 56 (10.3%) patients presented other anamnestic synchronous or metachronous tumors, while 80 showed gastric multifocality. Although we investigated potential risk factors for other secondary tumors, the only correlation found was for lesions of the middle gastric third ($P = .01$). To investigate the correlation between stump and other neoplastic lesions, we evaluated the incidence of other tumors in totally gastrectomized patients, identifying 11 (10%) cases, which was not statistically significant compared with the incidence observed in patients treated with subtotal gastrectomy.

Comments

This multicentric retrospective study puts together the data collected from 4 Italian center members of the Italian Research Group for Gastric Cancer[7,14] on a consecutive subset of EGC patients operated on at least 15 years ago. Of note, our results reveal some information on the risk of GSC in EGC patients treated with subtotal gastrectomy. The cumulative risk observed in our patients was 2.6% at 10 years, 3.2% at 15 years, and 4% at 20 years. However, these rates are not high enough to be able to consider subtotal gastrectomy or

Table 2 Recurrence sites

Site	No. of patients	%
Liver	11	23.4
Peritoneum	5	10.6
Lung	3	6.4
Bone	3	6.4
Local lymph nodes	4	8.5
Multiple sites	11	23.4
Unknown	10	21.3

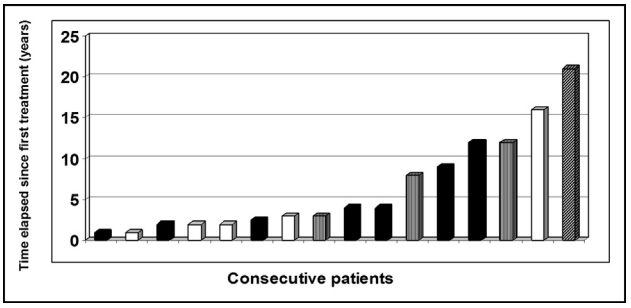


Figure 2 Time elapsed since first treatment in relation to the site of gastric stump carcinoma; subcardial cancer, solid black bars; diffuse stump carcinoma, bars with vertical black lines; anastomotic site carcinoma, bars with diagonal lines; white bars, unknown site.

reconstruction techniques as risk factors for GSC, especially if we take into account the 13.5% 20-year global risk of recurrence estimated in our series of EGC. The length of the follow-up period was based on literature data that define the mean interval between the first surgical intervention and diagnosis of GSC as shorter for cancer-treated patients (6.8 to 7.5 years)[1,2] than for patients treated for benign disease (20 years).[3] Median follow-up was less than 15 years because 82 patients were aged 75 years and over at diagnosis, many of them dying from other causes. Consequently, the median follow-up was less than the 15-year period planned.

GSC was observed in 3% of our patients, similar to rates reported by other eastern authors (.8% to 3.6%) for subtotal gastrectomy in EGC patients[5,6,15] and much lower than the 8.2% reported by Nakajima in 633 endoscopically treated EGC patients.[9] Although the difference in GSC incidence may be attributable to the duration or accuracy of follow-up, it may also be because of the fact that this cancer is sometimes considered stump relapse and other times a new cancer originating in the gastric stump. As no accepted guidelines exist and as different ranges have been proposed in the

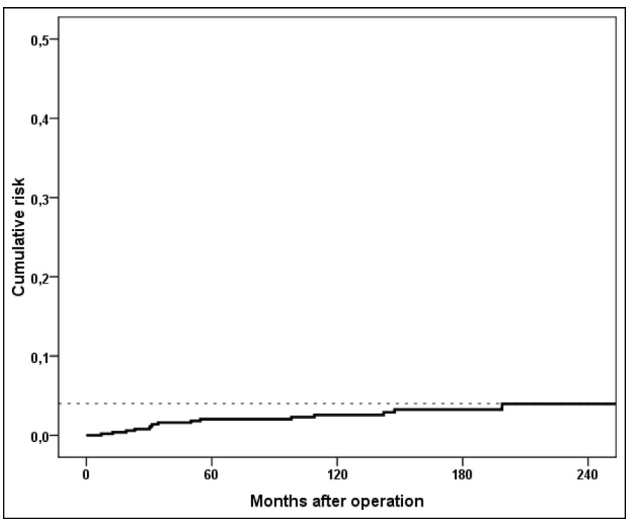


Figure 3 Cumulative risk of GSC calculated according to Kaplan–Meier method in 539 patients with EGC treated by subtotal gastrectomy. A risk of 4% at 20 years was estimated.

literature to define relapse, synchronous, or metachronous gastric stump cancer,[3,8,9] we decided to consider our case series as a single group (10 patients with stump lesions detected less than 4 years after primary surgery and 6 patients diagnosed with GSC after 8 years of follow-up).

Although it can be hypothesized that patients reoperated on 1 year after the first surgery probably had *missed* multifocal lesions rather than metachronous tumors, such as those detected 8 years after the surgical treatment, it is difficult to differentiate between disease relapse, synchronous cancer, or new GSC when 3 or 4 years have passed since primary EGC surgery. Multifocality is considered by some authors as a risk factor for GSC; Fujita et al[16] observed 4.7% of GSCs out of 153 patients with multifocal lesions. Although smaller secondary lesions missed at the preoperative workup are usually sited at the lower gastric third, the possibility of an upper location cannot be ruled out,[17] but only a small number of patients with GSC can be considered as mistreated at the first surgical intervention. In the present case series and in a previous work on 98 multifocal EGCs, distal EGC rarely presented upper secondary lesions in a different gastric third and no patients with the main EGC sited at the lower third presented a synchronous secondary lesion in the upper third.[18] None of the patients with multifocal EGC in either study were subsequently diagnosed with GSC.

Another issue concerning stump recurrence concerns whether inadequate resection margins can cause local stump relapse. In a previous retrospective study, we evaluated 11 surgically treated EGC patients with resection line involvement (RLI) at a median follow-up of 8 years. Very few of these patients showed local relapse and none with resection line involvement developed GSC.[19]

The role of anastomosis after gastric resection has been studied as a potential risk factor for GSC. Although B2 reconstruction after benign disease is considered as a preneoplastic condition[20] and the risk of developing GSC is estimated as 4- to 7-fold greater after 40 years,[4] in patients operated on for gastric cancer this correlation has rarely been evaluated. We are aware of the limitations of our study because of the lack of randomization and to the low number of Roux-en-Y and B1 anastomoses performed. However, even though there are no supporting statistical data, we did observe a similar incidence of stump cancer in patients submitted to Roux-en-Y (1 patient) and B1 reconstruction (2 patients).

A recent nationwide Japanese survey revealed differences in 309 GSCs previously submitted to B1 (207 patients) or B2 (102) anastomosis for gastric cancer.[3] In the study, patients with B2 anastomosis generally developed stump carcinoma at the anastomotic site, whereas for patients submitted to B1 reconstruction, GSC was generally observed in a nonanastomotic area. Unlike Tanigawa's experience, we observed several subcardial cancers in patients who underwent B2 anastomosis. Other authors, considering reflux as one of the factors most widely involved in GSC, correlated the site of the lesions with different pathogenetic mechanisms. In Sinning's opinion,[4] duodenogastric reflux is responsible for premalignant lesions in the anastomotic region, leading more frequently to a diffuse GSC histotype. Conversely, dysplasia, more frequent in the body of the gastric stump, may result in intestinal-type cancer. We did not observe this correlation in our study.

Of note, all cases of GSC occurred in patients previously operated on for intestinal-type gastric cancer, and the same histological type was found in the GSCs. Almost all GSCs occurred in men and it is unclear why reflux, if considered as a risk factor, only seems to affect men; the 222 women in our study showed a much lower incidence of the disease. Considering its high prevalence in men and intestinal histologic type, GSC in our patients shows strong similarities with gastric cancer of the upper third. We could thus hypothesize that most of these cases represent new gastric carcinomas of the upper third, raising some questions about the real carcinogenic effect of bile reflux.

A higher incidence of second primary cancer ranging from 3.2% to 10% is frequent in EGC patients.[5,21] These data, age adjusted, are much higher than standardized incidence (2.3%) or recurrence rates (estimated at 2.1%).[5] In 2006, Sinning et al[4] hypothesized that achlorhydria with bacterial growth (especially anaerobes) could induce carcinogenesis in the stump; if that were the case, it could cause a higher incidence of second neoplasia after subtotal gastrectomy, especially in B2 anastomosis where duodenal juice reflux worsens stump hypochlorhydria. Although our data confirm the high number of second tumors in these patients, we do not agree with this hypothesis. In fact, observing our own experience and considering the 116 patients submitted during the same period to total gastrectomy with Roux-en-Y anastomosis, which excludes duodenal reflux as a preneoplastic condition, we found a similar incidence (10%) of second tumors.

Conclusions

Our ECC patients who underwent subtotal gastrectomy had a low incidence of GSC, even after 20 years, while the risk of recurrence and incidence of other tumors were much higher. The only risk factors for GSC we observed were histologic intestinal type and male sex. We also found that multifocal EGC was not related to a high incidence of GSC. No correlation was seen between the site of GSC and histologic type or reconstruction technique. Although there is no firm evidence, we believe that B2 anastomosis can be performed, when indicated, without a high specific cancer-related risk. Molecular studies are needed to understand the real nature of this particular tumor and we believe that at present no differences can be drawn between cancer relapse and new carcinoma. In the absence of specific guidelines and studies conducted in this setting, the only possible definition for this subset of lesions is that of GSC.

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