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Gastric Stump Cancer After Distal Gastrectomy for Benign Disease: Clinicopathological Features and Surgical Outcomes

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ABSTRACT

Purpose. The purpose of the present study was to analyze clinicopathologic features and long-term prognosis of gastric stump cancer (GSC) arising in the remnant stomach 5 years or later after partial gastrectomy for benign disease.

Methods. We reviewed the results of 176 patients resected with curative intent for GSC at 8 Italian centers belonging to the Italian Research Group for Gastric Cancer (GIRCG). The median (range) follow-up time for surviving patients was 71.2 (6–207) months.

Results. One hundred forty-six patients were men, the mean age at the time of diagnosis was 69.2 years, and the great majority (167 cases) underwent Billroth II reconstruction. R0 resection was achieved in 158 (90 %) patients, and in 94 (53 %) lymph node dissection was ≥D2. Postoperative mortality and complication rates were 6.2 and 43.2 %, respectively. T1 tumor was diagnosed in 45 (25 %) cases. Lymph node metastases were evident in 86 patients (49 %). Thirteen patients had involvement of the jejunal mesentery nodes (pJN+); five cases were T2–T3 and eight cases were T4. Overall 5-year survival rate was 53.1 %. Five-year survival rates were 68.1, 37.8, and 33.1 % for pT1, pT2-3, and pT4 tumors, respectively ($P = 0.001$). Five-year survival rate was 56.5 % for node-negative tumors (pN0), 32.3 % for tumors with nodal metastases without involvement of jejunal mesentery nodes (pN+), and 17.1 % for tumors with involvement of jejunal mesentery nodes (pJN+) ($P = 0.002$).

Conclusions. Our study suggests that an aggressive surgical approach can achieve a satisfactory outcome in GSC.

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Patients with prior resection of the distal stomach for peptic ulcer are at increased risk of developing gastric stump cancer (GSC). This tumor is characteristically considered as a distinct clinical entity, and it is defined as a gastric cancer that arises in the remnant stomach more than 5 years after primary surgery for benign disease.[1–3] In Western centers, its incidence ranges between 2.4 and 6 % of all gastric cancer patients.[3–7]

Early diagnosis of GSC might be difficult, because most patients are asymptomatic.[8] GSC is usually described as a tumor with poor prognosis and low resectability rates in the range of 38–40 % because of extended lymph node metastases and infiltration of adjacent organs. The reported 5-year survival rates ranges from 7 to 25 %, even after curative resection.[9] In the present study, we reviewed clinicopathologic features and surgical outcome of GSC in an Italian multicenter cohort.

PATIENTS AND METHODS

Definition

GSC was defined as a gastric cancer occurring in the remnant stomach 5 years or later distal gastric resection for benign disease.[2,4] Tumors diagnosed as recurrence after distal gastric resection for malignant disease or metachronous gastric adenocarcinoma were excluded from the analysis.

GSC was classified as: (a) anastomotic when the bulk of the tumor involved the anastomotic site; (b) extra-anastomotic when the tumor was located outside the anastomotic site; and (c) diffuse when the tumor involved the entire gastric remnant. Patients affected by cancer involving the esophagogastric junction were not included in the study.

Study Population

This study analyzed 176 patients resected with curative intent for GSC from January 1990 and December 2012 in eight Italian centers (Department of Surgery of the University of Verona, Department Surgery of the University of Brescia, Department of Surgery of the Catholic University of Rome, Department of Surgery of Forlì, Department of Surgery of the University of Siena, Second Clinical Surgery of the University of Padua, Division of Surgical Oncology of the Humanitas Hospital of Milan, Division of Surgery of the Rovereto Hospital) belonging to the Italian Research Group for Gastric Cancer (GIRCG).

No patient in the cohort underwent preoperative chemotherapy and/or radiotherapy, or received adjuvant chemotherapy. The study was approved by the local ethics committees.

Extent of Resection and Lymphadenectomy

The main goal of surgery was to achieve a potentially curative (R0) resection. Complete resection of the gastric remnant with jejunal mesentery nodes was performed in any case. The extent of lymph node dissection as well as the need for splenectomy or other adjacent organ resection was established by the operating surgeon in order to achieve a complete resection. Postoperative complications were graded according to the modified Clavien–Dindo classification system.[10]

Particularly, lymphadenectomy and lymph node retrieval were classified and standardized in accordance with the second English edition of the Japanese Gastric Cancer Association (JGCA) guidelines: dissection of group 1 nodes (D1); dissection of group 1 and 2 nodes (D2); dissection of group 1, 2, and 3 nodes (D3). Although lymph node stations were not collected separately in all cases, the incidence of metastasis for each single station was calculated as the percentage of patients with positive nodes in that station among patients with separate dissection of that station and with reference to the depth of invasion.[11]

STAGING AND HISTOLOGICAL CLASSIFICATION

Tumors were staged according to the pathological classification (pTNM) of the 7th Edition of the International Union Against Cancer (UICC).[12] Lymph node involvement was classified according to the number (UICC) [12] and site (JGCA) of nodal metastasis.[11] The histological classification followed the criteria of Lauren.[13]

Follow-up and Survival Analysis

A total of 152 of the 176 patients were regularly followed-up with a standardized protocol.[14] Median follow-up time for surviving patients was 71.2 (range 6–207) months.

Survival curves were estimated using the Kaplan–Meier method and compared by the log-rank test. The time of survival measured was obtained starting from the date of surgery to the date of death. Multivariable analysis was performed by Cox regression model by taking into account the following risk factors: age (higher than median vs. median or below), sex (male vs. female), tumor location (extra-anastomotic and diffuse vs. anastomotic), Lauren histotype (nonintestinal vs. intestinal), R category (R1–2 vs. R0), M category (M1 vs. M0), T category (pT2–T3 and pT4 vs. pT1), type of lymphadenectomy (D2–3 vs. D1), and extent of lymph node involvement considered according to TNM classification (pN1, pN2, pN3a and pN3b vs. pN0), as well as site of nodal involvement (patients with nodal metastasis but negative jejunal mesentery nodes and patients with nodal metastasis in jejunal mesentery nodes vs. node negative patients). Causes other than gastric cancer were included in the survival analysis (overall survival). Analyses were performed using the Statistical Package for the Social Sciences, SPSS 16.0 for Windows, XP (SPSS, Chicago, IL, USA).

RESULTS

Principal Clinicopathological Characteristics

The main clinicopathological findings of the 176 patients under study are reported in Table 1.

One hundred forty-six patients were men (83 %). The median and mean age at the time of diagnosis was 70 and 69.2 (range 42–87) years, respectively. The mean interval between primary distal gastric resection and the development of GSC was 34.6 (range 8–57) years. The great majority of patients (167 cases) underwent Billroth II reconstruction and 10 patients Billroth I.

Extent of Resection and Short-term Results

Resection of one or more adjacent organs often was performed together with gastrectomy (70 patients). Splenectomy (37 cases) and resection of the transverse colon (9 cases) were the procedures most frequently associated. Extended (≥D2) lymph node dissection was performed in 94 (53 %) patients. Complete tumor (R0) resection was achieved in 90 % of the cases.

TABLE 1 Clinicopathological characteristics of the GSC patients

Characteristics	Number of patients	
Sex	Male	146 (83)
	Female	30 (17)
Mean age (years)		69.2; range 42–87
Primary operation	Billroth I	10 (5)
	Billroth II	167 (95)
Lymphadenectomy	D1	82 (47)
	≥D2	94 (53)
Histotype	Intestinal	104 (59)
	Diffuse	44 (25)
	Mixed	28 (16)
Tumor site	Anastomotic	71 (40)
	Extra-anastomotic	73 (42)
	Diffuse	32 (18)
T category	T1	45 (25)
	T2–T3	56 (32)
	T4a	42 (24)
	T4b	33 (19)
N category	N0	90 (51)
	N1	21 (12)
	N2	25 (14)
	N3a	32 (18)
	N3b	8 (5)
M category	M0	164 (93)
	M1	12 (7)
Type of resection	Gastrectomy	106 (60)
	Extended gastrectomy	70 (40)
	Spleen	37 (21)
	Colon	9 (5)
	Liver	3 (2)
	Pancreas	2 (1)
	Others	3 (2)
	Combined	16 (9)
Curability	R0	158 (90)
	R1	11 (6)
	R2	7 (4)

Values in parentheses are in percentage

Seventy-six patients (43.2 %) developed postoperative general and/or surgical-related complications. Eleven patients died (postoperative mortality 6.2 %). Pulmonary complications (11.9 %), anastomotic leaks (10.2 %), and cardiovascular complications (4.5 %) were the most frequently observed complaints (Table 2). According to the modified Clavien–Dindo classification system, complication rates for grades I, II, IIIa, IIIb, IVa, IVb, and V were 5.7 % (10/176), 15.3 % (27/176), 5.1 % (9/176), 4.5 % (8/176), 2.8 % (5/176), 3.4 % (6/176), and 6.2 % (11/176), respectively.

TABLE 2 Postoperative complications in the 176 patients studied

Type of complications	Number of patients
Surgical-related	
Anastomotic leak	18 (10.2)
Abdominal abscess	5 (2.8)
Abdominal hemorrhage	5 (2.8)
Pancreatic fistula	3 (1.7)
Anastomotic hemorrhage	2 (1.1)
Wound infection	2 (1.1)
Bowel infarction	2 (2.1)
Paralytic ileus	2 (2.1)
Biliary fistula	1 (0.6)
Severe pancreatitis	1 (0.6)
Lymphorrhea	1 (0.6)
Others	5 (2.8)
General	
Pulmonary	21 (11.9)
Cardiovascular	8 (4.5)
Multiple	
One or more of the previous	12 (6.8)
Total	76 (43.2)

Values in parentheses are in percentage

Histopathological Staging and Lymph Node Involvement

In our study, one of four tumors was diagnosed as an early gastric cancer, and one of two were without lymph node metastasis. Moreover, 12 (7 %) patients were diagnosed with metastatic disease at the time of surgery: 9 patients suffered from hepatic metastasis and 3 from peritoneal metastasis. Tumor location was anastomotic in 71 (40 %) cases, extra-anastomotic in 73 (42 %) cases, and diffuse in 32 (18 %) cases.

A total number of 3,376 lymph nodes were dissected with a mean (SD) number per case of 19.2 (5.8) and a median number of 16 (range 5–66). Lymph node metastases were found in 86 patients (49 %), with a total of 664 metastatic lymph nodes. The mean (SD) and median number of metastatic lymph nodes for node-positive patients were 7.7 (7) and 5 (range 1–45), respectively.

Table 3a, b show lymph node involvement according to depth of tumor invasion. Among the 13 patients with involvement of jejunal mesentery nodes (pJN+), this was the only site of nodal metastases in 4 cases of anastomotic tumors (31 %).

Survival

At the follow-up end date, 24 patients were lost at follow-up procedure and therefore were excluded from

TABLE 3 Lymph node involvement according to depth of tumor invasion

(a) Incidence (%) of lymph node metastasis according to the UICC classification[12]

Depth of invasion	N stage					
	N0	N1	N2	N3a	N3b	N+
T1a–T1b	43/45	1/45	1/45	0/45	0/45	2/45
	(95.6)	(2.2)	(2.2)	(0)	(0)	(4.4)
T2–T3	27/56	11/56	5/56	9/56	4/56	29/56
	(48.2)	(19.6)	(8.9)	(16.1)	(7.1)	(51.8)
T4a–T4b	20/75	9/75	19/75	23/75	4/75	55/75
	(26.7)	(12)	(25.3)	(30.7)	(5.3)	(73.3)
Total	**90/176**	**21/176**	**25/176**	**32/176**	**8/176**	**86/176**
	(51.1)	**(11.9)**	**(14.2)**	**(18.2)**	**(4.5)**	**(48.9)**

(b) Incidence (%) of metastasis in the JGCA lymphatic stations [11]

Depth of invasion	Lymphatic station										
	No. 1	No. 2	No. 3	No. 4sa	No. 4sb	No. 7	No. 8	No. 9	No. 10	No. 11	No. J[a]
T1a–T1b	0/24	0/22	1/23	0/21	0/22	1/13	0/15	0/8	0/9	0/7	0/6
	(0)	(0)	(4.3)	(0)	(0)	(7.7)	(0)	(0)	(0)	(0)	(0)
T2–T3	4/19	3/17	3/18	0/16	1/18	3/9	1/12	2/10	0/8	0/10	5/9
	(21)	(17.6)	(16.7)	(0)	(5.5)	(33.3)	(8.3)	(20)	(0)	(0)	(55.5)
T4a–T4b	6/38	5/39	17/42	3/34	7/35	6/29	3/21	3/11	3/13	2/11	8/13
	(15.8)	(12.8)	(40.5)	(8.8)	(20)	(20.7)	(14.3)	(27.3)	(23.1)	(18.2)	(61.5)
Total	**10/81**	**8/78**	**21/83**	**3/71**	**8/75**	**10/51**	**4/48**	**5/29**	**3/30**	**2/28**	**13/28**
	(12.3)	**(10.3)**	**(25.3)**	**(4.2)**	**(10.7)**	**(19.6)**	**(8.3)**	**(17.2)**	**(10)**	**(7.1)**	**(46.4)**

[a] Jejunal lymph nodes

survival analysis, 91 patients died, and 61 patients were alive. The overall 2-, 3-, and 5-year survival rates for the 152 patients were 67.1, 55.9, and 53.1 %, respectively. Median (95 % confidence interval [CI]) survival time was 42.5 (range 13.4–71.6) months after R0 resection and 9.7 (range 0–21.1) months when residual (R1–2) tumor was present ($P = 0.001$). Figure 1 shows survival curves according to the depth of tumor invasion. Five-year survival rates were 68.1, 37.8, and 33.1 % for pT1, pT2–3, and pT4 tumors, respectively ($P = 0.001$). Figure 2 reports survival curves according to nodal involvement. Five-year survival rate was 56.5 % for node-negative tumors (pN0), 32.3 % for tumors with nodal metastases without involvement of jejunal mesentery nodes (pN+) and 17.1 % for tumors with involvement of jejunal mesentery nodes (pJN+) ($P = 0.002$).

Multivariable analysis performed by Cox regression model controlling for sex, age, tumor location, Lauren histotype, curability, M category, T category, and extent of lymphadenectomy-confirmed N category, classified according to the 7th UICC Classification, to be an independent predictor of survival ($P = 0.011$). When positive-node patients were considered according to involvement of mesentery jejunal nodes, no statistical significance was observed [RR for pN+ with respect to pN0: 1.33 (95 % CI 0.78–2.26); RR for pJN+ with respect to pN0: 1.94 (95 % CI 0.88–4.26); $P = 0.239$].

DISCUSSION

Several investigations have been conducted to evaluate clinicopathological characteristics of patients with GSC, but most of them involved patients with previous gastric resection for cancer.

Although cancer can develop in the remnant stomach of patients with previous benign or malignant lesions, these tumors seem to be two different entities. Namely, the patients with previous cancer develop stump carcinoma in a significantly shorter time interval than those with prior benign disease.[15,16] Indeed, the most important factor presumed to be responsible for the development of GSC is duodenogastric reflux, whereas cancer after gastric resections for malignancy probably originates from the same precancerous conditions which had already existed before the initial operation.[15,17,18] Moreover, the discrepancies in the extent of gastric resection for benign or malignant

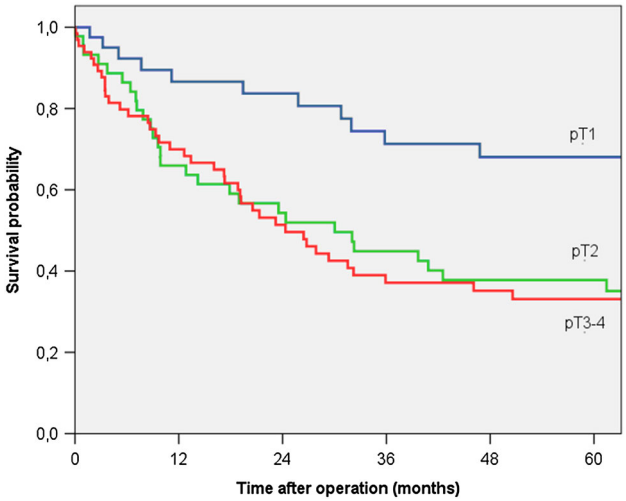

FIG. 1 Kaplan–Meier estimates of overall survival probability of the cohort under study who completed the follow-up procedure (152 patients) according to depth of tumor invasion. Median (95 CI) survival times were: beyond the observation period for pT1 tumors, 30 (range 13.3–46.8) months for pT2 tumors and 24.3 (range 15.5–33.2) months for pT3–T4 tumors ($P = 0.001$)

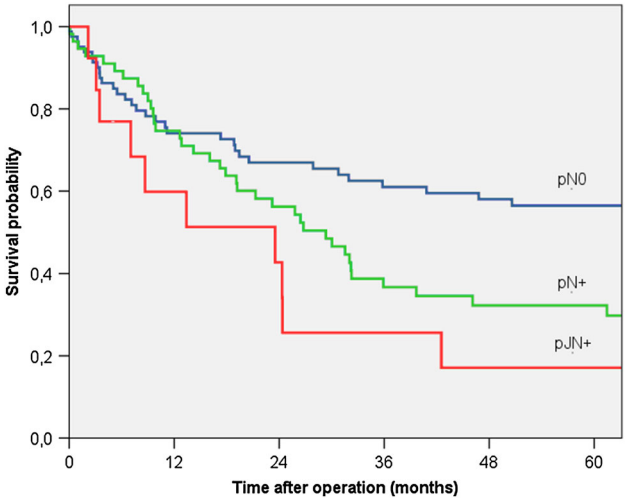

FIG. 2 Kaplan–Meier estimates of overall survival probability of the cohort under study who completed the follow-up procedure (152 patients) according to level of nodal involvement. Median (95 CI) survival times were: 88.2 (range 6.7–169.7) months for node-negative tumors (pN0), 29.3 (19.8–38.9) months for node-positive tumors (pN+), and 23.5 (range 0–47.9) months for pN+ tumors with involvement of jejunal mesentery nodes (pJN+) ($P = 0.002$)

disease and lymph node dissection, which is performed only in case of cancer, will lead to different pathways of local invasion and lymphatic spread.[15,18,19]

This Italian multicenter study only deals with GSC arising after gastric resection for benign disease. GSC remains a substantial clinical concern.[6] Indeed, gastric resection for benign disease was commonly performed until the late 1980s, and it is still less frequently conducted in case of emergent and life-threatening complications of peptic ulcer disease, such as bleeding and perforation, refractory ulcer disease, and recurrent ulcer with gastric outlet obstruction.[20–22] Because patients develop the tumor after a long latency period, which can be more than 30 years (as in our cases), GSC will continue to be encountered by surgeons.[4–7,23–25]

Several authors have reported a higher risk of developing GSC in men and after Billroth II reconstruction. In the present series, the great majority (83 %) of patients affected by GSC were men, and 167 (95 %) underwent Billroth II reconstruction. The male predominance could be explained with the higher incidence of peptic disease in men.[8] With regards to the type of surgical reconstruction, it has been found a fourfold increased risk of developing gastric carcinoma as a consequence of Billroth II procedure in comparison to Billroth I,[26] but it should be considered that in Italy, until 1980, Billroth I was less popular in surgical treatment of peptic disease.[3,8,25,27–29]

Despite the relatively high rate of cases with early cancer (25 %), and with no lymph node metastasis (51 %), surgeon performed extended (D2) or superextended (D3) lymphadenectomy in 94 patients (53 %), and gastrectomy with combined resection of one of more adjacent organs in 70 (40 %). We registered a relatively higher frequency of D1 (47 %) than that reported in previous studies (22-32 %),[3,19,30,31] because this multicenter study included patients operated on between January 1990 and December 2012. Indeed, especially during the first period of study, the superiority of D2 lymphadenectomy was not demonstrated, hence some of the centers were less prone to adopt extensive lymphadenectomy. Another reason for this proportion of D1 lymphadenectomies is that a huge number of patients were at an advanced age at the moment of surgery. This is demonstrated by the median age of the cohort (70 years) and by the percentage of patients $\geq$75 years (approximately 30 %). Indeed, multivariable analysis demonstrated a superiority of D2–D3 versus D1 lymphadenectomy [RR for D2–3 with respect to D1: 1.65 (95 % CI 1.03–2.63); $P = 0.036$], but we believe that such a debated issue was beyond the purpose of a study with this sample size.

We registered a high rate (90 %) of curative resection (R0), which was similar to the rates of 85 and 91 % reported in two recent studies, where the surgical management was based on an aggressive surgical approach.[4,7] This therapeutic strategy, recommended by several authors, includes complete removal of the whole remnant stomach with resection of adjacent organs in requiring cases, together with an extended lymphadenectomy.[5–7,32]

In the present series, the postoperative morbidity (43.2 %) and mortality (6.2 %) resulted in higher than previous reports of GIRCG in gastric cancer surgery.[33]

These results can be attributed to the major effort a surgeon should manage to treat this tumor compared with conventional gastric cancer: for instance, the low incidence of GSC, the presence of adhesion between the gastric stump and other organs due to the initial surgery, and the common removal of adjacent organs.[2,31,32] Moreover, morbidity and mortality observed in this series is probably related to median patient age (70 years) and to associated organ resection, which was quite frequent (70 cases).

Previous studies conducted on early gastric stump cancer reported a low incidence of nodal involvement, which is less than 6 %.[34–36] We found 45 patients (25 %) affected by early cancer, of which only 2 (4.4 %) presented lymph node metastases. These pathological findings support that endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) can be useful for the treatment of selected cases of early gastric stump cancer.[36,37]

Some authors have investigated the pattern of lymphatic spread of GSC in comparison with the upper third primary gastric cancer. Their results suggested that these two types of gastric tumors have a different lymphatic spread,[3,22,36] and our results seems to confirm this findings. As we reported in a previous study, the main lymphatic flow drains from a tumor located in the upper third of the stomach into nodes along the lesser curvature, the right cardia, the left gastric artery, and the celiac artery.[38] In GSC, these lymphatic pathways have been cut off; indeed, previous partial gastrectomy, usually causes lymphatic leakage, blockage, and regeneration of lymphatic flow around the gastric stump and also induces abnormal lymphatic formation.[32,36] Moreover, as recently reported by Li et al.[39] because of initial distal gastrectomy, the total number of lymph nodes and the amount of metastatic lymph nodes are lower in GSC than in conventional gastric cancer.

Four patients with anastomotic GSC had jejunal mesentery nodes involvement without simultaneous invasion of any other lymph node station. This observation is in agreement with the rules of the Japanese classifications of gastric carcinoma that identified jejunal mesentery nodes as group 1–group 2 if the tumor invades the jejunum, and as group 2–group 3 if there is no jejunal invasion.[11]

Although in our experience, overall 5-year survival rate reached 50 % and seems to be better than in recent Western series,[4,6] it is consistent with previous studies.[3,5,24,31,36] This result might be related to the relatively high rate of early stage disease (25 %), as 5-year survival rate was approximately 35 % for patients with advanced forms. Early tumors showed the best prognosis (5-year survival rate was 68.1 %), although it was poorer compared to primary early gastric cancer. This outcome reflects the advanced age of the cohort under study, in which cardiovascular diseases were the leading causes of death (70 %).

The reported prognosis of patients with infiltrated lymph nodes in the jejunal mesentery is poor; Thorban et al.[4] reported a median survival of 13.2 months. In the present series, patients with metastases in jejunal mesentery nodes (pJN+) had the worst outcome (5-year survival rate was 17.1 % and median survival time was 23.5 months), although the difference with node-positive patients did not reach statistical significance.

In conclusion, the results of this study suggest that early diagnosis allows the best surgical outcome in patients with GSC. An aggressive surgical approach can achieve a satisfactory outcome in advanced stages.

DISCLOSURE All the authors declare that they have not potential commercial conflicts of interest relevant to this article.

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