

Resection Line Involvement After Gastric Cancer Surgery: Clinical Outcome in Nonsurgically Retreated Patients

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Abstract

Purpose Resection line infiltration (RLI) after surgical treatment represents an unfavorable prognostic factor in advanced gastric cancer. We performed a retrospective analysis of 89 patients with resection line involvement who did not undergo reoperation.

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Methods On behalf of the Italian Research Group for Gastric Cancer, we present the characteristics and outcome of 89 patients who were submitted to surgical resection for gastric cancer from 1988 to 2001 and did not undergo reoperation because of disease extension or associated pathologies.

Results RLI was significantly higher in patients with T4 tumors and diffuse histological type. Anastomotic leakages were observed in 4.8% of infiltrated esophageal resection margins, whereas 1.9% of infiltrated duodenal resection lines showed duodenal fistulas. Five-year overall survival of patients with RLI was 29%. Prognosis was not affected by RLI in early forms (100% 5-year survival); however, 5-year survival in T2 and T3 stages was significantly lower with respect to the same stages without residual tumor. The influence of RLI on prognosis was confirmed in N0 as well as in N1 and N2 patients. RLI also was an independent prognostic at multivariate analysis (odds ratio = 1.5; 95% confidence interval, 1.08–2.08; $P = 0.0144$).

Conclusions RLI significantly affects long-term survival of advanced gastric cancer. The impact on prognosis is independent of lymph node involvement. Patients in good general condition for whom radical surgery is possible should be considered for reoperation.

Introduction

Surgery is widely accepted as the “gold standard” for the first-line treatment of gastric cancer, and curative resection is the only therapy offering hope of a cure. One of the most important steps in surgery is the determination of the tumor margin and its distance from the resection line, which is usually established on the basis of histotype and

macroscopic type, which is wider in nondifferentiated and infiltrating carcinomas.

An infiltrated resection line (RLI) in patients undergoing radical surgery indicates a significantly poorer outcome in advanced gastric cancer [1, 2] but would not seem to influence prognosis in early gastric cancer (EGC) [3, 4]. Although numerous studies have confirmed the prognostic value of RLI in advanced gastric cancer and usually recommend a new resection if radicality can be achieved, the situation is not so clear-cut when extensive surgical treatment is needed or when associated diseases are present [1–5]. Another important but inadequately addressed issue concerns the incidence of complications, considered frequent and extremely serious when anastomotic leakage occurs in neoplastic tissue.

The present study provides a retrospective analysis of 89 patients from 6 Italian centers who did not undergo reoperation. All patients underwent close follow-up.

Patients and Methods

From 1988 to 2001, 2740 patients underwent resection for gastric cancer in 6 Italian Surgical Units. One hundred and fifty-eight (5.7%) patients presented one or more RLI and 89 of these were classified as R1 (microscopically involved RL). Patients were classified according to tumor size, Borrmann's macroscopic type [6], Lauren's histological type [7], and TNM classification [8]. All patients were submitted to open surgical treatment.

Subtotal gastrectomy was performed for tumors located in the lower two-thirds of the stomach, with removal of the greater and lesser omentum. Surgical reconstruction was performed on the basis of the experience of the various centers involved in this study, and consisted of gastrojejunal Billroth II or Roux-en-Y anastomosis.

Total gastrectomy was performed for tumors located in the upper gastric third, for Borrmann type 4 lesions, or when the macroscopic distance between the resection line and the tumor was considered to be <5 cm. Unfortunately, none of the 89 patients with RLI underwent frozen-section analysis of the resection line during surgery.

Although handsewn anastomosis was usually performed after subtotal gastrectomy, staple guns were used for esophagojejunal anastomosis and sometimes for duodenal stump. Roux-en-Y reconstruction was always performed after total gastrectomy.

D1 lymph node dissection was generally performed in elderly or critical patients, and en bloc D2 or occasionally D3 lymphadenectomy, in accordance with Japanese Gastric Cancer Association (JGCA) recommendations [6], were performed on the basis of each center's experience [9].

Surgical treatment was classified as radical (R0) only in the control group, nonradical with microscopic residual disease (R1), or nonradical with macroscopic residual disease (R2), according to UICC criteria.

Of the 2740 submitted to surgical treatment, 2154 were treated with curative intent (R0), whereas 586 were submitted to palliative surgery because of residual disease (121 R1 patients generally with only positive peritoneal fluid cytology and 307 R2 patients). A total of 158 of these presented an RLI, and only 89 presented microscopic involvement of the resection line. This study was designed to present the outcome of these 89 patients, considering patients submitted to radical surgery (R0) as the control group.

Patients were subdivided on the basis of resection line infiltration (esophageal, gastric, duodenal, multiple). Postoperative complications were classified as medical, surgical, or anastomosis-related. Morbidity and mortality were compared with those observed in patients without RLI.

Death from postoperative complications was considered if it occurred during hospitalization. Follow-up tests were suggested on the basis of patient conditions; ultrasound scan, serum marker evaluation, and endoscopy were generally recommended every 3 or 6 months.

Survival times were measured from the date of surgery to death. Univariate analysis was performed by tracing Kaplan–Meier survival curves [10], and comparison of survival curves was based on the log-rank test [11]. The correlation between RLI and other clinicopathological variables was assessed by using the multiple logistic regression model in multivariate analysis, and the role of the joint effect of the putative prognostic variables was evaluated by using a Cox proportional hazard model [12]. All *P* values were based on two-sided testing and statistical analysis was performed by using SAS[®] Statistical software [13].

Results

Patient characteristics are summarized in Table 1. Comparing the variables relating to neoplastic infiltration with lymphatic diffusion, histological type, macroscopic type, and tumor dimensions, the variables most at risk of resection line infiltration were T4 tumor, with a sevenfold increased risk (odds ratio (OR) = 7.38; *P* = 0.01), and diffuse histological type, with a threefold increased risk (OR = 3; *P* = 0.005).

Resection line infiltration was observed in the duodenum in 51 patients, in the esophagus in 21 patients, and in the gastric stump in 14 patients; 3 patients had more than one positive area of infiltration (2 esophagus + duodenum and 1 stomach + duodenum).

Table 1 Patient characteristics and survival

	R1 patients with RLI (<i>n</i> = 89)	5-year survival % (95% CI)	<i>P</i> value	R0 patients (<i>n</i> = 1995) ^a	5-year survival % (95% CI)	<i>P</i> value
Overall	89	29 (18–40)		1995	66 (63–68)	<0.0001
Histology						
Intestinal	40	36 (19–52)		1353	70 (67–73)	
Diffuse	46	24 (9–39)		519	54 (49–59)	
Mixed	3	0	<0.0001	111	67 (57–76)	<0.0001
Unknown	0			12		
Tumor stage						
T1	11	100		637	94 (92–96)	
T2	18	8 (0–24)		638	64 (60–69)	
T3	46	21 (7–34)		645	42 (37–46)	
T4	14	11 (0–32)	0.0006	71	22 (11–32)	<0.0001
Unknown	0			4		
Nodal status						
N0	23	71 (50–93)		790	92 (90–94)	
N1	21	25 (3–47)		535	57 (65–74)	
N2	24	11 (0–26)		251	28 (21–35)	
N3	15	0	<0.0001	161	11 (5–17)	<0.0001
Nx	6			258		
Tumor size (mm)						
<20	10	78 (51–100)		246	92 (88–95)	
20–49	28	18 (1–35)		641	68 (64–72)	
50–100	40	31 (15–48)		531	51 (46–56)	
>100	3	0	0.1383	35	15 (1–30)	<0.0001
Unknown	8			542		
Stage						
I	14	82 (60–100)		745	94 (93–96)	
II	17	45 (16–73)		342	65 (59–71)	
III	31	16 (2–30)		437	40 (34–45)	
IV	23	0	<0.0001	213	11 (6–17)	<0.0001
Unknown	4			258		
Lymphadenectomy						
≤D1	39	29 (15–43)		691	65 (61–69)	
>D1	44	30 (13–47)	0.483	1288	66 (63–69)	0.942
Unknown	6			16		
Macroscopic type						
Borrman 1	2	0		72	45 (33–58)	
Borrman 2	3	33 (0–87)		216	58 (50–65)	
Borrman 3	15	12 (0–33)		244	43 (36–50)	
Borrman 4	7	0	0.016	112	25 (16–33)	<0.0001
Unknown	62			1351		

^a A total of 159 patients without RLI were not included because they were lost to follow-up

D1 or D0 dissection was performed in 39 (43.8%) of 89 patients, with an average of 11.7 lymph nodes dissected (range, 5–50); 44 (49.3%) patients underwent D2 or D3 lymphadenectomy, with an average of 27.4 nodes dissected (range, 10–82). This information was not available for six patients.

In the control group, 34.6% of patients were submitted to D0/D1 dissection with an average of 11.1 lymph nodes dissected (range, 1–51), and 64.5% underwent D2/D3 lymphadenectomy with an average of 28.6 dissected (range, 10–108).

Table 2 Morbidity in patients with resection line involvement (RLI)

	R1 patients with RLI	R0 group
Surgical morbidity	12 (13.5)	232 (10.7)
Specific anastomotic morbidity	4 (4.5)	114 (5.2)
Nonsurgical morbidity	10 (11.2)	222 (10.3)
No morbidity	63 (70.8)	1570 (73.8)
Total	89 (100)	2154 (100)

Data are numbers with percentages in parentheses

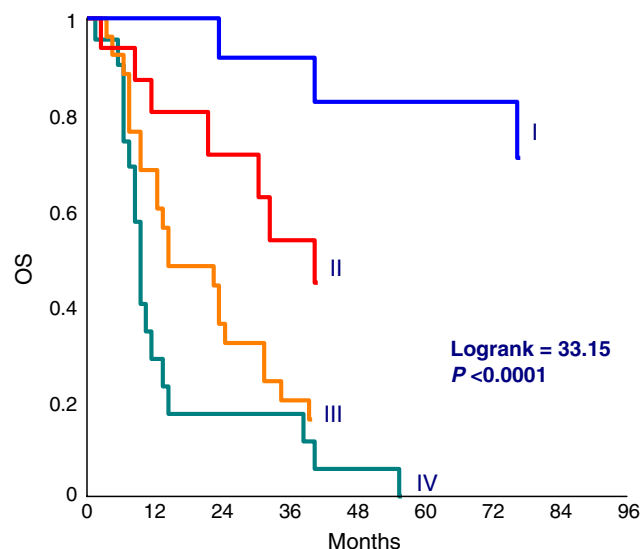
The complications observed were subdivided into surgical (12 cases, 13.5%), anastomosis-related (4 cases, 4.5%), and medical (10 cases, 11.2%), and were not significantly different from those observed in the control group (10.7%, 5.2%, and 10.3%, respectively; Table 2).

Patients were then subdivided on the basis of type of infiltrated resection line (Table 3). Evaluating these groups separately, we observed a similar incidence of esophagojejunal leakage after total gastrectomy in patients with a positive esophageal resection line with respect to that of the control group (4.8% vs. 7.9%), whereas for positive duodenal resection line infiltration, the incidence of duodenal fistulae was 1.9% compared with 0.3% in control subjects. However, 5.5% of patients with duodenal involvement presented complications at noninfiltrated esophageal or gastrojejunal anastomotic sites.

Postoperative mortality was 7.8%, which was higher than that of the control group (3.9%) but not significantly different from that of R1/R2 patients without RLI (8.1%).

After discharge, all patients were followed up for a median of 69 (range, 1–265) months. A total of 159 of the 2154 patients in the control group were lost to follow-up, leaving 1995 patients who could be evaluated for survival. Fifty-eight of our patients were submitted to adjuvant chemoradiotherapy, but because of the retrospective characteristics of our study and the long study period considered, enormous differences were observed in the anticancer treatments administered and it was not feasible to describe them.

Five-year overall survival for patients with R1 resection line infiltration (Fig. 1) was significantly lower than that of

**Fig. 1** Overall survival (OS) of patients with resection line involvement according to tumor stage (I–IV)

the control group (29% (95% confidence interval (CI), 18–40) vs. 66% (95% CI, 63–68); $P < 0.0001$), and median survival was only 24 months (Table 1). However, EGC patients with T1 tumors and a positive resection line had excellent 5- and 10-year survival rates (100% and 86% (95% CI, 60–100), respectively). On the contrary, resection line infiltration resulted in a significantly poorer 5-year survival for patients with T2 and T3 tumors with respect to the control group (8% (95% CI, 0–24) vs. 64% (95% CI, 60–69); $P < 0.0001$; 21% (95% CI, 7–34) vs. 42% (95% CI, 37–46); $P = 0.002$, respectively; Table 4).

Of the 55 patients who subsequently died from gastric cancer, only 31 showed a single specific site of recurrence, whereas the remaining 24 patients had multiple recurrences for which the first recurrence site was not identified. In the former group, 14 patients had diffuse carcinosis, 9 had local recurrences, 5 had liver or lung metastases, and only 3 had anastomotic recurrence.

Considering lymph node involvement, a significantly worse prognosis was observed in N0 (71% (95% CI, 50–93) vs. 92% (95% CI, 90–94); $P = 0.001$), N1 (25% (95% CI, 3–47) vs. 57% (95% CI, 52–62); $P = 0.003$), and N2

Table 3 Morbidity for different types of R1 resection line involvement (RLI)

	Duodenal R1 RLI	Gastric R1 RLI	Esophageal R1 RLI	Multiple R1 RLI
Surgical morbidity	4 (7.4)	2 (14.2)	6 (28.5)	0
Specific anastomotic morbidity	3 (5.5)	0	1 (4.8)	0
Non surgical morbidity	9 (16.7)	0	1 (4.8)	0
No morbidity	35 (68.7)	12 (85.8)	13 (61.9)	3 (100)
Total	51 (100)	14 (100)	21 (100)	3 (100)

Data are numbers with percentages in parentheses

Table 4 Five-year survival of R1 RLI /R0 patients

	R1 RLI	5-year survival % (95% CI)	R0	5-year survival % (95% CI)	<i>p</i> value
T1	11	100	637	94 (92–96)	0.836
T2	18	8 (0–24)	638	64 (60–69)	<0.0001
T3	46	21 (7–34)	645	42 (37–46)	0.002
T4	14	11 (0–32)	71	22 (11–32)	0.604
N0	23	71 (50–93)	790	92 (90–94)	0.001
N1	21	25 (3–47)	535	57 (52–62)	0.003
N2	24	11 (0–26)	251	28 (21–35)	0.009
N3	15	0	161	11 (5–17)	0.564
Stage I	14	82 (60–100)	745	94 (93–96)	0.025
Stage II	17	45 (16–73)	342	65 (59–71)	0.168
Stage III	31	16 (2–30)	437	40 (34–45)	0.001
Stage IV	23	0	213	11 (6–17)	0.235

patients (11% (95% CI, 0–26) vs. 28% (95% CI, 21–35); $P = 0.009$; Table 4).

It is interesting to note that survival in T2 patients with RLI was not influenced by lymph node involvement. In particular, survival in N0, N1, N2, and N3 patients overlapped, but this may have been due to the small number of patients involved. A similar trend was not observed in T3 patients with RLI, for which survival was significantly better in N0 cases. RLI also was confirmed as an independent prognostic factor at multivariate analysis (OR = 1.5; 95% CI, 1.08–2.08; $P = 0.0144$), together with N, T, and tumor size (Table 5).

Table 5 Results from a backward application of the Cox model

	HR (95% CI)	<i>P</i> value
Nodal status		
N1 vs. N0	3.65 (2.57–5.18)	<0.0001
N2 vs. N0	6.95 (4.81–10.04)	<0.0001
N3 vs. N0	11.59 (7.91–16.98)	<0.0001
Tumor stage		
T2 vs. T1	3.43 (2–5.9)	<0.0001
T3 vs. T1	5.68 (3.31–9.75)	<0.0001
T4 vs. T1	12.03 (6.48–22.35)	<0.0001
Tumor size (mm)		
20–49 vs. < 20	1.14 (0.7–1.85)	0.6036
50–100 vs. < 20	1.17 (0.71–1.91)	0.5434
>100 vs. < 20	2.38 (1.27–4.48)	0.0069
RLI		
Yes vs. no	1.5 (1.08–2.08)	0.0144
Histology		
Diffuse vs. intestinal	1.06 (0.86–1.31)	0.5689
Mixed vs. intestinal	0.8 (0.54–1.19)	0.277

Discussion

The incidence of a positive resection line in surgically treated gastric cancer patients shows wide variability (0.8–10.2% of cases) [1, 6, 8] and is always considered a bad prognostic factor. In our own experience, the incidence was 3.2% (5.7% if we also take R2 patients into consideration) and it was confirmed to be a significant ($P < 0.0001$) and independent prognostic factor ($P = 0.0144$).

The problem of the distance of the resection line from the tumor has been addressed by numerous authors and differs on the basis of the site involved, being different in the esophagus or duodenum. A 2-cm esophageal resection from the gastric cancer margin is generally considered safe when a histologically well-defined lesion is found. However, when undifferentiated tumor invasion is present, a resection of 4–7 cm of the esophagus may be necessary [14] because manual palpation or frozen sections may not detect the presence of skip submucosal foci [15]. Duodenal invasion, when present, generally extends approximately 2 cm beyond the pyloric ring, but a 4-cm invasion through submucosal or subserosal layers or lymphatic tissue also has been described [14–17]. In these patients it is advisable to perform an extemporaneous histological examination, although the risk of false-negative results persists in 19–21% of cases [16].

Some authors have reported that macroscopic Borrmann types III and IV, tumor and nodal stage, tumor location, and histologically nondifferentiated tumors [1, 18] are factors frequently linked to RLI. In our case series, a logistic regression model identified T4 tumors and diffuse histotype as the main factors associated with a higher risk of RLI. Surprisingly, Borrmann's macroscopic type IV, which represents the infiltrating growth type, did not prove to be a significant risk factor. This may be because we normally perform total gastrectomy for this type of tumor to guarantee wider margins, and also because of its strong

correlation with Lauren diffuse histological type. The latter would seem to be the real predominant risk factor for RLI.

RLI is generally reported to cause high surgical morbidity, as observed by Keighley in 1981, who described four anastomotic leakages in four total gastrectomies [19]. In another study of 137 total or proximal gastrectomies, Chan et al. [20] reported a 18.2% incidence of positive esophageal margins but did not observe an increase in morbidity or in the incidence of anastomotic leakage compared with patients with negative margins. Our experience confirms these data. In particular, the incidence of esophageal/duodenal leakages and mortality in patients with RLI was not higher than that of the control group.

Another interesting finding of our study concerns prognosis in relation to the potential disadvantages of further resection surgery [21]. All our patients were not reoperated on because of advanced age, associated disease, patient refusal, contraindications to thoracotomy, or when a new resection would have required extended procedures, such as duodenal pancreatectomy.

Although some authors recommend reoperation whenever technically feasible [1, 17], others advise only close follow-up to monitor potential anastomotic recurrence [5]. Cascinu et al. [22], comparing positive- and negative-resection lines in patients treated with D1 lymphadenectomy, observed a lower survival rate in N0 patients with RLI, and concluded that surgical retreatment may be indicated only in this subset of patients.

Kim et al. [23] observed that RLI was a significant and independent predictor of outcome, but poorer survival was observed only in patients with ≤ 5 positive lymph nodes and microscopically involved margins. He concluded that outcome is mainly determined by lymph node involvement rather than by residual cancer at the margin.

Our control group undergoing D2/D3 was much larger than the RLI group submitted to the same intervention (64.5% vs. 49.3%). This difference was due to the high incidence of elderly and high-risk patients in the latter group and may have influenced outcome. However, with respect to our results concerning lymphadenectomy, no prognostic differences were observed between patients submitted to more aggressive D2/D3 lymphadenectomy and those who underwent D1 ($P = 0.48$; Table 1).

In the present study, EGC patients with RLI had good survival rates [4]. Similar findings have been reported by other authors and also have been observed in patients subjected to endoscopic mucosal resection (EMR). Nagano et al. [24] conducted a study on 288 EGC patients with intramucosal lesions who presented lateral resection line involvement after EMR. Because no recurrences over time were observed, the authors proposed simple endoscopic monitoring for these patients. All our EGC patients presented only lateral infiltrated margins at the suture site. It

is, therefore, possible that poor blood supply at the resection margin may prevent cancer growth.

Notwithstanding such evidence from the literature and the results from our study, we still believe that a watchful waiting strategy in T1 patients should only be adopted after careful evaluation of the general risks associated with re-intervention, and bearing in mind the good survival rates of radically operated patients [25].

Conversely, a strong prognostic impact of RLI was observed in our patients with T2 tumors, which could, in our opinion, justify an interventive approach. Literature sources indicate that the decision to retreat, when technically feasible, often is based on the extent of lymph node diffusion, particularly when infiltration is absent or limited to level 1 stations. In the present study, a significant reduction in survival was seen for N0, N1, and N2 RLI patients with respect to control subjects, but this effect disappeared when we stratified on the basis of the T stage. In particular, patients with T2 tumors and RLI showed an invariably poorer prognosis in N0, N1, or N2 disease, suggesting that residual disease influences prognosis independently of the N stage. However, there may have been statistical bias because of the small number of T2 patients with RLI.

Patients with tumors involving the serosa (T3) and RLI showed a poor prognosis. In these patients, it is difficult to know for certain whether a new treatment would improve their prognosis, because T3 tumor progression generally results in peritoneal carcinomatosis [26]. However, there is some evidence to suggest that T3 N0 cases could potentially benefit from reoperation.

Some authors recommend a radical approach and even aggressive procedures, such as duodenopancreatectomy to obtain a clear duodenal margin [27]. In our opinion, such a procedure is too extensive to be considered in patients with microscopic duodenal involvement from gastric cancer, and its indication could only be defined in well-designed, prospective studies.

With regard to our data on recurrence sites, which were not statistically significant because of the small number of patients involved, only a few cases of local or anastomotic site recurrence were observed. In particular, three of the eight patients with esophageal margin infiltration showed anastomotic recurrence, one had local recurrence, and four had carcinosis. Furthermore, we observed a similar frequency of local recurrence, diffuse carcinomatosis, and distant metastases in the infiltrated duodenum subgroup.

One of the limitations of our study was the lack of a control group with RLI submitted to reoperation, which could have provided useful information about the benefit of retreatment. Although it also is clear that the relatively small number of patients evaluated would not lead to results with a high statistical power, we nevertheless

believe that our experience provides an overall clinical picture of the natural history of microscopic residual resection-line tumor in patients with gastric cancer.

Conclusions

Microscopic RLI after gastrectomy is an independent prognostic factor associated with poor long-term survival. Extemporaneous histological examination of the margin is always advisable in T4 or diffuse types of gastric cancer. Therefore, reintervention should be considered in T2 patients. Patients with EGC generally have a good prognosis and surgeons should carefully consider the operative risks associated with retreatment. Furthermore, the low incidence of postoperative complications in patients with RLI enables palliative surgery to be performed, even on potentially infiltrated tissue, when an improvement of symptoms is feasible.

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