

Does Resection Line Involvement Affect Prognosis in Early Gastric Cancer Patients? An Italian Multicentric Study

Paolo Morgagni, MD,¹ Domenico Garcea, MD,¹ Daniele Marrelli, MD,² Giovanni de Manzoni, MD,³ Giovanni Natalini, MD,⁴ Hayato Kurihara, MD,⁵ Alberto Marchet, MD,⁶ Giovanni Vittimberga, MD,¹ Luca Saragoni, MD,⁷ Franco Roviello, MD,² Alberto Di Leo, MD,³ Francesco De Santis, MD,⁴ Valerio Panizza, MD,⁵ Donato Nitti, MD⁶ for the Italian Research Group for Gastric Cancer Study (G.I.R.G.C.)

¹Department of General Surgery, Morgagni-Pierantoni Hospital, Via Forlanini 34, 47100, Forlì Italy

²Surgical Oncology Unit, University of Siena, Siena, Italy

³First Division of General Surgery, University of Verona, 37126 Verona, Italy

⁴Department of Surgery, Todi-Marsciano General Hospital, Todi, Italy

⁵Department of Surgery, Luigi Sacco Hospital, University of Milan, via GB Grassi 74, 20157 Milan, Italy

⁶Second Surgical Clinic, University of Padua, via 8 Febbraio 2, 35122 Padua, Italy

⁷Pathology Unit, Morgagni-Pierantoni Hospital, Via Forlanini 34, 47100 Forlì, Italy

Abstract

Background: Resection line involvement has been indicated as an important prognostic factor for gastric cancer. Its late detection renders the choice of treatment difficult for surgeons.

Materials and Methods: We describe the multicenter experience of a group of 11 patients with early gastric carcinoma (EGC) and positive resection confirmed at histological examination who did not undergo surgical retreatment for reasons of associated disease, surgical considerations on duodenal stump, or patient refusal.

Results: The gastric margin was involved in 4 patients, and 7 patients had duodenal resection line involvement. No surgical complications or postoperative deaths were observed. Five and 8-year survival was 100% and 86%, respectively. The only patient who relapsed did not have lymph node involvement and died from liver metastases, without local recurrence.

Conclusions: It is sometimes difficult to accurately define the resection line in gastric cancer surgery, especially in the early stages of disease, but because of the strongly negative prognostic value of an infiltrated margin, frozen sections are recommended if neoplastic invasion is suspected and a new resection is always recommended if possible. Nevertheless, the good prognosis of resected EGC patients with resection line involvement must be considered before submitting patients with associated diseases to radical surgical retreatment.

Table 1.
Patients with resection line (RL) involvement as a function of clinical pathological factors

T	N	M	Lymph-adenectomy	Resected lymph nodes	N+	Lauren's type	Macroscopic type	Size	Positive RL	Duodenal stump	Status	Follow-up (months)
1a	0	0	D1	15	0	INT	I	65	D	Manual	Alive	136
1a	0	0	D1	13	0	INT	III	10	G	Manual	Alive	115
1a	0	0	D2	20	0	DIF	III	30	D	Staple	Alive	39
1b	0	0	D2	20	0	DIF	III	50	D	Staple	Alive	60
1a	0	0	D1	11	0	INT	IIC	12	D	Staple	Alive	124
1a	0	0	D1	15	0	INT	III	20	G	Staple	Alive	127
1b	0	0	D1	13	0	DIF	I	10	G	Staple	Alive	99
1b	1	0	D1	6	2	DIF	IIC	25	D	Staple	Alive	24
1a	1	0	D2	62	3	DIF	IIC	10	G	Staple	Alive	50
1b	1	0	D1	17	3	DIF	III	35	D	Manual	Alive	133
1a	0	0	D2	10	0	DIF	IIB	10	D	Staple	Dead	77

Surgery is widely accepted as the first-line treatment for gastric cancer, and curative resection is the only therapy offering hope of a cure.

One of the most critical 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 the histotype and macroscopic type, being wider in non-differentiated and infiltrating carcinomas.

An infiltrated resection line (RL) in patients undergoing radical surgery indicates a significantly poorer outcome.^{1,2} However, in the event of delayed detection of margin infiltration, further surgery, even when possible, is not always advisable,^{1,3} and some authors report that retreatment may modify prognosis only in the absence of lymph node metastases.⁴

A singular setting is that of patients with early gastric cancer (EGC) and positive resection line is subsequently found. We describe our experience of 11 such patients who did not undergo surgical retreatment.

MATERIALS AND METHODS

From 1988 to 2001, 2740 patients underwent resection for gastric cancer in six Italian Surgical Units. One hundred and fifty-eight (5.7%) patients in whom a positive resection line was histologically confirmed were not surgically retreated for reasons of age, associated disease, or patient refusal. The present study evaluates 11 patients in this subgroup with mucosal or submucosal cancer and resection line involvement, representing 1.7 % of the 644 EGC patients operated on during this period (EGC constituted 23.5% of all the surgically treated gastric cancers).

Subtotal gastrectomy was performed for tumors located in the lower two thirds of the stomach, with removal of the greater and lesser omentum. This was associated with en-bloc resection of perigastric lymph nodes or dissection of first and second level lymph nodes, in accordance with Japanese Gastric Cancer Association (JGCA) recommendations.⁵ When possible, a macroscopic distance of more than 2 cm between the tumor and the upper resection margin was maintained. Hand-sewn anastomosis was generally performed, but staple guns were sometimes used for duodenal stump.

Histological type was based on Lauren's classification.⁶ Death from postoperative complications was considered a hospital mortality. Patients were seen every 6 months for the first 5 years and once a year thereafter. Routine follow-up tests included abdominal scan, chest x-ray, and serum CEA/CA19-9 levels. Gastroscopy was performed 6 months after surgery and once a year thereafter. Survival was calculated from the date of surgery, and only cancer-related mortality was taken into account. Death from other causes was considered censored.

Survival was analyzed using the Kaplan-Meier product limit method.⁷

RESULTS

Eleven patients presented EGC and resection line involvement. Six patients were males and 5 were females, with a median age of 62.6 years (range: 49–75 years). All lesions were sited in the lower two thirds of the stomach and patients underwent subtotal gastrectomy with BII reconstruction (8 patients) or Roux-en-Y reconstruction (3 patients). The clinical pathological characteristics of these patients are summarized in Table 1.

Table 2.
Patient survival

	No. of patients	No. of deaths	5 year survival (95% CI)	8 year survival (95% CI)
T1 (N0+N1)	11	1	100	86 (60–100)
T1N0	8	1	100	83 (54–100)
T1N1	3	0	100	100

All patients were treated with curative resection intent, and microinvolvement of the resection line, not suspected at the time of surgical treatment, was subsequently histologically confirmed. Four patients presented a positive proximal resection line, and 7 had distal infiltration. Staple guns were used to resect the duodenum in 5 of the patients in the latter group. Specimens were always carefully opened by the surgeon, who removed the staple line to verify the macroscopic distance of the resection margin from the tumor.

Six patients operated on before the D2 procedure became standard practice in all our centers or elderly patients with associated diseases were subjected to D1 lymphadenectomy, whereas the remaining 5 patients underwent D2 lymphadenectomy, with a median number of 12.5 (range: 6–20) and 23 (range:15–52) lymph nodes dissected for D1 and D2 procedures, respectively. Three patients presented first level lymph node metastases according to JGCA criteria and were classified as N1 according to the new TNM classification. None of the patients had second level lymph node metastases.

The median lesion size was 25.1 mm (range: 10–65 mm). Seven patients presented mucosal EGC and 4 had submucosal invasion. With regard to macroscopic type, 2 patients had type I EGC, 4 had type II (1 type IIb and 3 type IIc), and 5 had type III.

On the basis of Lauren's classification, 4 patients presented intestinal-type adenocarcinoma and 7 had diffuse-type carcinoma.

The gastric margin was involved in 4 patients and 7 had duodenal resection line involvement. No surgical complications or postoperative deaths were observed.

Surgical retreatment was not considered for these patients for reasons of age, associated diseases, patient refusal or, in the event of an infiltrated duodenal margin, because duodenocephalus pancreatectomy as an extension of the original resection was not considered achievable. In the absence of surgical alternatives, 3 of the 11 patients subsequently underwent complementary chemotherapy, decided upon in their own center and not based on standard protocols, because the impact of a

positive resection margin on the prognosis of EGC patients was still not fully understood.

The median follow-up was 93.4 months (range: 24–151 months), and no patients were lost to follow-up. One of the 11 patients developed liver metastases and died 77 months after surgery. None of the remaining 10 patients presented relapse.

Five-year and 8-year survival was 100% and 86% (95% CI = 60–100), respectively (Table 2). The only patient who relapsed did not have lymph node metastases, whereas 3 patients with N1 disease showed an 8 year survival of 100%.

DISCUSSION

A positive resection line has been reported in varying percentages (0.8%–10.2%) of surgically treated gastric cancer patients.^{1,8,9} The impossibility of manual palpation of the lesion in EGC renders the determination of resection line more difficult. In recent years, chromoendoscopy and magnifying endoscopy have led to a more accurate localization of the lesion; when this is near the surgical resection line, the use of an extemporaneous histological examination is always advisable.

Several studies have evaluated the extension of gastric cancer invasion when the esophageal or duodenal margin is involved to guarantee optimal surgical management. A 2 cm esophageal resection from the gastric cancer margin is generally considered safe when a histologically well-defined lesion is resected, but when undifferentiated tumor invasion is present, 4–7 cm of the esophagus may have to be resected¹⁰ because manual palpation or frozen sections may not suffice to detect the presence of skip submucosal foci.¹¹

Duodenal invasion, when present, generally extends about 2 cm beyond the pyloric ring, but a 4 cm invasion through submucosal or subserosal layers or lymphatics has also been described.^{11–14}

Clinical pathological factors that usually indicate a risk for positive resection line are macroscopic Borrmann

types III and IV,⁹ T and N stage, location, and histologically nondifferentiated tumors.^{1,14}

With regard to EGC macroscopic types, all patients with a positive resection line described by Fujimoto had excavated or superficial-type lesions.⁹ Huguier *et al.*, described 4 EGC patients with macroscopic flat-type tumors and RL involvement.¹⁵ Yamaguchi, commenting on the study of Hugier *et al.*, suggested that the use of routine frozen sections might be indicated only in flat-type EGC tumors.¹⁵ Conversely, we observed all macroscopic types except IIa, with a high prevalence of excavated lesions.

Resection line involvement is generally reported to cause high surgical morbidity, and Keighley *et al.*, in their 1981 paper, reported 4 anastomotic leakages in 4 total gastrectomies.¹⁶ Recently, Chan *et al.*, reviewing 137 total or proximal gastrectomies, reported an 18.2% incidence of positive esophageal margins but did not observe an increased morbidity or anastomotic leak incidence compared to patients with negative margins.¹⁷ Our experience confirms these data, and no surgical complications were observed in any of the 11 EGC patients with RL involvement.

Microscopic residual tumor, which is generally described as a significant prognostic factor,^{1,2,18} indicates poor survival, and several authors have proposed surgical retreatment when achieving a tumor-free resection line seems realistic.^{1,4} Other authors such as Papanichou *et al.*, after reporting unsatisfactory results from additional treatment, suggested monitoring these patients in order to treat only anastomotic recurrence.³ Cascinu *et al.*, comparing resection line-positive and negative patients treated with D1 lymphadenectomy, observed lower survival only in N0 patients with RL involvement and concluded that surgical retreatment may be indicated only in this subset of patients.⁴ Kim *et al.*, in a study of 47 resected patients with positive margins, maintained that this negative prognostic factor lost its significance in those who underwent D2 or D3 lymphadenectomy. Examining this subset, they found that the survival of patients who had ≤ 5 positive lymph nodes was significantly worsened by a microscopically involved margin and concluded that outcome is determined by the presence of >5 lymph nodes rather than by macroscopic residual cancer at the margin.¹⁹ Although D2 dissection is the standard surgical treatment for EGC in all our centers, in this retrospective study, 6 D1 and 5 D2 lymphadenectomies were performed for reasons explained previously.

With regard to EGC, Nakamura *et al.*, observed a good survival rate in 29 EGC patients and concluded that po-

sitive margins in EGC were of insignificant prognostic value.¹⁸ Our results confirm these findings and, despite the very modest survival rates in the literature for resected advanced gastric cancer patients with RL involvement, which our experience shows to be 9% at 5 years (95% CI 4–14) and 7% at 8 years (95% CI 2–11), we observed a 5 and 8 year survival of 100% and 86%, respectively, for the EGC patient subset in the present study. These rates are similar to those reported in a previous multicenter study of 584 patients in whom 5 year survival was 95% for N0 patients and 77% for N1 patients.²⁰ Furthermore, in 3 of our patients evaluated as N1 on the basis of both JGCA criteria and the 1997 TNM classification, prognosis was not influenced by the presence of positive lymph nodes and they were alive and disease-free at a median follow-up of 69 months.

Only 1 of the 11 EGC patients presented distant disease recurrence and subsequently died during the follow-up period, whereas the remaining 10 did not show any signs of relapse. It is somewhat difficult to evaluate these data, especially with regard to the increased risk of relapse observed in patients undergoing endoscopic resections, when complete or en-bloc resection is not guaranteed. It is not known whether the use of staple guns or a more extended lymphadenectomy or deeper surgical margins than those used for endoscopic resection could lead to better results in surgically treated EGC patients, and further studies investigating this issue are warranted.

In conclusion, resection line involvement after gastrectomy generally indicates a very poor prognosis and extemporaneous histological examination of the margin is always advisable for suspicious lesions. A new margin resection is always advisable, when possible, to ensure optimal results. Notwithstanding, the 11 EGC patients considered in the present study presented good survival at 5 and 8 years. Furthermore, no postoperative complications or mortality were observed. The decision to submit this category of patients to surgical retreatment, should, however, take into account the above-mentioned observations.

REFERENCES

1. Songun I, Bonekamp JJ, Hermans J, *et al.* Prognostic value of resection line involvement in patients undergoing curative resection for gastric cancer. *Eur J Cancer* 1996;32A:433–437.
2. Hallissey MT, Jewkes AJ, Dunn JA, *et al.* Resection-line involvement in gastric cancer: a continuing problem. *Br J Surg.* 1993;80:1418–1420.

3. Papachristou DN, Agnanti N, D'Agostino H, *et al.* Histologically positive esophageal margin in the treatment of gastric cancer. *Am J Surg* 1980;139:711–713.
4. Cascinu S, Giordani P, Catalano V, *et al.* Resection-line involvement in gastric cancer patients undergoing curative resections: implications for clinical management. *Jpn J Clin Oncol* 1999;29:291–293.
5. Japanese Research Society for Gastric Cancer. Japanese classification of Gastric Carcinoma (1st English edn), Tokyo, Kanehara, 1995.
6. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;64:31–349.
7. Kaplan EL, Meier P. Non parametric estimation from incomplete observation. *J Am Stat Assoc* 1958;53:457–481.
8. Sano T, Mudan SS. No advantage of reoperation for positive resection margin in node positive gastric cancer patients? *Jpn J Clin Oncol* 1999;29:283–284.
9. Fujimoto S, Takahashi M, Mutou T, *et al.* Clinicopathologic characteristics of gastric cancer patients with cancer infiltration at surgical margin at gastrectomy. *Anticancer Res* 1997;17:689–694.
10. Tsujitani S, Okuyama T, Orita H, *et al.* Margins of resection of the esophagus for gastric cancer with esophageal invasion. *Hepatogastroenterology* 1995;42:873–877.
11. Yokota T, Kunii Y, Teshima S, *et al.* Clinicopathologic prognostic features in patients with gastric cancer associated with esophageal or duodenal invasion. *Ups J Med Sci* 1999;104:217–230.
12. Kakeji Y, Tsujitani S, Baba H, *et al.* Clinicopathologic features and prognostic significance of duodenal invasion in patients with distal gastric carcinoma. *Cancer* 1991;68:380–384.
13. Kakeji Y, Korenaga D, Baba H, *et al.* Surgical treatment of margins of resection in gastric carcinoma and duodenal invasion. *J Surg Oncol* 1995;59:215–219.
14. Bozzetti F, Bonfanti G, Bufalino R, *et al.* Adequacy of margins of resection in gastrectomy for cancer. *Ann Surg* 1982;196:685–690.
15. Huguier M, Ferro L, Barrier A. Early gastric carcinoma: spread and multicentricity. *Gastric Cancer* 2002;5:125–129.
16. Keighley MR, Moore J, Lee JR, *et al.* Perioperative frozen section and cytology to assess proximal invasion in gastroesophageal carcinoma. *Br J Surg* 1981;68:73–74.
17. Chan WH, Wong WK, Khin LW, *et al.* Significance of a positive oesophageal margin in stomach cancer. *Aust N Z J Surg* 2000;70:700–703.
18. Nakamura K, Ueyama T, Yao T, *et al.* Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* 1992;70:1030–1037.
19. Kim SH, Karpeh MS, Klimstra DS, *et al.* Effect of microscopic resection line disease on gastric cancer survival. *J Gastrointest Surg* 1999;3:24–33.
20. Folli S, Morgagni P, Roviello F, *et al.* Risk factors for lymph node metastases and their prognostic significance in early gastric cancer (EGC) for the Italian Research Group for Gastric Cancer (IRGGC). *Jpn J Clin Oncol* 2001;31:495–499.