Original article

Early gastric carcinoma: spread and multicentricity

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Abstract

Background. In early gastric carcinoma (EGC), after subtotal gastrectomy, recurrent lesions limited to the gastric remnant are the cause of about 20% of deaths from recurrence. Therefore, it has been suggested to perform total gastrectomy in all cases of EGC.

Methods. We studied a case series of 82 consecutive patients operated on for an EGC, with a mean follow-up time of 72 months (range, 1–120 months). Subtotal distal gastrectomy was performed in 61 patients, total gastrectomy in 15, and other procedures in 6. Outcome measures were recurrence and causes of mortality, focusing on patients with resection line involvement and multifocal lesions.

Results. EGC was limited to the mucosa in 43 patients and had invaded the submucosa in 39. Ten patients had a lymph node involvement. In 4 patients having had a subtotal gastrectomy, resection line involvement was detected. In 3 patients, the involvement was detected preoperatively on frozen sections, and a re-resection was performed. In the fourth patient, the involvement was detected postoperatively, but follow-up endoscopies failed to show any residual tumor. In 17 patients, multifocal lesions were observed. No recurrence was observed in the gastric remnant of patients having undergone a subtotal gastrectomy.

Conclusion. In distal EGC, a subtotal gastrectomy may be performed under two conditions: (1) careful endoscopic and peroperative examination of the upper part of the stomach to detect multifocal lesions and (2) a systematic frozen-section assessment of the resection margin to avoid inadequate resection.

Key words Gastric carcinoma · Surgery

Introduction

In Western countries, the incidence of early gastric carcinoma (EGC), although steadily increasing, is far lower than in Japan. In Europe and in the United States, among patients presenting with gastric cancer, the rates of EGC vary from 8% [1–3] to 21% [4–7]. The prognosis is remarkably good, with 5-year survival rates of 80% or more [3,5–7], most patients dying either from benign causes or from malignant disease of other organs [9–12]. In multivariate analysis, lymph node metastases is the only significant prognostic factor for recurrence of EGC [7,12,13]. In patients with lymph node metastases, deaths are mainly due to lymphatic, hepatic, or peritoneal metastases. However, after subtotal gastrectomy, about 20% of deaths are caused by recurrent lesions limited to the gastric remnant [1,8,9,12,14]. Therefore, total gastrectomy has been proposed in all patients suspected of having EGC [7,15]. To the contrary, there are trends toward endoscopic resections, and a major effort is being made to identify patients suitable for a limited resection [16].

The aim of this study was to emphasize and to discuss two causes of missing a chance of cure in patients with an EGC: the presence of a positive margin or multifocal lesions.

Patients and methods

From May 1972 through June 1999, 547 consecutive patients underwent resection for gastric carcinoma at the Department of Digestive Surgery, Tenon University Hospital, Paris. EGC was found in 82 patients (15%; 95% confidence interval [CI], 12%–18%). There were 44 men and 38 women, with a mean age of 64 years (range, 24–84 years). Preoperative symptoms were epigastric pain ($n = 58$), nausea or vomiting ($n = 12$), upper-third bleeding ($n = 6$), dysphagia ($n = 2$), and

dyspepsia ($n = 4$). Weight loss was observed in 22 patients. The duration of the preoperative symptoms was 8.3 months (range, 16–48 months). Thirty-six patients (44%; 95% CI, 33%–55%) had a previous history of ulcer, gastric in 17 patients, and duodenal in 19. According to the classification of the American Society of Anesthesiology (ASA), 56 patients were classified as ASA I or II, 21 patients as ASA III, and 5 patients as ASA IV. All the patients underwent a preoperative gastroscopy with multiple biopsies.

The lesion was located in the lower third of the stomach in 44 patients, in the middle third in 25, in the upper third or in the gastric cardia in 11, and in a gastric stump in 2. At operation, the gastric wall was thickened in 35 patients, and normal in 37 patients. In 6 of these latter 37 patients, the tumor diameter was over 2 cm. Subtotal distal gastrectomy was performed in 61 patients, total gastrectomy in 15, subtotal proximal gastrectomy in 3, local excision in 1, and resection of a gastric stump in 2. All the patients had an R0 resection with no macroscopic residual tumor. A D2 lymphadenectomy was performed in 15 patients from 1991 through 1999 and a D1 lymphadenectomy in others. No patient received adjuvant therapy. Percentages were compared with the Fischer exact test. Survival curves were constructed using the Kaplan-Meier method. Mean follow-up time was 72 months (range, 1–120 months).

Results

Pathological findings are reported in Table 1. The mean size of the tumor was 2.3 cm (range, 0.8–12 cm). EGC was limited to the mucosa in 43 patients (52%; 95% CI, 49%–55%), and had invaded the submucosa in 39 patients. A lymphatic or a venous invasion was observed in 4 patients, all having a tumor invading the submucosa. Lymph node metastases were observed in 10 patients, 9 having a tumor invading the submucosa. Carcinoma was well differentiated in 42 patients (51%) and moderately or poorly differentiated in 40 patients (49%), with signet-ring cells in 26 patients.

In 4 patients, the margin of resection was histologically positive (7% of the subtotal gastrectomies). In 1

patient, resection line involvement was detected on postoperative histological examination. The patient was followed for 7 years without further treatment and there was not recurrence. In the 3 other patients, positive margins were found at the time of operation on frozen examination, and the 3 patients underwent a re-resection with another margin histological control. In 17 patients, multifocal lesions were observed (21%; 95% CI, 13%–30%). In 48 patients, intestinal metaplasia was seen on the resected specimen (59%; 95% CI, 48%–70%). Correlations between involvement of the resection line after subtotal gastrectomy, multifocal lesions, and the type and differentiation of the tumor are reported in Tables 2 and 3. The 4 patients with a first resection line involvement had a flat type. Multifocal

Table 2. Correlation between resection line involvement, type [16], and differentiation of the cancer

	Resection line	
	Normal ($n = 78$)	Invaded ($n = 4$)
Type [17]		
Protruded	20	0
Flat	33	4
Excavated	25	0
Differentiation		
Well	39	3
Moderately and poorly	39	1

Table 3. Correlation between resection line involvement, multicentricity, and type [16] and differentiation of the cancer

	Multicentricity	
	No ($n = 65$)	Yes ($n = 17$)
Type		
Protruded	15	5
Flat	27	10
Excavated	23	2
Differentiation		
Well	37	5*
Moderately and poorly	28	12*

* $P < 0.05$

Table 1. Histological findings

	Lymphatic or venous invasion		Lymph node involvement	
	No ($n = 78$)	Yes ($n = 4$)	No ($n = 72$)	Yes ($n = 10$)
Degree of penetration				
Mucosal ($n = 43$)	43	0	42	1
Submucosal ($n = 39$)	35	4	30	9

Fig. 1. Survival rates. Dashed line, Survival rates related to early gastric carcinoma (EGC); continuous line, overall survival rates

lesions were observed more often in moderately or poorly differentiated tumors (12/48; 25%) than in well-differentiated tumors (5/37; 14%; $P < 0.05$). Sixteen of the 17 patients with multifocal lesions underwent a subtotal gastrectomy, and 1 patient underwent a total gastrectomy. There were 3 postoperative deaths (1 acute pulmonary edema, 1 mesenteric infarction, and 1 hemoperitoneum).

The overall 5-year survival rate was 77% (Fig. 1). Eighteen patients died of non-related causes, including 3 malignancies, while 3 patients died of metastases of the EGC. One had a mucosal carcinoma without lymph node metastases and 2 had an EGC invading the submucosa with lymph node metastases. The specific 5-year survival rate was 90%. No recurrence was observed in the patient with the involvement of the resection line detected on postoperative histological examination. Similarly, none of the 16 patients with multifocal lesions who underwent a subtotal gastrectomy developed recurrence in the gastric remnant.

Discussion

The frequency of EGC in the present series (15%), and the demographics, did not differ from those of other European studies [18,19]. Pathological findings were quite similar to those of previously published reports with regard to depth of infiltration, lymph node involvement, or histological differentiation [6,8,19,20].

The duration of symptoms before diagnosis tended to be longer than in advanced carcinoma [19]. A previous history of peptic ulcer is not uncommon (44% in our

series). This may explain the duration of symptoms before diagnosis with the slow growth of EGC. Tsukuma et al. [21] followed 56 patients having an EGC proven on biopsies in whom surgical resection had been delayed or not conducted. Of these, 27 progressed to advanced cancer. The median duration of EGC before it became advanced was estimated to be 37 months. This suggests that EGC undergoes a period of slow growth before becoming advanced. Therefore, it would be more relevant to use the term "superficial carcinoma" rather than "EGC" [22].

We performed D2 resection, taking into account the retrospective comparative results of Maruyama et al. [23] and D1 since the results of the Dutch randomized study [24].

Spread

Endoscopically, despite extensive preoperative examination, determination of the tumor margin is impossible in half of the cases [15]. Japanese authors have suggested the performance of contrast endoscopy, using dye-spraying techniques, and endoscopic clipping of the gastric mucosa by biopsies at intervals of 1 cm [15]. However, the extent of resection is usually decided on clinical grounds by the surgeon at operation. Nevertheless, surgeons are not good at determining the adequacy of resection required to achieve microscopic clearance within the stomach [1,2]. At operation, the tumor margin of the flat type of EGC was so indistinct that the resection line was often difficult to determine. Surgeons had difficulty palpating the tumor and, therefore, in guessing the location of the proximal margin. In the present series, of the 64 patients who underwent a subtotal gastrectomy, the first resection line was invaded in 4. Kasakura et al. [15] have suggested that all patients must undergo total gastrectomy. However, the low rate of resection-line involvement suggests that subtotal gastrectomies should be performed under certain conditions, rather than total gastrectomies. As the resection margin is sometimes unclear and determination of the resection line is difficult, frozen-section examination of the margin of subtotal gastric resection seems to be a better method for avoiding both inadequate resection and unnecessary total gastrectomy. In our patients, additional resection was required in 3 patients after distal gastrectomy. Unfortunately, although it has been shown to be accurate and a valid approach, frozen-section assessment of the resection margin seems to be not widely used for EGC [2,15].

Multifocal carcinoma

The incidence of multiple cancer is higher in EGC than in more invasive cancer [25]. In the series reported by

Kodera et al. [25], of 271 EGCs, 84 (31%) were multiple. In other series, the rate of multifocal lesions was 9% (95% CI, 8%–10%) in six accumulated series [4,6,7,12,19,26]. The possibility of missing multiple foci, with increased risk of gastric remnant relapse, has been used as a rationale for routine total gastrectomy [7,15].

Nevertheless, after subtotal gastrectomy, the incidence of remnant cancer was not as high as expected, being 1.7% (95% CI, 0%–3.4%) in three accumulated European series, including the present study [5,18], and 1.1% in a Japanese study [9]. This might result from the fact that multifocal lesions are usually located in the same portion of the stomach [8] and that there is coresection of unrecognized lesions. Alternatively, it may be that those with distal multifocal lesions also had multifocal lesions in the stomach remnant, but, presumably, these did not result in recurrence [25]. In EGC located in the antrum, the risk of missing a proximal lesion is not high enough to justify a routine total gastrectomy [8]. However, multifocal lesions may be located in different portions of the stomach [7]. Therefore, it is important to evaluate the whole stomach with careful preoperative endoscopic examination, and examination during the operation, so as not to miss synchronous multiple cancer, mainly in the upper part of the stomach [8].

In conclusion, in EGC of the antrum, a subtotal gastrectomy can be performed once multifocal lesions of the upper part of the stomach are clearly excluded by endoscopy. Frozen section and negative margin control, especially in the flat type of ECG, are indicated in principle.

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Comment of two reviewers and the author's reply

Reviewer 1's comment

The major interest of this article is the precise diagnosis of tumor spread and multicentricity in gastric cancer surgery. The authors conclude that systematic frozen-section assessment of the resection line is necessary to avoid inadequate resection. I think that two points should be discussed in relation to their conclusion. First, in all the four cases with positive resection line involvement, the tumor was of the “flat type”. This means that systematic frozen-section might be omitted in tumors of

other types. Second, as the authors stated, multiple endoscopic biopsies are essential to determine the mucosal border of early gastric cancers. In other words, systematic step biopsies by trained endoscopists may be sufficient to determine the tumor spread in the majority of cases. Routine frozen-section assessment would be time- and cost-consuming, and we should narrow down the cases that truly require this examination.

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Author's reply

To Dr. T. Yamaguchi

We thank Doctor T. Yamaguchi for his comments. We agree that our results suggest the performance of frozen-section assessment of the resection line only in the flat type. However, in our series, the number of cases was small, and macroscopic configurations, such as mucosal fold patterns, are sometimes subjective [1]. Step endoscopic biopsies should be used to determine the tumor spread. Nevertheless, it is sometimes difficult to correlate the sites of biopsies and the level of the resection line.

Michel Huguier
On behalf of the authors
(L. Ferro, A. Barrier)

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Reviewer 2's comment

The article of Huguier and colleagues is an interesting Western report focused on multicentricity in early gastric cancer. The number of cases is quite high for a Western institution and the mean follow-up is very long. This topic is still matter of controversy, and I have some comments and questions for the author.

1. I think that it would be very important to know some data regarding the precise location of the secondary lesions in relation to the primary lesions, especially in the patients with the primary lesion located in the lower third of the stomach.
2. Three of your patients died of metastases. Could you please specify the type of recurrence in these patients?

3. What was the correlation between resection line involvement and multicentricity?
4. In your discussion you suggest the routine use of frozen sections of the resection margin after subtotal gastrectomy. In the recent literature there are some interesting studies on the use of intraoperative ultrasonography in the examination of the resection line [1,2]. What do you think about the use of this technique in the assessment of the resection line?

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Author's reply

To Professor C. Cordiano

We thank Professor C. Cordiano for his comments.

1. Our study was a retrospective one, and, unfortunately, we cannot specify the exact location of the secondary lesions. The rates of about 10% of multifocal carcinomas and less than 2% of recurrences after subtotal gastrectomy suggest that secondary lesions are usually close to the primary.
2. The metastases in the three patients were: peritoneal in two patients, and brain in one patient.
3. The four cases with resection line involvement were not multicentric.
4. We have no experience of intraoperative ultrasonography in early gastric carcinoma.

In the studies of Kodama et al. and De Manzoni et al., the aim was to assess depth of tumor in the gastric wall and lymph-node or hepatic metastasis. Nevertheless, it is an interesting suggestion to assess mucosal and submucosal spread in early gastric carcinoma using intraoperative ultrasonography to safely determine the resection line.

Michel Huguier
On behalf of the authors
(L. Ferro, A. Barrier)