



## Early Gastric Cancer: Ten Years of Experience

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**Abstract.** Gastric cancer is a disease in which the main treatment is surgical extirpation. The modifications introduced in the surgical treatment over the last decades were accompanied by a clear increase of survival, which reaches global values of 61% at 5 years in Japan. One of the reasons that contribute to this improvement is early diagnosis of the lesions. In the period between January 1, 1990 and December 31, 1999 662 patients with gastric adenocarcinoma were treated in the Service of Surgery 1 of our hospital; 110 were refused surgical treatment. Of the resected patients, 91 (21.4%) were classified as early gastric cancer according to the definition of the Japanese Society of Digestive Endoscopy. There were 30 women and 61 men, with a median age of  $60.2 \pm 15$  years; 3 patients had a preoperative diagnosis of gastric ulcer; 2 others were operated without recent histology; and 1 patient was urgently resected for a bleeding ulcer. In all the remaining patients biopsy confirmed the presence of cancer (89%) or serious dysplasia (4.6%). The lesions had been distributed essentially in the medium 1/3 (48.3%) and distal 1/3 of the stomach.

Subtotal gastrectomy was accomplished in 48 patients, total gastrectomy in 40, total desgastrogastrostomy in 3, and in 9 patients the surgery involved the spleen (8 patients) and the spleen and tail of the pancreas in 1 patient. Lymphadenectomy was not performed in 5 patients, lymph nodes by the first lymph node barrier were removed in 25 patients and by the second barrier in 61 patients (67%). Median tumor size was  $26 \pm 1.8$  mm. The lesion reached the mucosa in 46 patients and the mucosa and submucosa in 45. In 6 patients the removed lymph nodes were microscopically invaded (6.7%). Five patients died (5.7%). The median follow-up of the patients is  $41 \pm 26$  months; 7 patients died (8.1%) during this period; 4 died unequivocally of disease progression. The median survival of patients was 85% at 5 years and 80% at 10 years. In our series, survival was affected by the presence of invaded lymph nodes, not by the penetration in depth of the lesion or the size of the tumor.

Modifications in the surgical treatment of gastric cancer introduced in the last decades brought a clear increase of 5-year survival. This effect became particularly visible in Japan, whose surgeons present survival rates at 5 years of 61% in comparison to Western authors, whose results are approximately 40%, considering only radical surgery [1, 2]. One of the reasons that also contribute to this survival increase is early diagnosis, which allows the detection of more carcinomas in initial phases. In Japan this subgroup constitutes 50%–55% of all operated patients, being a

common clinical entity, but the same does not happen in Europe [3] and in the United States [4], where the frequency of early diagnosis does not surpass 15%.

The classic definition of early gastric cancer, as established in 1962 (gastric adenocarcinoma confined to the mucosa or submucosa, independently of the presence of lymph node invasion), includes different stages of the disease under the same name, in view of which, theoretically, disease prognosis by stage should be different. An accurate staging of the disease is influenced by the extension of the lymphadenectomy performed, since it is known that lymph node involvement, even in the lymph node belonging to the second barrier, is not rare and is a determinant factor of the final prognosis.

The present study was conceived to determine incidence, presentation form and diagnostic methods, treatment, and long-term survival of a consecutive series of patients with early gastric cancer treated in our hospital during the last 10 years.

### Materials and Methods

Between January 1, 1990 and December 31, 1999 we treated, in Surgery 1 Service of Hospital Geral de Santo António, 662 patients with gastric adenocarcinoma. All the data from patients with gastric adenocarcinoma, operated or not, were prospectively registered in a specific computerized database on a personal computer. Follow-up data of all patients were obtained in follow-up consultation. Recurrences and probable cause of death were included only after direct contact with the patient or a member of the family.

All patients were followed every 3 months during the first 2 years of disease, and every 6 months between the 2nd and the 5th years. Starting from the 5th year, routine surveillance became annual. All the data obtained in consultation are reviewed monthly and registered. The data not obtained in consultation, relative to some patients treated in other institutions or deceased out of the hospital, are registered from an interview with a direct kinsman of the patients or from the data supplied by the other institution.

Complication and surgical mortality rates were studied by chi-

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square test and Fisher's exact test. The survival was calculated through the method of Kaplan-Meier. For the comparison of the curves of obtained survival, we used the log-rank test; the level of considered significance was  $p < 0.05$ .

## Results

### Presentation

One hundred ten patients (16.7%) were refused surgical treatment; the main reasons for this decision were the presence of disseminated disease at the time of the diagnosis and the lack of operability conditions because of very advanced age or of important biological limitations.

Five hundred fifty-two patients were submitted to laparotomy. Resection was possible in 425 patients (64% of all observed cases). Of this group, 91 cases (21.4%) are included in the definition of early gastric carcinoma, as established by the criteria of the Japanese Society of Investigation of Gastric Cancer [5]. The group comprised 30 women and 61 men, with a median age  $\pm$  S. D. of  $60.2 \pm 15$  years. The youngest patient was 25 years old and the oldest was 85. Twenty-two patients were older than 70 years and 6 older than 80 years.

The main complaints were epigastric pain (50%) and dyspeptic syndrome (34%). Three patients were admitted with upper gastrointestinal bleeding for gastric ulcers, 8 patients were diagnosed in routine endoscopy for vomiting, and 3 were operated for gastric ulcers. Forty-four patients had symptoms for less than 6 months, 24 for less than a year, and 23 patients had complaints for more than 12 months. Five patients had lost more than 10% of their body weight when admitted to hospital.

### Diagnosis

All patients had upper gastrointestinal endoscopy. Three patients were admitted after an episode of upper gastrointestinal bleeding for gastric ulcer. Other imaging methods for staging included computed tomography (CT) scan (55%) upper gastrointestinal barium examination (43%), and endoscopic ultrasonography (2.2%).

Preoperative histology of adenocarcinoma was obtained in 81 (89%) patients. In 4 (4.6%) the diagnosis was high grade dysplasia/in situ carcinoma. Three patients were operated without preoperative recent biopsies (one urgently resected due to bleeding gastric ulcer); 3 others had gastric ulcers that did not respond to medical treatment. The biopsies did not give malignancy indications.

### Surgical Treatment

Distribution of the lesions in the stomach is shown in Figure 1. The operations performed were dictated essentially by endoscopic location of the lesion and by the general condition of the patient. In relation to the stomach, subtotal gastrectomy was accomplished in 48 patients (52.7%), total gastrectomy in 40 (43.9%), and total desgastrogastrectomy in 3 patients (3.2%) with cancer in the gastric stump. Surgery involved the spleen in 8 patients (8.8%) and the spleen and tail of the pancreas in 1 patient (1.1%).

Lymphadenectomy was not performed in 5 patients, lymph nodes of the first barrier (perigastric lymph nodes) were removed

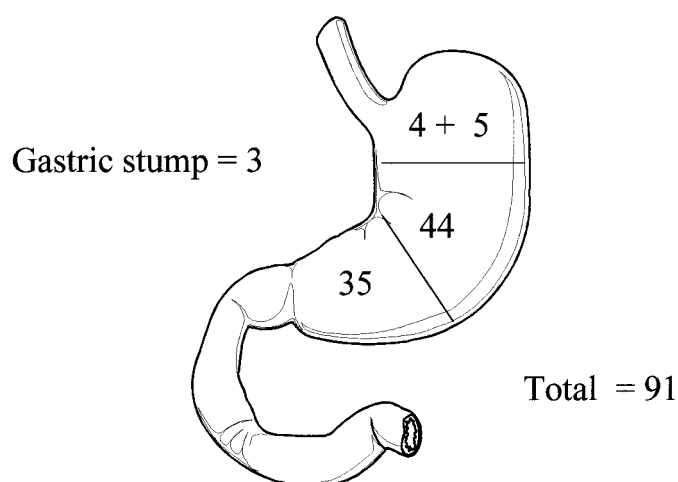


Fig. 1. Topographic distribution of lesions in the stomach.

in 25 cases (38.4%), mainly because of advanced age and related comorbidities; lymph nodes of the second barrier were removed in 61 patients (67%).

### Complications

The most frequent complications observed were cardiopulmonary, affecting about 25% of the patients of the series. Complications directly related to surgery are listed in Table 1. Complication rate showed no statistical significance when studied by chi-square test and Fisher's exact test.

Operative mortality rate observed at day 30 was 5.7% (5 patients). Three died of surgical complications, 1 of acute myocardial infarction, and 1 of pulmonary infection. Three patients died after total gastrectomy (7.5%) and 2 after subtotal gastrectomy (4.2%). These numbers also did not reveal statistical significance.

### Pathology

Most lesions were located in the body and antrum of the stomach. In 2 patients (2.2%) the existence of multicentric tumors was verified. The size of the lesions oscillated between a minimum of 3 mm and a maximum of 105 mm, with an average of  $26 \pm 1.8$  mm. The penetration of the lesions in depth, in the gastric wall, reached the mucosa in 46 patients (5 in situ carcinomas–5.5%) and the mucosa and submucosa in 45 patients (49.5%). The average number of lymph nodes was 13 by surgical specimen (range 0–47). Six patients had lymph node involvement (6.7%): in 4 the carcinoma invaded the mucosa and in 2 the mucosa and submucosal layer.

The majority of patients (89.1%) were in stage Ia of the classification pTNM. The final stages of all patients are shown in Table 2.

### Follow-up

Median follow-up  $\pm$  S.D. of the patients was  $41 \pm 26$  months (range 3–110). Eighty-one patients are alive and free from disease.

Seven patients died in this period (8.1%), 2 without evidence of

**Table 1.** Surgical complications related to procedure.

	Intraabdominal leaks	Intraabdominal abscesses	Peritonitis	Acute pancreatitis	Anastomosis stricture	Mortality
Subtotal gastrectomy ( <i>n</i> = 48)	1 <sup>a</sup>	2 <sup>b</sup>	1		2 <sup>c</sup>	4.2%
Total gastrectomy ( <i>n</i> = 40)	1 <sup>b,d</sup>	5		1 <sup>e</sup>		7.5%
Total desgastrogastrectomy ( <i>n</i> = 3)		1				0%
Total ( <i>n</i> = 91)	2 (2.2%)	8 (8.8%)	1 (1.1%)	1 (1.1%)	2 (2.2%)	5.7%

<sup>a</sup>Duodenal stump leakage.

<sup>b</sup>Esophagojejunal leakage: patient died of intraabdominal sepsis.

<sup>c</sup>Late complications: dilatation of the stricture was the only procedure.

<sup>d</sup>Patient died of intraabdominal sepsis.

<sup>e</sup>Patient died of multiorgan failure.

**Table 2.** Pathologic staging (pTNM) classification of the 91 patients.

T	N	M	Stage	Patients	%
Is	0	0	0	4	4.3
Is	1	0	IB	1	1.1
1	0	0	IA	81	89.1
1	1	0	IB	3	3.3
1	2	0	II	2	2.2

Is: in situ carcinoma.

disease and 1 of unknown cause. Four patients died unequivocally of progression of the disease: 2 by hepatic metastasis (at month 20 and 27), 1 for peritoneal carcinosis (at month 65), and 1 for disseminated disease with bone and soft tissue metastasis (at month 20). The crude survival of the series, including the operative mortality, was 85% at 5 years and 80% at 10 years. Statistical analysis demonstrated that there is no valid statistical relationship between survival and the parietal penetration of the tumor in the mucosa or mucosa and submucosa ( $p = 0.67$ ) or its superficial extension in the gastric epithelium ( $p = 0.38$ ) when we analyzed tumors of less than 2 cm and tumors of 2–4 cm. Patient survival was clearly affected ( $p = 0.001$ ) by the presence of invaded lymph nodes in the surgical specimen.

## Discussion

It is accepted by most authors that improvement of prognosis of gastric cancer is only possible if the diagnosis is made in early phases of the disease, which happens in Japan and other countries. An early diagnosis obtained with the wide and liberal use of endoscopy brings about the detection of larger number of early cancers, whose percentage can reach 17% to 27% of the total of the detected lesions [6, 7]. This number, elevated when Western countries are considered, is still substantially inferior to the numbers in the Japanese literature, in which about 50% of the patients operated have lesions confined to the mucosa and submucosa [8]. The rate of 21.7% in our series must, for this reason, be observed with caution, since our hospital is considered as a referral center for gastric surgery and the number is reported in relation to the total number of resected patients.

The distribution of the lesions by sex follows the pattern observed in another published series [9–11] being more frequently observed in men. The average age of patients is 3 years less than the median age of all our patients with gastric cancer (62.8 years), but age is clearly greater than the median age published in the Japanese series [12–14]. This fact is particularly important when

we consider morbidity and mortality. Also important in our series is the fact that the majority of our patients are in the 7th and 8th decades of life.

All patients had, before surgery, at least one endoscopy; malignant disease was diagnosed by biopsy in 89%. One patient was urgently operated due to bleeding gastric ulcer, and 2 were operated without recent histology in the context of benign disease, after an episode of bleeding. In 3 patients we performed surgery for gastric ulcer and cancer was a microscopic diagnosis.

In the staging of the remaining patients, diagnosis methodology was guided essentially for the elimination of distant metastasis by CT scan or abdominal ultrasonography; we did not have access to endoscopic ultrasonography in the referred period.

Surgical treatment followed the same guidelines that we use in gastric cancer surgery: resection with proximal safety margin of 7–8 cm with lymphadenectomy for the second barrier lymph nodes, just as defined by the Japanese authors. The topography of the lesion, patient's age, and associated illness conditioned the extension of gastric resection, as well as lymphadenectomy in some cases. Multicentricity of the tumor, which can reach a prevalence of 9% [15] or higher, has been used as argument, in some series, for total gastrectomy. The incidence of synchronous lesions in our series was 2 patients (2.2%), and they were found in the operative specimen, after total gastrectomy; on the other hand, careful follow-up of the patients with subtotal resections through endoscopy did not demonstrate the appearance of metachronous tumors in the remaining gastric stump.

No patients had microscopic invasion of the resection margin. Although it is debatable which margin is necessary in the treatment of early lesions, we argued for margins of 7–8 cm because of the intraoperative difficulty of location of the lesion by the surgeon (because it cannot be palpated), our lack of previous knowledge in relation to the lesion's parietal penetration, and the possibility of the lesion's proximal microscopic extension [16].

Incidence of lymph node metastasis in early cancer reaches different values in the literature, being usually greater than 10% [12, 17]. Extension of lymphadenectomy in these lesions is a controversial issue, the Western school, generally speaking, more conservative and adept at limited resection (first lymph node barrier-D1), and the Japanese school adept at more aggressive resection usually for second lymph node barrier (D2 type). On the other hand, the relationship is known between transmural invasion and the rate of positive lymph nodes: 0%–11% for mucosa invasion and 2%–29% for the mucosa and submucosa [12, 17, 18]. Knowing that the presence of positive lymph nodes is a main determinant of gastric cancer prognosis and having not observed,

in our patients, an increase of mortality related to second barrier lymphadenectomy (results not published), we think we should keep the same type of lymph node resection used for all gastric cancers.

Lymphadenectomy by the second barrier was performed in 67% of the patients. Six patients had positive lymph nodes (6.7%). In 4 the lesion just reached the mucosa and in the remaining ones the mucosa and submucosa. In 5 of these patients a D-2 type lymphadenectomy was used, and 2 patients had positive lymph nodes in the common hepatic artery group. In 5 of these patients the relation between invaded/resected lymph nodes is greater than 0.2, which constitutes a bad prognostic factor [19]. The factors mentioned above corroborate our position in favor of a wide lymph node clearance, which whenever possible should be of the D-2 type; some Japanese authors believe that this practice can have a beneficial effect in the survival of patients with tumors reaching the submucosa [20, 21].

The main morbidity of our patients involved cardiopulmonary problems (25% of the patients, unpublished results), which are essentially attributable to the advanced age of the group. In relation to surgical complications the most prevalent was intra-abdominal fluid collection (8.8%), sometimes secondarily infected, which led to surgical or ultrasonography-oriented drainage. The mortality observed (5.7%) was due to the evolution of preestablished diseases in 2 cases and in 3 of complications directly related to the surgery performed; these patients were in their 7th, 8th, and 9th decades of life. An analysis of the type of operation performed (total gastrectomy/subtotal gastrectomy) did not demonstrate differences in mortality between the two operations.

No adjuvant therapy was performed in patients that survived the surgery, whether or not there were invaded lymph nodes or parietal invasion of the tumor.

Our experience does not include endoscopic mucosectomy, endoscopic laser ablation, or atypical gastric resection by video-laparoscopy. The first technique provides extremely trustworthy diagnosis before surgery, which was not possible in our hospital for lack of technical means (endoscopic ultrasonography). This technique became available starting in January 2000. For the same reason we were previously unable to provide mini-invasive surgery, but we can now use it in patients of high surgical risk, with lesions of small metastatic potential and in certain locations where the extirpation of the entire gastric wall is contemplated [27]. Destroying the tumor by laser has the problem of not providing tissue for the pathologist, which makes the method a palliative one.

Crude survival of our patients, 85% at 5 years, 80% at 10 years, is inferior to the 90%–100% survival mentioned by Japanese authors [12, 13, 17, 22], but it is comparable to values of 70%–90% at 5 years and 60%–80% at 10 years presented by Western authors [16, 23, 24]. We think that the differences may be caused by a larger surgical mortality in the Western world because of older patients with a smaller performance index. Once statistical correction of these factors is made, we think that, considering the same type of resection and lymphadenectomy, differences among Japanese and Western series will greatly diminish.

Routine follow-up of these patients includes once-a-year endoscopy in cases of subtotal resection, and radiologic (CT, US) and other investigations adapted to the complaints or the clinical picture of the patient. Synchronous or metachronic neoplasias, in the gastric stump or in other organs, are frequently mentioned in

the literature [16, 25, 26] and could be responsible for a high mortality rate in the follow-up of the patients [26]. They manifest as Hodgkin disease, leiomyosarcoma, cancer of the endometrium, colon, and neoplasias, and they are, in our opinion, the main reason for careful surveillance of these patients, although we have not found any metachronic tumor in follow-up of our patients.

**Résumé.** Le traitement du cancer de l'estomac est l'ablation chirurgicale. Les modifications introduites ces dernières décennies sont accompagnées d'une nette amélioration de la survie, ayant atteint globalement 61% à 5 ans au Japon. Une des raisons de l'amélioration est le diagnostic plus précoce des lésions. Pendant la période entre le 1 jan 1990 et le 31 dec 1999, nous avons traité 662 patients porteurs d'adénocarcinome gastrique dans le service de Chirurgie I de notre hôpital; 110 n'ont pas eu de traitement chirurgical. Parmi les patients ayant eu une résection, 91 (21.4%) ont été classés comme porteurs de cancer gastrique au début selon la classification de la Société japonaise de l'endoscopie digestive. Il y avait 30 femmes et 61 hommes, d'un âge moyen de  $60.2 \pm 15$  ans. Le diagnostic préopératoire a été un ulcère gastrique chez trois patients, deux autres patients ont été opérés sans histologie récente et un patient a été opéré en urgence pour ulcère hémorragique. Chez tous les autres patients, la biopsie a confirmé la présence de cancer (89%) ou de dysplasie sévère (4.6%). Les lésions ont intéressé essentiellement le tiers moyen (48.3%) et distal de l'estomac. Une gastrectomie subtotale a été réalisée chez 48 patients, une gastrectomie totale chez 40, une dégastrogastrectomie totale chez trois et chez neuf patients, on a réalisé une splénectomie (8 patients) ou une spléno pancréatectomie caudale (1 patient). Aucune lymphadénectomie n'a été réalisée chez cinq patients, 25 ont eu une lymphadénectomie D1 alors que 61 ont eu une lymphadénectomie D2 (67%). La taille moyenne de la tumeur a été de  $26 \pm 1.8$  mm. La lésion a atteint la muqueuse chez 46 patients et la sous-muqueuse chez 45. Chez six patients, les ganglions enlevés étaient envahis microscopiquement (6.7%). La mortalité a été de cinq (5.7%) patients. La médiane de suivi des patients a été de  $41 \pm 26$  mois, avec sept (8.1%) patients décédés pendant cette période: quatre de façon non-équivoque de leur maladie. La médiane de survie des patients a été de 85% à 5 ans et de 80% à 10 ans. Dans notre série, la survie a été affectée par la présence de ganglions lymphatiques envahis, sans rapport avec la profondeur ou la taille de la lésion.

**Resumen.** El cáncer gástrico es una entidad nosológica cuyo tratamiento es fundamentalmente quirúrgico. Las modificaciones, realizadas durante las pasadas décadas, a las técnicas exérecitas del cáncer gástrico han dado origen a un incremento evidente de la supervivencia, que en Japón alcanza hasta el 61% a los 5 años. Una de las causas determinantes de esta mayor supervivencia es el diagnóstico precoz de las lesiones cancerosas. En el Servicio de Cirugía I de nuestro hospital, se trataron entre 01/01/1990 y el 31/12/1999, 662 pacientes con adenocarcinoma gástrico; en 110 pacientes el tratamiento quirúrgico no se consideró indicado. De los pacientes sometidos a resección gástrica, 91 (21.4%) fueron diagnosticados de acuerdo, con la clasificación y definición de la Sociedad Japonesa de Endoscopia Digestiva, como cáncer gástrico precoz. Se trataba de 30 mujeres y 61 varones cuya edad media fue de  $60.2 \pm 15$  años; de todos ellos, 3 fueron diagnosticados antes de la intervención como portadores de una úlcera gástrica y otros dos, fueron intervenidos de urgencia, sin estudio anatomopatológico reciente, por presentar un estómago sangrante. En los restantes pacientes la biopsia confirmó en el 89% de los casos la existencia de un cáncer o de grave displasia (4.6%). Las lesiones cancerosas se localizaban sobre todo en el 1/3 medio (48.3%) y 1/3 distal del estómago. En 48 enfermos se realizó una gastrectomía subtotal, en 40 una gastrectomía total, en 3 una desgastrogastrectomía total; en 8 pacientes la resección gástrica se acompañó de una esplenectomía y en 1 de esplenectomía y resección de la cola del páncreas. En 5 pacientes no se realizó linfadenectomía alguna, en 25 la linfadenectomía se limitó a la 1ª barrera linfática y en 61 se extendió hasta la 2ª barrera linfática (67%). El tamaño promedio del cáncer fue de  $26 \pm 1.8$  mm. En 46 casos la tumoración afectaba exclusivamente a la mucosa, mientras que en 45 pacientes estaban afectadas la mucosa y submucosa gástricas. Sólo en 6 pacientes se constató invasión tumoral de los ganglios linfáticos extirpados (6.7%). La mortalidad fue del 5.7% (5 casos). El seguimiento medio alcanzó los  $41 \pm 26$  meses registrándose



durante este periodo 7 fallecimientos (8.1%) de los que 4 se debieron, sin duda alguna, a la progresión del cáncer. La supervivencia media a los 5 años fue del 85% y a los 10 del 80%. En nuestra serie, la supervivencia guarda estrecha relación con la invasión metastásica de ganglios linfáticos y no con el crecimiento en profundidad del tumor, ni con el tamaño del mismo.

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