Five year monitoring of endoscopic treatment for early gastric cancer in Colombia

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Received: 23-10-09
Accepted: 11-11-09

Summary

Early gastric cancer (EGC) is being diagnosed more frequently as each day passes. This is true not only in Japan but around the world. Even though the endoscopic treatment is relatively simple, our field does not yet have enough experience in long term monitoring after successful endoscopic treatment. For this reason we undertook this study and targeted the following objectives: 1. To determine the efficiency of endoscopic treatment in curing EGC. 2. To investigate the incidence of recurrence of tumors after five years of monitoring.

Materials and Methods. Between March 2002 and June 2004 we prospectively included patients who were diagnosed with EGC at El Tunal Hospital and monitored for at least 5 years. Endoscopic diagnoses were done according to the classification of the Japanese Society. Patients diagnosed with types I, IIa and IIb of less than 20mm and which were histologically well-differentiated or moderately differentiated were endoscopically treated.

Results. 11 patients were included in this study. 63.6% were men. The average age was 66.1 years. All the EGCs were found in the gastric body. Loop resection was performed on seven patients, resection and injection with plastic cup on 1 patient, injection and band placement on 1 patient, traction and loop resection (double channel endoscopy) on two patients. The resection was incomplete in 2 patients. The average monitoring time was 71.3 months (60 to 84 months). There were no incidences of tumor recurrence.

Conclusions. Mucosectomy is a simple, safe and curative method for EGC. It is easily performed by a well-trained gastroenterologist.

Key words

Early cancer, mucosectomy, healing, recurrence.

Gastric cancer (GC) is a highly prevalent entity in the world. In 2002, there were 900.000 new cases and 700.000 deaths (1). Globally, it is the fourth most frequent type of cancer and the second cause of death by cancer (2) explaining 10% of these (3). Although in Japan (4) and Colombia (5), it is the leading cause of death by cancer. In the latter, its incidence is approximately 10 times higher than in the USA (5). More than 90% of the EGC's are adenocarcinomas (6) and the rest are less frequent tumors such as lymphomas, gastrointestinal stromal tumors (GIST) and carcinoid tumors (7). GC is a multifactor disease that fundamentally depends on three factors, which are: the agent, genetic aspects of the guest, and environmental aspects such as little ingestion of fresh fruits and vegetables, high ingestion of salt, smoking, etc. (7-10). It develops through multiple steps that can last 20 or more years (7, 8) and it appears in stomachs that have atrophic gastritis and intestinal metaplasia. It has been estimated that 10% of patients with gastric atrophy can develop this tumor in a 15 year period (7, 8). The main etiological agent of distal or none-cardiale GC's and the type MALT lymphomas is *Helicobacter pylori (H. pylori)* (8, 9). There are two histological types of GC: intestinal and diffuse (11, 12), which has clear differences from an epidemiologic, histopathologic, endoscopic, clinical and pathogenic point of view (6, 8). The intestinal type are the most frequent in places with high prevalence where they have a higher prognosis and happen more often in men, as of age 50, even though they can also occur in

young ages (6, 7) and most happen in underdeveloped countries 6-8). In places with a low prevalence or low risk, as in many underdeveloped countries, its incidence has decreased in the last decades (13). The high morbidity of this tumor is fundamentally due to its late diagnosis when the tumor is in advanced states wherewith 5 year survival is less than 10% (14) which is why the best strategies to fight this feared entity is prevention, early detection and early treatment. Early GC (EGC) is a tumor bound to the mucus or sub mucus, independent of the presence or absence of metastasis to the lymphatic nodes (15), who's prognostic is excellent if detected and opportunely treated in order to achieve survival time superior to 90% for 5 years, which notably contrasts with advanced GC (15, 16). In EGC management, the therapeutic endoscopy plays an important role and it is the treatment of choice when the tumor meets the criteria for the endoscopic approach. It is the standard therapeutic modality in Japan (17, 18) and it is being used more often outside of this country (19, 20). This endoscopic treatment is comparable in many aspects to conventional surgical treatments, with the advantages that it is less invasive and cheaper (15, 16). Within endoscopic modalities, these are included: endoscopic resection of the mucous (mucosectomy or ERM) sub mucous endoscopic dissection (SED) and ablative techniques such as laser, argon plasma or hot tube (20, 21). Due to the extremely low incidence of lymphatic compromise in patients with confined mucous disease, endoscopic local treatment implies that most of these can be cured with similar results to conventional surgical treatment (18, 21-23). On the contrary, patients whose sub mucous is compromised are accompanied by metastasis in 10 to 30% (24). Taking into account that early GC is diagnosed more frequently each time, not only in Japan but in other countries such as ours (25), as well as the relative ease for endoscopic treatment for EGC and the little experience in our work field in long term monitoring, we decided to start this investigation to offer endoscopic treatment to patients who we diagnosed with EGC and were monitored during a term superior to the following objectives:

1. Determine the efficiency of endoscopic treatment in EGC healing
2. Investigate the incidence of tumor recurrence.

MATERIALS AND METHODS

Prospective study which took place in EL TUNAL HOSPITAL, an institution with a third level of complexity. Patients were included in the study to whom, a routine high digestive endoscopy was performed to in a usual manner (26) requested by their physician, EGC was diagnosed through endoscopy and was confirmed through histology. The diagnosis trough endoscopy was performed according to the classification of the Japanese Society of Gastric Cancer Investigation (15) in the following manner: type I: protruding or exophytic lesion; type II: shallow or flat lesion; and, type II: I ulcerated or depressed lesion. Type II includes three subtypes depending on whether it is elevated (IIa), flat (IIb) or depressed (IIc). Also, there are combined types that include complex configurations. The protruded type (type I or IIa) with a diameter less than 25mm and the excavated type (IIc) with a diameter less than 20 mm rarely produce metastasis to the lymphatic nodes. Those who were diagnosed this EGC are considered candidates to endoscopic treatment if they met the following characteristics (21): Gastric cancer type I, IIa, IIb and a size less than 20mm. The histological type must be a well or moderately differentiated adenocarcinoma. Patients with EGC with one or more of the following characteristics were excluded: Lesions greater than 20mm ulcerated or depressed (type IIc) lesions (type III) and diffused lesions.

The protocol of investigation and the informed consent were approved by the Ethics and Investigation committee in the institution where the investigation took place. All the patients signed the informed consent. The protocol followed by the patients included in the present study was the following. Once the GC diagnosis was histologically confirmed the following lab exams were performed: CBC, prothrombin time, partial thromboplastin time, computed tomography (CT) of abdomen (to rule out lymphadenopathy), and when possible, gastric EUS was performed. In a prospective and systematic manner, in a specific form designed for this investigation, the following information was gathered: age, gender, symptoms that prompted the referral to endoscopy, presence of symptoms or warning signs, location and morphological characteristics of the tumor, gastric histology out of the injury (atrophy, metaplasia).

Endoscopic resection of the EGC. Fasting for at least six hours, usual form endoscopy, sedation with midazolam and/ or propofol administered by an anesthesiologist. The methods used for the endoscopic resection were the following:

1. Loop excision according to the technique described by Tada in 1982 (27)
2. Injection and resection with plastic cup (28)
3. Injection and varicose ligation resection (28)
4. Traction and loop excision using double-channel endoscope (29).

All the patients were investigated for *H. pylori* through histology and/ or rapid urease test performed by ourselves according to published recommendations (30) and if it was positive, eradication therapy with standard triple therapy was performed for 14 days (20 mg proton bomb

inhibitor on an empty stomach and before dinner, 1 g amoxicillin twice a day and 500g clarithromycin twice a day). The infection's verification was performed, six weeks after completing therapy, through the described histology and rapid urease test. It was decided to treat *H. pylori* while taking into account the recommendation to avoid GC recurrence (31).

Endoscopic monitoring. The endoscopy was repeated four weeks after the resection, every three months for the first year, every six months during the last three years and then every year.

Statistical Analysis

The data was typed in Excel and the calculations were performed through Stata 9.0 statistical package. The ordinal or nominal categorical variables were expressed in percentages and, the numerical variables were expressed in measures of central tendency and dispersion measures (standard deviation). Statistical tests were evaluated with a significance level of 5% ($p < 0.05$).

RESULTS

From March of 2002 to June of 2004, 11 patients were included who met the requirements of having received endoscopic treatment for EGC and completed the monitoring for at least 5 years. Seven were men (63.6%). The average age was 66.1 +/-14.1 years, with ranges between 40 (one patient) and 80 years. They all presented dyspeptic symptoms with an average evolution time of 14 months prior to the endoscopic diagnosis. Two patients (18.2%) showed alarm symptoms: one had hematemesis while the other showed weight loss.

EGC location: All the tumors were found in the gastric body: five in the proximal third, major curve, five in the middle third and one in the distal third.

Morphologic characteristics: Type I: 4 patients (36.4%), Type IIa: 6 patients (54.5%), Type IIb: 1 patient.

Size of the lesions: The average diameter was 11.2mm with a range from 9 to 15mm.

Endoscopic resection technique used: loop resection: 7 patients (83.6%); injection and resection with plastic cup: 1 patient; injection and band placement: 1 patient; and resection with traction handle (dual-channel endoscope) 2 patients.

*Histology of the Tumors:*_Well differentiated intestinal: 8 patients (72.7%); moderately differentiated: 3 patients (27.3%).

In nine lesions, the histology informed tumor free edges and in two, the lateral edges were compromised by the tumor. One of the patients was a 65 year old woman with a 10mm tumor located in the middle third of the gastric body which was dried through injection and polipeptomy loop and, the histology was moderately differentiated intestinal GT. In the monitoring, a scar was found with no residual lesion from the histology. It was remitted to surgery (subtotal gastrectomy) and, the histological study of the surgical specimen did not find a tumor despite several cuts being made. Another patient with positive lateral edges was a 63 year old woman who also had megaloblastic anemia. The lesion was in the distal third of the gastric body minor curve. The lesion was dried out with polipeptomy loop and the pathologist informed a well differentiated adenocarcinoma. In the endoscopic monitoring, a scar was found whose biopsy showed no tumor. From the experience with the latter, it was decided not to take her to surgery and in the 60 month monitoring to date, no tumor recurrence has been found.

Tumor depth: Mucus in only 9 patients (82%), proximal third submucuous (SM1) in two patients.

Gastric histology outside of the tumor: Chronic gastritis in all patients (100%), gastric atrophy in 9 patients and intestinal metaplasia in seven of these.

Infection due to *H. pylori:* All patients had this infection which was successfully eradicated.

Evolution (monitoring): To date, the average monitoring is 71.3 months with a minimum of 60 months and a maximum of 84 months. In none of the patients has tumor recurrence been found.

DISCUSSION

This is the first report published in Colombian literature that shows a monitoring superior to 5 years in these patients. In none of our monitored patients has there been tumor recurrence or new tumors. From on oncologic point of view, it can be considered that these patients are cured. The favorable evolution of these patients, such as the absence of complications, coincides with the experience of Japanese investigators who are pioneers in this method of treatment (16-18, 23). The obtained success is probably related to the strict monitoring of the indications for endoscopic resection of the EGC (17, 21, 23, and 32). Over more than a decade ago, Nakamura (32) noted that endoscopic mucosectomy was not to be applied to undifferentiated depressed carcinomas located in the gastric mucus, proper of the zone of folds in the gastric body and bottom, even in the smallest forms, because of the high frequency of submucus infiltration and linitis plastica. In the present report, endoscopic resection was incomplete in two patients (18.1%) which may be considered within the informed range from out authors, which go from 6.6%, 10.6% to 20% (33, 34). Nonetheless, in our patients with edges compromised by the tumor, the

lesion was relatively small (10mm) in comparison to the experience of experimented endoscopists who found this inconvenient in lesions greater that 20mm (33, 34), which probably reflects that in these first cases performed by us, we were still in the learning curve, even though none of our two patients with tumors in the edges in the piece send to pathology, was a tumor found by surgery (one patient) nor by endoscopic monitoring. We consider that the most probable explanation for this fact is that the remnant tumor cells in the stomach in the place of EGC resection can be destroyed by the heat generated by the polipeptomy loop. The finding of *H. pylori* all of these patients can reflect the clearly established association of EGC with this infection (35). In the patients monitoring, we have not found metachronic tumors and that may be related to the eradication of *H. pylori* included in our management protocol since it has recently been proven for the first unequivocal time, that eradicating the infection in early tumors reduces the probability of new EGC (36). In this study it was found that in a three year monitoring, 9 patients who had *H. pylori* eradicated, a metachronic GC appeared in contrast to 24 appearances in the group in which it was not eradicated. Despite this evidence, the monitoring must continue since more than 80% of the patients in this study had lesions precursors to GC such as atrophy and intestinal metaplasia and, the eradication of the infection under these circumstances can not eliminate the totally of GC risk as demonstrated in a high incidence zone of GC in China (37). The extensive Japanese experience with endoscopic treatment of incipient gastric cancer has shown infrequent systematic complications, rare operational and post-operational complications, and a good quality of life after its application and, it has been it has been chosen as the method of choice for those cases with the already described indications (17, 22, 23, and 32). Likewise, it constitutes a certain therapeutic possibility for those cases of a very advanced age, concomitant affection of high risk, or simply for those cases where surgical treatment is denied; having to mention a significantly lower price than conventional surgery. We want to highlight that an adequate communication between the endoscopist and the pathologist, which is achieved by examining the freshly excised material, through a complete description of the procedure, lesion type, localization of the number of fragments and a particular reference if the mucosectomy was monitored by additional biopsies in some margin that the endoscopist can consider doubtful of residual tumor lesion. Recently, endoscopic submucus dissection (ESD), which is a mainly spread technique through East Asia for early gastric cancer treatment (38), which has broadened the spectrum of lesions for endoscopic management since through it, not only lesions greater than 20mm (type IIc and type III) in "a single piece", but it has also decreased the rate of local recurrence in post treatment endoscopy (39). There are also reports on the example of this technique in managing other types of malign and benign lesions (40, 41). However, this technique requires experienced and skilled gastroenterologists who have been trained, as well as the use of certain endoscopic equipment, such as the IT (insulation-tipped) Knife (42). Currently a controversy arises as to whether it is better to use a DES or a mucosectomy in lesions less than 20mm since there are groups who perform a DES to patients in a systematic manner when they could have performed a simple mucosectomy which is less complex and less risky for the patient. In a recent study (43), this controversy was directly addressed and both methods were compared. 177 patients who met the requirements for mucosectomy were randomized to DES or mucosectomy. The objectives were to compare the rate of partial resection, total resection, recurrence and complications. The study concluded that in small lesions (<15mm), both methods were comparable and the authors recommended that in these types of lesions, a mucosectomy must be performed rather than a DES as some groups prefer.

In conclusion, this report constitutes one of the Latin American series with the longest monitoring of patients with EGC treated by endoscopy. It has been demonstrated that: 1. It is the most secure method, for lesions confined to the mucus, as well as the most healing for this pathology (absence of the tumor after five years), 2. It is a simple procedure easily performed by a trained gastroenterologist, 3. It requires a minimum infrastructure in most EGC, 4. Each day, more experience is acquired outside of Japan. However, for lesions of greater size (20mm), complex and expensive accessories are required for submucus dissection (SMD).

As with all malign diseases, the ideal to avoid morbidity due to GC would be primary prevention of the tumor; but, to date, the benefits achieved by eradicating *H. pylori* are not satisfactory and therefore the best strategy to face this pathology continues to be an early diagnosis and treatment (an early diagnosis is useless without an appropriate treatment) (44). Therefore, gastroenterologists from high GC prevalence, like ours, should continue to painstakingly search for EGC and offer high digestive endoscopy to all adult people with dyspepsia, independent of whether they present or do not present alarm symptoms, as well as start endoscopic treatment to the lesions that, as we have mentioned, are as efficient as surgery (45) with the discussed advantages.

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