ORIGINAL PAPER

The endoscopic and morphological forms of early gastric cancer

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Abstract

The early gastric cancer is an endoscopic notion in which gastric cancer is strictly placed to mucosis and submucosis without extensive manifestations. It is the form with favorable prognosis and better survival at 5 and 10 years. Our study tries to systematize the debut forms of early gastric cancer and their association with the lesions with malignisation risk. We also try to evaluate the incidence of endoscopic and histopathologic forms of early gastric cancer found in an internal medicine division. Our study included 435 patients with gastric cancer endoscopic and histologic diagnosed. Statistically, 64.36% were men and 35.64% were women, the mean age 48 ± 7 years. The endoscopic forms of early gastric cancer were type I: protruded in 19 cases, type II: superficially in eight cases, type III: excavated in six cases. Early gastric cancer is diagnosed with difficulty, it represents in 7.58% of the gastric cancer, being most frequently asymptomatic. The endoscopic forms frequently found in early gastric cancer in the population were type I: protruded and type IIa: superficially elevated. The histopathological examination is compulsory at this form of gastric cancer, while in advanced gastric cancer endoscopy is often sufficient for diagnosis. Analysing the histopathological results of cases diagnosed with early gastric cancer we found: 22 cases with intestinal type and 11 cases diffuse type. Microscopically, 15 were intramucosal and 18 had submucosal invasion. I and IIa lesions were predominantly located at the antrum and are histologically differentiated adenocarcinoma. Differentiated carcinoma frequently produces an elevated lesion and the border is well demarcated. There are frequent opportunities to detect gastric cancer in the early phase and the patient can expect a complete cure by the surgical operation or endoscopical mucosal resection.

***Keywords*:** early gastric cancer, type I: protruded adenocarcinomas, type IIa: superficially elevated adenocarcinomas, type III: excavated adenocarcinomas, malign lymphomas, stomach sarcomas.

Introduction

Gastric cancer represents the second cancer cause of death in the world. Adenocarcinomas represent almost 90% of the malign gastric tumors, 10% being malign nonepitelial neoplasic (malign lymphoma and stomach sarcoma). The process of gastric carcinogenesis involves favorable factors, such as an exaggerated intake of salt, Helicobacter pylori, especially roots cagA positive, nitrates and nitrites, polycyclic hydrocarbons, alcohol, smoking. Gastrectomy antecedents, Biermer or Menettrier disease, adenomas and gastric ulcer are also considered factors of risk. Genetic predisposition is another cause (families with gastric cancer or twins with gastric cancer). Gastric cancer may often be multifactorial involving both inherited predisposition and environmental factors [1–5].

Gastric carcinomatosis is a multiple process, which implies more stages: superficial gastritis, atrophic gastritis, intestinal metaplasy, severe epithelial dysplasy and finally gastric cancer [6, 7]. It has been demonstrated that in gastric cancer appears an uncontrollable proliferation as well as a deficiency of apoptosis.

The molecular mechanisms responsible for the development of gastric adenocarcinoma are not entirely known. For example, in the intestinal type one can mainly observe the amplification of mutations of c-erb B2, C-MET genes and E cycline, mutations K-RAS gene, non-activation of p53, p16, MGMT and MLH1 genes, while in the diffuse type it has been observed reduction or losing of cadherin functions, non-activating p53 gene and amplification of K-SAM, C-MET genes and E cicline [8–12].

Early gastric cancer (EGC) is defined as gastric cancer confined to the mucosa or submucosa, regardless of the presence or absence of lymph node metastasis. As proposed by the Japanese Society of Gastroenterological Endoscopy early gastric cancer is defined as adenocarcinoma that is limited to the gastric mucosa and submucosa regardless of whether regional lymph nodes are involved or not (T1Nx). This definition reflects an appreciation that EGC represents a subset of gastric cancers that has a favorable prognosis compared to invasive gastric cancer that extends beyond the submucosa (T2–4Nx) [7].

Material and methods

The early gastric cancer is an endoscopic notion referring to gastric cancer strictly placed to mucosis and submucosis without extensive manifestations. It is the form with favorable prognosis and better survival at 5 and 10 years.

Our study included 435 patients with gastric cancer, diagnosed by endoscopic and histopathological examination between January 2000 and July 2007 in the IInd Internal Medicine Department and the IIIrd Surgery Department. Statistically, there were 64.36% men and 35.64% women, the mean age 48 ± 7 years. Using the above criteria, the endoscopic distribution of gastric cancer was: 33 cases diagnosed with early gastric cancer (7.58%) and 402 cases with advanced gastric cancer (92.42%) (Figure 1).

This high prevalence of advanced gastric cancer, it is a delicate question and its justification is complex and depends on many elements like the late presentation of patients at physician, incomplete and superficially examination by the physician and deficiency of radiological examination in this type of gastric cancer. The upper digestive endoscopy and histopathological examination from mucosal biopsy were performed in all cases. The histopathological examination was made in The Department of Pathology, Emergency County Hospital of Craiova.

Esophagogastroduodenoscopy has a diagnostic accuracy of 95%. This relatively safe and simple procedure provides a permanent color photographic record of the lesion. This procedure is also the primary method for obtaining a tissue diagnosis of suspected lesions. Biopsy of any ulcerated lesion should require at least six biopsies taken from around the lesion because of variable malignant transformation. The pieces were processed in Pathology Lab of same hospital. All specimens were fixed in 15% buffered neutral pH formaldehyde and paraffin-embedded. Histological sections were stained using current techniques: Hematoxylin–Eosin, trichromic van Gieson and Giemsa (for *Helicobacter pylori*). We used Laurén histological classification with two main types of gastric carcinoma: type I (intestinal) or type II (diffuse). Adenocarcinoma of the stomach is subclassified according to histologic description as follows: tubular, papillary, mucinous, or signet-ring cells, and undifferentiated lesions. Researchers also employ a variety of other classification schemes. An appealing feature of classifying patients according to the Lauren system is that the descriptive pathologic entities have clinically relevant differences.

In selected cases, endoscopic ultrasound may be helpful in assessing depth of penetration of the tumor or involvement of adjacent structures. Double-contrast upper gastrointestinal series and barium swallows may be helpful in delineating the extent of disease when obstructive symptoms are present or when bulky proximal tumors prevent passage of the endoscope to examine the stomach distal to an obstruction (more common with gastroesophageal (GE)-junction tumors). Chest radiograph is done to evaluate for metastatic lesions.

CT-scan or MRI of the chest, abdomen, and pelvis assess the local disease process as well as evaluate potential areas of spread (i.e., enlarged lymph nodes, possible liver metastases) [13, 14]. The goal of obtaining laboratory studies is to assist in determining optimal therapy. A complete blood cell count can identify anemia, which may be caused by bleeding, liver dysfunction, or poor nutrition. Electrolyte panels, liver function tests, carcinoembryonic antigen (CEA) and cancer antigen (CA) 19–9 also are essential to better characterize the patient's clinical state.

Results

Analyzing the results we obtained in our study, we retained the following aspects.

The onset in early gastric cancer (Figure 2) was by:

- Dyspeptic ulcer-type symptoms in five cases (15.15%);
- Gastritis symptoms in five cases (15.15%);
- Vague discomfort and cramps in 11 cases (33.34%);
- Without symptoms in 12 cases (36.36%) – random discovery by endoscopic or radiological investigations for other symptoms.

The macroscopically types (Figure 3) found in early gastric cancer were:

- Type I: protruded – 19 cases (57.5%). In this cases the macroscopically aspect was like: (1) malignant polyps with different sizes 1–2 cm and sessile, non-molar form without shrinking at implantation place or (2) pediculate and molar form, aspect of cylindrical, protruded formations, with shrinking at implantation place (Figure 4).
- Type II: superficially – eight cases (24.2%) (seven cases type IIa: superficially elevated). The diagnosis in these cases was very difficult, because the lesions were similarly with normal mucous membrane or other not significant injuries (gastritis lesions or drug erosions) and was made by multiple biopsies (Figure 5).
- Type III: excavated (malignant niche) – six cases (18.1%). The differential diagnosis between this type and benign niche was made by macroscopically aspects, but also by histopathological examination (Figure 6).

Analyzing the reasons for upper digestive endoscopy indication (Figure 7), we established:

- In five cases (15.15%) the diagnosis was made at periodically reexamination for atrophic gastritis from pernicious anemia. In this cases, the early gastric cancer was type I: protruded and it is associated with histamine resistant gastritis.
- In 16 cases (48.48%) the indication for upper digestive endoscopy was periodically inspection at patients with stomach operated for duodenal or stomach ulcer – 2/3 resection and transit restored by various anastomosis (gastroduodenale or gastro-jejunal anatomosis). The diagnosis was made at reexamination: in 11 cases after 10 years and in other three cases after seven years, from surgical interventions. We found the following endoscopic forms: eight cases with type II, three cases with type I, and three cases with type III or excavated.

▪ In nine cases (27.27%) – the diagnosis was suggested by macroscopical modifications of the polyp and histological confirmed after the biopsy, during control for gastric polyposis. This early cancer gastric was type I: protruded.

▪ In three cases (9.1%) the diagnosis was made by biopsy. The biopsy was performed for differential diagnosis in stomach ulcer with gastritis symptoms. The endoscopic type of early gastric cancer diagnosed was type III: exacavated.

Helicobacter pylori gastritis is a risk factor for the development of gastric cancer. The results of several studies indicate that gastric adenomas, which are considered premalignant lesions, may also be associated with *H. pylori* gastritis. However, it is not clear whether there are different patterns of gastritis in these patients compared with patients with gastric cancer or patients with *H. pylori* gastritis alone. In our study, only 23 patients (69.6%) with early gastric carcinoma were infected with *H. pylori.*

The endoscopic examination combined with punction biopsy from injuries was made in all cases. Analysing the histopathological results of cases diagnosed with early gastric cancer we found: 22 cases with intestinal type and 11 cases diffuse type. Microscopically, 15 were intramucosal and 18 had submucosal invasion. Therefore, undifferentiated carcinoma is more infiltrative than the differentiated carcinoma.

Case reports

We present the case of a 69-years-old male, admitted in the IInd Medical Clinic of the Emergency County Hospital of Craiova for upper abdominal discomfort. Endoscopic examination revealed an irregular, nodular lesion in the antrum area (Figure 4). Biopsy revealed a well-differentiated tubular adenocarcinoma for the antrum lesion (Figure 8). Distal gastrectomy with sufficient duodenal resection was performed. The patient was infected with *H pylori*.

The next case is a case of a 76-years-old woman with type IIa: superficially elevated gastric cancer (Figure 4). The height of the type I lesion is more than twice that of the normal mucosa, but the height of IIa is less than twice the thickness. Therefore, this lesion cannot be distinguished easily between type I and IIa. Histologically, the lesion is papillary type limited to the mucosa (Figure 9).

This small lesion is an IIa type early cancer, and the cancer cells are restricted to the lamina propria of the mucosa. We can observe atypical glands at the surface layers of the mucosa. The atypical glands show a sufficient degree of cellular and structural atypia to enable the diagnosis of a well-differentiated tubular adenocarcinoma. Slightly elevated lesions like IIa are frequently found.

However, the degree of cellular atypia of some of the cases is not high and the pathological diagnosis must be gastric adenoma. If the pathological diagnosis is adenoma, surgical resection is never performed. Many cases of IIa are located at the antrum, whereas more than half of the IIc cases are located at the corpus. Accordingly, we can say that IIa arise predominantly from the antrum, and IIc arise from the corpus.

An irregular mucosa is frequently observed by endoscopic examination, and we classified it as a IIa + IIc early gastric cancer, because some parts are elevated and others depressed. The histological picture shows signet ring cell type, and the carcinoma has infiltrated the sub-mucosal layer (Figure 12). This is significant in deciding the indication of endoscopical mucosal resection.

Type III is a rare lesion. There is deep central ulceration, and the cancer cells remain in the mucosa of the ulcer edge. The endoscopic and macroscopic pictures of some cases look like IIc. However, histologically the carcinoma infiltrates the muscularis propria. Therefore, this appears to be an IIc-like advanced cancer (Figure 6).

A flat and erosive lesion is sometimes found. Histologically, signet ring cell type and mucinous type can be observed in the mucosa of the most part of the lesion, but poorly differentiated cancer cells have infiltrated the submucosa and muscularis propria in a small area (Figures 10 and 11).

Discussions

Gastric cancer is one of the most common malignancies in the world, although regional variations in incidence exist. About 95% of diagnosed gastric cancers are adenocarcinomas, with a much smaller percentage classified as non-Hodgkin lymphomas or leiomyosarcomas.

The development of gastric adenocarcinoma is associated with environmental as well as genetic factors. High dietary levels of nitrates, complex carbohydrates, and salted, pickled, or smoked foods have been linked to this malignancy. A history of smoking has been found to double the risk of transition from chronic atrophic gastritis to dysplasia, although no similar risk has been shown with alcohol use.

Individuals with an increased genetic risk for gastric cancer include those with hereditary non-polyposis colorectal cancer as well as those with familial polyposis coli. Particular polymorphisms affecting expression of the cytokines IL-1 beta and its receptor, and TNF alpha have been associated with increased risk of gastric cancer. The decreasing incidence of stomac cancer observed in developed countries has been attributed to improvement in living conditions [3, 9, 15].

Gastric cancer can be divided into two major categories: early and advanced. Early gastric cancer is characterized by limitation of the cancer cells to the mucosa or sub-mucosal layer, whereas in advanced cancer, the cancer cells infiltrate the proprial muscle layer or serosa. Early gastric cancers are macroscopically classified into five types: I: protruded, IIa: superficially elevated, IIb: superficially flat, IIc: superficially depressed, and III: excavated. Numerous cases show combined shapes, such as IIc + IIa, I + IIa, IIc + III, and IIa + IIb + IIc. Gastric adenoma cannot be differentiated from IIa macroscopically.

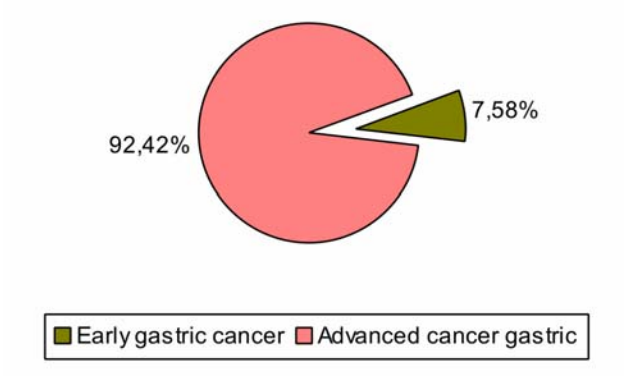

Figure 1 – ***The incidence of the early gastric cancer in the endoscopic forms of gastric cancer***

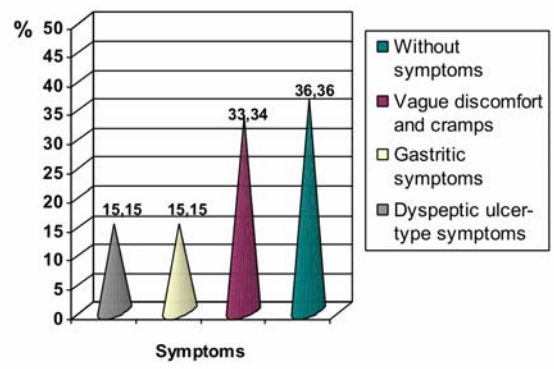

Figure 2 – ***The clinical onset forms of early gastric cancer***

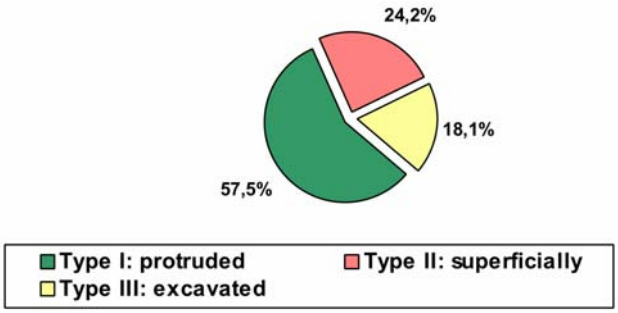

Figure 3 – ***Incidence of endoscopic forms of early gastric cancer***

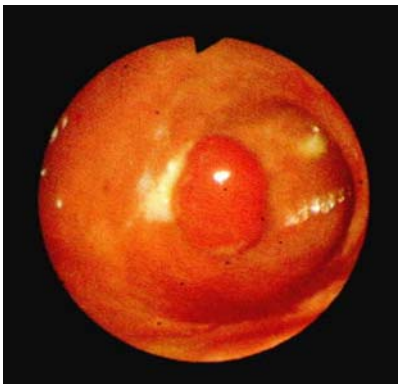

Figure 4 – ***Type I: protruded of early gastric cancer (endoscopic form)***

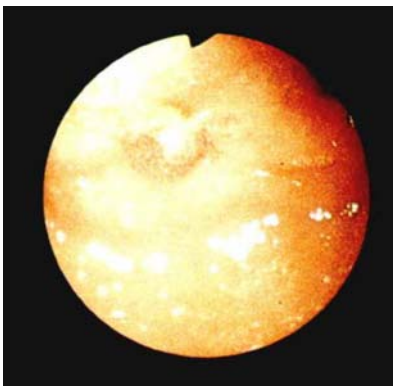

Figure 5 – ***Type IIa: superficially elevated of early gastric cancer (endoscopic form)***

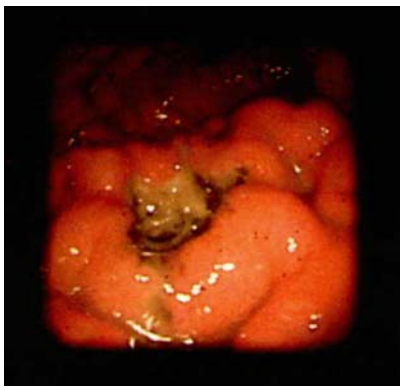

Figure 6 – ***Type III: excavated of early gastric cancer (endoscopic form)***

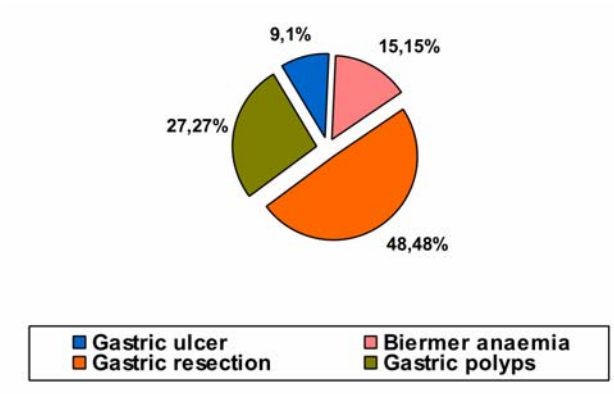

Figure 7 – ***Association of early gastric cancer with malignant risk lesions***

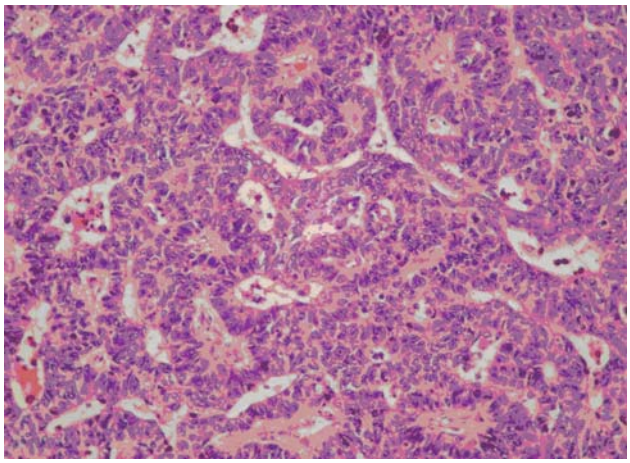

Figure 8 – ***Gastric adenocarcinoma: tubopapillary type***

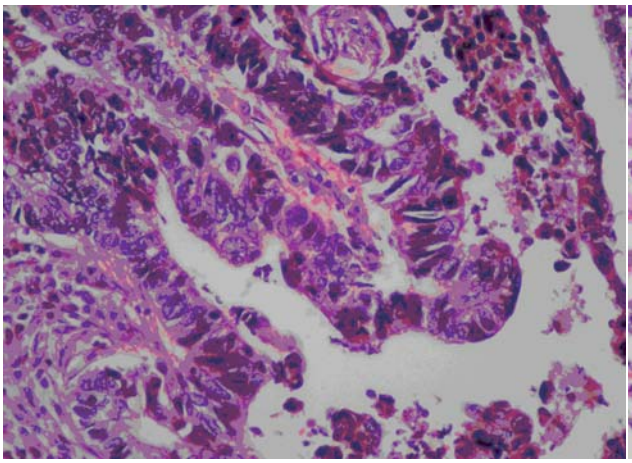

Figure 9 – ***Gastric adenocarcinoma: papillary type***

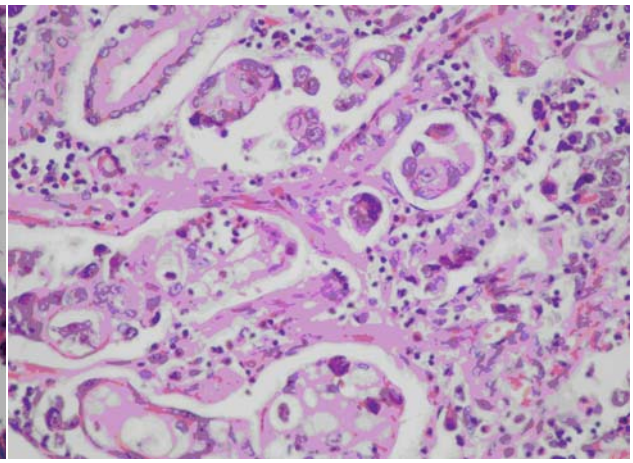

Figure 10 – ***Gastric adenocarcinoma: signet ring cell type***

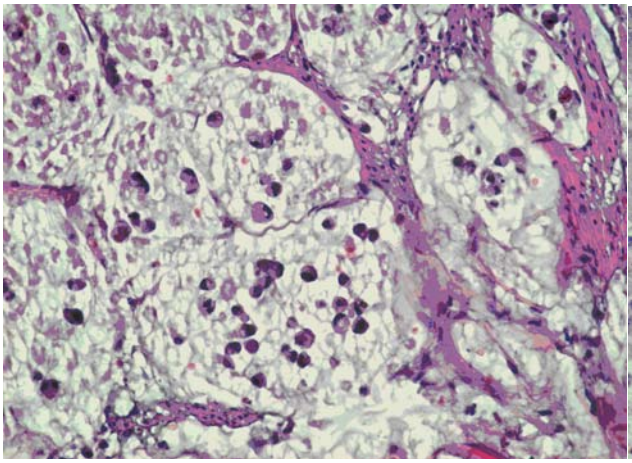

Figure 11 – ***Gastric adenocarcinoma: mucinous type***

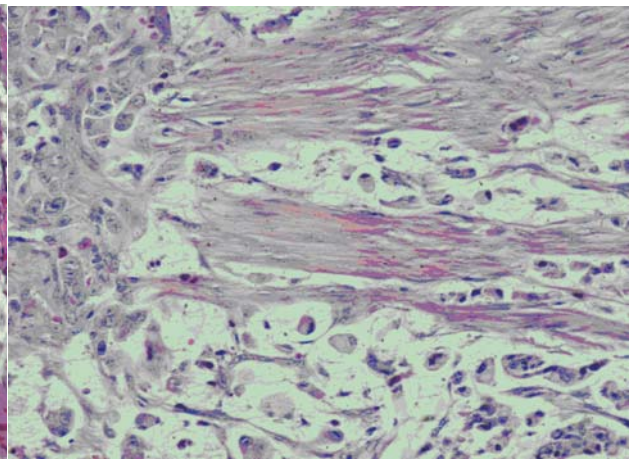

Figure 12 – ***Gastric adenocarcinoma: signet ring cell type with invasion to the muscle layer***

The histological characteristics of early gastric cancer are similar to those of advanced cancer. IIa and IIc are the major types of early gastric cancer. IIa lesions are frequently located at the antrum and predominantly are differentiated (intestinal) carcinomas. IIc lesions are frequently located at the corpus and predominantly are undifferentiated (diffuse) carcinomas. Differentiated carcinoma is expansive, whereas undifferentiated carcinoma is infiltrative.

Type I and IIa early cancers develop into Borrmann 1 and 2 type advanced cancers, while IIc and III early cancers develop into Borrmann 3 and 4 type advanced cancers via an IIc-like advanced cancer. Differentiated carcinoma is thought to arise from intestinal metaplasia, while undifferentiated carcinoma arises from the foveolar epithelium. Gastric cancer develops slowly from the early to the advanced phase over a long period of probably longer than 10 years. Therefore, there are frequent opportunities to detect gastric cancer in the early phase and the patient can expect a complete cure by the surgical operation or endoscopical mucosal resection [7, 16–19].

Gastric adenocarcinoma can be classified according to histology, as either intestinal or diffuse types. It has been hypothesized that the intestinal type develops in sequential fashion from superficial gastritis, to chronic atrophic gastritis, intestinal metaplasia, dysplasia, and carcinoma. A parallel sequence has not been detected for the diffuse type of gastric cancer [17–19].

Intestinal, expansive, epidemic-type gastric cancer is associated with chronic atrophic gastritis, retained glandular structure, little invasiveness, and a sharp margin. The pathologic presentation classified as epidemic by the Lauren system is associated with most environmental risk factors, carries a better prognosis, and shows no familial history [8, 23–25].

The second type, diffuse, infiltrative, endemic cancer, consists of scattered cell clusters with poor differentiation and dangerously deceptive margins. Margins that appear clear to the operating surgeon and examining pathologist often are determined retrospectively to be involved. The endemic-type tumor invades large areas of the stomach. This type of tumor is also not recognizably influenced by environment or diet, is more virulent in women, and occurs more often in relatively young patients. This pathologic entity is associated with genetic factors (such as E-cadherin), blood groups, and a family history of gastric cancer [21, 22].

Histological types of the early phase carcinoma are the same as those of advanced carcinoma, and the classification of pap, tub1, tub2, por1, por2, sig and muc

can be used. Histological classification according to the macroscopic types of the carcinoma is demonstrated.

Many American and European pathologists [7] do not agree on early gastric cancer, because they have assumed that the histological pictures of early gastric cancer in Japan are different from those of advanced cancers. However, the histological characteristics of gastric cancer are the same at every stage of cancer development. Therefore, undifferentiated carcinoma is more infiltrative than the differentiated carcinoma.

Primary gastric lymphoma accounts for about 3% of cancers in the stomach. These lesions arising from the mucosa also are known as Mucosa-Associated Lymphoid Tissue Tumors (MALToma), and are B-cell tumors. Numerous studies have reported an association between *H. pylori* colonization and the development of MALToma. Further evidence for the link between *H. pylori* and MALToma comes from the observation that remission of the tumor often, but not always, occurs with eradication of the organism [20–23].

Therefore, the incidence of lymph node metastasis was higher in the undifferentiated carcinoma cases. IIa lesions are predominantly located at the antrum and are histologically differentiated adenocarcinoma [24, 25].

Differentiated carcinoma frequently produces an elevated lesion and the border is well demarcated. Lymph node metastasis is rare. IIc lesions are predominantly located at the corpus and are histologically undifferentiated adenocarcinoma. Undifferentiated adenocarcinoma is infiltrative and produces IIc and III lesions. Some IIc lesion cases consisting of undifferentiated adenocarcinoma show lymph node metastasis. Therefore, endoscopic mucosal resection can be safely performed in IIa cases, but not in IIc cases.

Conclusions

Early gastric cancer is diagnosed with difficulty and it represents 7.58% of the gastric cancer, being most frequently asymptomatic.

The most frequently clinical symptoms were: dyspeptic ulcer-type symptoms (15.15%), gastritis symptoms (15.15%), abdominal discomfort and cramps 33.34%. The early cancer is asymptomatic in 36.36% cases.

The endoscopic forms frequently found in early gastric cancer in population were type I: protruded and type IIa: superficially elevated. I and IIa lesions were predominantly located at the antrum and are histologically differentiated adenocarcinoma. Differentiated carcinoma frequently produces an elevated lesion and the border is well demarcated.

There are frequent opportunities to detect gastric cancer in the early phase and the patient can expect a complete cure by the surgical operation or endoscopical mucosal resection. Lymph node metastasis is rare. IIc lesions are predominantly located at the corpus and are histologically undifferentiated adenocarcinoma.

Undifferentiated adenocarcinoma is infiltrative, produces IIc and III lesions, and could determinate lymph node metastasis. Therefore, endoscopic mucosal resection can be safely performed in IIa cases, but not in IIc cases.

The endoscopic diagnosis of early gastric cancer is often made at periodically reexamination for operated stomach, gastric polyposis, histamine resistant, atrophic gastritis from pernicious anemia or differential diagnosis in stomach ulcer. This diseases can be considered gastric lesions with malignant high risk and that require periodically endoscopic examination.

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