Early Gastric Cancer

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ABSTRACT

Early Gastric Cancer (EGC) is a carcinoma limited to the gastric mucosa or submucosa without the involvement of any lymph node. In Indonesia, the prevalence of EGC in 1980 was 2.2% and 1.7% for Jakarta and Medan, respectively. From 1980-1987 in Surabaya, the prevalence was 9.1% from all gastric cancers.

Gastric mucosal abnormalities include atrophic gastritis, which is frequently accompanied by achlorhidria *or* hipochlorhidria *and pernicious anemia, and the presence of an ulcer or polyp were believed to be precarcinogenic factors. Environmental factors, life style, age, sex, genetic factors, race, as well as dietary factors, especially intake of foods containing* N-nitrosa (N-nitrosa compound) *might play a role as risk factors for EGC. H.pylori infection also causes an increased risk for EGC.*

The diagnosis of EGC is based on physical examination, occult blood in stool sample, cytology, double contrast roentgenologic examination, gastroscopy, gastrobiopsy, and radioactive phosphor. There are no tumor markers specific for EGC. Histologically, EGC is classified into intestinal *and* diffuse infiltrative *EGC. In 1962, the Japanese Research Society for Gastric Cancer made a classification for EGC based on gastroscopy, fluoroscopy, histopathology and microscopic examinations. In Japan, detection for EGC was performed by spraying the gastric mucosa with* methylen blue *during endoscopy, which will stain intestinal mucosa and spare normal mucosa. Early detection of EGC in Japan was performed through mass screening of people ages 40-50 years with recent dyspepsia, by means of endoscopy, biopsy, and upper GI tract radiological examinations. Endoscopic Ultrasonography (EUS) is the most accurate tool to determine EGC staging, particularly those with non-ulcerative lessions.*

The choices of treatment for EGC are surgical therapy or Endoscopic Mucosal Resection (EMR). EMR is a localized therapy, and it is indicated for EGC without metastases, for patients unwilling to undergo operation, or for those who are bad candidates for operation.

The prognosis for EGC does not depend upon microscopic classification, but mostly on the depth of gastric mucosal invasion, spread to regional lymph nodes, and the presence of distant metastases. By establishing the diagnosis of EGC, the prognosis is usually better, for the treatment can be given at an earlier stage.

Key words: *Early gastric cancer, diagnosis, treatment*

INTRODUCTION

Early gastric cancer (EGC) was defined in 1962 by Japanese Research Society for Gastric Cancer as a carcinoma limited to the mucosa or submucosa without lymph node involvement [1]. All gastric cancers that have passed the muscle layer accompanied or unaccompanied by metastasis to surrounding organs or other body parts are classified as advanced gastric cancer (AGC).[2]

In the United States, gastric cancer is the number 9 most frequent malignancy in men and number 15 in women. The incidence of gastric cancer in 1985 was 11.9 cases for every 100,000 men and 5.3 in 100,000 women. While in 1993, 24,000 people in the United States were expected to suffer from gastric cancer, 13,000 of which to the point of death.[3]

Japan is known to be the country with the highest incidence of gastric cancer in the world,[4] gastric cancer

being the number one cause of death in the nation.[3] The incidence of gastric cancer in Japan is 84 for every 100,000 men.[3] Other countries, such as Costa Rica, Columbia, Singapore, and Iceland are also countries with a high incidence of gastric cancer. Sujono Hadi reported data from Indonesia demonstrating a relatively low incidence rate in indigenous Indonesians (± 1-2%), but an approximately 19% incidence rate in those of Chinese decent.[2]

Data specific for early gastric cancer reported by the Birmingham Cancer Registry from a registry of 13,228 cases of gastric cancer during the years 1960 to 1969 mentioned an incidence rate of 0.7%.[5] In Japan, as a nation that pays a great deal of attention to early gastric cancer, developments in technology and diagnostic methods were able to detect almost 10,000 cases of early gastric cancer annually, which consists of 40-50% of all gastric cancers (quoted from 1). In Indonesia, the incidence rate for early gastric cancer in 1980 is 2.2% in Jakarta, 1.7% in Medan, and 1.4% in Surabaya. Data for years 1981 to 1987 in Surabaya demonstrates an early gastric cancer of 9.1% of all 186 cases of gastric cancers.[6]

Because most patients come with symptoms associated with the gastrointestinal system, particularly dyspepsia, early investigations of dyspepsia symptoms should increase the detection of early gastric cancer.[5]

PATHOGENESIS

The etiology of gastric cancer is still unclear. However, several observations that has been conducted may be used to explain the pathogenesis:[2]

1. Abnormal mucosal changes
2. Epidemiological observations
3. Changes in various components

ABNORMAL MUCOSAL CHANGES

Hurst (1929) and Konjetzky (1936) were the first to investigate the presence of abnormal mucosal changes that often cause the development of gastric cancer. Another common abnormality is atrophic gastritis that is often accompanied by achlorhydria or hypochlorhydria. It has also been mentioned that gastric cancer would not occur in normal gastric mucosa.

Several benign changes in the gastric mucosa, such as ulcer, polyp, and pernicious anemia that often occurs at various levels of atrophic gastritis are pre-carcinogenic factors.[2] It has been mentioned that 3% of ventricular ulcers will undergo malignant changes, while 5-10% of pernicious anemia has a risk of turning into gastric cancer. While in gastric polyp, our attention is more focused on villous adenoma, since reports of its potential rate for turning malignant is 69%.[3]

EPIDEMIOLOGICAL OBSERVATION

Environmental conditions, life style, age, sex, genetic factors, and race may play roles as risk factors for the development of gastric cancer.

a. Age: The incidence of gastric cancer increases progressively after the age of 35 to 85 years (1 per 100,000 to 96.1 per 100,000).[3]
b. Sex: The risk for the development of gastric cancer worldwide is higher in men than in women, ranging from 1.7 (Iran) to 9 (South Africa) times higher.[3]
c. Race: African Americans have a 3 times higher risk for gastric cancer than white Americans.[3] In countries such as Chile, Japan, Iceland, Finland, Austria, Russia, and Scandinavia, the frequency for gastric cancer is very high compared to in other countries.[1] Studies report that Japanese who have lived a long time in the United States have a lower incidence rate of gastric cancer than those living in their country. We can thus conclude that life style plays an important role.[7,8]
d. Genetic factors:
    - Familial history: a study of family history found that gastric cancer is associated with a 2-3 times increased risk in first generations.[3]
    - Blood type: A blood type or specific substance of the Lewis group has a 15-20% risk of suffering from gastric cancer.[3]
    - Familial syndrome: Peutz-Jeghers Syndrome (multiple GI hamartomas polyps, melanic pigmentation) that is autosomal dominantly inherited has been mentioned to increase risks of gastric cancer, but only in cases of gastric hamartoma.[3]
    - Hereditary autosomal dominant mutation of the E-cadherin (CDH1) gene has been found in families with diffuse gastric cancer. Hereditary diffuse gastric cancer is an early gastric cancer that develops at a young age.[9]
e. Diet: Welvaart and Zwaveling (1981) reported a clear correlation between diet and gastric cancer. Smoked and roasted meat that is often eaten in countries with a high incidence rate of gastric cancer. Excessive sodium intake and the use of preserved foods is commonly found in countries with a high incidence rate of gastric cancer.[8]

A substance that has received great attention is the N-nitrose compound substance that is formed in foods

that contain nitrates (smoked, slated, and acidified foods). In the gaster, nitrates are changed into nitrites that then undergo secondary or tertiary reaction to form nitrosamine substances that are carcinogenic. A better freezing system has reduced the need for nitrates, thus reducing the risk for gastric cancer. Fresh fruits and vegetables, especially those containing vitamin A and C, inhibits the transformation of nitrates into nitrosamines.[3,6] Full cream milk also reduces the risk of gastric cancer.[6]

HELYCOBACTER PYLORI AND GASTRIC CANCER

Data from the United States and Europe demonstrates that the presence of H. pylori infection (Hp) increases the risks for gastric cancer up to 6 times, and is found in almost 50% cases of gastric cancer. The mechanism that supports this is that chronic inflammation due to Hp infection causes atrophic gastritis with reduced gastric acid and secondary increase of the number of bacteria that produces the nitrosamine carcinogen from a nitrate diet. The most recent study by Kuipers et al in Hp infected patients treated with proton-pump inhibitors demonstrate an increased risk for atrophic gastritis compared to those that underwent anti-reflux surgery. Thus, gastric cancer increases with the more dispersed use of this drug. In the United States, the risk rate for gastric cancer from asymptomatic Hp infected individuals is low (less than 1%).[10]

In the mean time, in an Asia-Pacific consensus conference on the treatment of Hp infection in 1997 in Singapore released several statements on the correlation between Hp infection and gastric cancer:[11]

- Hp infection is a risk factor for gastric cancer in the people of Asia.
- Recently, it has been found that there is no proof that the eradication of Hp infection cures atrophic gastritis and/or intestinal metaplasia.
- There is no sufficiently strong proof that eradication of Hp infection reduces the risks or prevents the development of gastric cancer.
- Hp infection is not a risk factor for gastric cancer in the cardiac region.
- In Asia and the Pacific, the prevalence of cagA positive Hp infection is very high, but it is useless to use as a marker for the development of gastric cancer. This is on the contrary to findings in Europe and North America, where a strong correlation between gastric cancer and cagA positive Hp was found.
- There is no proof that early gastric disease in Asia is a different disease entity.
- There is now recent proof that screening for individuals with asymptomatic Hp infection and successful treatment reduces the incidence of gastric cancer.

HISTOPATHOLOGY

Approximately 3% of all operated benign ulcers are associated with carcinoma of the mucosa, both near and far from the ulcer. Findings of early gastric disease take the form of rough mucosa with mildly pressed mucosal folds, sometimes with protruding borders or image similar to coral stones in the mucosa, but very well covered that it is often passes unsuspected.[7] The carcinoma rarely spreads to lymph nodes. The reported rate is 0-3%, for carcinoma of the mucosa, and 9-19% for carcinoma of the submucosa.[1]

Lauren (1965) classified the histology of early gastric cancer into 2 types, the intestinal and diffuse infiltration types. The intestinal type is characterized by an atypical tubular structure layered with bacillary, disorganized thoracic epithelial cells with enlarged, hyperchromatic or vesicular nuclei and a granular cytoplasm. In the diffusely infiltrative type, the shape and differentiation of the cells vary, from polygonal, round, foam cells with vacuolar cytoplasm, or signet rings, spread sporadically or clustered into small groups or in a chord-like shape, spread out in the gastric mucosa. Hirayama classified the intestinal type as well-differentiated, and the diffusely infiltrative type as undifferentiated.[12]

Biopsy in the area around the peptic ulcer may demonstrate pre-cancerous changes in the form of dysplasia. Dysplasia of gastric epithelial cells is a pre-invasive lesion with increased carcinomatous evolution in line with the degree of histological changes.[13] It is difficult to differentiate dysplasia and reactive epithelial atypia, and there have been proof that pure dysplasia may be a predisposition for gastric cancer, which can be detected in the early stages with multiple biopsy regimens and close observation. A combination of endoscopic biopsy and the brushing method for cytological evaluation increases the sensitivity rate of the diagnosis.[7]

CLASSIFICATION

Based the on findings from gastroscopy, fluoroscopy, histopathology, and microscopic examination, endoscopic experts from Japan from the Japanese Research Society for Gastric Cancer in 1962, early gastric cancer is classified into several types as follows:[2,7]

Type I. Protruded Type
- polypoid carcinoma similar to Borrman I
- invasion of carcinoma cells only limited to the mucosa and submucosa
- irregular shape, irregular surface, bleeding
- with or without surface ulceration

Type II. Superficial Type

Classified into 3 subtypes:

IIa. Elevated Type
- little elevation of the gastric mucosa
- almost alike with type I but more widely distributed and spread out

IIb. Flat Type
- no elevations or depression is found on the mucosa
- no mucosal color change

IIc. Depressed Type
- irregular border and surface
- clubbing or nick of mucosa folds
- hyperemic or hemorrhagic border
- adherent mucous with a dirty layer
- island-like residue

Type III. Excavated Type
- carcinomatose ulcer similar to Borrman II

A patient may suffer from 2 or more early gastric cancers, such as IIc + III or III + IIc, IIa + IIc, IIa + IIb + III, etc., where the first Roman numeral is more dominant than the one that follows.

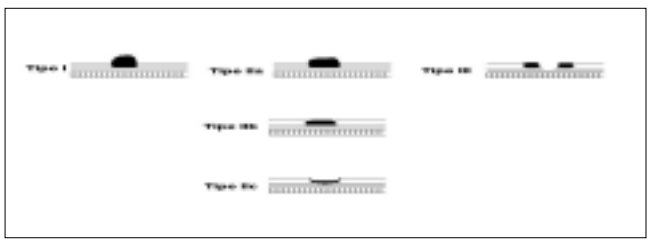

Figure 1. Scheme for Macroscopic Types of Early Gastric Cancer[2,12]

CLINICAL FINDINGS

Patients with early gastric cancer are detected clinically, since they come with recent dyspepsia or with unrelenting gastric ulcer. Even though symptoms like those of peptic ulcer have been heard for 20 years in several patients, weight loss might be a different signal, where clinical history do not point to carcinoma.[7]

DIAGNOSIS

The diagnosis of gastric cancer is made from physical examination, stool blood smear with the Benzidine test, cytological evaluation, double contrast X-ray, gastroscopy, gastrobiopsy, and radioactive phosphor.[2]

There are no specific tumor markers for early gastric cancer.[6] The first clues are obtained from endoscopic biopsy results demonstrating malignant cells. The endoscopic image of the gaster may seem normal, but most demonstrate a rough coral-like mucosa. Gastric biopsy can easily detect diffuse carcinomatous changes.[7]

Endoscopic evaluation of patients over 45 years of age with new symptoms of dyspepsia can increase the detection of early gastric cancer to 26%, and increase the number of operable patients to 63%.[14] According to Thomas, there might be adequate consideration to perform endoscopy on patients over 45 years of age prior to medication. Even though there is yet sufficient proof for this, this may be one of the means for early detection.[15]

DYE-SPRAYING TECHNIQUES

In Japan, early gastric cancer detection is performed using this technique, where the gastric mucosa is sprayed with methylene blue during endoscopy. The dye colors the intestinal mucosa but does not affect normal mucosa, while cancerous tissue is not colored. This technique is not used in the West.[7]

EARLY DETECTION

Early detection of early gastric cancer in Japan has made great developments. Endoscopy experts in the United States often discuss reports from Japan on early gastric cancer.[7]

Careful gastric cytological evaluation has been proven to be useful in the 1950s to 1960s for the early gastric cancer detection. In Japan, they conducted screening for the detection of early gastric cancer through mass surveys. The protocol is open, where everyone 40-50 years of age with new symptoms of dyspepsia has to undergo endoscopy, biopsy, and upper gastrointestinal tract X-ray. Special attention is paid to patients with type III intestinal dyspepsia. However, such early detection is not performed in Europe and the United States due to a difference in the health insurance system and based on the consideration of a low incidence rate for early gastric cancer.[3,4] Such early detection has increased the rate of diagnosis from 3% to 34.5%.[3]

ENDOSCOPIC ULTRASONOGRAPHY (EUS)

For now, EUS is still the most accurate device to establish the stage of early gastric cancer, particularly for non-ulcerative lesions.[16] If both EUS and conventional endoscopy is performed to determine the stage of early gastric cancer invasion, the accuracy of the degree of the lesion is increased, reducing the shortcomings of conventional endoscopy in determining the stage of early gastric cancer, particularly in the gastric corpus. As a comparison, the accuracy rate for conventional endoscopy and EUS according to a study by Hideo Yanai et al are 72.2% and 64.8% respectively.[17,18] Japan is a nation that has succeeded in developing the device. There are several ultrasound catheter probes that have been used in the development of EMR in Japan, such as probes 7, 5, 12, 15 and 20 MHz. The accuracy rate for EUS is 20 MHz for mucosal or submucosal staging of 72.3%, which can provide imaging to the muscular mucosa. Nevertheless, the efficacy of 20 MHz EUS has not been well agreed upon in early gastric cancer.[19]

In EUS, the image of the normal gastric wall is visualized as follows:[17]

- mucosa: a combination between the first hyperechoic layer and the second hypoechoic layer
- submucosa: the third hyperechoic layer
- muscularis propia: the fourth hypoechoic layer
- serous and subserous: the fifth hyperechoic layer

Findings of early gastric cancer are interpreted by determining tumor invasion according to the structure of the four gastric walls, where lesions are classified as EUS-M (mucosa), EUS-SM (submucosa), and EUS AD (advanced).[17]

TREATMENT

Several literatures mention that the choice of treatment for early gastric cancer is surgical treatment or endoscopic mucosal resection. The most important treatment procedure is to differentiate mucosal cancer and tumor that has invaded to deeper submucous layer, since this influences the choice of treatment, whether endoscopy or surgery should be performed.[17]

If early gastric cancer is found in asymptomatic patients with negative X-ray and endoscopic findings, total gastrectomy should be considered, except when a specific localized lesion is found.[7]

ENDOSCOPIC MUCOSAL RESECTION (EMR)

Endoscopic treatment is a local treatment indicated for early gastric cancer without metastasis.[19] EMR may be an alternative treatment for patients who refuse surgery or those who are bad candidates for surgery.[20] The role and benefits of EMR are increased in the treatment of early gastric cancer.[18]

Criteria for lesion that can be treated by means of EMR are as follows: [18]

1. Elevation type of < 2 cm
2. Depression type without ulceration < 1 cm

Successful treatment of early gastric cancer with EMR usually has the following characteristics: [18]

1. Is limited to the mucosa
2. Has a diameter of < 20 mm
3. There are no intramural ulcer changes
4. Is histologically classified as well-differentiated adenocarcinoma

The EMR techniques that are used are as follows: [18]

1. Double channel endoscopy
2. Aspiration mucosectomy and band ligation

For treatment, lesions are classified into 2 types:

1. Completely Resected (can undergo complete resection): the vertical and horizontal cutoff lines are not found following the first EMR.
2. Incompletely Resected (cannot undergo complete resection): vertical and horizontal cutoff lines are unclear following the first EMR.

Lesions that are incompletely resected may undergo either laser therapy, EMR and laser therapy, ethanol injection with heater probe coagulation, or heater probe coagulation alone.[1]

The most common complication of EMR is bleeding, which usually occurs in lesions over 30 mm in diameter. Thus, EMR is not recommended in lesions over 30 mm and for deep submucous infiltration. Perforation very rarely occurs.[18,20]

Nevertheless, other imaging modalities are needed to evaluate the extent of tissue involvement and the presence of lymph node metastasis prior to mucosectomy. EMR is a difficult and risky procedure. Even though there have been many satisfying results of many studies on EMR, in principle, an ideal technique should be easy to use, easy to obtain, and effective.[20]

PROGNOSIS

The prognosis for gastric cancer is not determined by the microscopic classification of the type of cancer, but most depends on the stage of invasion into the gastric wall, metastasis to regional lymph nodes, and the presence of distant metastasis.[6]

Early gastric cancer has a longer doubling time compared to its metastasis and advanced gastric cancer. For example, the doubling time of early gastric cancer in Japan is reported to range between 1.6 to 9.5 years, while that of advanced gastric cancer ranges from 69 to 305 days with a 17.7 to 60.2 days range for tumor metastasis to the abdominal wall.[7] By establishing the diagnosis of early gastric cancer, the prognosis is generally better, since rapid treatment measures can be taken.[2] Patients with positive cytological results without a detectable microscopic lesion is said to be able to survive without treatment for 5 to 6 years before the development of advanced lesions.[7] Histopathologically, the intestinal type early gastric cancer has a better prognosis compared to the diffuse infiltrative type.[12]

The survival rate reported by the Birmingham Cancer Registry for 1960-1969 in 90 patients with early gastric cancer was 57.8%.[5] Tsuhuma et al from the Centre for Adult Disease reported a survival rate of 34 out of 56 observed cases of early gastric cancer that has not undergone surgical treatment (64.5%).[21] While the 5-year survival rate for patients that undergo early gastric cancer is over 90%.[3,7,22] While they concluded that early diagnosis and treatment reduces the mortality in gastric cancer.[21,22]

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