The art and science of painting in early gastric cancer: is there a role for ablation therapy?

Clinicopathologically gastric adenocarcinomas can be divided into the following subtypes: intestinal type (fungating or polypoid, ulcerating, superficial spreading), diffusely spreading type (linitis plastica), and esophagogastric junction cancers. Gastric cancer is the world's second leading cause of cancer death; however, its prevalence is variable worldwide. In the United States, gastric cancer has fallen to the 13th most common cancer diagnosis and the 8th cause of cancer death. This is the sequela of a steady decline in the incidence since 1930 when it was the number one cancer killer, accounting for 38% of cancer deaths. While the incidence of gastric-body cancer has declined in the United States and in much of western Europe, there has been an increase in adenocarcinomas of the gastric cardia and the esophagogastric junction. The reasons for these trends remain obscure. There is inconsistent classification of gastric cardia and distal esophageal tumors in the literature, because many or most of these represent a distal spread of adenocarcinoma arising from specialized intestinal metaplasia of the distal esophagus or the esophagogastric junction. In Japan, gastric cancer remains among the most common cancers and causes of cancer death. This high incidence of gastric cancer is seen in other regions, including Costa Rica, China, Brazil, Yugoslavia, Poland, and Germany.[1] Genetic predispositions, *Helicobacter pylori* infection, diet, and other environmental factors have been implicated. In these regions, it is the intestinal-type gastric cancers that have the highest prevalence. These cancers originate intramucosally and occur predominantly in the gastric body and the antrum. The high incidence of gastric cancer in Japan has prompted broad population screening to identify early curable lesions. While partial or total gastrectomy may be curative in most patients with early gastric cancer (EGC), such surgery is accompanied by a considerable morbidity. These conditions have promoted interest in staging and therapy for EGC. Much of what we know about staging and the minimally invasive of EGC has come from Japanese endoscopic surgeons. Endoluminal management of early intestinal-type gastric cancer is the focus of this editorial.

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EGC is defined as cancer confined to the mucosa or the submucosa, with or without lymph-node metastasis. However, for practical purposes, EGC amenable to endoluminal therapies for curative intent are those EGC without lymph-node metastasis. EGC has an improved prognosis, with >90% 5-year survival after gastrectomy with removal of primary and secondary lymph nodes.[2,3] This compares favorably with the dismal <5% 5-year survival in patients with advanced disease. Operative resection is the standard treatment for EGC in western countries, usually in the form of subtotal gastrectomy. Endoscopic treatment of EGC with no metastases when using ablation and/or resection techniques has been adopted in Japan, and may be effective therapy in selective patients in the west.[4] Mass screening programs in Japan where the incidence of gastric cancers is 3- to 5-fold greater than in the west, have raised the percentage of early lesions detected, such that more than 45% to 50% of gastric adenocarcinomas treated in Japan are early stage lesions.[5] Conversely, EGC represents less than 10% of all gastric cancers diagnosed in countries other than Japan. However, this variance is changing, with EGC now being recognized more frequently outside of Japan, a change generally attributed to the widening use of endoscopy.[6,7]

In contrast to thermal ablation therapy, EMR for early gastric cancer achieves a high level of cure and reduces the reliance on pretreatment staging by providing the resected specimen for histopathologic evaluation.

A lower incidence of gastric cancer in the west does not support screening. Therefore, in the absence of mass screening programs, we have early endoscopic examination of any patient with dyspeptic symptoms, especially patients who are elderly, as the only practical approach to increasing the frequency of diagnosis of EGC.[8,9] Of 1900 cases of EGC in the registry of the National Cancer Center in Tokyo, 95% arose against a background of atrophic gastritis.[10] Chronic atrophic gastritis accompanied by intestinal metaplasia is recognized as a precursor of EGC, and vigilance of the endoscopist should be heightened when atrophic gastritis

is found on routine examination. In the west, chronic gastritis with intestinal metaplasia is associated with early and advanced gastric cancer. Therefore, individuals with a history of long-standing *Helicobacter pylori* infection (even after eradication) are at increased risk for developing gastric cancer and may benefit from surveillance.[11] Specifically, this would include patients with chronic gastritis, gastric intestinal metaplasia, gastric polyps (adenomatous and hyperplastic), a history of peptic ulcer disease, and prior gastric surgery, and also who are first- and second-generation Asian immigrants.

During endoscopy, the stomach should be well distended to allow inspection of the entire surface. Intestinal-type gastric cancers are found most commonly in the antropyloric region and the lesser curve. Biopsy specimens should be obtained from areas of discoloration (erythema or pallor), ulceration, nodularity, protrusion, or depression. The location of samples from the surface irregularities should be well documented to allow reidentification at subsequent endoscopy. We commonly perform 4-quadrant biopsies from the antrum, the body, the fundus, and the cardia to assess the distribution of intestinal metaplasia and dysplasia. However, it is unproved whether this approach improves the detection of early lesions. Adenomatous and hyperplastic gastric polyps should be removed, and careful examination of the surrounding gastric mucosa should be performed.

Improvements in endoscope-viewing optics have enabled an increase in the detection of EGC. Chromoendoscopy, including the use of high-resolution or magnification endoscopes, is intriguing. Contrast agents and vital stains may be applied by direct or indirect methods. Contrast agents (e.g., indigo carmine) have been used to diagnose otherwise inconspicuous lesions, to determine the lesion's surface extent, and to speculate its depth of infiltration. Vital stains (e.g., methylene blue) are intended to distinguish areas of dysplasia. Efficacy of chromoendoscopy for the detection of EGC is highly technique and interpretation related. Researchers rely on subtle changes in the mucosal surface relief and by uptake. While these techniques have contributed to improved outcomes in Japan, they remain of unproved value for routine use in the west.[12]

The TNM staging system for gastric cancer may be used to predict the prognosis and direct therapy. Histologic analysis of surgically resected gastric cancer specimens limited to the mucosa showed lymph-node metastases in only 0.5% to 3% of patients. Tumors that extend into the submucosa have lymph-node metastases in 10% to 30% of resected specimens.[4,13] In determining if EGC is suitable for endoscopic therapy, morphologic and EUS staging has been applied.

By taking into account features of morphology, surface relief pattern, histologic grading, and size, EGC lesions can be selected for attempted endoscopic therapy as an alternative to surgery in selective patients with a minimal risk of concurrent lymph-node metastases.[14] The classification of the Japanese Gastroenterological Endoscopy Society generally is used to describe the macroscopic features of EGC.[15] Such lesions are classified as protruding (type I), superficial or flat (type II), or excavating (type III). Type I cancers are polypoid lesions that protrude into the lumen. In type II, different degrees of flatness are recognized: a minimally elevated lesion, type IIA, appears at endoscopy as a plaque; a truly flat lesion, type IIB, is detected only as discoloration of the mucosal surface (pale or irregularly erythematous) and a finely nodular irregular surface; type IIC is minimally depressed, like a shallow ulcer, except that the edge is irregular or discolored. Type IIC is the most common type in Japan, currently accounting for 75% of EGCs. Type III occurs only rarely in Japan (1%), in contrast to Europe and the United States, where type III is the most common (30%-65%) and type II is the least common (8%-20%).[9,16] The presence or the absence of convergence of folds radiating from the lesion's central point provides a surface relief pattern of added significance.

If the surface of a type I lesion is smooth and is void of ulceration, it is likely that the malignancy remains confined to the mucosa. A type IIB or IIC lesion without fold convergence or bank formation (nodular elevated margin) is most often a mucosal cancer. If there is fold convergence in association with a type IIC lesion with only irregular tapering of the folds, the cancer is likely to be mucosal. However, if these folds end abruptly at the lesion, exhibit clubbing, or have nodular margins, it is likely that the cancer has invaded the submucosa. When the base of the depression is firm and unyielding to biopsy forceps, the depth of involvement is at least submucosal. If an ulcerative lesion is surrounded by an elevated, nodular margin (bank), the lesion is likely to be an advanced cancer. These empirically derived criteria are widely used by Japanese endoscopists to estimate the depth of penetration of the cancer. In one study of over 200 cases, these criteria predicted histologic depth of involvement with an accuracy of almost 70%; the depth was overestimated in 20% and underestimated in 10%.[14] The diameter of the lesion alone is not a reliable criterion for depth of invasion, except when smaller than 1 cm, in which case, the cancer is almost always mucosal. The same investigators also report that the risk of lymph-node metastases was only 0.2% in mucosal cancers if scars or ulcers were absent.[17]

Lymph-node metastases were found in only 0.5% of EGC that is well differentiated.[18]

Based on the above, the Japanese Research Society for Gastric Cancer established criteria for lesions suitable for endoscopic resection therapy: (1) well-differentiated adenocarcinoma-type morphologic I or IIA limited to the mucosa without ulceration and a maximum diameter of 20 mm, (2) well-differentiated adenocarcinoma type IIC limited to the mucosa without ulcers and a maximum diameter of 10 mm. When these criteria are applied, the risk of lymph-node metastasis accompanying EGC is 1.7%.

EUS is used to determine the pretreatment T and N stage. EUS may be performed with echoendoscopes or catheter