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EDITORIAL

Strategies for gastric cancer in the modern era

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Abstract

Gastric cancer is one of the most common neoplasms in Japan, and it is also the second leading cause of cancer-related deaths worldwide. Nowadays, infection with *Helicobacter pylori* (*H. pylori*) is a known risk factor for the development of gastric cancer. Therefore, gastric cancer should be considered as an infectious disease, and in fact, prophylactic eradication of *H. pylori* may prevent the development of metachronous gastric carcinoma. Before the role of *H. pylori* was understood, a different approach was used. Recently even after the cancer has developed, some newer therapeutic approaches have been pursued. These newer treatments have been summarized as "minimally invasive therapies" and use endoscopic or laparoscopic techniques. In addition, robotic approaches are being developed that seem to hold a great potential to change the surgical approach. Since basic understanding and treatment of the disease have both changed significantly over the last decade, we present a review of current advances in gastric cancer research and therapy.

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Key words: *Helicobacter pylori*; Endoscopic submucosal dissection; Laparoscopy-assisted distal gastrectomy; Gastric cancer; Robot

INTRODUCTION

In recent years, our understanding of the causes of gastric cancer has led to new therapies. The eradication of *Helicobacter pylori* (*H. pylori*) is now considered to be a key therapy for prevention of carcinogenesis. Even if patients still develop the disease, there are also new optimal therapies for both the early and advanced stages of cancer. In the case of early gastric cancer, the use of endoscopic submucosal dissection (ESD) and laparoscopy-assisted gastrectomy (LAG) is spreading widely, especially in Japan. In the case of advanced cancer, LAG and some new chemotherapeutic drugs are now available for treatment. Our strategies for treating gastric cancer are quite different from those used 10 years ago. Therefore, we present a review of current advances in gastric cancer research and treatment, from carcinogenesis to the most recent therapies.

CARCINOGENESIS

Both of genetic and environmental factors are thought to be involved in the carcinogenesis of gastric cancer. Although rare, E-cadherin mutation is reported as a genetic factor in hereditary diffuse gastric cancer[1] while food and infection are important environmental factors. A large number of studies have indicated that high intake of salted[2], smoked, pickled, and preserved foods (rich in nitrite, and preformed N-nitroso compounds) are associated with an increased risk of gastric cancer[3]. However, it is widely

recognized that the most important carcinogenic factor in gastric cancer is *H. pylori* infection. A meta-analysis report has indicated that the patients with gastric histology who are first-degree relatives of gastric cancer patients show significantly higher prevalence of *H. pylori* and higher risk of developing gastric cancer[4]. This suggests we could reduce gastric cancer by changing the environment.

After the effect of *H. pylori* was discovered by Marshall *et al*[5], it became accepted as the most common cause of gastritis. Etiologically, *H. pylori* is involved in gastric ulcers, duodenal ulcers, gastric mucosa-associated lymphoid tissue lymphomas[5], and is the most important cause of gastric cancer[6] based on both large epidemiological studies and animal experiments. Other *Helicobacter* species have also been identified in the liver[7], gall bladder[8,9], bile[10], and pancreas[11] from human samples. Our report also revealed the carcinogenic effect on biliary and pancreatic cell lines[12,13]. Similar to these reports, *Helicobacter* species were also believed to be one of the most important carcinogenic organisms and have been implicated in human carcinogenesis. *H. pylori* infection has clearly been established as a risk factor for gastric cancer. In gastric cell lines infected by *H. pylori,* NF-κB activity[14] and IL-8 secretion is[15] increased, and if the strain expresses CagA protein, the product of the *cagA* gene, malignancy is further increased. CagA is one of the most important and well-known virulent factors delivered into gastric epithelial cell lines by a bacterial type IV secretion system[16]. Moreover, CagA localizes to the inner surface of the plasma membrane and undergoes tyrosine phosphorylation by Src family kinases. Tyrosine-phosphorylated CagA then interacts with and activates SHP-2 phosphatase, a bona-fide oncoprotein deregulation factor, which is involved in a variety of human malignancies[17]. These results help to elucidate the way in which Shp-2 functions downstream of a receptor tyrosine kinase to promote the activation of the Ras-Erk pathway with potential therapeutic applications in cancer treatment[18]. CagA also binds to and inhibits PAR1b/MARK2 polarity-regulating kinase to disrupt tight junctions and epithelial apical-basolateral polarity. These CagA activities may collectively contribute to the transformation of gastric epithelial cells. Indeed, transgenic expression of CagA in mice results in the development of gastrointestinal and hematological malignancies, indicating that CagA is the first bacterial oncoprotein that acts on mammalian cells. The oncogenic potential of CagA may be further potentiated in the presence of chronic inflammation, which aberrantly induces activation-induced cytidine deaminase (AID), a member of the DNA/RNA-editing enzyme family. Ectopically expressed AID may contribute to *H. pylori*-initiated gastric carcinogenesis by increasing the likelihood of epithelial cells acquiring mutations in cancer-related genes[19]. As for the causal link between CagA and *in vivo* oncogenesis, wild-type CagA transgenic mice showed gastric epithelial hyperplasia and some of the mice developed gastric adenocarcinomas of the stomach. Hematological malignancies such as myelodysplastic/myeloproliferative neoplasms are also caused by gain-of-function SHP-2 mutations. Such pathological abnormalities were not observed in transgenic mice expressing phosphorylation-resistant CagA. These results provide the first direct evidence for the role of CagA as a bacterial oncoprotein that acts on mammalian cells and further indicate the importance of CagA tyrosine phosphorylation, which enables CagA to deregulate SHP-2, in the development of *H. pylori*-associated neoplasms[20].

PREVENTION OF CANCER

There is no doubt that *H. pylori* infection is strongly related to the genesis of gastric cancer. It follows that the eradication of *H. pylori* has some clinical benefit. For instance, the eradication of *H. pylori* may improve the hemoglobin and serum ferritin levels[21]. One large clinical trial in Japan conducted prospective post-eradication evaluations in 1342 consecutive patients with peptic ulcer disease who had received *H. pylori* eradication therapy. A total of 1120 patients were followed for more than a year. Gastric cancer developed in 8 of 944 patients cured of *H. pylori* infection and 4 of 176 who had persistent infection. In this study, only the patients with gastric ulcers developed gastric cancers. In patients with gastric ulcer, persistent infection was identified as a significant factor for the risk of developing gastric cancer. Eradication of *H. pylori* may reduce the risk of developing gastric cancer in patients with gastric ulcer[22]. In another Japanese multicenter randomized controlled trial, 544 patients with early gastric cancer, newly diagnosed and planning to have endoscopic treatment or in postresection follow-up, were randomly assigned to receive *H. pylori* eradication therapy. Patients were examined endoscopically at 6, 12, 24 and 36 mo after this assignment. The primary endpoint was diagnosis of new carcinoma at another site in the stomach. Analyses were conducted with the intention to treat. At the 3-year follow-up, metachronous gastric carcinoma had developed in 9 patients from the eradication group and in 24 patients from the control group. Prophylactic eradication of *H. pylori* after endoscopic resection of early gastric cancer should be performed to prevent the development of metachronous gastric carcinoma[23]. Based on the results from these studies, eradication after endoscopic resection of early gastric cancer is recommended. It is expected that eradication of *H. pylori* may also reduce the incidence rate.

EARLY GASTRIC CANCER THERAPY

Endoscopy

Early gastric cancer is defined as a neoplasm confined to the mucosa or submucosa, regardless of regional lymph node metastasis. Because the presence of lymph node metastasis has a strong influence on a patient's prognosis, a gastrectomy with complete removal of primary and secondary lymph nodes has been the standard treatment for early gastric cancer. The average 5-year survival rate of patients with early gastric cancer exceeded 90% according to the Japanese and European data from several studies[24-26]. The incidence of lymph node metastasis in early gastric cancer is reported as only 3% in intramucosal cases and

20% in submucosal cases[27]. Because of the comparatively lower risk of lymph node metastasis, surgery may an be excessive treatment for many early gastric cancers. Endoscopic resection is similar to surgery in efficacy but less invasive and more cost-effective. In addition, endoscopic resection allows accurate histological staging of cancer, which is critical in deciding whether additional treatment is necessary. Thus, endoscopic mucosal resection (EMR) has been widely accepted in Japan as a first-line treatment for early gastric cancer where there is no clinical evidence of lymph node metastasis. This practice is also gaining acceptance in other countries. Recent improvements in endoscopic treatment technique and technology have resulted in a new EMR method, ESD. The ESD method has brought great changes in the endoscopic resection of early gastric cancer, and an extension of the indication of ESD to include lesions of more than 2 cm is expected[28]. Standard ESD consists of 3 main steps. First, fluids are injected into the submucosal layer to separate it from the muscular layer. Second, circumferential cuts are made around the lesion. Third, the connective tissue of the submucosa is dissected under the lesion. The transparent hood attached at the end of the endoscope provides lesion counter traction and makes it easy to dissect the submucosal layer. The ESD technique has made it possible to remove not only large lesions but also lesions with ulcer scars and recurrent tumors after endoscopic resection. Because of severe submucosal fibrosis, these lesions have been too difficult to remove with conventional EMR. Disadvantages of ESD with regard to its technical difficulties and complications include bleeding and perforation. Bleeding during the procedure sometimes requires cessation of the procedure. However, with improvements in endoscopic technique and technology, we have gradually been able to manage bleeding during the procedure using endoscopic clipping, hemostatic forceps, APC, and other methods[29]. Nowadays, ESD is widely performed in Japan and is becoming a standard technique among Japanese endoscopists[30]. The risk of perforation during ESD is approximately 1%-4%, significantly higher than for conventional EMR. Perforation has been one of the most dangerous complications and it requires emergency surgical treatment. However, perforation of the stomach is currently managed conservatively without peritoneal dissemination by complete endoscopic enclosure with endoclips[31]. The endoscopic enclosure method has been attempted instead of emergency surgical treatment because the stomach is always clean during ESD. In Japan, ESD is clinically indicated for early gastric cancer, meeting not only the general criteria for EMR but also the extended criteria, which include lesions over 2 cm in diameter and ulcerative lesions. Based on retrospective data, the risk of lymph node metastasis in early gastric cancer is thought to be relatively low. Recently, a phase Ⅱ trial of ESD to expand the indication for early gastric cancer (JCOG 0607 study) has been initiated to evaluate the efficacy and safety of ESD for early gastric cancer. In the future, further extension of the indication for ESD should be considered. The combination of ESD with laparoscopic lymph node dissection, which has already been reported, might reduce surgery for early gastric cancer with risk of lymph node metastasis[32]. Further more, endoscopic full-thickness resection is currently under development in animal models, and has the potential to treat advanced gastric cancer using endoscopy in humans as well[33].

Laparoscopy

Since its description by Kitano *et al*[34] in 1991, laparoscopy-assisted distal gastrectomy (LADG) has been adopted for the treatment of early gastric cancer and has been performed worldwide, especially in Japan and Korea. In 1997, Goh *et al*[35] published the early results of 118 LADGs based on a questionnaire sent to 16 surgeons across 12 countries. They found that 10 of those surgeons deemed LADG to be superior to conventional open distal gastrectomy (ODG) because of faster recovery, reduced pain, and better cosmesis. Unfortunately, only 4 prospective randomized controlled trials (RCTs) have been published[36-39]. This may be due to the difficulty of conducting a large RCT in Japan, where LADGs are most frequently performed, because of the high incidence of early gastric cancer found in Japanese patients. This meta-analysis showed LADG for early gastric cancer is associated with lower morbidity, less pain, faster bowel function recovery, and shorter hospital stay. Recently, a phase II trial has been started in Japan to evaluate the safety of LADG for clinical stage I gastric cancer. A total of 170 patients will be enrolled in this study by expert laparoscopic surgeons from 16 institutions over 1 year. The primary endpoint to be determined is incidence of anastomotic leak and pancreatic fistula. The secondary endpoints are overall survival, relapse-free survival, proportion of LADGs completed, proportion of conversion from LADG to open gastrectomy, surgical morbidity, and short-term clinical outcomes[40]. In Korea, a phase Ⅲ, multicenter, prospective, randomized trial was conducted which included a total of 342 randomized patients (LADG, 179 patients; ODG, 163 patients) on the morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer. This study found no significant differences between the 2 groups in age, gender, and comorbidities. The postoperative complication rates of the LADG and ODG groups were 10.5% (17/179) and 14.7% (24/163), respectively ($P = 0.137$)[41]. After established laparoscopic surgery, less invasive laparoscopic surgery, such as single incisional laparoscopic surgery (SILS) or natural orifice translumenal endoscopic surgery (NOTES), is most likely to be performed. We have successfully performed less invasive surgery, such as SILS for cholecystectomy, hernioplasty, or for less invasive colectomy with a SILS port (Covidien, Mansfield, MA, USA), and we expect in the near future we will be able to manage the less invasive LADG with a SILS port.

Robotic surgery

As early as 2002, we started using robotic surgery for LADG for early gastric cancers with the voice-controlled robot AESOP (Figure 1). At that time, LADG was usu-

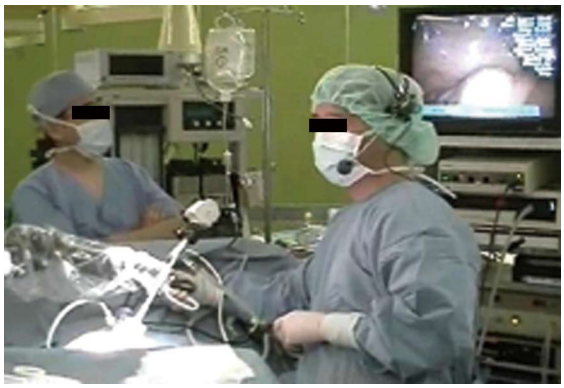

Figure 1 Laparoscopy-assisted distal gastrectomy with the voice- controlled robot AESOP. AESOP holds the laparoscope.

ally performed by three surgeons but by implementing this robotic system, it was possible to perform the procedure with only two surgeons. The robot AESOP has now been replaced by the da Vinci system and robotic gastrectomy is being performed around the world. The short-term results of conventional and robot-assisted minimally invasive procedures have been examined in gastric cancers[42] and these results support the feasibility of robotic surgery.

ADVANCED GASTRIC CANCER THERAPY

Operative therapy

Generally, advanced gastric cancer is treated by open surgery although a few institutions perform laparoscopic surgery and have good outcomes. A Korean group reported a retrospective multicenter study in which LAG was performed on 1485 gastric cancer patients. The results showed that 50 of 1417 patients (3.5%) had recurrences, 1.6% (19/1186) in early gastric cancer and 13.4% (31/231) in advanced gastric cancer[43]. A Chinese group reported a retrospective study that compared the use of LADG and ODG for advanced gastric cancer in which 78 patients who underwent LADG were compared with 90 patients who underwent ODG. No significant differences in the complication rate (7.7% *vs* 10.0%) between LADG and ODG were observed, supporting the feasibility of using LADG for advanced gastric cancer[44]. Another study was designed to assess long-term outcomes after laparoscopic gastrectomy with D2 dissection. The charts of 60 patients who underwent laparoscopic surgery were reviewed retrospectively, 56 laparoscopic subtotal gastrectomies and 4 laparoscopic total gastrectomies. Two postoperative deaths were reported. The mean hospital stay was 10 d, the mean follow-up was 30 mo, and the cumulative overall 5-year survival rate was 78%. Survival at 5 years for early gastric cancer was 94% and survival at 4 years for advanced gastric cancer was 53%. Thus, laparoscopic gastrectomy for cancer represents a valid alternative to open surgery with minimal morbidity and acceptable long-term survival[45]. An additional report from Japan described laparoscopic gastrectomy performed with regional lymph node dissection in 612 cases of gastric malignancies between 1998 and 2006. Distal gastrectomy was performed in 485 cases, proximal gastrectomy in 42 cases, and total gastrectomy in 85 cases. In all the cases, D1 or D2 lymph node dissection was performed according to the general rule of the Japanese Gastric Cancer Association. The result was quicker recovery in the laparoscopic gastrectomy cases than in the open cases. The postoperative complications using this technique were within a permissible range. No statistical difference was seen in the survival curve after surgery between the laparoscopic group of advanced cases, preoperatively diagnosed as surgical T2N1 or lower, and the open group[46]. This suggests that the laparoscopic technique is not only less invasive but also similar in safety and curative ability compared with open gastrectomy. Therefore, in the near future, laparoscopic gastrectomy may become the standard therapy for gastric cancer regardless of the stage.

Chemotherapy

Recently the report of a huge meta analysis report revealed postoperative adjuvant chemotherapy for resectable gastric cancer based on fluorouracil regimens increased five-year overall survival by about 5% (from 49.6% to 55.3%) compared with surgery alone[47]. S-1 which is also new oral fluoropyrimidine formulation, is especially favored in Japan. Additionally, the recent introduction of active new-generation agents such as taxanes, irinotecan (CPT-11), oxaliplatin, and capecitabine, offers hope for markedly improving patient outcomes. Docetaxel, as well as the other new-generation agents, plays a key role in the development of new-era chemotherapy. The incorporation of taxanes has provided several regimens, such as docetaxel/cisplatin/5-fluorouracil (5-FU) (DCF), that could become standard treatments. The DCF regimen is already regarded as a standard treatment option in advanced gastric cancer in selected patients in good condition. In various treatment settings, attention has been focused recently on innovative approaches involving the incorporation of biological agents, such as cetuximab, bevacizumab, everolimus, and sunitinib, into docetaxel-containing combinations. The ongoing clinical trials of a number of new regimens will clarify their clinical benefits in gastric cancer treatment. Along with the development of more active docetaxel combination regimens, the identification of predictive biomarkers for each regimen has been intensively studied recently[48]. The role of trastuzumab in curative gastric cancer treatment needs to be studied, as well as monotherapy, maintenance therapy, and second-line treatment in the palliative setting[49]. Amplification of the HER2 gene and over-expression of the HER2 protein in gastric cancer have been shown in a large number of studies. HER2 positivity, which can be detected in approximately 20% of patients, is a characteristic associated with poor prognosis. Preclinical *in vitro* and *in vivo* studies have demonstrated that trastuzumab and lapatinib are effective in different gastric cancer models and have, thus, led to the initiation of clinical studies. In the first phase III study, the ToGA trial, HER2-positive patients with advanced gastro-esophageal and gastric adenocarcinoma were randomized to receive 5-FU/capecitabine and cisplatin either alone or in

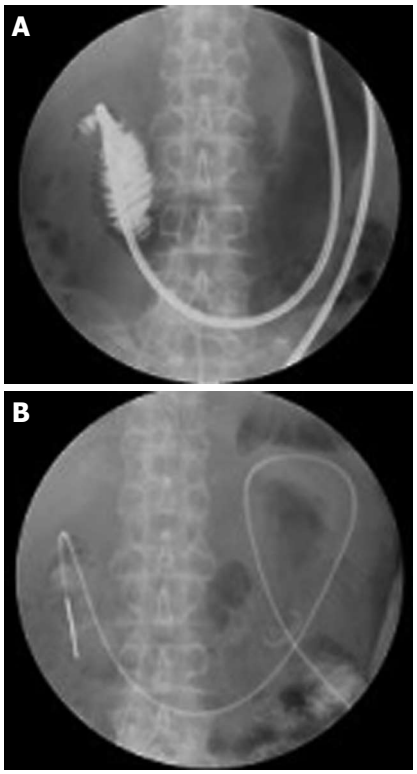

Figure 2 Transgastrostomic ultrathin scope passing through the pyloric stricture (A) and percutaneous endoscopic jejunostomy feeding tube placed for palliative therapy (B).

combination with trastuzumab. A statically significant gain in the overall survival was seen in the patients who received the combined treatment of trastuzumab and chemotherapy. It is expected that the encouraging results from the ToGA trial will have an immediate impact on the management of patients and that routine HER2 testing of patients with advanced gastric cancer will be initiated within a relatively short period of time[50].

Palliative therapy

In cases of non-curative gastric cancer, patients sometimes suffer from nausea or vomiting due to bowel stenosis. In such cases, ordinary nasogastric tube drainage or bypass operation is worth considering. However, a nasogastric tube is not completely effective and the bypass operation is too invasive. Therefore we often apply endoscopic palliative therapy for such patients, generally with an ultrathin gastroscope. An ultrathin gastroscope is used to pass a severe tumor stricture, advance a guide wire beyond the stenosis, and insert a feeding tube or stent beyond the stricture. However, it may be easier to reach deep strictures using a transgastrostomic fistula route rather than a transoral route. We used the fistula formed during percutaneous endoscopic gastrostomy (PEG) or duodenostomy and an ultrathin endoscope to treat deep upper-gastrointestinal strictures. These endoscopic techniques are very useful to avoid surgical management, such as bypass operation, in executing difficult approaches involving the duodenum and proximal jejunum. In the case of pyloric stenosis, we have

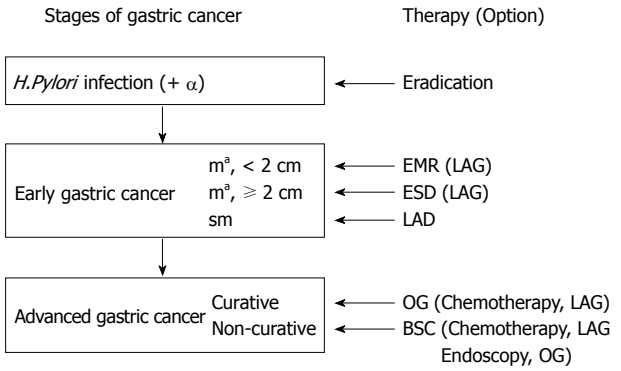

Figure 3 New strategies for gastric cancer. If a patient develops cancer and even if it is diagnosed at an early stage, it may be resectable using less invasive endoscopic submucosal dissection or laparoscopy-assisted gastrectomy (LAG). In the case of advanced stage cancers, instead of open gastrectomy, LAG may also be possible and newer, more effective chemotherapy may be applicable. In case of non-curative advanced gastric cancer, various less invasive therapies may be feasible as best supportive care. m[a]: Except for poorly differentiated adenocarcinoma; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; OG: Open gastrectomy; BSC: Best supportive care.

performed percutaneous endoscopic jejunostomy (PEJ) to insert a transgastrostomic jejunal tube as an alimentation method. In such cases, the pyrrolic stricture prevented passage because of intragastric flexing, so we chose a trans-PEG approach, which was facilitated by the ultrathin scope (Figure 2A). An ultrathin transnasal gastroscope was used to pass the severe tumor strictures. A guide wire was inserted beyond the stenosis, and a PEJ feeding tube was inserted in its place (Figure 2B). The patient continued to be fed by the PEJ tube in the same manner as the PEG tube. As in this case, we often insert a tube or stent for palliation. Even if the stricture is more distal, using this method it is possible to insert the stent using this method[51]. Currently, athrough the scope stent is also available[52], and we also use it in palliative therapy instead of in operations. Otherwise very aggressive operations are used as a palliation. A few surgeons perform peritonectomy for a patient who has carcinomatosa peritonitis due to gastric cancer. In other situations, such as pseudomyxoma, mesothelioma, or some colon cancers, some studies have shown good outcomes, especially with intraperitoneal hyperthermic chemotherapy[53]. However, few studies show good outcomes for gastric cancer.

CONCLUSION

The study of gastric cancer is evolutionally advancing. Simultaneously, therapies for gastric cancer are undergoing dramatic change. This is true especially in Japan, where gastric cancer is often detected at an early stage and cured by minimally invasive therapy, such as ESD or laparoscopic surgery. This therapy is gradually being adopted for use worldwide. In the near future, the eradication of *H. pylori* may become a common prophylactic therapy, and minimally invasive robotic surgery, such as robotic prostatectomy, may become a mainstream surgical therapy. Since the treatment of stomach cancer is changing rapidly and we have to have new strategies for gastric cancer (Figure 3), it

is imperative that we have the most currently information available in order to provide the most effective treatment.

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