

Treatment of Gastric Cancer in Japan

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Although the incidence of gastric cancer has decreased because of the lower rate of *Helicobacter pylori* infection, it still accounts for a large number of deaths in Japan. Gastric cancer is mainly treated by resection, and the rate of radical resection is high in Japan because approximately 50% of cases are diagnosed at an early stage. Treatment advances have increased the number of endoscopic submucosal dissections, and development of laparoscopic surgery and robot-assisted surgery as minimally invasive approaches has yielded results similar to those of conventional surgeries, at least in the short term. Cases for which resection is contraindicated are treated with chemotherapy if performance status can be maintained. Although anticancer drugs are continuously under development, treatment outcomes remain unsatisfactory. As Japan becomes a super-aging society, the number of refractory cases is projected to increase. Therefore, evidence of any benefit for minimally invasive surgery and function-preserving surgery needs to be reported quickly. In this paper, we discuss gastric cancer treatment modalities recommended in the fifth edition of the gastric cancer treatment guidelines and describe recent research findings. (J Nippon Med Sch 2021; 88: 156–162)

Key words: gastric cancer, endoscopic resection, surgical resection, chemotherapy

Introduction

Although the incidence of gastric cancer is declining because of the decrease in the rate of *Helicobacter pylori* infection, the mortality rate for gastric cancer remains high. In 2018, gastric cancer was the second and fourth most common cause of death among men and women, respectively, in Japan¹. The primary treatment modality for gastric cancer is resection, but the rate of open resection for distal advanced cancer with previous chronic atrophic gastritis is diminishing as the rate of *H. pylori* infection decreases. In Japan, treatment for gastric cancer is generally decided in accordance with the fifth edition of the Gastric Cancer Treatment Guideline, which is prepared by the Japanese Gastric Cancer Association (Fig. 1). Approximately 50% of gastric cancer cases in Japan are diagnosed at an early stage; thus, the rate of minimally invasive resection, such as endoscopic, laparoscopic, and robotic surgery, is high. Advanced gastric cancer for

which radical resection is not indicated is primarily treated with chemotherapy. Although new anticancer drugs have been developed, the prognosis for advanced gastric cancer remains unsatisfactory. This review discusses the latest evidence on endoscopic resection, surgical resection, and chemotherapy as primary treatment modalities for gastric cancer.

Endoscopic Resection

According to the National Database of the Ministry of Health, Labour and Welfare, 54,470 (53.2%) of the 102,315 gastric cancer operations in 2017 were endoscopic resections, and the rate is increasing². There are two types of endoscopic treatment: endoscopic mucosal resection and endoscopic submucosal dissection. In endoscopic mucosal resection the mucosa of the stomach is raised, the lesion is snared with a steel wire, and high-frequency ablation is performed^{3,4}. In endoscopic submucosal dissec-

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Treatment of Gastric Cancer

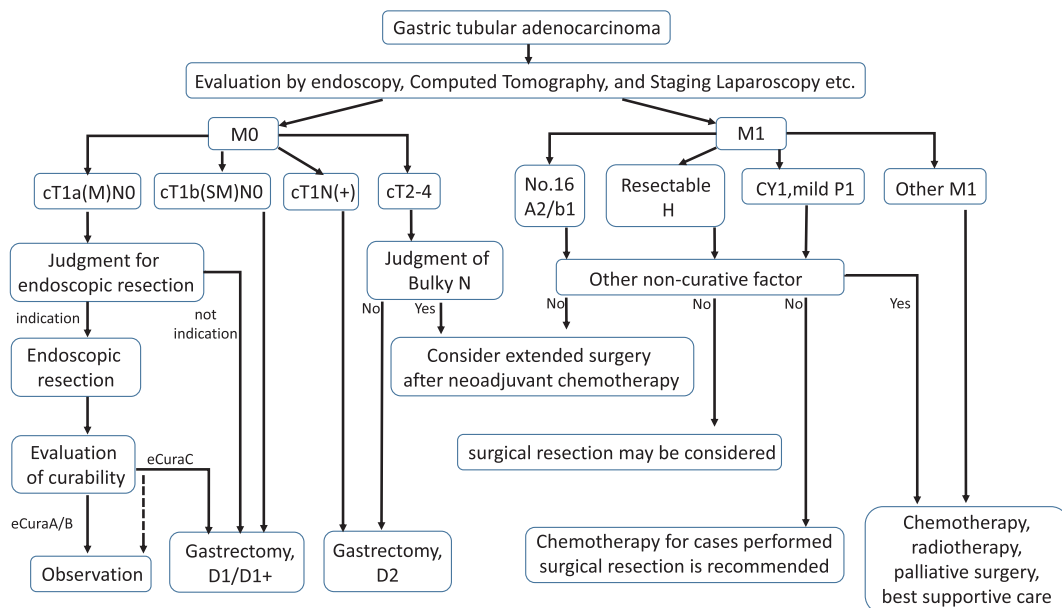


Fig. 1 Flowchart for treatment selection in gastric cancer
 Excerpted and modified from the fifth edition of the Gastric Cancer Treatment Guideline



Fig. 2 Endoscopic submucosal dissection procedure

The mucosa around the lesion is incised with a high-frequency device, followed by concurrent dissection of the submucosa and resection of lesions.

tion the mucosa around the lesion is incised with a high-frequency device and the submucosa is then dissected and excised⁵⁻⁷. Development of the endoscopic submucosal dissection procedure has enabled complete resection of lesions and is an important advance in endoscopic treatment (Fig. 2). The fifth edition of the Gastric Cancer Treatment Guidelines recommends endoscopic resection for cT1a early gastric cancer lesions with a <1%

estimated risk of lymph node metastasis. Endoscopic treatment has absolute and expanded indications, both of which are determined based on tumor size, pathological type, and presence or absence of ulcerative findings^{8,9}. However, endoscopic treatment may also achieve cure, even in patients who do not satisfy the above indications. Endoscopic treatment can be considered a “relative indication” for patients who refuse surgery or cannot un-

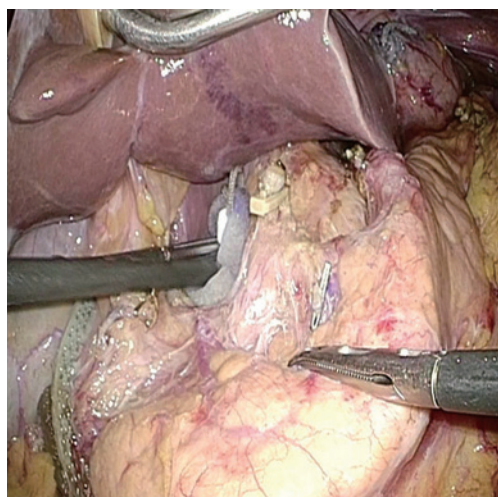


Fig. 3 Laparoscopic dissection of a lymph node
Suprapancreatic lymph node dissection via laparoscopy.
The procedure achieves outcomes comparable to those of
open surgery.

dergo surgery because of comorbidities. This “relative indication” will likely increase as we become a super-aging society.

Laparoscopic and endoscopic cooperative surgery (LECS)¹⁰-first reported by Hiki et al. in 2008-was developed to treat gastric submucosal tumors. The original method involves full-thickness resection that perforates the stomach wall and thus is contraindicated for gastric cancer because of concerns regarding dissemination. However, a non-perforating LECS approach, such as a combination of laparoscopic and endoscopic approaches for neoplasia with non-exposed technique¹¹ and non-exposed endoscopic wall inversion surgery¹², has been recently developed. This approach does not open the gastric cavity and may thus be used in gastric cancer. For example, full-thickness resection by LECS and/or sentinel node navigation surgery may be a treatment option for cases in which the depth of cancer invasion deviates from the “relative indication” in the absence of clinical lymph node metastasis. It can also be performed when endoscopic submucosal dissection is technically difficult.

Surgical Resection

According to the 2017 National Database, 48,485 (47.3%) of the 102,315 gastric cancer operations were surgical resections, among which 21,291 procedures (44.5%) were performed laparoscopically². Surgical resection involves lymph node dissection and gastrectomy for advanced gastric cancer or early gastric cancer with a high risk of lymph node metastasis. The fifth edition of the Gastric Cancer Treatment Guidelines recommends radical gas-

trectomy for M0 patients for whom endoscopic resection is contraindicated (or eCura C after endoscopic submucosal dissection). Furthermore, if regional lymph node swelling is greater than 3 cm, extended surgery after neoadjuvant chemotherapy should be considered. Surgery alone may be considered for resectable H, minor P1, and CY1. Meanwhile, extended surgery after neoadjuvant chemotherapy is recommended for para-aortic lymph node (No. 16a2/b1) metastasis alone (Fig. 1).

Gastric surgery can be classified as total gastrectomy, distal gastrectomy, pylorus-preserving gastrectomy, and proximal gastrectomy. Although segmental resection and local resection are commonly performed, they are regarded as investigational surgical techniques. Lymph node dissection is decided according to clinical T and/or N factor, and D1 or D1+ dissection is indicated for cT1 lesions and D2 dissection for cT2 or cN (+) lesions. The range of lymph node dissection (eg, D1/D1+/D2) is determined for all four surgical procedures, and D2 is exclusively defined for total and distal gastrectomies. Therefore, the standard surgical modality for advanced cancer with cT2 or higher or cN (+) lesions is total gastrectomy or distal gastrectomy. For cT1N0 tumors, a more conservative surgery, such as pylorus-preserving gastrectomy or proximal gastrectomy, may be considered. The choice depends on tumor location and the need to preserve stomach function. Although there is no definite evidence, extended dissection of D2 or higher may be performed, such as splenectomy, for advanced gastric cancer invading the upper greater curvature.

Laparoscopic surgery-first reported in 1991 by Kitano et al.¹³-has become widely used over the last 30 years, in conjunction with improvements in surgical skills, development of novel medical devices, and increased emphasis on posttreatment quality of life¹⁴ (Fig. 3). A 2016 questionnaire survey on endoscopic surgery, distributed by the Japanese Society of Endoscopic Surgery¹⁵, showed that laparoscopic surgeries outnumbered open surgeries, and a 2010 clinical trial (JCOG0703) reported that laparoscopy-assisted distal gastrectomy was safe¹⁶. On the basis of these results, the fourth edition of the Gastric Cancer Treatment Guidelines recommended that laparoscopic surgery be considered as an option in general clinical practice for cStage I cancer that is indicated for distal gastrectomy. In addition, the safety of laparoscopic proximal gastrectomy and total gastrectomy was proven in clinical trials (JCOG1401)¹⁷. Accordingly, the Gastric Cancer Treatment Guidelines Committee recommended laparoscopy-assisted total gastrectomy and laparoscopy-



Fig. 4 The da Vinci surgical system

Photograph of the da Vinci Xi surgical system developed by Intuitive Surgical in the United States.

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assisted proximal gastrectomy as standard treatments for cStage I gastric cancer. Laparoscopic treatment for advanced gastric cancer was found to be safe in a joint clinical trial in Japan and South Korea (JLSSG0901)¹⁸. Patient follow-up is ongoing, and the results, including outcomes, are expected to influence current treatment guidelines.

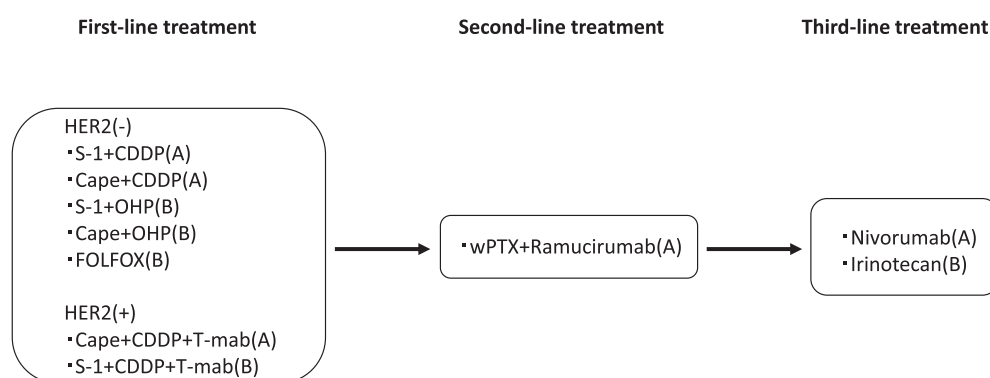
Laparoscopic surgery techniques are close to optimal, at least in high-volume centers, and laparoscopic surgery is thus projected to be more widely used for expanded indications and in cases of advanced cancer. The da Vinci Surgical System, developed by Intuitive Surgical in the United States (Fig. 4), became more widely used after Ishida et al.¹⁹ first reported robot-assisted gastrectomy in Japan, in 2009. The major features of this system are its multi-joint movement, tremor filtering, and three-dimensional view, which enable highly accurate, “millimeter unit”, surgery. An analysis of short-term postoperative outcomes found that robotic surgery achieved a lower rate of grade ≥ 3 Clavien-Dindo complications and shorter hospital stays²⁰. The drain amylase level on postoperative day 1 was also significantly lower for this technique²¹. Therefore, many surgeons believe that robotic surgery achieves short-term results that are almost equivalent to those of laparoscopic gastrectomy, if the surgeon is experienced. The exponential increase in the number of robot-assisted operations, since insurance began covering these procedures, in 2018, suggests that it

will become the main surgical approach in the future, if the cost can be reduced.

We reviewed evidence on laparotomy procedures. The JCOG9501 trial investigated whether D2 plus No. 16 dissection was superior to standard D2 dissection for T2 or worse gastric cancer with no macroscopic metastasis to the para-aortic node²². Unfortunately, there was no significant difference in 5-year survival between the two groups, and prophylactic No. 16 dissection was not established as a standard treatment. As mentioned above, extended surgery after neoadjuvant chemotherapy is considered for patients with clinical metastasis limited to the No. 16 lymph node area.

Total gastrectomy with splenectomy has long been performed in Japan as curative surgery for gastric cancer patients with advanced lesions in the upper part of the stomach. However, the JCOG0110 trial found that non-splenectomy was noninferior to splenectomy²³. Furthermore, incidences of postoperative complications were higher in the splenectomy group. As a result, No. 10 was deleted from the definition of D2 dissection for total gastrectomy in the fifth edition of the Gastric Cancer Treatment Guideline. However, “lesions invading the curvature line” were excluded from the case selection; thus, it is important to understand that the significance of splenectomy for such cases has not yet been determined. We believe that splenectomy should be performed for sufficient dissection in patients with clinically suspected metastasis in No. 10. However, surgeons must take care to avoid complications such as pancreatic fistula and intraperitoneal abscess. Future studies should attempt to accumulate evidence on the usefulness of splenectomy for cases of greater curvature invasion.

Bursectomy for advanced cancer, which aims to remove micrometastases that may be present in the bursa, is a procedure that has long been performed by Japanese surgeons. The randomized controlled trial (RCT) JCOG 1001 investigated whether bursectomy was superior to omentectomy in standard gastrectomy for T3/T4a gastric cancer but was discontinued because the survival curve of the bursectomy group was slightly lower than that of the omentectomy group in interim analysis. Further, the amount of bleeding, operation time, and rate of postoperative pancreatic juice leakage were significantly higher in the bursectomy group than in the omentectomy group²⁴. Therefore, the usefulness of bursectomy was rejected in the fifth edition of the Gastric Cancer Treatment Guideline. Ongoing RCTs (JCOG1711) are examining the noninferiority of omitting omentectomy²⁵.



Abbreviation: S-1: tegafur•gimeracil•oteracil potassium, CDDP: cisplatin, Cape: capecitabine, OHP: oxaliplatin, FOLFOX: fluorouracil+calcium levofolinate hydrate+oxaliplatin combination treatment, T-mab: trastuzumab, wPTX: paclitaxel weekly administration

The parentheses after the regimen indicate the level of evidence.

※Partially excerpted and modified from the Gastric Cancer Treatment Guideline 5th Edition

Fig. 5 Chemotherapy regimen recommended for unresectable/recurrent gastric cancer
Excerpted and modified from the fifth edition of the Gastric Cancer Treatment Guideline

Collection of data on radical resection after neoadjuvant chemotherapy was delayed in Japan, partly because more than 50% of gastric cancers are diagnosed at an early stage. The results of the first Japanese RCT on neoadjuvant chemotherapy (JCOG 0501) were reported in 2018²⁶. In this trial, patients with scirrhous gastric cancer (type 4) or type 3 gastric cancer ≥ 8 cm were considered eligible for resection but had poor outcomes, and the effectiveness of neoadjuvant chemotherapy can be expected. JCOG 0501 attempted to confirm the superiority of neoadjuvant chemotherapy with S-1 plus cisplatin plus surgery plus postoperative S-1 adjuvant chemotherapy over standard D2 dissection surgery plus postoperative S-1 adjuvant chemotherapy. However, contrary to expectations, 3-year survival did not significantly differ between the standard treatment group and neoadjuvant chemotherapy group (62.4% vs 60.9%, respectively). Thus, neoadjuvant chemotherapy has not been established as a standard treatment. An RCT of neoadjuvant chemotherapy with S-1 plus oxaliplatin for cT3/4 and N (+) (JCOG 1509) is ongoing²⁷.

Chemotherapy

Chemotherapy for gastric cancer is broadly classified as treatment for unresectable or recurrent cases, postoperative adjuvant chemotherapy, and neoadjuvant chemotherapy. Here, we describe the first two treatments, for which evidence is strong.

Chemotherapy for Unresected/Recurrent Gastric Cancer

Figure 5 shows the recommended chemotherapy regi-

men for unresected/recurrent gastric cancer in the fifth edition of the Gastric Cancer Treatment Guidelines. Chemotherapy for unresectable or recurrent gastric cancer is expected to improve clinical symptoms during progression and prolong overall survival. However, it is not a curative modality. The indications are a performance status of 2 or higher, stable function of major organs, and absence of severe comorbidities. Advances in chemotherapy drugs have increased response rates; however, median survival remains about 6-14 months^{28,29}. The principal chemotherapeutic agents for gastric cancer are 5-FU, levofolinate calcium, S-1, capecitabine, cisplatin, oxaliplatin, irinotecan, docetaxel, paclitaxel, nab-paclitaxel, trastuzumab, ramucirumab, and nivolumab. Chemotherapy for gastric cancer can be administered as monotherapy or combination therapy, as shown in Figure 5. The Japan Gastric Cancer Society Guidelines Committee recommends pembrolizumab after second-line treatment (evidence level B); trifluridine, tipiracil, and hydrochloride (TAS-102) after third-line treatment (evidence level A); and trastuzumab deruxtecan after third-line treatment for human epidermal growth factor receptor 2 (+) gastric cancer (evidence level A). These recommendations are all based on the results of RCTs³⁰⁻³². During regimen selection, it is important to consider a treatment strategy that uses the drugs pyrimidine fluoride, platinum, taxane, irinotecan, ramucirumab, and nivolumab, as these are known to prolong survival.

Adjuvant Chemotherapy

Adjuvant chemotherapy is administered to prevent recurrence after curative resection. S-1 for 1 year, or cape-

citabine plus oxaliplatin for 6 months, is the gold standard of adjuvant chemotherapy for pStage II, IIIA, and IIIB gastric cancer in the 13th Edition of the Japanese Classification of Gastric Carcinoma. This recommendation is based on the results of the ACTS-GC study^{33,34} and CLASSIC study³⁵. However, adjuvant chemotherapy using the above regimen is inadequate for Stage III gastric cancer. Thus, Japan and South Korea conducted a joint RCT (JACCRO GC-07)³⁶ that investigated whether addition of docetaxel to oral fluoropyrimidine improves the efficacy of chemotherapy for gastric cancer. Overall survival was better for the S-1 plus docetaxel arm than for the S-1 alone arm. The Japan Gastric Cancer Society Guidelines Committee thus recommends S-1 plus docetaxel for pStage III gastric cancer (evidence level A).

Conclusion

Although surgery is the most improved treatment modality for gastric cancer in Japan, outcomes for surgical treatment of advanced gastric cancer have worsened. The current goal of surgical resection is to preserve gastric function and achieve R0 resection without perioperative complications. The proportion of frail patients is projected to increase with the super-aging of the Japanese population, and some patients are already difficult to treat according to current guidelines. Improving treatment outcomes for gastric cancer will require a multidisciplinary approach combining endoscopy, drug treatment, and surgery as part of a well-balanced treatment strategy, especially for frail patients.

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