Guidelines for Diagnosis and Treatment of Carcinoma of the Stomach

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Overview

Objective of Guidelines

Gastric Cancer Treatment Guidelines for doctors in clinical practice is designed to 1) provide appropriate indications for gastric cancer treatment, 2) reducing disparities in treatment among different institutions, 3) improve the safety and efficacy of treatment, 4) avoid unnecessary treatment to reduce both personal and economic burden, and 5) disclose the Guidelines to the public for mutual understanding between patients and doctors. The Guidelines represent a consensus regarding approaches to treatment, not control individual treatment modality different from the Guidelines.

In addition, the Guidelines are expected to be interpreted easily for the understanding of the general public.

Principles of Guidelines

The Guidelines provide a consensus regarding treatment indications, not discuss the technical aspects of each treatment. To show appropriate treatment indications; 1) each treatment is introduced in relation to the progression of cancer without excess or deficiency, 2) evaluation of treatment efficacy is evidence-based, 3) treatment is evaluated primary by the survival period, while symptom relief, tumor shrinkage and improvement of QOL are also evaluated, 4) treatment efficacy for clinical practice is principally presented, but promising experimental treatments in some institutes are also included when needed. Accordingly, treatment options for individual stages are shown in two parts of clinical practice and experimental study. Then, principles of indication and criteria details of each treatment modality are provided. In addition to *Discussion*, the data and literatures supporting the guidelines are included in *References*.

The guidelines will be continually-revised as treatments advance according to the following procedure.

Guideline Process

For preparation of guidelines, guideline-developing group and guideline-assessment group independently established under Guidelines Developing Committee of JGCA make a draft of the guidelines. Getting the feedback from the discussion of the Consensus meeting of the Association and opinions from outside the Association, a final plan is compiled and validated with approval of the Association. The revision of guidelines has the same procedure. If the guidelines prove to be unsuitable after implementation, it should be reported to the Committee for the next revision.

How to Use Guidelines

This guidelines is published as a booklet for the widespread use in the scene of gastric cancer treatment and also available on the website of the Association.

Informed Consent (IC) is a premise of decision-making for gastric cancer treatment. Doctors are expected to simply explain the details of each treatment modality referring to the guidelines and help patients to make decisions on their own. It is recommended to use written documents for the procedure of IC. When treatment modality different from the guidelines is employed, doctors are required to explain the reason and obtain full understanding from patients.

Discussion

I Treatment Decision-Making by Stage

Treatment options for gastric cancer by preoperative/intraoperative stage are shown in Table 1 and 2. The treatments recommended for clinical practice are listed in Table 1, and those without evidence or experimental treatments in some institutes are in Table 2. When experimental treatment is conducted, doctors are expected to explain the reason in advance, ensure accurate understanding from patients, and obtain informed consent documents from them.

Table 1 Treatment options by stage for clinical practice

	N0	N1	N2	N3
T1 (M)	**IA** · EMR (en bloc resection) (differentiated type, ≤ 2.0 cm in diameter, no ulceration in cases of depressed-type · Modified surgery-A (other than those above)	**IB** · Modified surgery-B (≤ 2.0 cm in diameter) · Standard surgery (≥ 2.1 cm in diameter)	**II** · Standard surgery	**IV** · Extended surgery · Palliative surgery · Chemotherapy · Radiation therapy · Palliative care
T1 (SM)	**IA** · Modified surgery-A (differentiated-type, ≤ 1.5 cm in diameter) · Modified surgery-B (other than those above)			
T2	**IB** · Standard surgery	**II** · Standard surgery	**IIIA** · Standard surgery	
T3	**II** · Standard surgery	**IIIA** · Standard surgery	**IIIB** · Standard surgery	
T4	**IIIA** · Extended surgery (combined resection)	**IIIB** · Extended surgery (combined resection)		
H1, P1 CY1, M1 Relapse				

1 Modified Surgery-A & -B: resection less than standard surgery (see below 2). They include omentum-preserving procedure, omission of omento-bursectomy, pylorus-preserving gastrectomy (PPG), and vagus-preserving procedure. According to the extent of lymph node dissection, modified surgery is classified into surgery-A (D1+α dissection) and

surgery-B (D1+β dissection).

· Dissected lymph nodes for α: No. 7 irrespective of the location of lesions, and additionally No.8a in cases with lesions located in the lower-third of the stomach.

· Dissected lymph nodes for β: No.7, 8a, 9

2 Standard surgery: resection of two-thirds of the stomach with D2 dissection

3 Extended surgery (combined resection): standard surgery with combined resection of the involved organs

4 Treatment options by stage are based on macroscopic staging during surgery. If there is any doubt about indication for modified surgery, standard surgery is recommended.

Table 2 Treatment options by stage for clinical study

	N0	**N1**	**N2**	**N3**
T1 (M) **>2.0 cm**	**IA** · EMR (piecemeal resection) · ESD (endoscopic submucosal dissection) · EMR (laser treatment for incomplete resection)	**IB** · Laparoscopy-assisted gastrectomy	**II**	**IV** · Extended surgery (combined resection, dissection) · Reduction surgery · Chemotherapy (systemic or regional) · Hyperthermochemotherapy
T1 (SM)	**IA** · Wedge or segmental resection · Laparoscopic wedge resection · Laparoscopy-assisted gastrectomy			
T2	**IB** · Laparoscopy-assisted gastrectomy	**II** · Postoperative adjuvant chemotherapy	**IIIA** · Postoperative adjuvant chemotherapy	
T3	**II** · Postoperative adjuvant chemotherapy · Neoadjuvant	**IIIA** · Extended surgery (dissection) · Postoperative adjuvant	**IIIB** · Extended surgery (dissection) · Postoperative adjuvant	

	chemotherapy	chemotherapy · Neoadjuvant chemotherapy	chemotherapy · Neoadjuvant chemotherapy
T4	**IIIA** · Chemotherapy · Neoadjuvant chemotherapy · Postoperative adjuvant chemotherapy · Radiation therapy	**IIIB** · Extended surgery (combined resection, dissection) · Chemotherapy · Neoadjuvant chemotherapy · Postoperative adjuvant chemotherapy	
H1, P1 **CY1, M1** **Relapse**			

1) Extended surgery (dissection): extended gastrectomy with extended lymphadenectomy.
2) Extended surgery (combined resection, dissection): gastrectomy with combined resection of involved organs and extended lymphadenectomy.

II Types of Gastric Cancer Treatment and its Indication

Endoscopic Mucosal Resection (EMR)

Endoscopic mucosal resection (EMR) is a technique to resect an area of mucosa including diseased site in the stomach and retrieve the removed tissues for histological evaluation by endoscopy. The principal methods includes injection of solution into submucosa as a safety cushion, snaring of the lifted mucosa by a looped wire, and cut using diathermy current. There are methods of EMR such as strip biopsy,[1] endoscopic double snare polypectomy (EDSP),[2] endoscopic resection with local injection of HSE (ERHSE),[3] endoscopic mucosal resection using a cap-fitted panendoscope (EMRC),[4] and so forth. Endoscopic submucosal dissection technique is recently employed and its procedure consists of incision of surrounding mucosa of lesions and dissection of the submucosa of the involved area with endoknife e.g. insulated-tipped (IT) knife,[5] hook knife (Hooking Knife Method),[6] flex knife (thin-type snare, flex knife method).[7]

To determine indications of EMR, precise estimation of depth of invasion and pathological types of tumor is essential.

1) Principles of Indication

· Tumor with little possibility of lymph node metastasis, which can be removed *en bloc* according to its location and size.

2) Criteria Details

· Macroscopic mucosal cancer (cM) of differentiated type (pap, tub1, tub2) less than 2 cm in diameter.

· No ulceration or scar in cases of depressed type, irrespective of macroscopic type.

Modified Surgery

As compared with standard surgery (resection of two-thirds of the stomach with D2 dissection), modified surgery refers to reduction of the extent of lymph node dissection and gastrectomy, including options such as omission of omento-bursectomy and omentum-preserving procedure. If the extent of lymph node dissection is reduced to D1+α, it is defined as modified surgery-A. If D1+β, it is defined as modified surgery-B.

Since laparoscopic surgery has been covered under health insurance in 2002, increasing facilities have come to perform this surgical technique as promising, minimally-invasive surgery. However, laparoscopic surgery hasn't been standardized yet, still at the stage of clinical study.

1. Modified Surgery-A

1) Principles of Indication

· T1 cancer not indicated for EMR with little possibility of lymph node metastasis, that is expected to be cured with D1+α dissection.

2) Criteria Details

· Macroscopic mucosal cancer (cM, sM) not indicated for EMR without lymph node metastasis (sN0).

· Macroscopic submucosal cancer (sSM, sSM) of differentiated type less than 1.5 cm in diameter without lymph node metastasis (sN0).

2. Modified Surgery-B

1) Principles of Indication

· T1 cancer not indicated for modified surgery-A in spite of little possibility of lymph node metastasis.

2) Criteria Details

· Macroscopic submucosal cancer (cSM, sSM) without lymph node metastasis (sN0).

· sT1 cancer less than 2.0 cm in diameter without lymph node metastasis (N0) that is expected to be cured with D1+β dissection.

Standard Surgery

This is the standardized surgical procedure primarily for radical gastrectomy, involving the resection of two-thirds of the stomach with D2 lymph node dissection.

1) Principles of Indication

· Cancer without involved organs (less than T3 cancer) that is expected to achieve curability-A or -B with D2 dissection.

2) Criteria Details

· sSM cancer not indicated for modified surgery.

· sT2-sT3 sN0-N2 cancer that is diagnosed as having no peritoneal metastasis (P0) nor hepatic metastasis (H0) according to preoperative and intraoperative diagnosis.

Extended Surgery

Extended surgery is defined as gastrectomy more than standard surgery, including combined resection of involved organs or D2+α/D3 lymph node dissection. To establish evidence of extended surgery, surgical safety and better survivals than those of standard surgery should be evaluated.[8-12]

When opening the abdominal cavity, the presence or absence of isolated tumor cell is examined with peritoneal lavage diagnosis in the surrounding of the stomach or Douglas pouch. Pathological examination is recommended if possible in cases with nodules suspected hepatic, peritoneal, or distant lymph node metastasis.

1) Principles of Indication

· Primary or metastatic tumor directly invading the surrounding organs, in which combined resection is the only treatment for cure.

· Cancer with metastasis to Group 2 lymph nodes (N2 or more), in which D2+α or D3 lymph node dissection is essential to achieve curability-B.

Reduction Surgery

Reduction surgey is defined as gastrectomy in cases developing non-curative factors such as hepatic or peritoneal metastasis but without tumor-related symptoms such as bleeding, stricture, or pain. The aim of reduction surgery is to decrease the amount of tumor with resection of the stomach, delay the development of symptoms, and extend the survival, but this surgery is still at the level of clinical trial without established evidence.

Palliative Surgery

Urgent symptoms such as bleeding, stricture, or malnutrition are frequently developed in advanced gastric cancer. Palliative surgery is performed to prevent such symptoms in spite of unresectable metastasis.[13]

In cases with stricture, palliative gastrectomy is recommended if performed safely, and gastrojejunostomy (bypass surgery) is conducted if gastrectomy is difficult.

1) Principles of Indication

· Unresectable cases with urgent symptoms such as bleeding, stricture, or malnutrition.

Perioperative Management

Preoperative accurate diagnosis, experienced surgical technique, and enough knowledge and experience of perioperative management are essential to performing surgery with safe.

1. Confirmed diagnosis of gastric lesion

It is required to diagnose the spread of primary tumor and clinical staging including invasion to the surrounding tissues (organs). The diagnosis of localization and depth of invasion are conducted using endoscopy or biopsy (sometimes, endoscopic ultrasonography). Upper gastrointestinal series is used to examine the extent of resection and involved location in the stomach. Ultrasonography and CT scan are performed to observe the invasion to adjacent organs and metastatic lesions. Diagnostic laparoscopic examination is routinely used as evidence of treatment decision-making in

Western countries, but still at the stage of clinical study in Japan.

2. Preoperative Management

More and more patients develop preoperative complications such as high blood pressure, diabetes, schematic cardiac disorder, or respiratory complication with aging society and dietary westernization. Also, perioperative deep vein thrombosis and embolism is not negligible with increasing number of obese patients. It is necessary to consider social environment such as postoperative care as well as to make risk analysis carefully for elderly patients.

Clinical Pathway (CP)

CP aims to introduce standardized medical care according to evidence-based medicine (EBM) and guidelines to promote team medicine and provide patients-oriented medicine of high-quality. CP includes examination, medicine and injection, treatment, follow-up, activity, cleanliness and excretion, safety, education and IC, variances, and signature on the vertical charts, and the course from admission to discharge on the horizontal charts.

Postoperative Follow-up

Patients undergoing gastrectomy should be followed systematically for treatment of postoperative symptoms, lifestyle guidance, and early detection of recurrence or second cancer depending on risk of recurrence with endoscopy, US, and CT scan. At five years or later after surgery, basic checkups are recommended every year. Also, it is required to treat or prevent postoperative disorders such as macrocytic and megaloblastic anemia following total gastrectomy.

Chemotherapy

Chemotherapy for unresectable advanced or recurrent gastric cancer has come to achieve high response rate due to recent progress, although it is still difficult to bring about complete cure with this treatment modality. Clinical trials inside and outside Japan showed that median survival time has been about 6-9 months. The present task of chemotherapy is to delay the development of clinical symptoms and expand survival.

Clinical efficacy of chemotherapy was confirmed in randomized controlled trial of PS 0-2 cases on best supportive care (BSC) group versus chemotherapy group, in which long-term survival of chemotherapy group was demonstrated.[14-17] In a small number of cases, long-term survival (more than 5 years) was obtained. Therefore, chemotherapy is considered to be the first choice of treatments for cases with unresectable advanced or recurrent gastric cancer, or non-curative resection.

Chemotherapy of fluorinated pyrimidine (5-FU, etc.) combined with cisplatin (CDDP) is promising as standard regimen for the treatment of gastric cancer, but specific regimen cannot be recommended at present from results of clinical trials inside and outside Japan.

1) Principles of Indication

· Unresectable advanced, recurrent cancer, or Non-curative resection cases (curability-C) with good performance status and well-maintained organ function.

2) Criteria Details

· sT4 cancer or cases with a high degree of lymph node metastases (lots of N3s) with PS 0-2.

· Primary or recurrent case with peritoneal metastasis (P1), hepatic metastasis (H1), or other distant metastasis (M1) with PS 0-2.

· Non-curative resection cases with PS 0-2.

Postoperative Adjuvant Chemotherapy

There have been little evidences on significant survival benefit in the clinical trials of single- or multiple-agents combined chemotherapy for prevention of recurrence from microresidual tumor after curative resection.[18,19] The results of three randomized controlled trials were reported after publication of the first edition of the guidelines; two were negative studies,[20,21] and the other showed a significant difference but not reliable with small number of 137 cases as well as survival rate of only 12 % in surgery alone group. On the other, two meta-analyses on randomized controlled trials were reported,[22,23] each of which demonstrated significant better results of chemotherapy group but concluded, as in the case of established meta-analysis, that postoperative chemotherapy could not be a routine practice until large-scale clinical trials comparing with surgery alone group are conducted using survival as primary endpoint. The results of large-scaled randomized controlled trials in Japan showed that postoperative chemotherapy is not essential in cases of T1 cancer in spite of the presence or absence of lymph node metastasis and node-negative T2 cancer. Therefore, these cases should be excluded from clinical trials on adjuvant chemotherapy.[24,25]

1) Principles of Indication

· Cases with some possibility of recurrence after resection of curability-A or -B

2) Criteria Details

Adjuvant chemotherapy should be conducted only under clinical trial. However, pT1 or pT2pN0 cancer is excluded from the trial, and should be observed without adjuvant chemotherapy after curative resection of gastric cancer, in principle.[25,26]

Neoadjuvant Chemotherapy

Neoadjuvant Chemotherapy is a multimodality therapy to resect residual primary tumor or metastasis after downsizing tumor or subsiding micrometastasis with chemotherapy. In addition to intrinsic deflection evaluated by response rate and resection rate, survival advantage assessed by survival rate is employed as ultimate evaluation criteria. Some reports presented cases obtaining long-term survival in unresectable gastric cancer.[27-29] The results of phase II trials for resectable, locally-advanced cancer (stage IIIa, IIIb, IV) in Germany was also reported,[30] but there has been no confirmed evidence of survival advantage in phase III trials. It is required to conduct clinical trials aiming at evaluation of treatment efficacy for the introduction of neoadjuvant chemotherapy.

1) Principles of Indication

· Moderately-advanced cancer that can achieve curability-B with surgery alone but with high risk of recurrence. This aims at the control of micrometastasis.

· Advanced gastric cancer that can achieve curability-B with chemotherapy and surgery. Intended for tumor downsizing.

2) Criteria Details

· cStage II-IIIb cancer, that is, cT3-4 cN1-2 P0 H0 cancer. The treatment should be performed under randomized control

trial with surgery alone after safety and response rate are confirmed in phase II trial.

· cT3-4 cN2-M1(LYM) P0 H0 cancer.

Postoperative Adjuvant Chemoradiotherapy

MacDonald *et al* reported that randomized controlled trial with 556 cases demonstrated significant survival benefit of adjuvant chemoradiotherapy over surgery alone.[31] However, 90 % of dissection in this trial was D0/D1 surgery followed by chemoradiotherapy undergone for insufficient local control. In this sense, this trial doesn't directly apply to clinical practice in Japan where D2 dissection is being performed as standard technique.

Immunotherapy, Immunochemotherapy

It was reported that combination therapy of nonspecific immunomodulator with chemotherapy contributed to survival benefit after gastrectomy,[32] while many have been negative about this treatment. The evaluation has not been established yet. Also, clinical assessment of studies on adoptive immunotherapy or tumor-specific vaccine therapy is still insufficient. It is required to carry out clinical trials to establish the clear evidence on life prolongation.

Folk medicine including health food has little scientific basis or evidence with lack of clinical trials.

Radiotherapy

Radiotherapy alone cannot achieve curability because sensitivity of gastric cancer for radiotherapy is small. On the other, it is effective for controlling pain caused by bone metastasis or cancer invasion.

Hyperthermochemotherapy

Clinical study has been conducted on hyperthermochemotherapy as a multimodality therapy combining hyperthermotherapy with chemotherapy, aiming to prevent recurrence or improve prognosis of peritoneal dissemination. It is required to establish the safety of this treatment and carry out clinical trials of high-quality.

Palliative Care

Palliative care is an essential part of clinical practice related to all fields of cancer care, which can be provided actively to the patients without possibility of cure and their families. The purpose of this modality is to relieve pain and other physical symptoms, or to solve psychological and social problems. This treatment has special importance especially for patients at terminal stage of care. Communication skill and symptom management technique are required for palliative care. In addition to usage of drug, radiotherapy and mental therapy are included. The clinical trials on pain control and symptom management are under implementation.

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