



## *Special article*

# Gastric cancer treatment guidelines in Japan

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### Abstract

**Recent developments in treatment modalities for gastric cancer have allowed the selection of a variety of treatments, and this has resulted in some confusion in daily practice. The Japan Gastric Cancer Association issued the first edition of *Gastric cancer treatment guidelines* in March, 2001 to provide a common basis of understanding of the extent of disease and selection of proper treatment among doctors, patients, and their families.**

**Key words** Gastric cancer treatment guidelines · Stage-oriented treatment · Standard treatment · EBM

### Introduction

Recent developments in treatment modalities for gastric cancer, on one hand, have allowed clinical oncologists a broad range of treatment options for patients with gastric cancer of various stages, and, at the same time, have caused some confusion and institutional differences in the selection of optimal treatment modalities. The Japanese Gastric Cancer Association (JGCA) issued the first version of their gastric cancer treatment guidelines (GLs) for doctors in March 2001, and those for patients in December 2001, with the aim of providing a reference for both clinical oncologists and patients how to select optimal treatments for various stages of disease. This article, which is a short summary of the Nishi Memorial Lecture given at the fourth International Gastric Cancer Association (IGCA) meeting in New York, in May, 2001, will serve to give a quick general view of JGCA gastric cancer treatment guidelines in response to the numerous inquiries from

IGCA members, because the English edition of these GLs is not yet formally available.

### Purpose of GLs

As stated above, GLs aim to provide standard indication for doctors and patients to select the proper treatments for gastric cancer according to the clinical stages of disease. Accordingly, the use of GLs is expected to reduce differences in treatment selection by institutions and doctors, to improve treatment results by eliminating improper treatment practices, and to improve mutual understanding of the extent of disease and on treatment modalities between doctors and patients. Unlike the aim of GLs in western countries, the JGCA GLs primarily do not aim to reduce medical expenses in the health care system, but their use is expected to bring about cost-effectiveness as the result of the proper practice of gastric cancer treatments.

### Principles

1. GLs provide standardized indications of the optimal treatment modality according to the clinical stage of each patient, but do not deal with the technical aspects of treatment.
2. GLs are principally described based on evidence-based medicine (EBM) as much as evidence is available, although the GL Development Committee sometimes faced difficulties because of lack of evidence in regard to various aspects of treatments.
3. Survival time is the primary endpoint of treatment results, although relief of symptoms, tumor shrinkage, and quality of life (QOL) are considered to be secondary endpoints.
4. Recommendations for daily practice are listed in the GLs, and some promising, but not yet confirmed,

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treatment modalities are also recommended to be investigated as clinical trials.

### Target of GLs and how to use them

The JGCA provides GLs for all doctors and patients, who are going to make their treatment decisions on a common basis. GLs will facilitate the mutual understanding of treatment decisions between doctors and patients or their families. If doctors are planning to offer treatments different from those in the GLs, they are expected to explain the reasons for this difference to patients, and to when they obtain informed consent.

### Revision of GLs

Treatment GLs should be always reviewed and revised associated with developments in the treatment of gastric cancer. A panel of the GL Development Committee of the JGCA is in charge of periodical review and revision, and discussion and proposals from members of the IGCA and JGCA are always welcome for this purpose.

### Available treatment modalities for gastric cancer

The treatment modalities for gastric cancer available now in Japan are: endoscopic mucosal resection (EMR), laparoscopic gastrectomy, modified gastrectomy A and B (MG A and B), standard gastrectomy, extended gastrectomy, chemotherapy, radiotherapy, multimodality therapy (including neoadjuvant and adjuvant chemotherapy, immunochemotherapy, hyperthermochemotherapy), and terminal care.

### Stage-oriented treatment indications

GLs show treatment indications according to the clinical stage (JGCA classification [1]). The T category in the JGCA classification is identical to that in the TNM, but the N category is different from the TNM, and is based on the anatomical lymph node stations.

#### Treatments for stage IA (T1N0)

EMR or modified gastrectomy (MG) is indicated for this stage according to the following instructions (Table 1).

EMR is indicated for patients with small mucosal cancer with no lymph node metastasis. Our database [2] suggests that intestinal-type mucosal cancer less than

**Table 1.** Treatment indications for stage IA disease

Depth of invasion	Histology	Size	Indication
Mucosa (M)	Differentiated	≤2cm	→ EMR
Mucosa (M)	Other		→ MG A
Submucosa (SM)	Differentiated	≤1.5cm	→ MG A
Submucosa (SM)	Other		→ MG B

EMR, Endoscopic mucosal resection; MG A and MG B, modified gastrectomy A and B

**Table 2.** Type of gastrectomy

Gastrectomy	Range of resection	Dissection	Option
MG A	<2/3	D1 + no. 7 <sup>a</sup>	Vagus-preserving
MG B	<2/3	D1 + nos. 7, 8a, 9	Pylorus-preserving Laparoscopic
Standard	≥2/3	D2	
Extended	≥2/3	D2 or D3	
	Combined resection		

<sup>a</sup> In lower-third cancer, no. 8a nodes should also be dissected

2 cm in diameter has no lymph node metastasis. En-bloc resection is preferable because of the possible risk of residual cancer remaining after EMR, and 2 cm is the technical upper limit of en-bloc resection. Accurate assessment of the depth of wall invasion, histological type, and size of tumor is mandatory before the selection of EMR. Fragmented, or piece-meal resection is allowed as a clinical trial if planned so as to allow complete reconstruction of piecemeal specimens. Mucosal cancer that does not meet the above conditions should be treated by MG A.

As shown in Table 2, modified gastrectomy (MG) is classified into MG A and B according to the extent of resection and lymph node dissection: gastrectomy of less than two-thirds of the stomach with dissection of D1 and no.7 (+8a) lymph nodes is designated as MG A (see Table 2 footnote), and modified gastrectomy with dissection of D1 and no. 7, 8a and 9 lymph nodes is designated as MG B.

MG A is also indicated for differentiated submucosal cancer less than 1.5 cm in diameter. Submucosal cancer that does not meet this condition should be treated by MG B. The type of gastrectomy is shown in Table 2.

Standard gastrectomy includes resection of more than two-thirds of proximal, distal, or total gastrectomy associated with D2 dissection according the size and location of the tumor. Regarding to the extent of D2 dissection, please refer to the *General rule of gastric cancer study* issued by the JGCA [1].

*Treatments for stage IB (T1N1, T2N0)*

As shown in Table 3, MG B or standard gastrectomy is indicated for stage IB cancer according to the T and N categories. If a T1N1 tumor is less than 2.0 cm in diameter, MG B is indicated, and a T1N1 tumor larger than 2.1 cm or a T2N0 tumor is treated by standard gastrectomy.

*Treatments for stage II (T1N2, T2N1, T3N0)*

Standard gastrectomy is indicated for all categories of stage II cancer. Table 4 shows the treatment indications for stage II disease.

Total or partial gastrectomy is indicated according to the size and type of tumor: partial gastrectomy is indicated for a T1 tumor when a tumor-free margin larger than 1.0 cm is available, or for well-demarcated T2-3 tumor when a tumor-free margin larger than 3.0 cm is available, or for intermediate or infiltrative T2-3 tumor with an available tumor-free margin larger than 5.0 cm; otherwise, total gastrectomy is indicated. Meta-analysis suggests that adjuvant chemotherapy is recommended for stage II or III cancer [3–5], but to date, there is no single regimen that shows effectiveness for post-operative adjuvant chemotherapy [6–12]. Clinical trials should be conducted to establish standard regimens for adjuvant chemotherapy.

*Treatments for stage IIIA (T2N2, T3N1, T4N0)*

Standard or extended gastrectomy is indicated for stage IIIA cancer according to the T or N categories, as shown in the Table 5.

Clinical trials of adjuvant and neoadjuvant chemotherapy are indicated for this stage. In T4 cancer, combined resection of involved organs is indicated, because the prognosis of patients with macroscopic residual tu-

mor (R1 surgery) is obviously worse than that in those without residual tumor [2].

*Treatments for stage IIIB (T3N2, T4N1)*

For stage IIIB, as for stage IIIA, standard or extended gastrectomy is indicated, according to the T and N categories (Table 6). Although the survival benefit of D3 for N2 cancer is not yet established, D3 is sometimes performed in Japan. A controlled randomized study comparing D2 and D3 was carried out in Japan, and its results may suggest new indications in this regard in the near future.

Combined resection of involved adjacent organ(s) is indicated for T4 cancer to achieve R0 resection. Adjuvant chemotherapy, neoadjuvant chemotherapy, and adjuvant radiotherapy should be performed in the setting of randomized controlled trials.

*Treatments for stage IV (N3, CY1, M1)*

Most cases of stage IV cancer cannot be curatively treated with surgery alone, except for those with N3 or T4N2 cancers. If N3 is the only determinant factor for stage IV, D3 surgery often achieves R0 resection.

There is no evidence of survival benefit of treatment modalities other than surgery for stage IV cancer, but some benefits are suggested for marginal life-prolongation, tumor shrinkage, and relief of symptoms. Chemotherapy is indicated for patients with unresectable tumor with good performance status (Table 7). Standard regimens of chemotherapy for late-stage cancer are not yet established, although combination chemotherapy with cisplatin (CDDP), and 5-fluorouracil (5FU) or its derivatives may be the regimen of preference and recommendation [13–15]. When patients with fair or poor performance status are subjected to chemotherapy, they should be carefully treated by experienced chemotherapists, with the in-

**Table 3.** Treatment indications for stage IB disease

Depth of invasion	Size	Lymph node	Indication
T1 (M,SM)	≤2.0 cm	N1	MG B
T1 (M,SM)	≥2.1 cm	N1	Standard
T2 (MP,SS) <sup>a</sup>		N0	Standard

<sup>a</sup>MP, Muscularis propria layer; SS, subserosal layer**Table 4.** Treatment indications for stage II disease

Depth of invasion	Lymph node	Indication
T1	N2	Standard
T2	N1	Standard
T3	N0	Standard

**Table 5.** Treatment indications for stage IIIA disease

Depth of invasion	Lymph node	Indication
T2	N2	Standard
T3	N1	Standard
T4	N0	Extended

**Table 6.** Treatment indications for stage IIIB disease

Depth of invasion	Lymph node	Indication
T3	N2	Standard
T4	N1	Extended

**Table 7.** Treatments for stage IV disease

Patients with M1 lesion(s) with good PS (0–2)
Chemotherapy, radiotherapy, or best supportive care (reduction surgery)
Patients with severe symptoms, such as bleeding, stenosis, and malnutrition
Palliative surgery (resection, bypass, gastrostomy, enterostomy)
Patients with T1-3N3 or T4N2-3 lesions without M1
Extended radical gastrectomy

PS, Performance status

formed consent of the patients, otherwise they should not be treated with aggressive therapy, but with best supportive care [16–18]. Improvement in patients' QOL is the endpoint of therapy for this late-stage cancer.

## Discussion

There are some issues to be kept in mind when these GLs are extrapolated to countries outside Japan, because treatment results may vary with various factors in regard to diagnosis, treatment, and patients' condition.

GLs indicate treatments for diseases based on the clinical stages, but readers should be aware that the Japanese stage classification is different from those of the International Union Against Cancer (UICC)/AJCC system, mainly because of the difference in N categories. Careful reference to the Japanese classification [1] is necessary in this matter. The UICC/AJCC stage system cannot be used to plan treatment, because of its numeric system N staging.

There may be various arguments regarding the clinical significance of lymph node dissection, because all clinical trials in western countries [19–22] were negative for a survival benefit of D2 node dissection. However, the survival benefit in these trials seems to be biased because of technical and patient factors; namely, the high incidence of postoperative complications and high operative mortality rates. Regardless of this high-level negative evidence for lymph node dissection, Japanese surgeons and some in western countries [23] still favor D2 dissection, and Oncology Practice GLs issued by the National Comprehensive Cancer Network in the United States [24] also recommend D2 dissection as their preference for resectable gastric cancer.

It is regretted that the GLs were not able to make any recommendations, as a daily practice, for standard chemotherapy regimens for advanced gastric cancer, although many favorable reports are available regarding the response rates of new anti-cancer drugs. However, these reports do not meet our conditions of recommendations for standard therapy, because the

regimens show no or marginal survival benefit, with moderate or severe toxicity. Survival benefit for advanced gastric cancer may be achieved by multimodality therapy, i.e., by combinations of surgery, chemotherapy, and/or radiation therapy, in future trials.

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## Appendix

Treatment results with standard gastrectomy are shown by tumor site in Table 8.

The data are based on the Nationwide gastric cancer registry, 1991, described in the 13th edition of *The general rules of gastric cancer study*. All causes of death were counted in the calculation of 5-year survival rates.

**Table 8.** Five-year survival rates (%) of patients treated with standard gastrectomy (D2 dissection) according to tumor site

	+E	U	M	L	Whole	Total
IA	71.4 (7)	88.0 (225)	95.1 (910)	93.0 (854)	100.0 (8)	93.4 (2004)
IB	68.8 (21)	82.5 (163)	91.0 (300)	86.6 (243)	57.1 (7)	87.0 (734)
II	44.9 (28)	63.7 (117)	72.7 (200)	66.1 (198)	66.6 (19)	68.3 (562)
IIIA	33.7 (30)	44.6 (137)	57.0 (150)	53.0 (167)	17.0 (25)	50.1 (509)
IIIB	21.7 (24)	26.2 (73)	35.4 (71)	35.2 (98)	10.1 (28)	30.8 (294)
IV	16.1 (40)	17.1 (120)	23.2 (92)	13.6 (152)	11.0 (67)	16.6 (440)
Total	35.9 (150)	61.3 (835)	82.6 (1723)	74.8 (1712)	25.6 (154)	73.7 (5044)

Figures in parentheses show numbers of patients  
Data from the Nationwide gastric cancer registry, 1991  
U, Upper; M, middle; L, lower third of the stomach; whole, whole stomach; +E, involvement of esophagus