Introduction to JGCA gastric cancer treatment guidelines

The Japanese Gastric Cancer Association (JGCA) issued the first version of gastric cancer treatment guidelines (GL) in March 2001. This article aims to introduce an outline of treatment guidelines for doctors' reference outside Japan, because an English version is not yet published by JGCA.

1) **Purpose of GL**

GL aim to provide a standard indication for doctors to select the proper treatments of gastric cancer according to the clinical stages of patients. Accordingly, GL expect to reduce differences in treatment selection by institutions and doctors, to improve in the treatment results by eliminating improper treatments, and to improve in the mutual understanding on the extent of disease and treatment modalities between doctors and patients. Unlike in the western countries, JGCA GL primarily do not aim to reduce the medical expense in the health care systems, but expect financial improvement as the result of proper acceptance of this GL.

2) **Principles**

- GL provide standardized indication of utmost treatment modality according to the clinical stage of each patient, but do not deal with the technical aspect of treatment.
- GL are described based on the Evidence-based medicine (EBM) as possible as evidences are available, though guideline-developing committee faced to difficulties because of lack of evidence in various aspects of treatments.
- Survival time is the primary endpoint of treatment results, though relief of symptoms, tumor shrinkage, and QOL are considered as the secondary endpoint.
- Recommendations for daily practice are listed in GL, and some promising, but not yet confirmed treatment modalities are also recommended to investigate as the clinical trials.

3) **How to use GL**

JGCA provides GL for doctors and patients, who are expected to refer to GL at every step of treatment decision. GL will facilitate the mutual understanding on treatment decision between doctors and patients, or their families. If doctors are going to offer treatment different from GL, doctors are expected to explain the reasons of difference to patients, and get the informed consent.

4) **Available treatment modalities for gastric cancer**

Following are the available treatment modalities for gastric cancer in Japan:

Endoscopic mucosal resection (EMR), laparoscopic gastrectomy, modified gastrectomy A and B, standard gastrectomy, extended gastrectomy, chemotherapy, radiotherapy, multimodality therapy including neoadjuvant and adjuvant chemotherapy, immunochemotherapy, hyperthermochemotherapy, and terminal care.

5) **Stage-oriented treatment indications**

GL show treatment indication according to clinical stages (JGCA classification).

i) Stage IA (T1N0)

EMR or modified gastrectomy (MG) is indicated to this stage according to the following instruction.

Table 1 Treatment indication for Stage IA

Depth of invasion	Histology	Size		Indication
Mucosa(M)	differentiated	□ 2cm	→	EMR
Mucosa(M)	else		→	MG A
Submucosa(SM)	differentiated	□ 1.5cm	→	MG A
Submucosa(SM)	else		→	MG B

EMR should be indicated to patients with small mucosal cancer with no lymph node metastasis. Our database suggests that intestinal type mucosal cancer less than 2cm in diameter has no lymph node metastasis. En-bloc resection is preferable because of risk of residual cancer left behind EMR, and 2cm is the upper limit of en-bloc resection. Then, accurate assessment of the depth of wall invasion, histological type and size of tumor is mandatory before carrying out EMR. Mucosal cancer that does not meet this condition should be treated by MG A. MG A is also indicated to the differentiated submucosal cancer less than 1.5cm in diameter. Submucosal cancer that does not meet this condition should be treated by MG B. Type of gastrectomy is shown in Table 2.

Table 2 Type of gastrectomy

Gastrectomy	Range of Resection	Dissection	Option
Modified A Modified B	< 2/3 < 2/3	D1 + No.7* D1+No.7,8a,9	Vagus preserving Pylorus preserving Laparoscopic
Standard	□ 2/3	D2	
Extended	□ 2/3 Combined resection	D2	D3

* In case of lower third cancer, No.8a nodes should be dissected.

Standard gastrectomy includes proximal, distal or total gastrectomy associated with D2 dissection according to 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 JGCA.

ii) Stage IB (T1N1, T2N0)

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

Table 3 Treatment indications for Stage IB

Depth of invasion	Size	Lymph node		Indication
T1(M,SM)	□2.0cm	N1	→	Modified B
T1(M,SM)	□2.1cm	N1	→	Standard
T2(MP,SS)*		N0	→	Standard

* MP:muscularis propria layer, SS:subserosal layer

iii) Stage II (T1N2, T2N1, T3N0)

Standard gastrectomy is indicated to Stage II cancer regardless of T, N-categories.

Table 4 Treatment indications for Stage II

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

Adjuvant chemotherapy is recommended for stage II cancer, but there is no established regimens for postoperative adjuvant chemotherapy up to date. Clinical trial should be done to establish the standard regimens of adjuvant chemotherapy.

iv) Stage IIIA (T2N2,T3N1,T4N0)

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

Table 5 Treatment indications for Stage IIIA

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

Clinical trials of adjuvant and neoadjuvant chemotherapy are indicated to this stage. In case of T4 cancer, combined resection of involved organs and/or adjuvant radiotherapy may be indicated, because the prognosis of patients with macroscopic residual tumor (R1 surgery) is obviously worse than those without residual tumor.

v) Stage IIIB (T3N2, T4N1)

Same as in the case of Stage IIIA, standard or extended gastrectomy is indicated to Stage IIIB according to T and N categories. Though the survival benefit of D3 for N2 cancer is not yet established, D3 is frequently performed in the daily practice in Japan. Controlled randomized study of D2 vs. D3 is now undertaken in Japan, and its results may indicate new indication in this regard.

Table 6 Treatment indications to Stage IIIB

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

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

vi) 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 may have a potential of R0 surgery.

Table 7 Treatment indications to Stage IV

* In patients with M1 lesion(s),but with good PS(0-2):
  Chemotherapy, Radiotherapy, or Best supportive care
  (Reduction surgery)
* In patients with urgent symptoms: bleeding, stenosis, malnutrition etc
  Palliative surgery (resection, by-pass, gastrostomy, enterostomy)
* In patients with T1-3N3 or T4N2-3 lesions without M1:
  Extended radical gastrectomy

There are no evidences of survival benefit of these treatment modalities for stage IV

cancer, but some benefits are suggested for a marginal life-prolongation, tumor shrinkage and relief of symptoms. Chemotherapy is indicated to patients with unresectable tumor, but with good performance status. Standard regimens of chemotherapy for late stage cancer are not yet established, though the combination chemotherapy with CDDP, and 5FU or its derivatives may be the regimen of preference and recommendation. If patients with fair or poor performance status are subjected to chemotherapy, they should be carefully treated by experienced chemotherapists with informed consent of patients, otherwise should not be treated with aggressive therapy, but with best supportive care. Improvement in patients' QOL is the endpoint of therapy for this late stage cancer.

Treatment GL should be always reviewed and revised associated with the development in the treatment of gastric cancer. GL Developing Committee of JGCA is on charge of periodical reviewing and revision, and discussion and proposal from members of IGCA and JGCA are always welcome for this purpose.

Table 8 5-year survival rates of primary gastric carcinoma, after D2 dissection, according to the tumor location and Stage (13th Edition). The numbers in parentheses are the number of cases. Results of registered cases treated in 1991. Overall survival includes postoperative deaths. 8% of all registered cases were lost of follow-up.

	+E*	U	M	L	Whole*	Total
IA	71.4 (7)	88.0 (225)	95.1 (910)	93.0 (854)	100.0 (8)	93.4 (2030)
IB	68.8 (21)	82.5 (163)	91.0 (300)	86.6 (243)	57.1 (7)	87.0 (725)
II	44.9 (28)	63.7 (117)	72.7 (200)	66.1 (198)	66.6 (19)	68.3 (541)
IIIA	33.7 (30)	44.6 (137)	57.0 (150)	53.0 (167)	17.0 (25)	50.1 (485)
IIIB	21.7 (24)	26.2 (73)	35.4 (71)	35.2 (98)	10.1 (28)	30.8 (273)
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 (4494)

+E: invasion to esophagus U: upper M: middle L: lower

whole： UML, MUL, MLU, LMU

Table 9 Treatment indications according to the clinical stages

<table>
<tr><td></td><td>N0</td><td>N1</td><td>N2</td><td>N3</td></tr>
<tr><td>T1(M)</td><td>IA
EMR
Mod.G(A)</td><td rowspan="2">IB
Mod.G(B)
Stand.G</td><td rowspan="2">II
Stand.G</td><td rowspan="5">IV
Ext.G
Pal.G
Chemotherapy
Radiation
Pal. care</td></tr>
<tr><td>T1(SM)</td><td>IA
Mod.G(A)
Mod.G(B)</td></tr>
<tr><td>T2</td><td>IB
Stand.G</td><td>II
Stand.G
Adj. chem*</td><td>IIIA
Stand.G
Adj. chem*</td></tr>
<tr><td>T3</td><td>II
Stand.G
Adj. chem*</td><td>IIIA
Stand.G
Adj. chem*</td><td>IIIB
Stand.G
Adj. chem*</td></tr>
<tr><td>T4</td><td>IIIA
Ext.G
Adj. chem*
Radiation*</td><td>IIIB
Ext.G
Adj. chem*
Radiation*</td><td></td></tr>
<tr><td>M1
Recurrence</td><td colspan="3">IV</td></tr>
</table>

I – IV：Japanese clinical stage classification according to T and N categories

EMR: endscopic mucosal resection

Mod.G(A): modified gastrectomy with D1+α dissection

Mod.G(B): modified gastrectomy with D1+ß dissection

Stand. G: standard gastrectomy with D2 dissection

Ext. G: extended gastrectomy

Pal. G: palliative gastrectomy and other surgical palliation

Pal. care: palliative care

Adj. chem：adjuvant or neoadjuvant chemotherapy.

* ：Treatment modalities with asterisk mark should be done as prospective clinical trials.

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