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Special article

The new Japanese Classification of Gastric Carcinoma: Points to be revised

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Summary of changes:

1. The previous version described clinical, surgical and conclusive staging. This version retains clinical and surgical staging, being the staging before and during definitive surgery respectively. Conclusive staging is now defined as final staging, and may include information for which there is no histological proof (e.g. hepatic metastases). Pathological staging has been introduced, and requires microscopic proof.
2. Lymph node staging has been extensively revised. A 3 tier system replaces the previous 4 tier system, and thus there are now 4 possible N stages (N0-3). The definition of some node groupings have been more precisely defined (No.11 and No.12).
3. Lymph node dissection is classified D0-3 based on the new nodal groups. Minor modifications of the extent of dissection have been made. "Optional" stations have been omitted.
4. Peritoneal cytology has been included in the staging system.
5. Subclassification of hepatic and peritoneal metastasis has been abandoned.
6. Rules for staging carcinoma of the remnant stomach have been introduced.
7. Rules to classify and evaluate endoscopic mucosal resection (EMR) have been introduced.
8. Subclassification of T staging has been introduced for T1 (M and SM) and T2 (MP and SS) tumors.
9. Nomenclature has been simplified: lower case letters are only used to define the "type" of staging (c clinical; s surgical; p pathological; f final). Tumor location is now defined as U (upper third), M (middle) or L (lower), replacing C, M, A. Proximal and distal margins are designated as PM and DM (previously OW and AW). LM and VM have been introduced for the lateral and vertical margins of EMR specimens.

Key words: general rules, staging of gastric carcinoma, Japanese Gastric Cancer Association

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Introduction

The General Rules (GR) for Gastric Cancer Study in surgery and pathology of the Japanese Research Society for Gastric Cancer (JRSGC) have been widely accepted among specialists inside and outside of Japan. The first Japanese edition of the GR was published in 1962 and the first English edition of the Japanese Classification of Gastric Carcinoma was published in 1995 [1] based on the 12th Japanese edition [2] of GR with full illustrations and detailed descriptions. To coincide with the establishment of the Japanese Gastric Cancer Association (JGCA) in 1998, the 13th edition of the GR and second edition of the JGCA classification is published after correction and revision of the 12th and 1st edition, respectively.

The GR have contributed to establishing standard rules for clinical and pathological hadling and recording of gastric cancer. This enabled evaluation of the treatment results of different institutions, accumulation of nationwide data and eventually the establishment of treatment standards for gastric cancer. The Japanese staging system is specifically intended for use during treatment planning. In contrast to the UICC TNM there has been much more detailed classification of lymph nodes, and subdivision of patients with liver or peritoneal metastasis.

In the past, clinical and surgical staging which was used to decide treatment planning was solely based on the macroscopic findings and therefore much less accurate than microscopic findings, which was available only after treatment. Thus pathological, i.e., microscopic, staging was strictly distinguished from other findings because of its accuracy and described as pT and pN. However, many trials now require intra-operative histological or cytological information (frozen section) to decide eligibility. Furthermore, diagnostic laparoscopic evaluation can change the accuracy of preoperative staging enormously. Thus histological information in

Table 1.

Type of findings	Time of diagnosis	Availability for treatment decision	Accuracy
Image diagnosis	Before treatment	Yes	Low
Laparoscopic findings	Before treatment	Yes	Moderate-high(histology)
Surgical findings: macroscopic	Before treatment	Yes	Moderate
Surgical findings: frozen section	Before or during treatment	Yes	Almost high
Macroscopic findings of resected material	During or after treatment	Yes for modification	Moderate
Frozen section of resected material	During or after treatment	Yes for modification	Almost high
Microscopic findings of resected specimen	After treatment	No	High

addition to simple tumor biopsy is often used in treatment decisions. In this manner, the simple categorization of clinical and pathological stages applied by UICC TNM has become difficult (Table 1). Because the Japanese staging system has been developed partly for treatment planning, emphasis has been placed on staging at distinct phases of patient management. Thus there has been clinical staging, surgical staging and final staging. Most of findings to decide final staging are pathological but not all. Therefore pathological staging is independently established.

Results of different treatments or different institutions have usually been evaluated by retrospective analysis. As prospective evaluation has increased in importance, it has become important to be able to define and compare pre-treatment staging. Such staging allows comparison of treatment results according to pretreatment staging rather than solely on final staging after pathology is available. Use of neo-adjuvant chemotherapy requires clear guidelines for clinical evaluation before chemotherapy.

Recently more and increasingly subtle lesions of mucosal cancer are being detected by endoscopy. Many of these lesions are treated by endoscopic mucosal resection (EMR) in Japan. Rules concerning lesions treated by EMR are included in this edition to provide definite guidelines for further evaluation of this treatment.

This Japanese classification is composed of the following four parts.

1. Basic rules for clinical, surgical, pathological, and final findings,
2. Specific rules for histological findings,
3. Group Classification of gastric biopsy specimens,
4. Response assessment of chemo/radio-therapy for gastric carcinoma.

I. Major changes in the revised edition

1. Principles of description

The anatomical extent of the tumor is one of the most important factors in treatment planning, as well as the strongest predictor of prognosis. In this revision, the description of the anatomical extent of gastric carcinoma is categorized according to the time of assessment and the methods used. Four assessments, defined as clinical (c), surgical (s), pathological (p) and final findings (f), should be described independently and should not be changed once classified. The timing of an assessment is expressed by lower case letters. The lower case 'f' may be omitted. Capital letter define the subject of staging – T, N, M. If a finding is not available, it should be designated as X for example pTX.

Clinical findings are defined as any findings before treatment. Findings at diagnostic laparoscopy are included in defined as a part of clinical findings. Therefore histological findings obtained by staging laparoscopy with biopsy or lavage cytology are in this category, because they are available before any treatment. In the near future, assessment of neo-adjuvant therapy will be carried out using the results of pretreatment (clinical) staging.

Surgical findings include any findings during definitive surgery, including frozen examination, needle biopsies, cytology, and macroscopic findings of the fresh resected specimens. Thus surgical staging is based on all pre- and intra-operative data and represents the total information available at the time of definitive treatment. Findings during therapeutic laparoscopy are defined as surgical findings.

Pathological findings are any findings based on the final histological examination of resected material.

Final findings are a summary of all information based upon clinical, surgical and pathological findings. If pathological information is not complete, then clinical or surgical findings are used as final findings.

2. Description of findings

1) Description of primary tumors

The symbols describing the primary tumor site are changed to U (upper third), M (middle third) and L (lower third). This is to remove the confusion generated by the use of the symbol C (cardia), as the histological "cardia" is much smaller than one third of the stomach.

Table 2. Incidence of lymph node metastasis and five-year survival rates of those having nodal metastasis in each station, according to the tumor location [3]

	L (distal third)		M (middle third)		U (Upper third)		LMU (entire stomach)	
Station	Incidence	5YSR	Incidence	5YSR	Incidence	5YSR	Incidence	5YSR
1	6.2	25.0	15.0	52.6	38.0	31.7	32.7	11.3
2	7.1	0.0	3.4	25.0	22.0	23.2	18.2	8.0
3	40.9	42.2	44.8	58.7	45.1	37.9	66.0	17.8
4	34.2	42.3	26.8	48.4	14.5	20.5	53.1	19.0
5	10.5	37.5	2.4	33.3	3.0	0.0	14.2	18.8
6	46.3	46.0	14.6	26.8	6.8	6.3	37.7	18.7
7	23.4	34.9	22.6	46.5	26.9	19.7	44.4	18.5
8	24.5	30.6	11.0	41.5	10.2	20.0	30.6	19.2
9	12.8	30.4	11.0	47.5	16.0	20.5	18.5	20.7
10	3.8	0.0	11.9	33.3	17.4	21.6	21.6	7.4
11	6.7	15.4	6.3	21.4	16.1	11.4	20.6	3.7
12	9.0	29.6	1.6	33.3	2.5	0.0	4.4	0.0
13	8.3	0.0	0.0	0.0	2.5	0.0	5.6	0.0
14	14.6	14.3	8.7	0.0	10.0	0.0	4.5	0.0
16	13.1	18.2	7.4	0.0	12.1	0.0	26.5	11.1

Incidence was calculated by dividing the number of patients with metastasis in each station by the number of patients who undeerwent dissection of that station. Survival rates of positive patients in each station were calculated irrespective of odal metastasis to other stations. 5YRSR, 5-year survival rate

Depth of tumor invasion should be recorded in T categories. In addition, tumor invasive depth is recorded as M (mucosa), SM (submucosa), MP (muscularis propria), SS (subserosa), SE (serosa-exposed) and SI (serosa-infiltrating). Thus subclassification of T1 and T2 are defined. The increase of early gastric cancers and wide application of EMR have led to sub-classification of submucosal lesions. To standardize the subclassification, SM1 is defined as those whose invasion is <0.5 mm from the muscularis mucosae and SM2 is as those whose invasion is ≥ 0.5mm. The description of carcinoma of the remnant stomach is newly established. These findings include the character of the lesion for which the first gastrectomy was performed, the interval between the first gastrectomy and the remnant stomach cancer, and the location of the second tumor.

2) Description of metastasis

(1) Lymph node metastasis. Major changes were made in the classification of lymph node groups. Grading was mainly decided by anatomical/physiological lymphatic flow studies in past editions. However, such classification produces many artificial "skip" metastasis with contradictory prognosis between two classes (i.e. N4 metastases being less significant than some N3 metastases). The areas to dissect according to the lymph node classification were therefore difficult to understand, and there was a discrepancy between the actual standard surgery and the theoretical D2/D3/D4 guidelines.

To address these issues, intensive review of the former classification was carried out and the efficacy of lymph node dissection was evaluated. Efficacy of dissection was evaluated by multiplying the incidence of metastasis by 5-year survival rate of patients with positive nodes in each station, according to the location of the primary tumor. The incidence was calculated by dividing the number of patients with metastasis in each station by the number of patients who underwent dissection of that station. The survival rate of positive patients in each station was calculated irrespective of nodal metastasis to other stations (Table 2,3) [3].

Based on these results, the lymph node classification was changed from 5 to 4 categories (N0, N1, N2, N3). Some regional lymph nodes, even some perigastric nodes, are excluded from the classification of regional lymph nodes for some tumor locations. Metastases in such nodes are considered as distant metastasis (M1). For example, the left paracardial lymph node (station No.2) metastasis from a lesion confined to the antrum implies as poor a prognosis as any distant metastasis. Disease in these nodes should therefore be defined as distant metastases. By this change the use of "optional" stations for defined dissection and the resultant inconsistencies have been avoided. As a result, the standard dissection for advanced carcinomas is a "D2" dissection, a literal dissection of all second tier stations, and a D3 dissection is presently regarded as an investigational treatment.

(2) Liver and peritoneal metastasis. The liver and the peritoneum are by far the most frequent sites of distant metastasis. The separate description for these two sites has been retained, but subdivision by the number or site

Table 3. Index of estimated benefit from lymph node dissection in each station, according to the tumor location [3]

Station	Lower third	Middle third	Upper third	Entire stomach
1	1.6	7.9	12.0	3.7
2	0.0	0.9	5.1	1.5
3	17.3	26.3	17.1	11.7
4	14.5	13.0	3.0	10.1
5	3.9	0.8	0.0	2.7
6	21.3	3.9	0.4	7.0
7	8.2	10.5	5.3	8.2
8	7.5	4.6	2.0	5.9
9	3.9	5.2	3.3	3.8
10	0.0	4.0	3.8	1.6
11	1.0	1.3	1.8	0.8
12	2.7	0.5	0.0	0.0
13	0.0	0.0	0.0	0.0
14	2.1	0.0	0.0	0.0
16	2.4	0.0	0.0	2.9

First, second, third and fourth tirs are n1–n4 by the Japanese classification, respectively. Each index roughly corresponds the percentage of patients who will benefit from dissection of each station.
Aggregation of the numbers in the second tier implies the benefit of D2 dissection over D1

Table 4. Curative potential of endoscopic mucosal resection

	depth	histology	ulcer in the tumor	VM, LM	ly·v
EA	T1	pap or tub	no ulcer	(–) no tumor infiltration within 1 mm* of LM	ly0 v0
EB	no residual tumors but not evaluable as "Resection EA"				
EC				VM(+) or LM(+)	

* 1 mm of lateral margin corresponds to approximately 10 normal glands pap, papillary adenocarcinoma; tub, ttublar adenocarcinoma; VM, vertical margin; LM, lateral margin

of metastases was abandoned. Thus liver metastasis is now described as H0 or H1, and peritoneal metastasis as P0 or P1.

(3) Peritoneal cytology. Rules concerning the results of cytological studies of the peritoneum surface, peritoneal lavage, or ascites are newly established. It has been confirmed that positive cytology is prognostically equivalent to distant metastasis [4–7]. Intraoperative cytology is available in most major Japanese hospitals. The results of cytological study are described as CY0 (negative) or CY1 (positive). Peritoneal washing is performed by instillation of 100–200 ml of normal saline after initial laparotomy with subsequent collection of 20–100 ml of the fluid. The specimen is examined by Papanicolaou or Giemsa staining. If further examination is necessary, other staining methods can be used.

3. Operative procedures

Classification of surgical approaches has been introduced to cater for the increased number of techniques in use. They include intraluminal endoscopy, laparoscopy, laparotomy, thoraco-laparotomy and others. Mucosal resection has been added to range of surgical treatments.

The symbols representing the proximal and distal surgical margins have been changed from OW and AW to PM (proximal margin) and DM (distal margin). As proximal and distal orientation is impossible in EMR specimens, lateral margin (LM) and vertical margin (VM) are evaluated. These findings are exclusively applied to EMR specimens.

4. Curative potential of EMR

A new classification for curative potential of mucosal resection using endoscopy or laparoscopy has been established (Table 4). The curative potential is evaluated based on the pathological findings. According to retrospective Japanese data, early gastric carcinomas have a high probability of cure if they meet the following criteria: 1) mucosal cancer (T1(M)), 2) no ulcerative change in the lesion, 3) papillary or tubular subtypes, 4) macroscopically superficial elevated type (IIa) of 2 cm or less

Table 5. Final Stage Grouping

	N0	N1	N2	N3
T1	Ia	Ib	II	
T2	Ib	II	IIIa	
T3	II	IIIa	IIIb	
T4	IIIa	IIIb		
H1,P1,CY1,M1				IV

in diameter or macroscopically superficial depressed type (IIc) of 1 cm or less in diameter. Prospective analysis is necessary to confirm that these guidelines are appropriate.

The incidence of lymph node metastasis with submucosal cancer is higher than that with mucosal cancer [8–11]. Submucosal cancer was divided into SM1 and SM2 for two reasons: First, when the tumor infiltrates into the submucosal layer by ≥0.5 mm, clinical diagnosis of tumor depth using endoscopic ultrasound is accurate. However almost all SM1 carcinomas are clinically diagnosed as mucosal cancer (T1(M)). Secondly, the incidence of lymph node metastasis from SM1 carcinoma is lower than that of SM2 lesions. We should carefully observe the patients treated by endoscopic mucosal resection, classified as "Resection EA" (Table 4), because longterm data on outcomes are not yet available. After getting sufficient data on such minimally invasive treatment, we will re-evaluate this classification.

II. Significance of the new classification

1. Stage grouping

There have been significant changes in stage grouping. Reduction in the number of lymph node groups from 5 to 4, has simplified the stage grouping. Stage IV is no longer subdivided (Table 5). Patients with any positive factor out of H1, P1, CY1 and M1, are classified as stage IV. Designating patients with positive cytology as Stage IV is a major change, justified by numerous reports of poor prognosis. The stage specific survival curves using the new criteria are shown in Fig. 1 (Nakajima T, unpublished data).

2. Curative potential of gastric resection

In the past curative potential of gastric resection was evaluated both surgically and conclusively using slightly different definitions. In this revision, curative potential is assessed using one single definition shown in Table 6. Resection A means no residual disease with high probability of cure; Resection C means definite residual disease; the other cases are classified as Resection B. A good correlation was found between this classification and the 5-year-survival-rate (Fig. 2) [4].

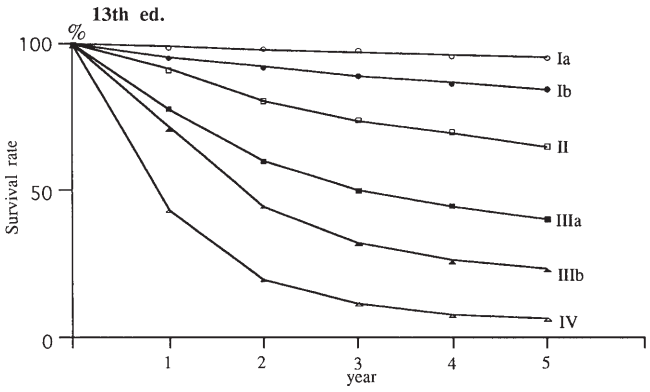

Fig. 1. Survival rate according to the new classification. (8,338 solitary gastric cancer resected at the Cancer Institute Hospital, Tokyo, between 1946 and 1997)

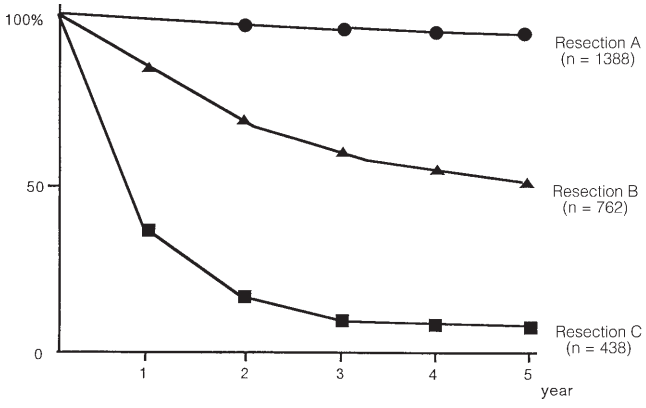

Fig. 2. Survival rate according to resection [4]

III. Harmonization with UICC TNM classification

An important issue for the JGCA is harmonization with the TNM classification of UICC [12], to allow international comparison of treatment results. The major differences between the two classifications is in the multiple categories used in the Japanese system (clinical, pathological etc) and in the N classification. The rationale for the new staging categories has been explained and we believe it has the advantage of being applicable pre- or intra-operatively. As far as the N classification is concerned, the revised TNM system is based on the number of lymph node metastases. It is easy to determine a patient's TNM N stage from Japanese medical records, but the reverse is usually not possible. Topographical evaluation of nodal metastases is unlikely to be introduced into the N classification of the TNM. Meticulous mapping of dissected lymph nodes and metastasis, which is required by the GR of JGCA, is regarded as too labor-intensive by Western surgeons and pathologists.

Table 6. Curative potential of gastric resection

	T	N·D	H	P	M	PM·DM
Resection A	T1 or T2	N0·D1,D2,D3 or N1·D2,D3	H0	P0	M0	(–) proximal and distal margin >5mm
Resection B	no residual tumors but not evaluable as "Resection A"					
Resection C	definite residual tumors					

Reliable N staging is potentially difficult. It is necessary to dissect and examine at least 15 lymph nodes for valid N staging in the new TNM classification. It is possible that in many countries the percentage of NX cases will increase due to the change of TNM classification, as 15 nodes may not be dissected or examined in many cases. It is unclear whether 6 of 6 positive nodes represents NX or N1 in the new TNM system. While such a patient is likely to be staged as N1, the true N stage is probably N2 or greater. Under the GR, a single positive second or the third tier node represents N2 or N3 disease. From the prognostic point of view, the new TNM classification does separate the stages well. This is because the probability of more distant nodal metastasis correlates with the total number of metastatic lymph nodes. Reports of multiple micrometastases in the lymph nodes of gastric cancer have appeared [13–15]. The prognostic significance of micrometastasis should be studied urgently. Another criticism is that the range of prognosis within one N-stage is wider in the new TNM classification than in the GR. Because the topographical evaluation of dissected lymph nodes is an established practice in Japan and has become accepted in many Asian, South American and even European institutions, there are no immediate plans to change this aspect of the GR. Further evaluation of both classifications should be carried out in the coming years.

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