

Comparison of Staging between the Old (6th Edition) and New (7th Edition) TNM Classifications in Advanced Gastric Cancer

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Abstract. *Background:* The aims of the present study were to compare staging between the old (6th edition) and new (7th edition) TNM classifications, and to evaluate the prognostic impact of extended lymph node dissection according to the new nodal staging in advanced gastric cancer. *Patients and Methods:* A total of 609 patients with advanced gastric cancer who had undergone curative gastric resection combined with extended lymph node dissection were enrolled in the present study. Survival curves were analyzed according to staging based on the TNM 6th and 7th editions and the Japanese Classification of Gastric Carcinoma (JCGC) 14th edition. *Results:* The 5-year survival rates and the consecutive stage survival with no significant differences were: IB 88%; II 74%; IIIA 53%; IIIB 39%; and IV 18% (IIIA vs. IIIB, $p=0.1307$) by the TNM 6th edition; IB 94%; IIA 85%; IIB 71%; IIIA 68%; IIIB 48%; IIIC 23%; and IV 13%; (IIB vs. IIIA, $p=0.7665$; IIIC vs. IV, $p=0.4156$) by the TNM 7th and JCGC 14th editions; N0 85%; N1 70%; N2 46%; N3 18%; and M1 13%; (N3 vs. M1, $p=0.8640$) by the TNM 6th edition; and N0 85%; N1 80%; N2 61%; N3a 46%; N3b 18%; and M1 13%; (N0 vs. N1, $p=0.2735$; N2 vs. N3a, $p=0.0663$; N3b vs. M1, $p=0.8640$) by the TNM 7th and JCGC 14th editions. *Conclusion:* The new classification according to the TNM 7th and the JCGC 14th editions does not always seem to be superior to the TNM 6th edition for the prognostic stratification of stages in patients who undergo curative resection for advanced gastric cancer. An extended lymph node dissection may be effective for N0-N3a, but not for N3b and M1 stages classified according to the new TNM 7th and JCGC 14th editions.

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Gastric cancer is one of the most common causes of cancer-related death worldwide (1). Complete removal of the primary lesion and metastatic lymph nodes is an essential and effective means for achieving cure in this carcinoma. Although the optimal extent of lymph node dissection is still a matter of controversy (2-5), D2 lymph node dissection has been performed as a safe and standard procedure for advanced gastric cancer in Japan and some other countries (6-11).

The TNM Classification of Malignant Tumours (TNM) and the Japanese Classification of Gastric Carcinoma (JCGC) (12-15) have been used widely for clinical practice and research when determining tumor stage in gastric cancer. Since the initial editions of the two systems were published in the 1960s, they have been revised many times, and comparison of the different classifications for gastric cancer has often been performed to improve the classification of gastric cancer (16-21). The 6th edition of TNM (TNM 6th) was revised in 2009 and the classifications of N- (extent of lymph node metastasis) and T- (degree of depth of invasion) categories have been changed in the new 7th edition of TNM (TNM 7th). Corresponding with this revision, the 13th edition of JCGC (JCGC 13th) was also revised, largely in 2010, and similar criteria to those of the TNM 7th edition in the N- and T-categories were adopted in the 14th edition of JCGC (JCGC 14th), which made it possible to handle classification using common rules. It is expected that this common standard will allow international comparisons of comparable clinical and pathological information, which will result in further progress in the management of this carcinoma.

Since the extent of lymph node dissection can affect the nodal stages (22-24), patients undergoing consistent D2 or more extended dissection for advanced gastric cancer may be a useful population for comparing staging between different classifications and evaluating the prognostic impact of extended lymph node dissection according to nodal staging. However, recent surgical results according to the new classification system based on long-term follow-up of patients with advanced gastric cancer have not been fully evaluated.

The aims of the present study were to compare staging between the old (TNM 6th) and new classifications (TNM 7th and JCGC 14th), and to evaluate the prognostic impact of extended lymph node dissection according to the current nodal staging in a recent series of patients who underwent consistent, extended lymph node dissection for advanced gastric cancer.

Patients and Methods

Over a 15-year period between June 1986 and May 2001, 695 patients with advanced gastric cancer had undergone curative gastric resection (R0 according to TNM 6th, TNM 7th and JCGC 14th) combined with lymph node dissection at Kitasato University East Hospital, Japan. Out of these patients, 86 were excluded, including 16 patients with simultaneous malignancy in other organs, 6 who had died due to operation-related death (mortality rate: 0.9%), 29 patients who had undergone limited D1 lymph node dissection and 35 patients with cancer of the esophagogastric junction who were defined as having esophageal cancer according to TNM 7th. The remaining 609 patients (406 males and 205 females, ranging in age from 21 to 86 years; average age 59.5 years) who had undergone gastrectomy (271 total, 335 distal and 3 proximal gastrectomies) with D2 or more extended lymph node dissection (D2 for 538 and D3 for 71 patients) were enrolled in the present study.

The clinical and pathological classifications were determined according to TNM and/or JCGC, as appropriate. For 63 patients with multiple gastric carcinomas (50 double, 12 triple and 1 quadruple), any lesion that invaded the deeper layer of the stomach or that had a larger diameter when multiple lesions invaded to the same layer was considered representative for these patients, in the present study. The main site of the tumor, macroscopic type, microscopic type, depth of tumor invasion (T-category), nodal status (N-category) and the postoperative course of all the patients were reviewed from the clinical and pathology records. Nodal status, including the number of dissected nodes and metastatic nodes, was reviewed from the pathology records. A total of 28,000 lymph nodes (range, 3 to 121 nodes/patient; average, 50.0 nodes/patient) had been dissected, and metastasis had been found histologically in 3,435 lymph nodes (12.3% of dissected nodes; range, 0 to 75 metastatic nodes/patient; average, 5.6 metastatic nodes/patient).

Survival curves for all 609 patients were analyzed according to stages based on TNM 6th, TNM 7th and JCGC 14th, using the Kaplan-Meier method and log-rank tests. The median follow-up time of the 373 survivors was 88.1 months. Stat View software (version 5.0, SAS Institute Inc., Cary, NC, USA) was used for all the statistical analyses and values of $p < 0.05$ were considered significant.

Results

The clinicopathological features of the 609 patients are presented in detail in Table I. In the 609 patients, 469 tumors (77%) were located mainly in the middle or lower-third of the stomach. Two hundred and forty-four tumors (40%) were macroscopically classified as Type 5 (non-classifiable carcinoma) and 346 tumors (57%) were histologically diagnosed as poorly-differentiated carcinoma.

The tumor invaded to the muscularis propria or subserosa (T2) in 441 patients (72%), to the serosa (T3) in 149 patients (24%), and to adjacent structures (T4) in 19 (3%) according to

Table I. Clinicopathological features of the study patients.

Factors (classification described)		No. of patients (%)
Main site of tumor (JCGC 13th, 14th edition)	Upper third Middle third Lower third	140 (23) 279 (46) 190 (31)
Macroscopic type (JCGC 13th, 14th edition)	Type 1 Type 2 Type 3 Type 4 Type 5	28 (5) 131 (22) 160 (26) 46 (8) 244 (40)
Microscopic type (JCGC 13th, 14th edition)	Papillary Tubular Poorly differentiated Mucinous Signet ring cell	13 (2) 197 (32) 346 (57) 38 (6) 15 (2)
Depth of tumor invasion (TNM 6th edition, JCGC 13th edition)	T2 T3 T4	441 (72) 149 (24) 19 (3)
Depth of tumor invasion (TNM 7th edition, JCGC 14th edition)	T2 T3 T4a T4b	161 (26) 280 (46) 149 (24) 19 (3)
Nodal status (TNM 6th edition)	N0 N1 N2 N3 M1*	219 (36) 227 (37) 82 (13) 52 (9) 29 (5)
Nodal status (TNM 7th edition, JCGC 14th edition)	N0 N1 N2 N3a N3b M1*	219 (36) 104 (17) 123 (20) 82 (13) 52 (9) 29 (5)

*M1, Metastasis to lymph nodes beyond the regional nodes.

TNM 6th and JCGC 13th criteria. The tumor invaded to the muscularis propria (T2) in 161 patients (26%), to the subserosa (T3) in 280 patients (46%), to the serosa (T4a) in 149 patients (24%) and to adjacent structures (T4b) in 19 patients (3%) according to TNM 7th and JCGC 14th criteria.

No lymph node metastasis was found in 219 patients (36%). The number of metastatic nodes was 1-6 (N1) in 227 patients (37%), 7-15 (N2) in 82 patients (13%), and more than 15 (N3) in 52 (9%) according to TNM 6th. The number of metastatic nodes was 1-2 (N1) in 104 patients (17%), 3-6 (N2) in 123 patients (29%), 7-15 (N3a) in 82 patients (13%) and more than 15 (N3b) in 52 patients (9%) according to the new TNM 7th and JCGC 14th criteria. Metastasis to lymph nodes beyond the regional nodes (M1) was found in 29 patients (8%) according to the classifications of both systems.

Figure 1 shows the survival curves of the 609 patients according to staging based on TNM 6th. The 5- and 10-year survival rates were 87.9% and 79.0% for stage IB, 74.3% and 61.8% for stage II, 52.7% and 46.7% for stage IIIA, 39.3% and

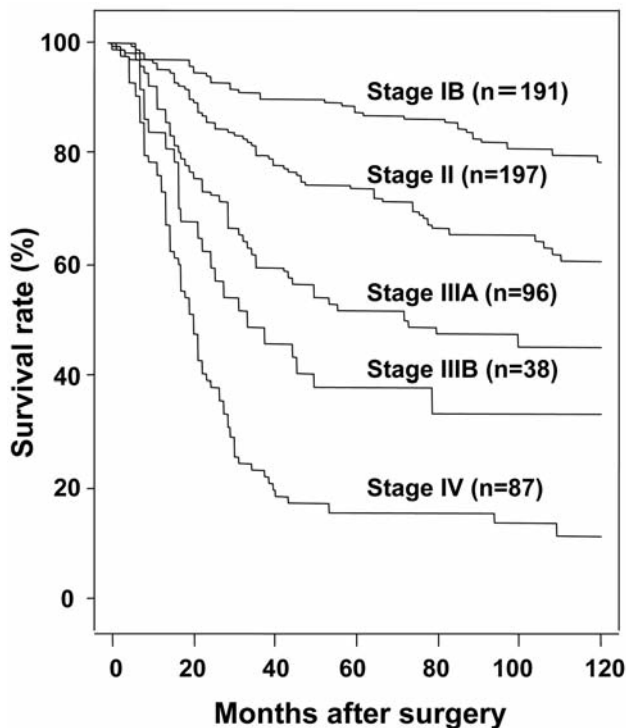


Figure 1. Survival curves of the 609 patients according to staging based on TNM (6th edition). Significant difference between stage 1B and II, $p=0.0002$; stage II and IIIA, $p=0.0016$; stage IIIB and IV, $p=0.0080$.

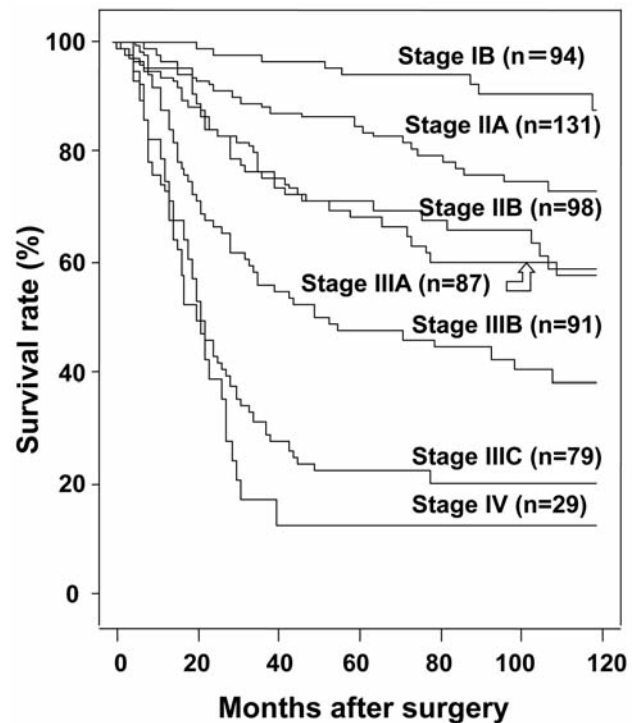


Figure 2. Survival curves of the 609 patients according to staging based on TNM (7th edition) and JCGC (14th edition). Significant difference between stage 1B and IIA, $p=0.0068$; stage IIA and IIB, $p=0.0243$; stage IIIA and IIIB, $p=0.0062$; stage IIIB and IIIC, $p=0.0004$.

34.9% for stage IIIB and 17.5% and 13.5% for stage IV, respectively. Significant differences were found between stage 1B and II, $p=0.0002$; stage II and IIIA, $p=0.0016$; stage IIIB and IV, $p=0.0080$, but not between stage IIIA and IIIB, $p=0.1307$.

Figure 2 shows the survival curves of the 609 patients according to staging based on TNM 7th and JCGC 14th. The 5- and 10-year survival rates were 94.3% and 87.9% for stage IB, 84.8% and 73.5% for stage IIA, 71.3% and 59.0% for stage IIB, 68.4% and 57.9% for stage IIIA, 48.0% and 39.0% for stage IIIB, 23.1% and 21.0% for stage IIIC and 13.4% and 13.4% for stage IV, respectively. Significant differences were found between stage 1B and IIA, $p=0.0068$; stage IIA and IIB, $p=0.0243$; stage IIIA and IIIB, $p=0.0062$; stage IIIB and IIIC, $p=0.0004$, but not between stage IIB and IIIA, $p=0.7665$; stage IIIC and IV, $p=0.4156$.

Figure 3 shows the survival curves of the 609 patients according to nodal staging based on TNM 6th. The 5- and 10-year survival rates were 84.6% and 75.5% for N0, 70.0% and 59.0% for N1, 45.7% and 42.1% for N2, 18.1% and 12.1% for N3 and 13.4% and 13.4% for M1, respectively. Significant differences in survival were found between N0 and N1, $p=0.0002$; N1 and N2, $p=0.0002$; N2 and N3, $p=0.0002$, but not between N3 and M1, $p=0.8640$.

Figure 4 shows the survival curves of the 609 patients according to nodal staging based on TNM 7th and JCGC 14th. The 5- and 10-year survival rates were 84.6% and 75.5% for N0, 79.9% and 71.2% for N1, 61.3% and 48.5% for N2, 45.7% and 42.1% for N3a, 18.1% and 12.1% for N3b and 13.4% and 13.4% for M1, respectively. Significant differences in survival were found between N1 and N2, $p=0.0014$; N3a and N3b, $p=0.0002$, but not between N0 and N1, $p=0.2735$; N2 and N3a, $p=0.0663$; N3b and M1, $p=0.8640$.

Discussion

The latest revisions may cause some differences in prognostic stratification based on staging between the old and new classification systems. Indeed, though no significant difference in survival time was found only between consecutive stage IIIA and IIIB ($p=0.1307$) of TNM 6th, no significant differences were found between the consecutive stages IIB and IIIA ($p=0.7665$) and IIIC and IV ($p=0.4156$), and survival curves of IIB and IIIC almost overlapped with those of IIIA and IV, respectively of TNM 7th and JCGC 14th. Furthermore, no significant difference in survival time was found only between nodal stage N3 and M1 ($p=0.8640$) of TNM 6th, while no significant differences were found not only between

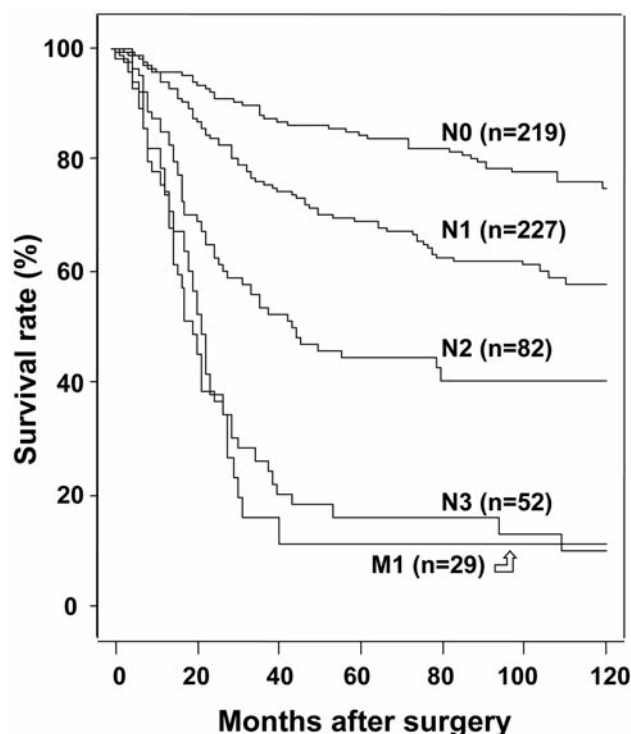


Figure 3. Survival curves of the 609 patients according to N-staging based on TNM (sixth edition). Significant difference between N0 and N1, $p=0.0002$; N1 and N2, $p=0.0002$; N2 and N3, $p=0.0002$.

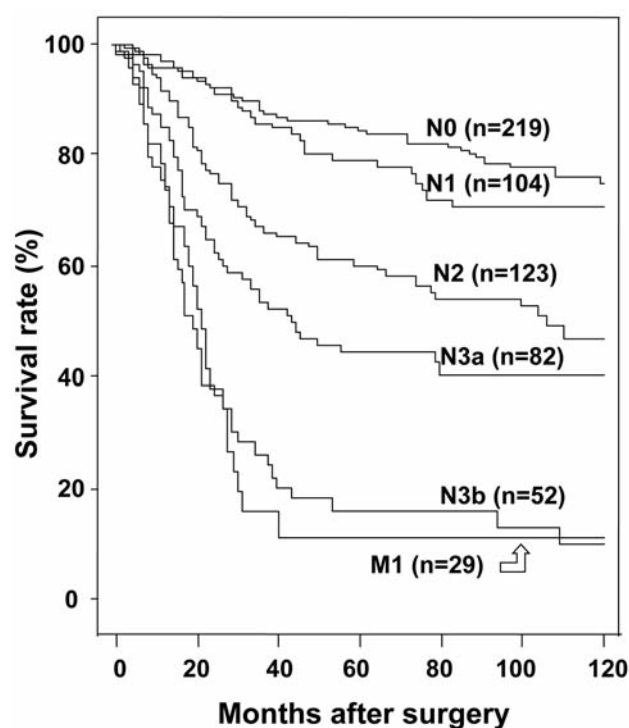


Figure 4. Survival curves of the 609 patients according to N-staging based on TNM (7th edition) and JCGC (14th edition). Significant difference between N1 and N2, $p=0.0014$; N3a and N3b, $p=0.0002$.

stage N3b and M1 ($p=0.8640$), but also between N0 and N1 ($p=0.2735$) and between N2 and N3a ($p=0.0663$) of TNM 7th and JCGC 14th. These findings indicated that disease and nodal stages based on the old TNM 6th may have reflected the prognosis more accurately than does the new TNM 7th in the patients of the present study. Thus, the classification according to the new TNM 7th and JCGC 14th does not always seem to be superior to the old TNM 6th for the prognostic stratification of staging in gastric cancer. Further studies with larger numbers of patients with gastric cancer are necessary to evaluate the validity and effectiveness of the new systems from various angles.

The optimal extent of lymph node dissection for gastric cancer has long been debated, even though previous randomized control trials (RCTs) have shown increased risks of postoperative complications and death, and failed to clearly demonstrate survival benefits of D2 compared to limited D1 dissection (2, 3). In addition, recent RCTs have shown that more radical lymph node dissection (D2 + paraaortic lymph node dissection) showed no evidence of survival benefit (25, 26). Therefore, D2 lymph node dissection is now performed as standard for advanced gastric cancer, if it can be performed safely. Definition of the degree of the extent of lymph node

dissection was not included in the new classification systems. Since the number of positive nodes was influenced by differences in the examined area of lymph nodes (22-24), a standard of the extent of lymph node dissection, such as D-number described in the JCGC 13th edition, is necessary to evaluate the validity of the current classifications and to improve them in the future.

Five- and ten-year survival rates of the patients with no metastasis or 1-15 metastatic regional lymph nodes, which corresponds to N0-N2 of TNM 6th or N0-N3a of TNM 7th and JCGC 14th, exceeded more than 40%, but fell to less than 20% when metastasis was seen in 16 or more regional nodes, or beyond the regional nodes, which corresponds to N3 or M1 of the TNM 6th or N3b or M1 of TNM 7th and JCGC 14th. Thus, these findings suggested that an extended lymph node dissection may be effective for N0-N3a stages according to TNM 7th and JCGC 14th and that metastasis to more than 15 regional nodes may be clinically equal in prognosis with M1 stage according to the classification of TNM 7th and JCGC 14th, which provides useful information when considering selection of postoperative adjuvant therapies or the introduction of new clinical trials after curative surgery for advanced gastric cancer.

In conclusion, the new TNM 7th and JCGC 14th classifications do not always seem to be superior to the old TNM 6th classification for the prognostic stratification of disease and nodal staging in advanced gastric cancer. Furthermore, D2 lymph node dissection may be effective for N0-N3a but not for N3b and M1 stages defined according to the new TNM 7th or JCGC 14th classification.

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