jgc
J Gastric Cancer 2011;11(2):78-85 • DOI:10.5230/jgc.2011.11.2.78
Review Article

Evaluation of the 7th UICC TNM Staging System of Gastric Cancer

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Since January of 2010, the seventh edition of UICC tumor node metastasis (TNM) Classification, which has recently been revised, has been applied to almost all cases of malignant tumors. Compared to previous editions, the merits and demerits of the current revisions were analyzed. Many revisions have been made for criteria for the classification of lymph nodes. In particular, all the cases in whom the number of lymph nodes is more than 7 were classified as N3 without being differentiated. Therefore, the coverage of the N3 was broad. Owing to this, there was no consistency in predicting the prognosis of the N3 group. By determining the positive cases to a distant metastasis as TNM stage IV, the discrepancy in the TNM stage IV compared to the sixth edition was resolved. In regard to the classification system for an esophagogastric (EG) junction carcinoma, it was declared that cases of an invasion to the EG junction should follow the classification system for esophageal cancer. A review of clinical cases reported from Asian patients suggests that it would be more appropriate to follow the previous editions of the classification system for gastric cancer. In addition, in the classification of the TNM stages in the overall cases, the discrepancy in the prognosis between the different stages and the consistency in the prognosis between the same TNM stages were achieved to a lesser extent as compared to that previously. Accordingly, further revisions are needed to develop a purposive classification method where the prognosis can be predicted specifically to each variable and the mode of the overall classification can be simplified.

Key Words: Stomach neoplasms, Neoplasm staging, Lymphnodes

Introduction

Tumor node metastasis (TNM) staging provides guidance for selecting the optimal treatment modalities. It also provides information on the prognosis for both physicians and patients. Furthermore, it is also used as a tool by which the treatment outcomes can be compared at hospitals and in different countries.

Disease staging based on the TNM classification currently provides a basis for staging almost all cases of a malignant tumor. This staging method is amended continuously and revised over time as new diagnostic or treatment methods have been developed. In the disease staging system, it is essential to determine if consistency can be acquired between the groups for which the same disease stage was determined and how the differentiation could be made between groups for which a different disease stage was determined. In addition, the applicability should be considered from a practical perspective. That is, it would be ideal to develop the staging system in such a manner that the specificity to each category should be assured and the overall classification should be simplified. In this regard, this study assessed the seventh edition of TNM staging. The TNM staging for gastric cancer has been included in the first edition of UICC TNM since 1966.(1) Since January, 2010, the revised seventh edition has been used. A review of the revisions on the seventh edition of TNM staging focused mainly on the classification of lymph nodes. In particular, changes were made for the fifth edition published in 1997 compared to previous editions.

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Received March 23, 2011
Accepted April 30, 2011

In other words, it was recommended that lymph nodes be classified based on the anatomical location. On the other hand, the fifth edition recommends that the lymph nodes be classified based on the number of lymph nodes with a metastasis. Major revisions on the current seventh edition include the following:

(1) Changes in the methods for classifying lymph nodes
(2) Changes in the definition of TNM stage IV
(3) Changes in the application of the disease staging to the eso-phago-gastric junction
(4) The classification of positive cases to a peritoneal washing cytology to a distant metastasis.

Given this background, this study analyzed the significance of these changes and examined the matters that need to be considered in the future classification of the disease stage.

The Scope of the Classification of Lymph Nodes with Metastasis

A revision was made for the definitions on the seventh edition when they were based on the number of lymph nodes observed on the fifth and the sixth edition. In other words, in the seventh edition, which unlike the previous classifications in that the number of lymph nodes with a metastasis of 1~6, 7~15 and ≥16 were classified as N1, N2 and N3, respectively, those in which the number of lymph nodes with a metastasis was 1~2, 3~6, 7~15 and ≥16 were classified as N1, N2, N3a and N3b, respectively. N3a and N3b were classified as the same stage. According to Ha et al.,(2) there was a significant difference in the survival rate between N3a and N3b. In particular, in the seventh edition, all cases with a metastasis in more than 7 lymph nodes were classified as N3. Compared to N1 or N2, there was a wider standard deviation in the number of lymph nodes with a metastasis (N1: 0.49, N2: 1.10 and N3: 13.77). This indicates that there is great variability in the number of lymph nodes with a metastasis in patients who belong to the N3 group. Based on the cut-off value of the number of lymph nodes with a metastasis of 30, N3 was subclassified into N3a (the number of lymph nodes with metastasis: 7~15), N3b (the number of lymph nodes with metastasis: 16~30) and N3c (the number of lymph nodes with metastasis: ≥31). This was followed by an analysis of the survival rate between the three subgroups in those patients with TanyN3M0. This showed that there was a significant difference in the survival rate between the three groups ($P<0.0001$). In addition, following a comparison of the survival rate between the TanyN3cM0 group and stage IV based on the degree of the invasion to the gastric wall, there was a significant difference in the survival rate between T3N3cM0 and stage IV and that between T4aN3cM0 and stage IV ($P=0.044$ and $P=0.007$, respectively). On the other hand, there was no significant difference in the survival rate between T4bN3cM0 and stage IV. In other words, T4bN3cM0 was classified as stage IIIc in the seventh edition but it was found to be too poor to have a significant difference in the survival rate compared to stage IV. As described herein, there was no significant difference in the survival rate, even though there was a significant difference and the other disease stages were determined, even in cases for which the same disease stage was determined on the TNM staging system in the seventh edition (In press). According to Huang et al.,(3) few cases with early-stage gastric cancer had more than 6 lymph nodes with a metastasis. These authors reported that there were almost no cases corresponding to N2 (7~15) and N3 (>15) based on the TNM staging on the fifth edition. They also noted that the difference in survival rate between N2 and N3 was significant after re-classifying N into N1 (1~3), N2 (4~6) and N3 (>6), even though there was no significant difference in the survival rate between N2 and N3. This point of view was reflected appropriately in the seventh edition of TNM staging. If one should analyze these study results, he or she would be skeptical about whether there would be a difference in the methods for applying the TNM staging to progressive gastric cancer and early-stage gastric cancer. Some reports have shown that the classification of lymph nodes proposed on the seventh edition was better in predicting the prognosis compared to the sixth edition(4-6) but there are also dissenting reports.(2,7) A further subclassification of the lymph nodes would be useful for predicting the prognosis of each case. Other aspects are present that would cause many problems with clinical applications due to a very complicated staging system. In consideration of this, further studies will be needed to develop a staging system by harmonizing the two aspects that classifications should be made more specifically and then be uncomplicated.

The Number of Lymph Nodes That Were Dissected

The sixth edition of UICC TNM staging system declared that a pathological examination should be performed to make an accurate assessment of the degree of lymph node metastasis in more than 15 lymph nodes. According to the seventh edition, based on the statement "Any cases in whom no metastases are detected in all

the lymph nodes with no respect to the number of lymph nodes dissected, even though the number of dissected lymph nodes was no greater than 16, could be classified as N0 group", revisions were made in that the dissection of more than 16 lymph nodes would not be mandatory (the classification is pNo if the examined lymph nodes are negative but the number ordinarily resected is not met.). Previous studies reported contradictory results in that correct disease staging could become difficult due to stage migration in cases in whom the number of dissected lymph nodes was insufficient.(8,9) Based on these revisions, stage migration could occur in many cases. According to Hundahl et al.,(10) based on the disease staging performed for cases of gastric cancer surgery in North America, the proportion of those with more than 15 lymph nodes dissected was at most 18%. One study examined the validity of staging for cases of esophagogastric (EG) junction cancer through a comparison between the adequate staging group where more than 15 lymph nodes were dissected and an inadequate staging group where less than 15 lymph nodes had been dissected.(11) They reported that the TNM staging could be performed accurately only in cases in whom more than 15 lymph nodes had been dissected. In particular, this would make it possible to accurately predict the prognosis of patients with progressive gastric cancer. According to INT-0116(12) and MAGIC Trial,(13) both of which were large-scale, randomized clinical studies conducted in America and Europe, the proportion of cases in whom a more extensive D2 lymph node dissection was performed was 10% and 41.4%, respectively. In addition, the proportion of cases in whom the D0 lymph node dissection, i.e., a less D1 lymph node dissection, was performed on 54% and 15.1%, respectively. According to ACTS-GC, a prospective, in randomized clinical study recently conducted in Japan, 99.8% of cases had a D2 lymph node dissection. This is contradictory to the above reports.

Of the total cases of gastric cancer surgery, which was performed at large-volume centers in Korea and the USA, the proportion of those in which less than 15 lymph nodes were dissected was 3% and 22%, respectively. A comparison of the survival rate of patients between the two hospitals during the same disease duration revealed the survival rates of patients with stage I/II/III to be significantly higher in Korea compared to USA.(14) One of the major causes of these results might be stage migration resulting from an insufficient lymph node dissection.

In cases in whom the dissection of more than 15 lymph nodes is an essential condition for the TNM staging, it might be impossible to determine the TNM stage in many patients from the USA and Europe. The current guidelines might have been loosened considering this in the seventh edition. In a future TNM staging system, the untoward effects called 'a lower standardization' can be prevented provided it is specified as the essential condition for TNM staging that more than 16 lymph nodes should be dissected.

The Proportion of Lymph Nodes with Metastasis

In the UICC and AJCC TNM Classification, the cuff-off point of the scope of lymph nodes with a metastasis has been revised continuously. To date, its gold standard has not been identified. Given this background, the proportion of lymph nodes with a metastasis relative to the number of dissected lymph nodes was divided into several segments. Some suggest that it should be used as a tool for assessing the degree of lymph node metastasis.(15-17) In addition, the proportion of lymph nodes with a metastasis exceeds the ability to predict the prognosis based on the pre-existing TNM Classification, even in cases of breast cancer, colon cancer and rectal cancer.(18-20) As reported by Lemmens et al.,(21) the proportion of lymph nodes with a metastasis was first proposed as a measure to overcome the limitations of a lymph node dissection. The methods for screening the lymph nodes with a metastasis were once assessed as the best tool for predicting the prognosis. This might not be superior to the classification based on the N category due to reasons such as the limitation in the number of dissected lymph nodes, the insufficiency in a consensus on the segment interval and the insufficiency in a consensus on the scope of lymph node metastasis. In cases for which surgery was performed with a smaller number of dissected lymph nodes in the USA and Europe, it might also be a good method that can be used alternatively to the pre-existing TNM classification.

Constituents Forming the TNM Stage IV

In the sixth edition, the TNM stage IV included M0 and M1, which showed a significant difference in the survival rate. Considering this, several authors reported that staging should be done in such a manner that stage IV should be differentiated into stages IVa and IVb according to M0 or M1.(22-25) Given this background, in the seventh edition, only distant metastasis-positive cases (M1) were classified as stage IV. Although there are many lymph nodes with a metastasis or the degree of invasion to the gastric wall is as high as possible, the corresponding cases were classified as stages other than stage IV. Therefore, differentiation

of the survival rate in stage IV cases was strengthened. Of the total M0 cases, no stage IV was determined in cases in whom both the degree of invasion to the gastric wall and that of a lymph node metastasis were relatively higher. The difference in the survival rate from stage IV would not be of statistical significance. As mentioned previously, highly-advanced T4b cases in whom the number of lymph nodes with a metastasis was greater than 30 were not classified as stage IV provided there was M0. Compared to the cases in whom stage IV was determined, a poorer prognosis was found. In these cases, a more advanced classification system is needed. Another classification system is a revision that positive cases to a peritoneal washing cytology are classified as a distant metastasis. There are various methods for performing a peritoneal washing cytology. Depending on the types of methods, there is a large discrepancy in the frequency of a positive cytology (cy+). According to Kodera et al.,(26) the rate of positive cases was found >20% on a routine cytology, 35% on immunohistochemistry and 50% on RT-PCR in cases of a serosa invasion-positive gastric carcinoma. In addition, there is a large discrepancy in the positive rates and median survival time (MST) of the positive cases between institutions. At the East Hospital of National Cancer Center of Japan, the positive rate and MST were 14% and 12 months, respectively, in cases of invasion to the subserosal layer or deeper (n=924). At the Central Hospital of National Cancer Center of Japan,(27) the positive rate and MST were 22.6% and 12 months, respectively, in cases of invasion to the muscular layer or deeper (n=996). At the MD Anderson Cancer Center in the USA,(28) the positive rate was 10.2% in cases of T1~T4b (n=381). After classifying these cases into the neoadjuvant chemotherapy group and non-neoadjuvant chemotherapy group, the MST was found to be 13 months and 7 months, respectively. According to reports from the Queen Elizabeth Hospital in the UK,(29) in 207 cases of T3 and T4a, the positive rate and MST were 7.2% and 13 months, respectively. Indeed, a peritoneal washing cytology is not a diagnostic regimen that is commonly performed at most hospitals. Accordingly, there should be guidelines for recording whether a cytology was performed, e.g. CYX. On the seventh edition of the UICC TNM staging system, positive cases to a peritoneal washing cytology are classified as a distant metastasis, except for which there are no definite guidelines for recording whether the cytology should be performed. Accordingly, if there are any positive cases in whom a peritoneal washing cytology was not performed and there was no concurrent presence of other lesions of a distant metastasis, these cases are not classified as stage IV. This might cause problems in establishing consistency between the TNM stages. According to the methods of the tests and because of the variability in the interpretation of test results, further revisions will be needed to examine whether a peritoneal washing cytology can be classified as a distant metastasis.

The TNM Staging in the EG Junction Carcinoma

According to Washington,(30) because there is variability in the prognosis of gastric cancer depending on the anatomical location at the sites of occurrence, cancers at the distal sites have a better prognosis. Accordingly, there is the possibility that the classification system developed the most appropriately for cancers at the distal sites might not be the best TNM staging. Accordingly, in an effort to improve the staging system for gastric cancer, only when the data obtained from Asians and Caucasians are referenced can the classification be applied from a worldwide perspective. In particular, regarding cases of the EG junction carcinoma, according to the sixth edition, based on the judgment of the physicians, classifications into the esophageal cancer or gastric cancer should be made. In the seventh edition, however, the primary goal of revisions to the TNM staging was to clear this confusion. The secondary goal is to homogenize the tumor (T) category for cases of gastrointestinal tumors occurring at the gastrointestinal (GI) tract extending from the stomach, small intestine and large intestine to the rectum. Therefore, attempts were made to simply the concept of the T-category, which is one of the essential factors for the classification of TNM stage. To achieve these goals, it was declared that the classification system for esophageal cancer be followed in cases of EG junction carcinoma and the previous confusion was resolved accordingly. On the other hand, there is no evidence demonstrating the validity of the application of the classification system for esophageal cancer rather than stomach cancer. Besides, there are reports that the same T category should be applied to all cancers occurring at this site because the GI tract is formed of a single tubular structure. On the other hand, this would be problematic because the anatomical difference between the organs was not considered. According to Hassan et al.,(31) the incidence of gastric cardia adenocarcinoma was increased with time and increased gradually to 42% of the total cases of gastric cancer in 1996. Clark et al.(32) reported that the incidence of cardia cancer and that of distal esophageal adenocarcinoma in Caucasians had increased. This led to the speculation that both disease entities have the same

pathogenetic origins. Dolan et al.(33) reported a similarity in the etiology, epidemiology and clinicopathological features between an adenocarcinoma of lower esophagus and cardia. These authors reported that these two carcinomas should be classified as the same disease entity. According to large-scale studies conducted on 1,002 cases of the EG junction carcinoma, Rüdiger Siewert et al.(34) reported that Type I (tumors with the center located from 5 cm to 1 cm above the EG junction) formed a specific category that should be considered as a lower esophageal cancer and most of these cases occurred in the Barrett's esophagus, which are the sites of intestinal dysplasia of the lower esophagus formed due to the EG regurgitation. In contrast, in Type II cases (tumors with the center located 1 cm above to 2 cm below the EG junction), the intestinal dysplasia formed in only 10% in the lower esophagus. In patients with Type III (tumors with the center located from 2 cm to 5 cm below the EG junction), the incidence of intestinal dysplasia was very low. Accordingly, there is great discrepancy between Type I cases. In other words, a Type II tumor is closer to gastric cancer at the proximal sites than a lower esophageal adenocarcinoma. In addition, according to studies on the lymphatic circulation, the lymphatic ducts originating from the lower esophagus bilaterally progress, i.e. the mediastinum superiorly and the celiac axis inferiorly. In cases of Type II and III, most lymphatic ducts progress to the celiac axis. For this reason, there is a difference in the pattern of lymph node metastasis between Types II and I tumors, which is also similar to Type III. In cases of Type II tumor, the esophagectomy has not improved the survival rate compared to an extensive gastrectomy. According to Kusano et al.,(35) the incidence of an EG junction carcinoma (Siewert Type II) was 10% in patients with progressive gastric cancer who had been treated surgically at the National Cancer Center of Japan from 2001 to 2005 and the incidence of Siewert Type I was approximately 1%. According to studies comparing the characteristics of gastric cancer between Asians and Caucasians,(36) the incidence of an EG junction carcinoma was 0.4%, which is much lower than the 18% observed in Caucasians. In addition, following the classification of an EG junction carcinoma into Siwert Types I and II, there were almost no cases of Type I in Koreans.(37) The incidence of upper gastric 1/3 cancer steeply increased sharply to 12.5% up to 1992. Since then, its increasing rate has been reduced markedly and showed a greatly different tendency compared to the higher increasing rate observed in Caucasians.(38) According to the staging system on the seventh edition of the UICC TNM, cases in whom the central region of carcinoma was located within 5 cm superior and inferior to the EG junction and then invaded the EG junction, were classified based on the classification system for esophageal cancer. To evaluate the validity of the changes in this classification system, 496 cases of an EG junction carcinoma were classified based on the classification system of esophageal cancer in the seventh edition at the Seoul National University Hospital. This was followed by an analysis of the difference in the survival rate between the stages. The survival rate was similar in stage I (n=230) and stage II (n=116) (P=0.948), but there was a significant difference in the survival rate between stages III (n=150) and II (P $<$ 0.001) and between stages III and I (P $<$ 0.001). A comparative analysis of the survival rate between the TNM stages after the same patient group was classified based on the TNM staging revealed a difference in the survival rate between stage I (n=241) and stage II (n=125) at a moderate degree of statistical significance (P=0.089). In addition, there was a significant difference in the survival rate between stages III (n=130) and II (P $<$ 0.001) and that between stages III and I (P $<$ 0.001). This suggests that the classification system for gastric cancer rather than the classification system for esophageal cancer reflects the difference in the survival rate between the TNM stages. One study examined the survival rates between the TNM stages in 4,027 cases of gastric cancer located more than 5 cm distal to the EG junction and 496 cases of the EG junction carcinoma. A comparison of the survival rate between the TNM stages in cases of the EG junction carcinoma, which had been classified based on the classification system for esophageal cancer and that for gastric cancer between the TNM stages, revealed a significant difference in the survival rate in stage II patients (P=0.021). Nevertheless, there was no significant difference in the survival rate between all the TNM stages (stage I, stage II and stage III) in cases of the EG junction carcinoma, which had been classified based on the classification system for esophageal cancer and gastric cancers occurring at other sites. This suggests that the current revisions might fulfill the classification system for both cancers at distal and proximal sites. Based on these results, there is a higher degree of differences for EG junction carcinomas based on the classification system for gastric cancer rather than the classification system for esophageal cancer (not pressed). The Japanese Society for Gastric Cancer defined carcinomas located within 2 cm superiorly and inferiorly to the EG junction as EG junction cancer in collaboration with the Japanese Society for Esophageal Cancer.(39) Controversial opinions exist regarding the treatment modalities for cases of EG junction cancer. Currently, there is some consensus that the optimal treatment modalities should be selected based on the distance of tumor invasion to the stomach or esophagus rather than the location of

the central region of the tumor. According to the 83th workshop of the Japanese Society for Gastric Cancer, on March 2011, "Progresses in the diagnosis and treatment of the esophago-gastric junction tumors", most Japanese surgeons considered an EG junction carcinoma to be a gastric cancer rather than an esophageal cancer for treatment. According to Rausei et al.,(40) EG junction carcinoma was included in the esophageal chapter based on the new TNM staging system according to the anatomical criteria '5 cm rule' proposed by Siewert but this was based on an obscure concept of the tumor epicenter. Accordingly in some cases, a gastric fundus tumor might also be considered as an esophageal cancer. Therefore, the current revision did not clarify the clinical issues that are well known regarding the EG junction carcinoma. Nevertheless, it did not discourage attempts to make a differentiation of an EG junction carcinoma from an esophageal or gastric cancer.

Conclusions

In the seventh edition of the UICC TNM staging, which has recently been revised, attempts were made to resolve the problems of previous editions of TNM staging. On the other hand, any noticeable matters have not been resolved. First of all, the N3 category was defined too extensively in the classification of lymph node metastasis. This achieved a simplification of the classification but it impaired the accuracy in predicting the prognosis in cases of progressive gastric cancer with a large number of lymph nodes with metastasis. Besides, it also did not clarify the minimum number of lymph nodes that should be dissected for appropriate TNM staging as shown previously. Therefore, it reduced the accuracy of TNM staging due to stage migration. Although it declared that it resolved the confusion of previous editions of TNM staging by specifying that the EG junction carcinoma should follow the classification system for esophageal cancer, it provided no clear evidence for this and did not resolve the previous issues. The edition also declared that positive cases to a peritoneal washing cytology should be considered a distant metastasis and then determined to be TNM stage IV. On the other hand, there are no standardized methods for this diagnostic regimen, which is not performed at many medical institutions, and deserves further consideration.

The most ideal TNM staging methods should be composed of simpler rules so that it may be used easily in a clinical setting. Simultaneously, it should also guarantee the consistency between the cases corresponding to the same TNM stage and the differentiation between those corresponding to different TNM stages. This is quite challenging to surgeons. Further revisions of the TNM staging will be needed to contain both of these aspects to develop a harmonized classification.

References

1. Sayegh ME, Sano T, Dexter S, Katai H, Fukagawa T, Sasako M. TNM and Japanese staging systems for gastric cancer: how do they coexist? Gastric Cancer 2004;7:140-148.
2. Ha TK, Kim HJ, Kwon SJ. Does the New UICC/AJCC TNM Staging System (7th Edition) Improve Assessing Prognosis in Gastric Cancer Compared to the Old System (6th Edition)? J Korean Gastric Cancer Assoc 2009;9:159-166.
3. Huang B, Zheng X, Wang Z, Wang M, Dong Y, Zhao B, et al. Prognostic significance of the number of metastatic lymph nodes: is UICC/TNM node classification perfectly suitable for early gastric cancer? Ann Surg Oncol 2009;16:61-67.
4. Qiu MZ, Wang ZQ, Zhang DS, Liu Q, Luo HY, Zhou ZW, et al. Comparison of 6th and 7th AJCC TNM staging classification for carcinoma of the stomach in China. Ann Surg Oncol 2011 Jan 19. [Epub ahead of print]
5. Deng J, Liang H, Sun D, Wang D, Pan Y. Suitability of 7th UICC N stage for predicting the overall survival of gastric cancer patients after curative resection in China. Ann Surg Oncol 2010;17:1259-1266.
6. Deng J, Liang H, Wang D. The feasibility of N stage of the 7th edition TNM for gastric cancer. Ann Surg Oncol 2011;18:1805-1806.
7. Bae JM, Kim SW, Kim SW, Song SK. Evaluation of prognostic values according to the new TNM classification in gastric cancer. J Korean Surg Soc 2011;80:23-28.
8. Deng JY, Liang H, Sun D, Zhan HJ, Wang XN, The appropriate cutoffs of positive lymph nodes to evaluate the prognosis of gastric cancer patients. J Surg Oncol 2008;98:343-348.
9. Bunt AM, Hermans J, Smit VT, van de Velde CJ, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. J Clin Oncol 1995;13:19-25.
10. Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: fifth edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. Cancer 2000;88:921-932.
11. Barbour AP, Rizk NP, Gonen M, Tang L, Bains MS, Rusch

VW, et al. Lymphadenectomy for adenocarcinoma of the gastroesophageal junction (GEJ): impact of adequate staging on outcome. Ann Surgl Oncol 2006;14:306-316.
12. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-730.
13. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
14. Strong VE, Song KY, Park CH, Jacks LM, Gonen M, Shah M, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. Ann Surg 2010;251:640-646.
15. Fukuda N, Sugiyama Y, Midorikawa A, Mushiake H. Prognostic significance of the metastatic lymph node ratio in gastric cancer patients. World J Surg 2009;33:2378-2382.
16. Persiani R, Rausei S, Biondi A, Boccia S, Cananzi F, D'Ugo D. Ratio of metastatic lymph nodes: impact on staging and survival of gastic cancer. Eur J Surg Oncol 2008;34:519-524.
17. Marchet A, Mocellin S, Ambrosi A, Morgagni P, Garcea D, Marrelli D, et al. The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. Ann Surg 2007;245:543-552.
18. Moug SJ, Saldanha JD, McGregor JR, Balsitis M, Diament RH. Positive lymph node retrieval ratio optimizes patient staging in colorectal cancer. Br J Cancer 2009;100:1530-1533.
19. Peschaud F, Benoist S, Julié C, Beauchet A, Penna C, Rougier P, et al. The ratio of metastatic to examined lymph nodes is a powerful independent prognostic factor in rectal cancer. Ann Surg 2008;248:1067-1073.
20. Van der Wal BC, Butzelaar RM, van der Meij S, Boermeeste MA. Axillary lymph node ratio and total number of removed lymph nodes: predictors of survival in stage I and II breast cancer. Eur J Surg Oncol 2002;28:481-489.
21. Lemmens VE, Dassen AE, van der Wurff AA, Coebergh JW, Bosscha K. Lymph node examination among patients with gastric cancer: Variation between department of pathology and prognostic impact of lymph node ratio. Eur J Surg Oncol 2011;37:488-496.
22. Ha TK, Kwon SJ. Subclassification of stage IV gastric cancer according to the presence of distant metastasis (IVa and IVb). J Korean Gastric Cancer Assoc 2006;6:173-180.
23. Park JM, Park SS, Mok YJ, Kim CS. pN3M0 gastric cancer: the category that allows the sub-classification of stage IV gastric cancer (IVa and IVb). Ann Surg Oncol 2007;14:2535-2542.
24. Li C, Yan M, Chen J, Xiang M, Zhu ZG, Lin YZ. Prognostic influence of sub-stages according to pTNM categories in patients with stage IV gastric cancer. J Surg Oncol 2009;99:324-328.
25. An JY, Ha TK, Noh JH, Sohn TS, Kim S. Proposal to subclassify stage IV gastric cancer into IVa, IVb, and IVM. Arch Surg 2009;144:38-45.
26. Kodera Y, Nakanishi H, Ito S, Nakao A. Clinical significance of isolated tumor cells and micrometastases in patients with gastric carcinoma. Gan To Kagaku Ryoho 2007;34:817-823.
27. Fukagawa T, Katai H, Saka M, Morita S, Sasajima Y, Taniguchi H, et al. Significance of lavage cytology in advanced gastric cancer patients. World J Surg 2010;34:563-568.
28. Badgwell B, Cormier JN, Krishnan S, Yao J, Staerkel GA, Lupo PJ, et al. Does neoadjuvant treatment for gastric cancer patients with positive peritoneal cytology at staging laparoscopy improve survival? Ann Surg Oncol 2008;15:2684-2691.
29. Nath J, Moorthy K, Taniere P, Hallissey M, Alderson D. Peritoneal lavage cytology in patients with oesophagogastric adenocarcinoma. Br J Surg 2008;95:721-726.
30. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg 2010;17:3077-3079.
31. Hassan HA, Sharma VK, Raufman JP. Changing trends in gastric carcinoma at a university medical center: a twelve-year retrospective analysis. J Clin Gastroenterol 2001;32:37-40.
32. Clark GW, Smyrk TC, Burdiles P, Hoeft SF, Peters JH, Kiyabu M, et al. Is Barrett's metaplasia the source of adenocarcinomas of the cardia? Arch Surg 1994;129:609-614.
33. Dolan K, Sutton R, Walker SJ, Morris AI, Campbell F, Williams EM. New classification of oesophageal and gastric carcinomas derived from changing patterns in epidemiology. Br J Cancer 1999;80:834-842.
34. Rüdiger Siewert J, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Ann Surg 2000;232:353-361.
35. Kusano C, Gotoda T, Khor CJ, Katai H, Kato H, Taniguchi H, et al. Changing trends in the proportion of adenocarcinoma of the esophagogastric junction in a large tertiary referral center

in Japan. J Gastroenterol Hepatol 2008;23:1662-1665.
36. Strong VE, Song KY, Park CH, Jacks LM, Gonen M, Shah M, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. Ann Surg 2010;251:640-646.
37. Kim HJ, Kwon SJ. Analysis of clinicopathologic difference between type II and type III cancers in Siewert classification for adenocarcinoma of the cardia. J Gastric Cancer 2004;3:143-148.
38. Jang JH, Beron RI, Ahn HS, Kong SH, Lee HJ, Kim WH, et al. Clinicopathological features of upper third gastric cancer during a 21-year period (single center analysis). J Gastric Cancer 2010;10:212-218.
39. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. Published online: 15 May 2011.
40. Rausei S, Dionigi G, Boni L, Rovera F, Dionigi R. How does the 7th TNM edition fit in gastric cancer management? Ann Surg Oncol 2010 Sep 29. [Epub ahead of print].