Special article

TNM-7th edition 2009 (UICC/AJCC) and Japanese Classification 2010 in Gastric Cancer. Towards simplicity and standardisation in the management of gastric cancer

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ARTICLE INFORMATION

Article history:
Received September 8, 2010
Accepted October 20, 2010

Keywords:
TNM (7th edition)
Gastric cancer
Lymphadenectomy
Japanese classification 2010

ABSTRACT

The 7th edition of the UICC/AJCC TNM, and a new revision of the Japanese Classification for Gastric Cancer and Treatment Guidelines (Japanese Gastric Cancer Association) have been available since the beginning of 2010. One of the most important changes consists on the redefining and simplification of type D1/D2 lymphadenectomy depending on the type of gastrectomy performed (previously it depended on the location of the primary tumour), and the adoption of numeric criteria of TNM-7th Edition to evaluate the level of lymph node involvement (before, according to the anatomical location of the groups as regards the primary tumour). These changes attempt to make therapeutic management easier and a more uniform comparison of results between countries. The importance of these modifications in both systems justifies this exhaustive analysis and update of the new concepts for a correct management of gastric cancer.

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TNM 7.ª edición 2009 (UICC/AJCC) y Clasificación Japonesa 2010 en Cáncer Gástrico. Hacia la simplicidad y estandarización en el manejo del cáncer gástrico

RESUMEN

Desde inicios de 2010 han entrado en vigor la 7.ª ediciónde el TNM (UICC/AJCC) y una nueva revisión de la Japanese Classification for Gastric Cancer and de la Treatment Guidelines (Japanese Gastric Cancer Association). Unas de las modificaciones más importantes consisten en la redefiniciónde simplificación de los tipos de linfadenectomía D1/D2 en función del tipo de gastrectomía realizada (anteriormente en función de la localización del tumor primario) y en la adopción del criterio numérico de la 7.ª edición del TNM para evaluar el grado de afectación ganglionar (antes según la localización anatómica de los grupos respecto al tumor primario). Estos cambios pretenden facilitar el manejo terapéutico y la
Introduction

Precise tumour staging is indispensable for reliable prognostic information, and to establish common treatment recommendations for tumours with similar characteristics. Different systems have been developed for evaluating the stage of gastric cancer tumours, which has impeded the interpretation and comparison of results between geographical locations.

The most commonly used system in Western countries is the TNM system proposed by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). The TNM staging system classifies tumours based on the extent of the primary tumour, involvement of regional lymph nodes, and the presence of distant metastasis, thus grouping cases by similar prognosis. This system is revised every 6-8 years, considering the input from new clinical, histopathological, and biological data that may influence patient prognosis.1,2

The Japanese Gastric Cancer Association (JGCA) used its experience compiled from over 4 decades through wide-ranging national registries and biannual meetings to elaborate an overarching review of the Japanese classification system and treatment guidelines. This new review, which came into effect during 2010, presented important modifications to previous editions in very relevant areas such as the definition of different types of lymphadenectomies and the evaluation of lymph node involvement, which no longer is based on the location of invaded lymph node groups, but rather on the number of infiltrated lymph nodes, a criterion that has been used by the TNM classification system since 1997.3,4

The modifications made to both systems are complimentary, and facilitate the treatment of patients in clinical practice. On the one hand, the recommendations established by the JGCA define and simplify the recommended treatment for tumours with common characteristics (for example, defining the different types of lymphadenectomy). On the other hand, the TNM system (UICC-AJCC) facilitates a simple tumour staging method that is both agile and reproducible, allowing for the evaluation of patient prognosis and treatment results, as well as the exchange of information between different hospitals and countries.

Until now, one of the greatest difficulties in interpreting and comparing results between Western countries and Japan has been the different evaluation criteria used for lymph node infiltration (pN) and the definition of tumour stages. This made other common criteria necessary in order to uniformly interpret results and exchange information between health centres.

During 2010, relevant modifications have come into effect in both staging systems that justify this update and review.

TNM (UICC/AJCC) 7th Edition 2009

In the TNM 7th Edition 2009, a series of modifications have been made to the different categories used for the definitions of primary tumour (T), regional lymph nodes (N), and distant metastasis (M), as well as to their grouping into different stages.

Primary tumour

The categories for T in gastric cancer have been modified to be coherent with those for the rest of the digestive system (oesophagus, small intestine, colon, and rectum). Thus, category T1 is subdivided into T1a (invasion of the muscularis mucosa and/or lamina propria) and T1b (invasion of the submucosa). T2 is invasion of the muscularis propria. The most significant changes appear in the category T3, which is now defined as infiltration of the subserosa without invasion of the visceral peritoneum or adjacent structures (classified in the 2002 edition as T2b), and in the category T4a, which is now considered as infiltration of the serosa or the visceral peritoneum (which beforehand was considered to be T3). Tumours that invade surrounding organs are now considered to be T4b (Table 1).

Regional lymph nodes

The classification of N also underwent important changes (Table 1). N1 is now defined as involvement of 1-2 regional lymph nodes. N2 is the presence of 3-6 infiltrated lymph nodes (this was previously considered as N1), and N3 is >7 lymph nodes. This new classification allows for defining lymph node involvement in the same way as for oesophageal cancer. However, as opposed to oesophageal cancer, the category of N3 in gastric cancer is subdivided into 3a (7-15 nodes) and 3b (≥16 nodes). The identification of lymph node infiltration by only isolated tumour cells (cell cluster ≤0.2 mm in size) using very sensitive immunohistochemical or molecular techniques continues to be considered as pN0.

Table 1 – Summary of the principal changes between the 2002 6th edition and the 2009 7th edition of the TNM

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>T1a Lamina propria</td>
<td>T1</td>
</tr>
<tr>
<td>T1b Submucosa</td>
<td>T1</td>
</tr>
<tr>
<td>T2 Muscularis mucosa</td>
<td>T2a</td>
</tr>
<tr>
<td>T3 Subserosa</td>
<td>T2b</td>
</tr>
<tr>
<td>T4a Perforation of the serosa</td>
<td>T3</td>
</tr>
<tr>
<td>T4b Invasion of adjacent structures</td>
<td>T4</td>
</tr>
<tr>
<td>N1 (1-2 nodes)</td>
<td>N1</td>
</tr>
<tr>
<td>N2 (3-6 nodes)</td>
<td>N1</td>
</tr>
<tr>
<td>N3a (7-15 nodes)</td>
<td>N2</td>
</tr>
<tr>
<td>N3b (≥16 nodes)</td>
<td>N3</td>
</tr>
</tbody>
</table>
Initial studies with few patients in Western countries, where locally advanced primary tumours are most common (T3-T4), have attested to the advantages given by subdividing the old category of pN1 (1-6) into two different categories (pN1: 1-2; pN2: 3-6).5 Our experience at the Hospital Mutua de Terrassa confirm these findings (Figure 1). However, data from a registry maintained by the Seoul National University Hospital involving 9582 patients (≥7 lymph nodes infiltrated: 2161 patients) who complied with the criteria of a single lesion, R0 surgery, and no deaths within the first 30 days, has shown a clear advantage when subdividing the old pN1 group.6 Another study performed by the National Cancer Institute with 9018 patients in Tokyo corroborated these results (Figure 2). Given the direct relationship between the level of invasion of the stomach wall by the primary tumour (T) and the number of infiltrated lymph nodes (N), it is probable that in Western studies, where the prevalence of the disease is lower but with a greater proportion of locally advanced tumours, researchers have greater difficulty in demonstrating the advantages of the new staging system. Even so, these modifications have allowed for a better evaluation of prognoses in less advanced tumours (<7 infiltrated lymph nodes) and has facilitated the adoption by the Japanese Classification system of the lymph node categories established by the TNM 7th edition.

Distant metastasis

The category of pM is defined only as a positive biopsy result for the metastasis location (pM1). The category of pM0 is therefore no longer considered valid; cases in which the extent of the tumour is determined without histopathological confirmation of a metastasis should be labelled as cM0.

Another aspect to keep in mind is that positive peritoneal cytology, which was not considered in previous versions of the UICC/AJCC staging system, is now considered to be M1 (stage IV), which was already integrated into earlier versions of the Japanese classification system.

Tumour stages

The grouping of TNM categories has also undergone important changes (Table 2). Under the new system, for example, a tumour catalogued as T2bN0 using the 6th edition from 2002 should now be staged as T3N0 (stage IIA), and another classified as T2bN1 (5 infiltrated lymph nodes) according to the 6th edition would now be classified as T3N2 (stage IIIa).

In the TNM 6th edition from 2002, all tumours with more than 15 infiltrated lymph nodes (pN3) were considered to be stage IV. Under the new edition, the number of infiltrated lymph nodes is no longer a criterion for defining stage IV. The new TNM edition recognises 5 different situations upon staging a tumour. ‘Clinical’ (cTNM) defines patient prognosis before the initial treatment given. ‘Pathological’ (pTNM) compiles the data from the surgical resection and histological analysis, providing a more precise prognosis and aiding in selecting candidate patients for adjuvant treatment. ‘Post-therapy’ includes clinical (ycTNM) or pathological (ypTNM) data after the patient has received chemo and/or radiation therapy, whether prior to surgery or as a primary treatment, which allows for estimating the response of the cancer to treatment. ‘Retreatment’ (rTNM) include clinical and pathological data when starting a new treatment method due to recurrence or progression of the disease, and helps define the new line of treatment. Finally, ‘Autopsy’ (aTNM) defines the extent of an unknown cancer that is identified during a necropsy.

All of these changes made to the definitions of tumour stages create the need for specifying the edition of the TNM used when expressing and comparing results.

Tumours in the gastroesophageal junction

One of the biggest advances made with the 7th edition of the TNM is with regard to tumours located in or near the gastroesophageal junction: tumours originating in the gastroesophageal junction or the stomach within 5cm of the junction and extending into the oesophagus are now staged as oesophageal adenocarcinomas.
The definition of primary tumours includes high-grade dysplasia such as Tis. The category of T1 is subdivided into T1a (invasion of the lamina propria and the submucosa) and T1b (invasion of the submucosa); and subdivides the category T4 into T4a (resectable tumour that invades the pleura, pericardium, or diaphragm) and T4b (non-resectable tumour that invades the aorta, vertebrae, trachea, etc.).

In earlier editions, the criteria used for evaluating lymph node involvement in oesophageal cancer depended on the location of infiltrated lymph nodes with relation to the location of the primary tumour. As such, in inferior thoracic oesophagus tumours, infiltrated lymph nodes in the celiac trunk were considered as metastases (M1a), and so in stage IV. In the 2009 edition, the criteria were radically modified in favour of numeric criteria, regardless of the location of the primary tumour (pN1 [1-2]; pN2 [3-6] and pN3 [≥7]). ‘Regional lymph nodes’ were re-defined as those that extend from the perioesophageal cervical space to the celiac trunk. The category M1 only includes distant metastases that are not in direct contact with the oesophageal tumour or invaded lymph nodes.

Sufficient evidence exists to confirm the existence of a direct proportional relationship between the number of resected lymph nodes and survival. This relationship has been attributed to the therapeutic effect of lymphadenectomies, although it may also be due to a stage migration phenomenon, since resecting more lymph nodes improves the N classification. Based on these data, the definition of an optimal lymphadenectomy depends on the T classification (pT1 ≥10 nodes; pT2 ≥20 nodes, and pT3-4 ≥30 nodes), although in general terms and based on analysis methods, the resection of between 12 and 22 nodes can be considered as adequate. In any case, as many regional lymph nodes as possible should be resected, limiting the morbidity associated with a radical lymphadenectomy.

This new manner of staging tumours in the gastroesophageal junction and those of the cardia within 5cm of the junction have generated some controversy, since it does not appear to respect the biological characteristics of the tumour, lacks a scientific foundation and shifts other classifications. The Siewert classification system, for example, has demonstrated to be very useful in the clinical setting, establishing different surgical recommendations based on the location of the primary tumour (Siewert type I: subtotal oesophagectomy with proximal gastrectomy; type III: extended total gastrectomy). Although the motives behind these changes are not immediately understandable, a future analysis of the results will allow for a real conclusion regarding the usefulness of staging cardial tumours as oesophageal, as well as an evaluation of the influence of different surgical techniques used in these cases.

Japanese classification system and treatment guidelines 2010

For over 4 decades, the Japanese Research Society for Gastric Cancer (JRSGC) has used data from national registries to establish a series of recommendations for the diagnosis and treatment of gastric cancer. These recommendations include a manual for manipulating the resected specimen and performing a histological analysis. Recently, the JGCA revised its classification system (Japanese Classification of Gastric Cancer, JCGC) and treatment guidelines (Japanese Gastric Cancer Treatment Guideline, JGCTG). The most relevant changes were the adoption of the classification system proposed by the TNM 7th edition and a simplification of the definitions for the different types of lymphadenectomy.

Table 2 – Tumour stages in the TNM 7th edition 2009 (UICC/AJCC)a

<table>
<thead>
<tr>
<th></th>
<th>N0</th>
<th>N1 (1-2)</th>
<th>N2 (3-6)</th>
<th>N3a (7-15)</th>
<th>N3b (≥16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 Mucosa/submucosa</td>
<td>IA</td>
<td>IB</td>
<td>IIa</td>
<td>IIb</td>
<td>IIb</td>
</tr>
<tr>
<td>T2 Muscularis propria</td>
<td>IB</td>
<td>IIA</td>
<td>IIb</td>
<td>IIIA</td>
<td>IIIA</td>
</tr>
<tr>
<td>T3 Subserosa</td>
<td>IIA</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIb</td>
<td>IIIb</td>
</tr>
<tr>
<td>T4a Serosa</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIb</td>
<td>IIIC</td>
<td>IIIC</td>
</tr>
<tr>
<td>T4b Surrounding organs</td>
<td>IIIB</td>
<td>IIIB</td>
<td>IIIC</td>
<td>IIIC</td>
<td>IIIC</td>
</tr>
</tbody>
</table>

Any T or N, M1: Stage IV.

aAdopted by the JCGC
Japanese classification system

Until now, one of the primary difficulties in interpreting the clinical experience gained in Japan has been the different method used for expressing the level of lymph node involvement. From its inception, the JCGC has used anatomical criteria for defining pN based on the location of the affected lymph nodes with regard to the primary tumour. The lymph node groups were previously defined as perigastric (first level), located throughout the branches of the celiac trunk (second level), or distant (third level), as shown in Table 3. The level of lymph node involvement was classified as: no evidence of lymph node invasion (N0), metastasis of only level 1 lymph nodes (N1), metastasis of level 2 lymph nodes but not level 3 (N2), and metastasis of level 3 lymph nodes (N3). Sufficient scientific evidence based on the accumulation of data from Japanese registries exists to demonstrate the reliability of this prognostic criteria.\(^{10,11}\) Additionally, in contrast to a numeric criterion, this topographical criterion provides information regarding the extent of the surgery performed (which groups have been resected) and the level of lymph node involvement, using biopsies from different levels in cases in which a lymphadenectomy surgical specimen is not available, such as in non-resectable tumours, palliative resections, and patients eligible for neoadjuvant therapy. Finally, given the possibility of evaluating the number of invaded lymph nodes in each resected group, the anatomical category of pN can be transformed into a numeric value, but not in the other direction.

However, this topographical system has been difficult to standardise due to the complexity associated with its use in daily practice, above all in countries in which the prevalence of gastric cancer is low. Several different Western and Japanese studies have demonstrated the advantages of a numeric criterion for establishing the prognosis of lymph node invasion. Some of these advantages are that the system is very simple, easy to reproduce, is more objective (since the different groups do not have to be separated for a histopathological analysis), and with a more precise prognostic value, according to some studies.\(^{12,13}\) This evidence, along with the desire to unify criteria with those from Western countries, has led the JGCA to adopt the numeric system used by the UICC. As we have seen, the prognostic information provided by each system of criteria is not mutually exclusive, but rather complementary. As such, in spite of having adopted the TNM 7th edition 2009 classification system for expressing prognostic results, Japanese surgeons will continue to identify and register lymph node groups according to their location in normal clinical practice for their pathological evaluation and later study for recommending the proper type of lymphadenectomy.

One of the aspects that have probably had the greatest influence on making the decision to adopt the numeric system has been the subdivision of the old category of pN1 (1-6) into pN1 (1-2) and pN2 (3-6). In Japan, where the proportion of initial stage tumours can constitute more than 50% of the total, the old pN classification system did not allow for precisely assessing the prognosis of these types of tumours.\(^{14,15}\)

The lack of agreement regarding the classification of tumours in the upper third of the stomach that extend into the oesophagus requires special attention. The Japanese classification system will continue to stage these tumours as gastric, without following the recommendations of the UICC/AJCC, which indicate that these should be staged as oesophageal adenocarcinomas. The JGCA considers that this modification ignores the current knowledge regarding lymph node dissemination and the biology of gastric cancer. Additionally, they argue that this criterion is in violation of the basic rules of the TNM system, since it would consider a tumour that has invaded an organ from a distinct primary location as originating in the invaded organ.

One of the greatest difficulties that existed in interpreting results from Japan and comparing them with those from Western countries was the disparity in the criteria used for defining tumour stages in each classification system. For example, as shown in Table 3, a stage IIIA tumour under the UICC/AJCC system could be categorised within a range from stage II to stage IV in the Japanese classification system. Using the same criterion for defining tumour stages (following the recommendations in the TNM 7th edition) will allow for comparing the experience and treatment given in different studies involving Japanese and Western patients alike.

Even though the new systems have already come into effect, it will now be necessary to specify the classification system used when presenting study results, since many studies have presented results using the recommendations set forth by previous editions.

Japanese treatment guide

Lymph node dissection is defined as D0 (null or incomplete dissection of level 1 lymph node groups), D1 (complete dissection of level 1 groups, but none from level 2), D2 (complete dissection of groups from levels 1 and 2, but not level 3) and D3 (dissection

<table>
<thead>
<tr>
<th>Tumour location</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antrum +/- duodenum</td>
<td>3, 4, 5, 6</td>
<td>1, 7, 8a, 9, 11p, 12a, 14v</td>
<td>4sb, 8p, 12b, 12p, 13, 16a2, 16b1</td>
</tr>
<tr>
<td>Antrum +/- body</td>
<td>1, 3, 4sb, 5, 6</td>
<td>7, 8a, 9, 11p, 12a</td>
<td>2, 4sa, 8p, 10, 11d, 12p, 13, 14v, 16a2, 16b1</td>
</tr>
<tr>
<td>Body +/- fundus +/- cardia</td>
<td>1-6</td>
<td>7, 8a, 9-11, 12a</td>
<td>8p, 12b, 12p, 14v, 16a2, 16b1, 19, 20</td>
</tr>
<tr>
<td>Fundus +/- cardia</td>
<td>1-3, 4sa, 4sb</td>
<td>4d, 7, 8a, 9-11</td>
<td>5, 6, 8p, 12, 16a2, 16b, 119, 20</td>
</tr>
<tr>
<td>Linitis</td>
<td>1-6</td>
<td>7, 8a, 9-11, 12a, 14v</td>
<td>8p, 12b, 12p, 16b2, 19, 20</td>
</tr>
</tbody>
</table>

of all lymph nodes of levels 1, 2, and 3). Until now, these different levels were defined based on the location of the primary tumour, resulting in a complex system that was difficult to remember. As such, the JGCA has established a new definition of the different types of lymphadenectomy (D) that allows for a much simpler management of this process, which can be used on a larger scale (Table 4). The 2010 Japanese classification eliminates the location of the primary tumour as the method used for defining the different lymph node levels, and establishes a new criterion based on the type of gastrectomy (total, distal subtotal, distal with pyloric preservation, or proximal).16 Both proximal and distal gastrectomy with pyloric preservation are included in the gastrectomy with functional preservation, which is only considered a possibility in the treatment of early gastric cancer in the JGCTG.

In spite of the fact that this new type of classification greatly simplifies its clinical applications, we must keep in mind that, contrary to the previous version, it is not based on an analysis of registry data. Taking into account the therapeutic value of a specific dissection of each lymph node group, our experience in the Hospital Mutua de Terrassa allows for demonstrating its viability in spite of a limited number of cases (Table 5). During the coming years, the data provided by large registries should demonstrate the clinical and prognostic usefulness of these changes.

Another novel modification is the elimination of the concept of D3 lymphadenectomy, which comes as a result of the trial in which it was shown that the para-aortic lymphadenectomy increased patient morbidity without improving survival over a D2 dissection (JCOG 9501).17,18 Even so, in cases in which the dissection includes groups 13, 14v, and/or 16, results can be evaluated as a D2+ lymphadenectomy.

In gastric tumours that invade the oesophagus, group 110 should be added to D1 lymphadenectomies and groups 19, 20, 110, and 111 should be added to D2 lymphadenectomies.

The new classification system continues to include splenectomies as part of the definition of D2.
lymphadenectomies in proximal third >T2 tumours eligible for a total gastrectomy. The results from the JCOG 0110 trial will allow for definitively establishing whether splenectomies can be avoided without compromising patient survival in cases involving these types of tumours. In this same study has demonstrated a greater morbidity and greater blood loss in the group that underwent splenectomies.

In addition to the modified definitions of lymphadenectomies and surgical techniques, the JGCTG (3rd edition) includes therapeutic recommendations according to the tumour stage (Table 6). In the chemotherapy chapter, the recommended treatment regimens are different from those in the European (ESMO) and American (NCCN) guidelines, which is due to the standardised use of S-1 in Japan.

To conclude, the modification of the new pN categories and the new definitions of types of lymphadenectomies attempt to simplify and standardise the surgical management of gastric cancer. The UICC, the AJCC, and the JGCA have put a great deal of effort into complementing each other and establishing a common language for expressing the clinical experience and results from around the world. All these important changes must be evaluated in coming years in order to assess their benefits.

Conflict of interest

The authors affirm that they have no conflict of interest.

Acknowledgements

The authors would like to thank Dr. Takheshi Sano of the Cancer Institute Hospital in Tokyo for the information provided for the elaboration of this manuscript.

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