



## Seventh tumor-node-metastasis staging of gastric cancer: Five-year follow-up

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**Conflict-of-interest statement:** None to declare.

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**Manuscript source:** Invited manuscript

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Received: April 20, 2016  
Peer-review started: April 21, 2016  
First decision: May 27, 2016  
Revised: June 10, 2016  
Accepted: July 20, 2016

Article in press: July 21, 2016  
Published online: September 14, 2016

### Abstract

Seventh tumor-node-metastasis (TNM) classification for gastric cancer, published in 2010, introduced changes in all of its three parameters with the aim to increase its accuracy in prognostication. The aim of this review is to analyze the efficacy of these changes and their implication in clinical practice. We reviewed relevant Literature concerning staging systems in gastric cancer from 2010 up to March 2016. Adenocarcinoma of the esophago-gastric junction still remains a debated entity, due to its peculiar anatomical and histological situation: further improvement in its staging are required. Concerning distant metastases, positive peritoneal cytology has been adopted as a criterion to define metastatic disease: however, its search in clinical practice is still far from being routinely performed, as staging laparoscopy has not yet reached wide diffusion. Regarding definition of T and N: in the era of multimodal treatment these parameters should more influence both staging and surgery. The changes about T-staging suggested some modifications in clinical practice. Differently, many controversies on lymph node staging are still ongoing, with the proposal of alternative classification systems in order to minimize the extent of lymphadenectomy. The next TNM classification should take into account all of these aspects to improve its accuracy and the comparability of prognosis in patients from both Eastern and Western world.

**Key words:** Gastric cancer; Staging system; Tumor-node-metastasis; Prognostic factors; Clinical practice

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**Core tip:** After five years since latest tumor-node-metastasis (TNM) classification for gastric cancer staging has been published, we reviewed Literature concerning its accuracy in prognostication and the impact on clinical practice of the statements introduced in 2010. While waiting for the next UICC/AJCC TNM classification for gastric cancer, open issues and new proposals are also critically discussed.

Rausei S, Ruspi L, Galli F, Pappalardo V, Di Rocco G, Martignoni F, Frattini F, Rovera F, Boni L, Dionigi G. Seventh tumor-node-metastasis staging of gastric cancer: Five-year follow-up. *World J Gastroenterol* 2016; 22(34): 7748-7753 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i34/7748.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i34.7748>

## INTRODUCTION

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related death<sup>[1]</sup>. In the era of stage adapted therapy, where effective tools both in preoperative staging and in peri-operative treatment (neoadjuvant and adjuvant therapy) are widely available, the importance of an accurate prognostication is crucial for the best possible management of gastric cancer patients.

A cancer staging system should describe the severity of a neoplasm according to the extent of primary tumor and of its spread, both local and distant; this allows clinicians to calculate prognosis, to compare groups of patients, and to determine the treatment strategy. As it should be used in an everyday clinical practice setting, an ideal cancer staging system has to be easily reproducible and applicable, both before and after treatment.

Since its first application in the staging of gastric malignancies in 1974<sup>[2]</sup>, the tumor-node-metastasis (TNM) staging system has been periodically modified, in order to ameliorate its accuracy in stratification of prognosis in gastric cancer patients.

The current TNM system for gastric cancer, although still improvable, well fulfills the above mentioned requirements.

In last five years different Authors analyzed usefulness of the seventh TNM classification and, up to now, it seems that different issues still require further improvements.

In this review, we summarize current opinions and controversies on the seventh classification of the TNM staging system for gastric cancer, introducing open questions and new issues which may integrate the traditional way of staging.

## LITERATURE RESEARCH

Recent Literature (from 2010 up to March 2016) was

evaluated on PubMed Central with combination of following MESH terms: gastric cancer and staging system, gastric cancer and TNM, esophago-gastric junction and staging, gastric cancer and distant metastasis. All abstracts were read separately by two different surgeons belonging to an Italian University Hospital, and scientific relevance of papers has been assessed mostly according to originality of the article, accuracy of the statistical method and number of patients. All of the selected papers were fully read by two or more surgeons, and only papers reported in References have been judged clinically and scientifically relevant.

## ADENOCARCINOMA OF ESOPHAGO-GASTRIC JUNCTION

Latest TNM classification made an effort to clarify recommendations about malignancies arising at or close to the esophago-gastric junction. According to anatomical criteria consistent with the 5-cm rule of Siewert Classification<sup>[3]</sup>, seventh TNM classification included esophago-gastric junction tumor in the esophageal chapter<sup>[4]</sup>. Unfortunately, this proposal might lead to classify as esophageal a tumor of the gastric fundus<sup>[5]</sup>. Hence, most Adenocarcinoma of esophago-gastric junction (AEGs), including adenocarcinomas of the cardia and subcardia, are now to be staged as esophageal adenocarcinomas rather than gastric cancers, although they actually originate from the gastric mucosa and consequently have different biological properties compared with genuine gastric and genuine esophageal cancers<sup>[6]</sup>; therefore cardia tumors still remain in a no-man's land of staging.

Actually, the esophago-gastric junction is a peculiar transitional area from squamous to glandular epithelium, which is different from epithelium of distal stomach. Concerning macroscopic anatomy, the intra-abdominal part of the esophagus, esophagogastric junction, and fundus are not totally covered by visceral peritoneum. These portions of the stomach are located extraperitoneally or retroperitoneally, which makes AEG more prone to infiltrate the serosa and more inclined to peritoneal metastasis; moreover, a different pathway of lymphatic metastases has to be considered<sup>[7]</sup>.

These anatomical differences related to the esophago-gastric junction imply a different oncological management as well as a different surgical approach than gastric or esophageal cancer: basically, the clinicians should early know the correct strategy and a reliable prognosis to present to their patients.

Although some authors reported better prognostication when AEG II/III tumors were staged as gastric cancer<sup>[8,9]</sup>, several studies advocate the introduction of a separate staging system for neoplasm of this "damned" anatomical district, as neither the esophageal

nor the gastric staging scheme could well stratify the prognosis of these patients<sup>[10-12]</sup>.

Staging of tumors arising from the esophagogastric junction should require further revision.

### **Distant metastasis (M)**

Regarding assessment of M parameter, Mx has been deleted. To be correct, the lack of information about status of anatomical districts far from primary tumor site must be considered as inappropriate.

In every day clinical practice, it means that an accurate staging process must be performed (both before and after treatment); this again, became even more important, since latest TNM classification included findings of positive peritoneal cytology (as well as omental tumor not part of continuous extension) in M1 category<sup>[4]</sup>.

After more than five years since this proposal, unfortunately, clinical practice has not been really modified: in fact, the routinely use of laparoscopic staging, which allows both retrieval of free fluid for cytologic examination and inspection of the entire peritoneal cavity, and thus eventual omental implants<sup>[5,13]</sup>, has not reached a wide diffusion yet<sup>[14]</sup>. This "bad habit" is responsible for understaging of disease or useless laparotomies in about 20% of cases<sup>[15,16]</sup>.

Moreover, since some studies reported outcomes of potentially curative resections after the clearance of peritoneal cytology (conversion from positive to negative after neoadjuvant chemotherapy)<sup>[17,18]</sup>, it might be responsible of sub-optimal treatment.

Actually, a standardization of the method used to perform peritoneal cytology is needed: in fact, different rates of positive cases with different techniques have been reported: > 20% on a routine cytology, 35% on immunohistochemistry and 50% on RT-PCR in cases of a serosa invasion-positive gastric carcinoma<sup>[19]</sup>.

This new change in the last TNM classification could be considered an improvement according to prognostic results. Nevertheless, it should suggest a more reliable compliance to clinicians.

### **Node (N)**

The cut off of metastatic regional lymph nodes in the N category was changed, too (N1 = 1-2 nodes; N2= 3-6 nodes; N3a= 7-15 nodes; N3b= more than 15 nodes)<sup>[4]</sup>. Moreover, the minimum number of required nodes reached 16, although this seems to be in contrast with the sentence (added in the previous edition) which allows to classify as pN0 also negative nodes tumors even if the minimum number of examined nodes is not met. This proposal seems to derive from the need to minimize non-homogeneity in the extent of lymphadenectomy.

Actually, lymph node staging is the main object of current controversies in TNM staging system. In last years, different authors compared the prognostic

power between the sixth and the seventh TNM classification, as well as they proposed possible alternative staging systems.

According to comparison studies, seventh TNM classification for gastric cancer provided a more detailed classification of prognosis than the sixth system<sup>[20,21]</sup>. With specific regard to the proposal of new staging criteria, lymph node ratio (LNR) gained increasing popularity. It is defined as the ratio between the number of positive nodes and the number of total examined nodes. Most studies concluded that LNR is superior to the traditional N stage in TNM system in stratifying the prognosis of gastric cancer patients<sup>[22-28]</sup>. LNR, and other alternative node staging system, such as LODDs (log of the ratio between the probability of being a positive lymph node and the probability of being a negative lymph node when one lymph node is retrieved)<sup>[29]</sup>, have been proposed especially in groups of patients with less than 15 retrieved nodes: thus, it seems that most of the attempts are made to justify a suboptimal surgery about lymphadenectomy, rather than to increase prognostic power of pathological lymph node staging<sup>[30,31]</sup>.

In this context, a possible further staging improvement could be to associate LNR (instead of the more complex LODDs) with the last numeric criterion.

### **Tumor (T)**

Regarding the T parameter, latest TNM classification has introduced high grade displasia (HGD) in Tis category; T1 category has been subdivided into T1a (tumors involving lamina propria or muscularis mucosae) and T1b (tumors involving submucosa), and T2b has been replaced with new T3 category, so that serosal involvement is now considered a T4 tumor (T4a category differently from T4b category assigned to tumors invading adjacent structures)<sup>[4]</sup>.

Inclusion of HGD in Tis category lead to a more aggressive approach to this histologic entity. According to latest Japanese guidelines for gastric cancer<sup>[32]</sup>, some histologic and dimensional criteria have to be met in order to perform endoscopic mucosal resection (EMR) or endoscopic submucosal dissection: therefore, preoperative diagnosis has to be even more accurate.

Furthermore, as distinguishing invasive carcinoma from HGD in gastric biopsy specimens is not always possible, EMR can also be proposed in order to obtain a more accurate histologic definition<sup>[33]</sup>.

Finally, new T3 category implied for the first time the definition of locally advanced disease for a tumor entirely contained into the gastric wall. As subserosal involvement may not be correctly evaluated during staging laparoscopy, EUS - which remains the first-choice imaging modality in preoperative T staging of gastric cancer - emerges again as a crucial step in pre-treatment staging<sup>[34]</sup>. Nonetheless, it is not always included in staging algorithm. De facto, although trial about perioperative chemotherapy have been

**Table 1 Stage grouping based on cluster analysis in the International gastric cancer association stage grouping**

	N0	N1	N2	N3a	N3b
T1	I A	I B	II A	II B	III B <sup>1</sup>
T2	I B	II A	II B	III A	III B <sup>1</sup>
T3	II A	II B	III A	III B	III C <sup>1</sup>
T4a	II B	III A	III A <sup>1</sup>	III B <sup>1</sup>	III C
T4b	III A <sup>1</sup>	III B	III B <sup>1</sup>	III C	III C

<sup>1</sup>Categories are different from 7<sup>th</sup> TNM grouping.

conducted even on T2 tumors<sup>[35]</sup>, at the moment T3 is often excluded from perioperative treatment strategy.

The change of Tis and T1 categories simplified the (endoscopic) management of early cancers. Even if the change of T3 category did not imply significant publications on the comparison between the sixth and the seventh TNM classification, in the future revisions it could be useful to reconsider a simplification of the staging related to the deep involvement of stomach wall.

## GROUP STAGING

Finally, the aforementioned revisions of the three parameters also resulted in a rearrangement of stage grouping. The most important feature in latest TNM is that only distant metastasis defines stage IV (very poor prognosis)<sup>[41]</sup>; this means that T4 and N3 are not necessarily considered signs of significantly advanced disease anymore. This could probably have been induced by an excessive optimism towards multimodal treatment, recruiting at the moment more advanced disease<sup>[36]</sup>. However, patients with N3b tumors do have a very scarce prognosis<sup>[37]</sup>, although they are considered same as N3a in stage grouping.

Dikken *et al.*<sup>[38]</sup>, testing latest TNM in prognostication of 2196 patients, found a decreased heterogeneity among stage groups, and observed that the increased complexity of the latest TNM is not accompanied by an improvement in prognostic accuracy of stage grouping. Regarding this aspect, Röcken *et al.*<sup>[39]</sup> proposed to reduce to 3 groups (instead of 7) M0 patients according to different combinations of the new T and N parameters: low risk group with > 60% 5-year survival rate, intermediate risk group with 20%-60% 5-year survival rate and high risk group with < 20% 5-year survival rate.

Since stage grouping is essential in prognostication (not in treatment planning), hopefully summing the three parameters, it is probably here that great simplicity and high accuracy has to be reached.

## CONCLUSION

Although many criticisms have been reported since seventh TNM classification was adopted, we may consider it a valuable tool in assessing the extent of

disease, and a good instrument in everyday clinical practice.

The International Gastric Cancer Association (IGCA) launched in 2009 a staging project with the aim of collecting gastric cancer data worldwide, in order to formulate a contemporary evidence based classification. This project collected data from 59 Institutions in 15 Countries and used them to validate the latest TNM classification: for both T and N it accepted the categories of the seventh TNM and then assessed a new stage grouping scheme (Table 1), which better stratifies prognosis also in patients with Siewert type II or III tumor. A relevant aspect of this new staging system is the split between N3a and N3b categories, derived from finding of worse survival in patients with more of 6 involved nodes. This new scheme could be introduced in next TNM classification<sup>[29]</sup> along with some implications of the above mentioned considerations: hence, this next staging solution, tested with data from both Eastern and Western patients, should allow to appropriately compare treatment results in different regions.

If the IGCA staging system at the moment does not add any new parameter, other Authors reflected on possible introduction of more details to improve accuracy of prognostication.

As specified, the role of LNR seems to be quite widely accepted, but other issues regarding lymph node involvement are still debated, such as the presence of isolated tumor cells, now classified as pN0(i+), which might be classified as pN1(i+), and the extra capsular extension of regional metastasis in adjacent tissues<sup>[39]</sup>.

Again, lymphatic and venous invasion have been proposed for a better definition of T category<sup>[40]</sup>, as well as the possible use of molecular findings (*i.e.*, HER2), but it is still to determine whether these data should be actually introduced in the TNM staging system or they should be considered as additional (and thus optional) prognostic factors.

In conclusion, further improvements are obviously needed, but if on one hand the integration with molecular and histopathological findings may give more precision to prognosis prediction, on the other hand it will certainly reduce the easy applicability of the staging scheme<sup>[39]</sup>.

Without any doubt we are going toward a more specific and precise staging system, and this requires strict statistical evaluations. While waiting for the perfect staging system, we should at first reach standardization of both surgical (use of staging laparoscopy, extent of resection, proper lymphadenectomy) and pathological technique (blocks of primary tumor, nodes count accuracy, immunoistochemistry of lymph nodes to detect isolated tumor cells, technique for peritoneal cytology), so that the future TNM classification will not be conditioned by the need of supply to inadequate surgery and/or inadequate pathological staging.



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**P- Reviewer:** Park WS, Zhang JZ    **S- Editor:** Ma YJ    **L- Editor:** A  
**E- Editor:** Ma S



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ISSN 1007-9327



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