

Sixth and seventh tumor-node-metastasis staging system compared in gastric cancer patients

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diagnosed stage differed in 32% of 241 patients based on the TNM edition used for the diagnosis. The patients in stage II according to the 6th edition who were reclassified as stage III had significantly worse prognosis than patients classified as stage II (5-year OS, 39% vs 71%). According to the 6th edition, 135 patients were classified as T2, and 75% of these patients migrated to T3 and exhibited a significantly worse prognosis than those who remained T2, regardless of lymph node involvement (37% vs 71%). The new N1 patients exhibited a better prognosis than the previous N1 patients (67% vs 43%).

CONCLUSION: 7th TNM allows new T2 and N1 patients to be selected with better prognosis, which leads to different staging. New stratification is important in multimodal therapy.

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Key words: Gastric cancer; Tumor-node-metastasis staging system; Survival analysis; Prognostic factor; Lymphadenectomy

Core tip: The 7th edition of the tumor-node-metastasis (TNM) staging system appears to exhibit improved accuracy in staging and prognostic stratification with more precise indication for adjuvant and neoadjuvant therapy in the multimodal treatment era. Our data show the importance of standardization of treatment and the type of surgical lymphadenectomy for comparing different experiences. Further studies are necessary to improve the TNM system, particularly regarding the parameter N and the division into substages.

Abstract

AIM: To investigate the clinical relevance and prognosis regarding survival according to the changes of the tumor-node-metastasis (TNM) in gastric cancer patients.

METHODS: We retrospectively studied 347 consecutive subjects who underwent surgery for gastric adenocarcinoma at the Division of General Surgery, Hospital of Busto Arsizio, Busto Arsizio, Italy between June 1998 and December 2009. Patients who underwent surgery without curative intent, patients with tumors of the gastric stump and patients with tumors involving the esophagus were excluded for survival analysis. Patients were staged according to the 6th and 7th edition TNM criteria; 5-year overall survival rates were investigated, and the event was defined as death from any cause.

RESULTS: After exclusion, our study population included 241 resected patients with curative intent for gastric adenocarcinoma. The 5-year overall survival (5-year OS) rate of all the patients was 52.8%. The

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INTRODUCTION

In addition to age, comorbidities, lesion site, macro- and microscopic type of tumor, quality of surgery and residual tumors, the main factors that influence the long-term survival of patients with gastric cancer are (1) the depth of tumor penetration into the gastric wall (T parameter); (2) the amount of the metastatic regional lymph nodes involved (N parameter); and (3) the presence of distant metastases (M parameter).

The tumor-node-metastasis (TNM) classification of cancer was developed between 1943 and 1952 by Prof. Pierre Denoix at the Institute Gustave-Roussy. In 1987, the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM classifications were unified. The following are the main objectives of the classifications: to aid the clinician in the planning of treatment, to provide an indication of prognosis, to assist in the evaluation of the results of treatment; to facilitate the exchange of information between treatment centers, to contribute to the continuing investigation of human cancer and to support cancer control activities^[1,2]. Since January 1st 2010, the UICC/AJCC TNM 7th edition differs from the previous version regarding some aspects of the T parameter and is completely renewed regarding the N parameter (Table 1).

Particularly, the subserosa infiltration by the tumor, which was previously classified as T2b, is now classified as T3, and the perforation of serosa changed from T3 to T4a. Regarding the parameter N, the UICC/AJCC TNM 7th edition changes the lymph nodes “cut-off”. Tumors classified as N1 in the 6th edition with more than 2 positive nodes are classified as N2 in the 7th edition, while N2 is classified as N3a, and N3 is classified as N3b. In the new stratification by stage, the number of substages is increased. According to the 7th edition, only patients with distant metastases are classified as the fourth stage. Another important change to the criteria concerns distant metastases. In the new edition of the TNM staging system, a positive peritoneal cytology is considered as M1.

Several studies, which were mostly performed in eastern countries, have demonstrated the superiority of the 7th edition TNM criteria and highlighted issues still in dispute for improvement.

The aim of the present study is to compare the sixth and the seventh edition of the TNM classification in patients who underwent surgery for gastric cancer in a single center to confirm the superiority of the new edition regarding its prognostic stratification and reliability. We considered the parameters T, N and the lymph node ratio (LNR) individually regardless of stage as additional prognostic parameters. We observed and followed how these changes in the allocation of pT and pN parameters according to the two editions of the classification affect

Table 1 Tumor-node-metastasis staging system 6th and 7th edition

TNM staging system 6 th edition				TNM staging system 7 th edition			
Stage	T	N	M	Stage	T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
I A	T1	N0	M0	I A	T1	N0	M0
I B	T1	N1	M0	I B	T2	N0	M0
	T2a	N0	M0		T1	N1	M0
	T2b	N0	M0	II A	T3	N0	M0
II	T1	N2	M0		T2	N1	M0
	T2a	N1	M0		T1	N2	M0
	T2b	N1	M0	II B	T4a	N0	M0
	T3	N0	M0		T3	N1	M0
III A	T2a	N2	M0		T2	N2	M0
	T2b	N2	M0		T1	N3	M0
	T3	N1	M0	III A	T4a	N1	M0
	T4	N0	M0		T3	N2	M0
III B	T3	N2	M0		T2	N3	M0
IV	T4	N1	M0	III B	T4b	N0, N1	M0
	T4	N2	M0		T4a	N2	M0
	T4	N3	M0		T3	N3	M0
	T1	N3	M0	III C	T4a	N3	M0
	T2	N3	M0		T4b	N2, N3	M0
	T3	N3	M0	IV	AnyT	AnyN	M1
	Any T	Any N	M1				

determining the prognosis and the type of treatment for these patients.

MATERIALS AND METHODS

Patient cohort

We retrospectively studied 347 consecutive patients who underwent surgery for gastric adenocarcinoma at the Division of General Surgery, Hospital of Busto Arsizio (Varese), Italy from June 1998 through December 2009. For the survival analysis, we excluded the following patients: (1) patients with distant metastases; (2) patients who underwent surgery without curative intent; (3) patients with tumors of the gastric stump after gastric resection for benign disease; (4) patients with other tumors at the time of diagnosis; and (5) patients with a large involvement of the esophagus requiring total esophagectomy.

None of the patients considered for inclusion in the study underwent neoadjuvant chemotherapy or radiochemotherapy. Because of the heterogeneous and unsystematic indication for adjuvant chemotherapy, treatment protocols and number of cycles, details of the postoperative chemotherapy were not considered in this study.

Regarding the surgical method, en bloc resection of the primary tumor and lymphatic drainage area was routinely performed. D2 lymphadenectomy was performed in 87% of patients, while the remaining 13% underwent a D1 lymphadenectomy according to the Japanese Guidelines^[3,4]. The principles of tumor resection and lymphadenectomy by experienced surgeons were similar among all the resected patients. No local excision was performed.

Follow-up

For all patients, a regular 6th month follow-up within 5

Table 2 Univariate survival analysis of clinicopathologic variables in 241 patients *n* (%)

Variable	<i>n</i> (%)	5-year overall survival rate (%)	<i>P</i> value
All	241	52.80	
Sex			0.740
Female	116 (48.1)	50.40	
Male	125 (51.9)	54.30	
Age (yr)			0.000
1 (≤ 50)	14 (5.8)	78.60	
2 (51-60)	18 (7.5)	32.00	
3 (61-70)	78 (32.3)	57.50	
4 (71-80)	87 (36.1)	57.30	
5 (> 80)	44 (18.3)	35.20	
Site			0.006
S	40 (16.6)	33.30	
M	50 (20.7)	70.80	
I	150 (62.2)	51.50	
Surgery			0.400
Total gastrectomy	191 (79.3)	53.10	
Subtotal gastrectomy	50 (20.7)	52.60	
Lauren			0.500
Intestinal	150 (62.2)	56.50	
Diffuse	58 (24.0)	48.50	
Mixed	15 (6.2)	33.90	
T stage (6 th edition)			< 0.0001
T1	64 (26.6)	86.20	
T2	135 (56.0)	45.40	
T3	37 (15.3)	23.30	
T4	5 (2.1)	0.00	
T stage (7 th edition)			< 0.0001
T1	64 (26.6)	86.20	
T2	33 (13.7)	71.00	
T3	102 (42.3)	37.30	
T4	42 (17.4)	20.50	
N stage (6 th edition)			< 0.0001
N0	81 (33.6)	77.30	
N1	73 (30.3)	55.70	
N2	50 (20.7)	27.60	
N3	37 (15.4)	22.90	
N stage (7 th edition)			< 0.0001
N0	81 (33.6)	77.30	
N1	39 (16.2)	67.50	
N2	35 (14.5)	43.00	
N3	86 (35.7)	25.90	
Stage (6 th edition)			< 0.0001
I	87 (36.1)	76.40	
II	59 (24.5)	61.50	
III	55 (22.8)	24.40	
IV	40 (16.6)	21.20	
Stage (7 th edition)			< 0.0001
I	70 (29)	85.60	
II	56 (23.3)	61.50	
III	115 (47.7)	27.00	
Lymph node ratio			< 0.0001
I (0)	81 (33.6)	77.30	
II (0.01-0.09)	41 (17.1)	65.40	
III (0.1-0.25)	50 (20.7)	44.50	
IV (> 0.25)	69 (28.6)	21.00	

S: Superior; M: Middle; I: Inferior.

years from surgery consisted of the following procedures: serum tumor biomarker and laboratory biochemical examinations, radiological and UltraSound imaging, endoscopic control (1/year) and physical examination. Annual follow-ups after 5 years were performed until the patients

died. In this study, a period of 120 mo was considered as the end of the patient's observation. The median follow-up was 48 mo (range: 0-120 mo).

Statistical analysis

The depth of primary tumor invasion (T) and lymph node involvement (N) were classified according to the 6th and 7th UICC/AJCC edition TNM classification. All patients were restaged using the 6th and 7th editions of the UICC/AJCC TNM staging system. Survival curves were estimated using the Kaplan-Meier method^[5]. The overall survival (OS) rates were investigated, and the event was defined as death for any cause. The Log rank test was used to identify the differences between the survival estimates of the different patient groups. Hazard ratio (HR) and 95%CI were also generated. A *P* value of less than 0.05 was considered significant. All tests were two-tailed. Statistical analysis and graphics were performed with MedCalc Software bvba, Mariakerke, Belgium.

RESULTS

From June 1998 until December 2009, a total of 347 patients in our department underwent surgery for gastric adenocarcinoma. After exclusion, the study population consisted of 241 resected patients, and 112 patients are currently alive.

The clinical and pathological characteristics are shown in Table 2. The median age was 71 years (range: 37-94 years), and 51.9% of the patients (*n* = 125) were male.

Total gastrectomy was performed in 191 (79%) patients, and subtotal gastrectomy was performed in 50 (21%) patients.

A D2 lymphadenectomy was performed in 208 (87%) patients. The median number of lymph nodes retrieved was 37 (range: 5-100); the value reached 40 (range: 13-100) in D2 lymphadenectomy and 16 (range: 5-45) in D1. The incidence of positive node patients was 67%. The 5-year overall survival of the 241 patients was 52.8%, and the ten-year overall survival was 34.7%. In the univariate analysis, age, site, T parameter, N parameter and Stage were significantly associated with overall survival.

We also studied the LNR as a prognostic factor among parameters of the univariate analysis. We considered 4 cutoff based on Marchet *et al*^[6] (Table 2).

Survival analysis by stage

Stage migration occurred in 33% of the patients: 19.5% of the Ist stage were reclassified to IInd stage, and 33.9% of the IInd stage patients were reclassified as IIIrd stage. All the patients we considered as stage IV in the 6th ed. of the TNM staging system were reclassified as IIIrd stage using the 7th edition TNM staging system.

The patients classified as stage II according to the 6th edition and reclassified as stage III exhibited significantly worse prognosis than the patients who remained in stage II (5-year OS, 71% *vs* 39%; *P* = 0.01, HR = 2.3, 95%CI: 0.9-5.8) (Figure 1).

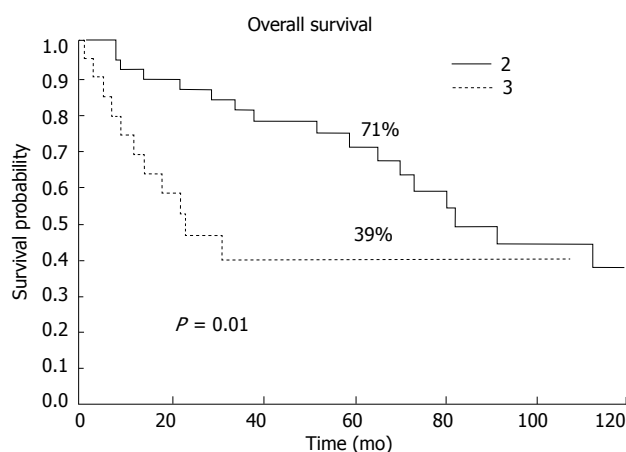


Figure 1 IInd stage patients according to the 6th edition of the tumor-node-metastasis staging system reclassified as IInd or IIIrd stage according to the 7th edition of the tumor-node-metastasis staging system.

Important changes regarding the survival rates and stage reclassification were observed in our analysis. As shown in Table 3, the patients assigned stages using the sixth edition (orizontally) exhibit a statistically significant difference in the prognosis when reclassified in a different stage according to the seventh edition criteria. However, a statistically significant difference in the prognosis was not observed when comparing the prognosis of patients assigned stages using the seventh edition criteria (vertically) with the stages assigned using the sixth edition (Table 3).

Regarding the substages in the 7th edition, the 5-year survival rates are comparable between substage I B and II A (5-year OS 59% *vs* 55%; $P = 0.8$). However, there is a significant difference regarding the survival probability at 5 years among substages III A, III B and III C (5-year OS III A: 47%, III B: 20%, III C: 24%; $P = 0.07$). The patients who belong to substage III C exhibit similar survival to M+ patients.

Survival analysis by T category

We also analyzed the T category on T2b patients reclassified as T3 in the new edition of the TNM. In our population, 135 T2 patients were classified according to the 6th edition (56%), and 75% of these patients were reclassified as T3 using the most recent revision of the TNM system. The 5-year survival rates of the migrated patients and the patients who remained as T2 were 71% and 37%, respectively ($P = 0.008$, HR = 2.1, 95%CI: 1.3-3.5) (Figure 2A). The T2aN+ patients exhibited significantly better survival compared with the T2b patients with lymph node involvement (N+) according to the 6th edition (5-year OS 73% *vs* 37%; $P = 0.009$, HR = 2.5, 95%CI: 1.4-4.4) (Figure 2B).

Survival analysis by N category

Patients stratified according to the N-stage using the 6th and 7th editions of the TNM are now classified as N1 with the 7th edition and exhibit a 5-year OS probability

Table 3 Stage migration from the sixth to seventh edition of the tumor-node-metastasis system

6 th edition TNM	Stage (patients)	7 th edition TNM			P
		I	II	III	
I		70	17		0.004
II			39	20	0.040
III				55	
IV				40	
P			0.09	P (II-III) = 0.3 P (IV-III) = 0.1	

TNM: Tumor-node-metastasis.

of 67%. The N2 patients classified according to the 7th edition. TNM exhibit a 5-year OS of 43% ($P = 0.04$) (Figure 3).

DISCUSSION

In this retrospective study, we focused on the major changes between the 6th and 7th edition of the TNM system regarding gastric cancer. The analysis of this migration reveals the most important prognostic factors and possible modifications introduced in multimodal treatment.

We observed an OS of 52.8%. That goes to 54% of survival in the D2 type of lymphadenectomy that represented 87% of the sample. In our study population, more than 50% of the patients were diagnosed with T2 lesions according to the 6th edition regarding the parameter of infiltration of the tumor in the gastric wall (T parameter). Other studies reported variable incidences of T2 (Sarela *et al*^[7]: 30%; Marchet *et al*^[8]: 32%; Nitti *et al*^[9]: 51.4%; Park *et al*^[10]: 30%; Lu *et al*^[11]: 40%).

In our study, 102 out of 135 patients (75%) classified as T2 according to the 6th edition of the TNM system were reclassified as T3 based on the 7th edition of the TNM system. The shift exhibits a statistically significant prognostic difference in 5-year OS regardless of nodal involvement (Figure 2).

Our results concerning the prognostic differentiation between T2 and T3 are also confirmed by other studies^[12,13]. Sarela *et al*^[7] reported a statistically significant difference between patients classified as T2N1 and T3N1, (56% *vs* 44%; $P = 0.3$). Fotia *et al*^[14] obtained different results (74% *vs* 67% for T2 to T1 to 5 years; $P = 0.2$).

Recently, Marchet *et al*^[8] reported 5-year survival values of 67% for T2 and 52% for T3. When N+ patients were included in their analysis, 5-year survival rates of 66% and 47% were obtained for T2N+ and T3N+. In conclusion, the results of this study emphasize the prognostic value of T2/T3 categories and the importance of identifying subgroups of patients (T2b 6th edition) that may benefit from adjuvant chemotherapy. Based on our results, these patients would also be candidates for neo-adjuvant treatment^[15-17].

The renewal of the lymph node cut-off (N parameter) has allowed us to select patients with better prognosis

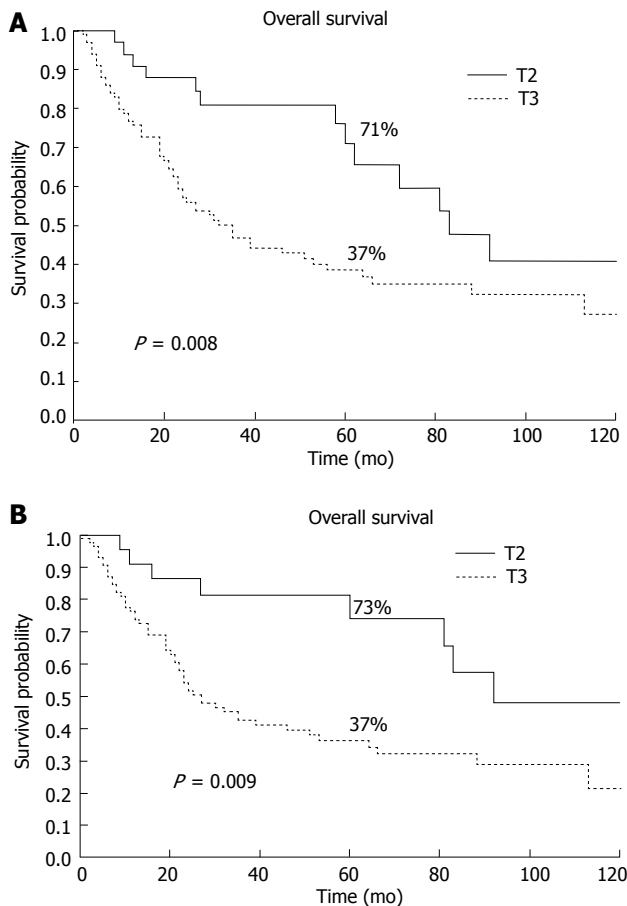


Figure 2 Overall survival. A: T2 patients according to the 6th edition of the tumor-node-metastasis (TNM) staging system reclassified as T2 or T3 with the 7th edition; B: T2N⁺ patients according to the 6th edition of the TNM staging system reclassified as T2 or T3 with the 7th edition.

(new N1). The involvement of 1-2 lymph nodes was associated with a better prognosis in our cases than patients with N2 (3-6 positive nodes). The 5-year OS rates were 67.5% for N1 and 43% for N2; ($P = 0.04$). Similar results were obtained from the study published by Ahn *et al*^[13] (N1: 76.5% *vs* N2: 58%).

In our analysis, we did not investigate the difference between N3a and N3b because of the small sample size. However, according to other reports, a possible reclassification of the N3 category would be desirable because N3a and N3b exhibit significant differences in survival^[13,18,19].

The analysis of the LNR (lnf+/lnftot) showed good prognostic stratification among the 4 curves ($P < 0.0001$). Some studies have described the usefulness of the LNR in Japan and South Korea^[20,21].

As demonstrated by the work of Kong *et al*^[22], the power of the differential staging of the LNR system was fortified with a higher number of examined lymph nodes and represents appropriate N-staging.

In a retrospective multicenter study of 1853 patients operated for gastric cancer, Marchet *et al*^[6] showed that the LNR was an independent prognostic factor regardless of the type of lymphadenectomy.

Wang *et al*^[23] showed that the “TNratioM System” may predict survival more accurately in patients who undergo

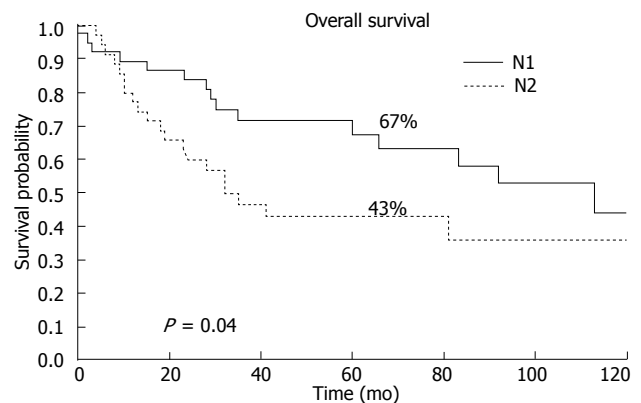


Figure 3 Comparison between N1 patients and N2 patients according to the 7th edition of the tumor-node-metastasis staging system.

limited lymph node analysis.

The changes in the parameters N and T have generated stage migration, which confirms the superiority of the 7th edition of the TNM system. The new TNM edition groups patients with similar prognoses and separates subjects with different prognoses better than the previous version of the TNM system (Table 3). Similar rates of survival are shown in the analysis by Marrelli *et al*^[24]. Evaluating the substages in our population, we observed that the 5-year survival values were similar between I B and II A. Similar findings were reported in a large series of western patients with gastric cancer^[18].

A significant difference regarding the 5-year survival was observed between the substages of stage III (III A, III B and III C). In a study by Wang *et al*^[12] on 1503 patients, the tumor size (> 5 cm or < 5 cm) was a determining factor in the differentiation of the prognosis between I B and II A. According to Wang *et al*^[12], three subgroups of the fourth stage exhibit different biologic behaviors of relapse or metastasis models and need further analysis.

In conclusion, the 7th edition of the TNM system seems to have improved accuracy in staging and prognostic stratification, the 7th edition provides more precise indication for adjuvant and neoadjuvant therapy in the multimodal treatment era, our data show the importance of standardization of treatment and the type of surgical lymphadenectomy to compare different experiences and further studies are necessary to improve the TNM system particularly regarding the parameter N and the division into substages.

COMMENTS

Background

The Union for International Cancer Control and the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system is the most important classification of tumors. The main objectives of TNM cancer staging are to help the clinician plan the treatment, to give an indication of prognosis and to evaluate the results of treatment. In the new edition of the TNM (7th) staging system, there are important changes in the field of gastric cancer.

Research frontiers

The 7th edition of the TNM system appears to exhibit improved accuracy in staging and prognostic stratification. Different experiences need to be compared to

improve the reliability of the TNM classification system.

Innovations and breakthroughs

The TNM 7th edition differs from the previous version regarding gastric cancer on some aspects of the T and M parameters and is completely renewed regarding the N parameter. Several studies, which were predominantly performed in Eastern countries have demonstrated the superiority of the new edition criteria and the highlighted issues still require improvement.

Applications

The study results suggest that the 7th edition of the TNM system is superior to the previous version regarding prognostic stratification. However, further studies are necessary to improve the TNM system particularly regarding the N parameter and the division into substages.

Terminology

The TNM classification uses three parameters to divide the patients into different stages: depth of tumor penetration into the gastric wall (T parameter), the number of metastatic regional lymph nodes involved (N parameter) and the presence of distant metastases (M parameter).

Peer review

The retrospective study compares the 6th and 7th edition of the TNM classification in a single Italian institution to confirm the superiority of the new edition for prognostic accuracy. According to the experience, standardization of surgical therapy and a multidisciplinary approach are necessary to develop a multimodal tailored treatment.

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