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Classification of Lymph Node Metastases from Carcinoma of the Stomach: Comparison of the Old (1987) and New (1997) TNM Systems

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Abstract. The pN classification of gastric cancer is currently based on the distance of metastatic nodes from the primary tumor (TNM—1987). The UICC (Union Internationale Contre le Cancer) has recently proposed a new classification system based on the number of the involved nodes (TNM—1997). The present prospective study is aimed at verifying whether the two classifications (1) assign approximately a similar rank to individual patients and (2) give comparable prognostic information. The Cox regression model was used to evaluate the prognostic significance of either the distance or the number of positive nodes, controlling for sex, age, site, histology and depth of tumor invasion, in a group of 175 patients who underwent curative surgery for gastric cancer from March 1988 to October 1997. Among the patients classified as N1 and N2 according to TNM—1987, 81.8% (36/44) and 35.8% (19/53), respectively, were coded as N1 and N2 by the new classification. The survival probabilities of N1 and N2 categories were similar in both classifications. The N2 category of TNM—1987 comprised also 10 cases with >15 positive nodes (N3 category of TNM—1997), who presented a large excess mortality (RR = 35.14 with respect to N0). When the site and number of positive nodes are combined in a new variable, both appear to be important from a prognostic point of view. Both anatomic location and number of nodes with metastasis are important predictors of survival in gastric cancer patients. Caution should be used when replacing the old classification with the new one, as they group patients in a different way.

The TNM system for the classification of tumors has become the principal method for assessing the prognosis for cancer patients and to provide a reliable means for reporting and comparing the results of treatments. The unified staging system, published in 1987 [1], was the result of an agreement between the Union International Contra Cancer (UICC), the American Joint Committee on Cancer (AJCC), and the Japanese Cancer Committee (JCC) that was reached in Geneva in May 1985.

In this previous TNM system for gastric cancer, the N classification was based on the site and the distance of the metastatic nodes from the primary tumor [2, 3]. As for breast and colorectal cancer, the prognostic significance of the number of metastatic lymph nodes with gastric cancer has been emphasized by several reports [4–7], and some authors suggested that the number of nodes with metastasis exerts a larger effect on survival than the anatomic level of involved nodes [8–10].

Therefore to simplify the pN classification and to reduce errors when deciding the sites of dissected nodes after en bloc resection, the UICC has proposed a new classification system based on the number of involved nodes [11].

The aims of the present study were to (1) verify whether individual patients have a similar rank in the new classification based on the absolute number of metastatic lymph nodes and in the old classification based on the distance of metastatic nodes from the primary tumor; and (2) determine if this new classification gives the same prognostic information as the previous classification.

Materials and Methods

Between March 1988 and October 1997 a series of 262 patients suffering from primary gastric carcinoma underwent gastric resection in the First Department of General Surgery, University of Verona. Complete removal of the tumor (R0 resection) was achieved in 216 patients by gastrectomy; in 188 patients an extended or superextended lymphadenectomy (≥ D2) was performed, with 15 or more lymph nodes dissected. Seven patients who had died in hospital and six in whom liver or peritoneal metastases had been removed were excluded from the analysis. Thus overall 175 patients were recruited for the study.

Among the 175 patients, the total number of dissected lymph nodes was 6439. The mean number of dissected nodes per case was 36.8 ± 16.1 (range 15–108), and the mean number of metastatic nodes was 5.34 ± 7.75 (range 0–42) in the overall series and 8.6 ± 8.3 (range 1–42) when excluding N0 cases. Tumors were staged according to the old and new pathologic tumor node metastasis classifications (pTNM) [2, 11]. Because the cutoffs adopted in the new TNM system are not naturals cutoffs as were those of the old TNM system (anatomic location of the stations), a preliminary evaluation of the new TNM was performed in the present series. Patients with at least one positive node were grouped into five classes approximately of the same

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Table 1. Joint distribution of the 175 gastric cancer patients according to the two TNM classification systems.

	New TNM (1997)				
Old TNM (1987)	N0	N1 (1–6 nodes positive)	N2 (7–15 nodes positive)	N3 (≥ 16 nodes positive)	M1a (N3–N4)
N0	66				
N1		36 (81.8%)	8 (18.2%)		
N2		24 (45.3%)	19 (35.8%)	10 (18.9%)	
M1a (N3–N4)					12

Percent frequencies in parentheses are row percentages.

Table 2. Main demographic and clinical characteristics of 175 patients who underwent R0 resection for gastric cancer with and removal of 15 or more lymph nodes between March 1988 and April 1996.

		Univariate survival analysis	
Variable	No. (%)	Percent 5-year survival rate (95% CI)	*p*
Sex			
Men	119 (68)	53 (43–63)	0.018
Women	56 (32)	74 (59–85)	
Age (years)			
< 58	58 (33.1)	68 (51–80)	
58–69	59 (33.7)	62 (47–74)	0.034
≥ 70	58 (33.1)	51 (36–64)	
Site			
Upper third	51 (29.1)	44 (28–59)	
Middle third	45 (25.7)	73 (57–84)	0.064
Lower third	79 (45.1)	62 (47–73)	
Histology			
Intestinal	97 (55.4)	70 (58–79)	
Diffuse	78 (44.6)	48 (35–60)	0.015
T classification			
T1 (tumor invasion of mucosa and submucosa)	55 (31.4)	89 (72–96)	
T2 (tumor invasion of muscularis propria or subserosa)	39 (22.3)	73 (52–86)	
T3 (tumor invasion of serosa)	70 (40.0)	37 (25–49)	< 0.001
T4 (tumor invasion of adjacent structures)	11 (6.3)	18 (1–52)	
N classification according to TNM—1987			
N0 (no regional nodes metastasis)[a]	66 (37.7)	93 (82–97)	
N1 (metastasis in perigastric nodes within 3 cm of the edge of the primary tumor)	44 (25.1)	52 (35–67)	
N2 (metastasis in perigastric nodes > 3 cm from the edge of the primary tumor or in the other regional nodes)	53 (30.3)	35 (20–50)	< 0.001
M1a (metastasis in nonregional nodes/N3-N4)[b]	12 (6.9)	16 (1–48)[d]	
N classification according to TNM—1997			
N0 (no regional nodes metastasis)	66 (37.7)	93 (82–97)	
N1 (metastasis in 1–6 regional nodes)	60 (34.3)	56 (40–69)	
N2 (metastasis in 7–15 regional nodes)	27 (15.4)	30 (13–49)	< 0.001
N3 (metastasis in >15 regional nodes)	10 (5.7)	0[c]	
M1a (metastasis in nonregional nodes/N3-N4)	12 (6.9)	16 (1–48)[d]	

Lymph node involvement was classified according to both TNM staging systems (1987 and 1997). Five-year survival rates are calculated by the Kaplan-Meier method and the *p* value by the log-rank test.

[a]Regional nodes are the perigastric nodes along the lesser (1, 3, 5) and greater (2, 4d, 4sb, 4sa, 6) curvatures and the nodes located along the gastric (7), common hepatic (8), celiac (9), and splenic (10, 11) arteries and hepatoduodenal nodes (12).

[b]Nonregional nodes are retropancreatic (13), mesenteric (14), and paraaortic (16) lymph nodes.

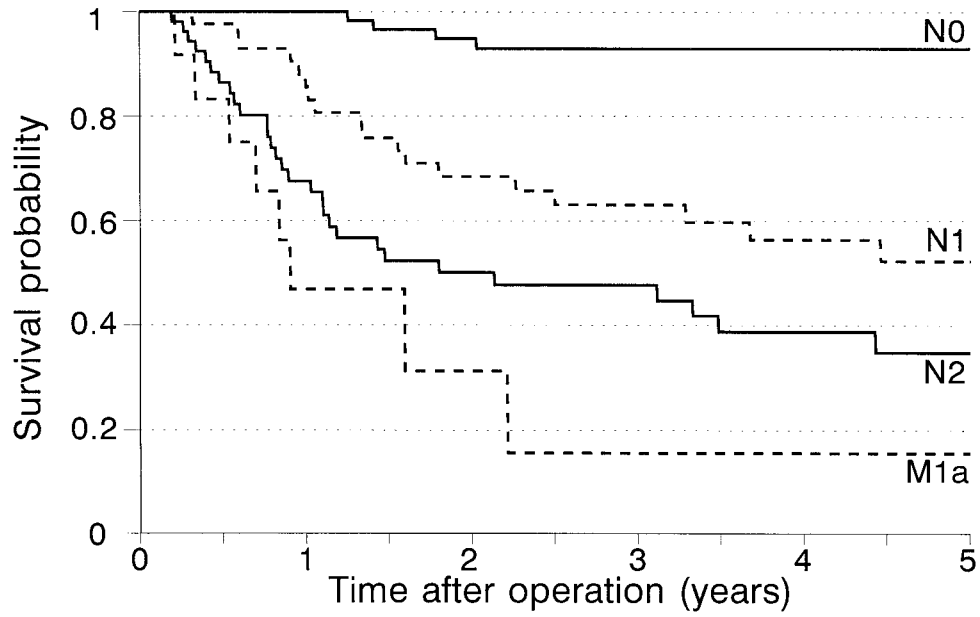
[c]No patients alive after 13 months.

[d]Three-year survival rate.

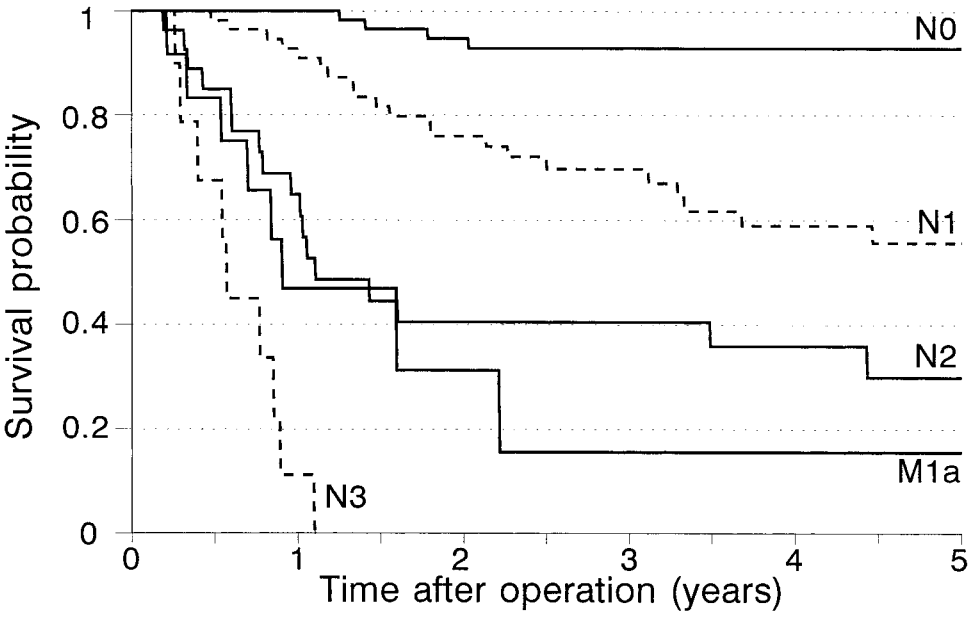
size, and the progressive worsening of prognosis in these groups with respect to N0 patients was analyzed. The median follow-up for surviving patients was 49 months (range 6–118 months).

Statistical Analysis

Only cancer-related mortality was taken into account for survival analysis, and deaths from different causes ($n = 6$) were considered as censored observations at the time of death. Univariate analysis was carried out by the Kaplan-Meier method and the log-rank test [12]. Multivariate survival analysis was accomplished through the Cox regression model [13] by taking into account the following risk factors: age, sex, tumor location (fundus, corpus, antrum), histology (intestinal versus diffuse), depth of invasion, and nodal involvement, expressed either as the site or the absolute number of metastatic lymph nodes. Because the latter variables were



N0	66	59	51	38	32
N1	44	35	27	21	17
N2	53	31	21	16	12
A M1a	12	5	2	1	1



N0	66	59	51	38	32
N1	60	49	38	28	22
N2	27	16	10	9	7
N3	10	1	--	--	--
B M1a	12	5	2	1	1

Fig. 1. A. Kaplan-Meier estimates of survival probability in 175 patients who underwent curative surgery for gastric cancer, according to the N classification based on the distance of the metastatic nodes (TNM—1987). **B.** Kaplan-Meier estimates of survival probability in 175 patients who underwent curative surgery for gastric cancer, according to the N classification based on the number of metastatic nodes (TNM—1997).

closely correlated, their impact on survival was evaluated separately by performing two different analyses. In addition, the two variables were joined to build up a new variable with the following levels: N0; N1 with 1–6 positive nodes; N1 with 7–15; N2 with 1–6; N2 with 7–15; N2 with >15 positive nodes; M1a (N3–N4) (Table 1).

Table 3. Results of preliminary multivariate analysis after grouping patients in classes of approximately the same size.

No. of involved nodes	No. of cases	Relative risk (95% CI)
0	66	1
1–2	26	3.96 (1.16–13.46)
3–4	18	2.28 (0.54–9.59)
5–6	16	4.82 (1.30–17.90)
7–10	17	7.89 (2.18–28.53)
≥ 11	20	10.86 (3.08–38.31)
M1a (N3–N4)	12	9.10 (2.43–33.89)

Results

The main demographic and clinical characteristics of the cohort are presented in Table 2, together with the univariate survival analysis. It can be appreciated that all T classifications and all possible sites of involvement were represented in the study base. Moreover, the mean age (63.3 ± 11.9 years), the male/female ratio (2:1), and the frequency distribution of histology according to the Lauren classification were comparable to other series reported in the current literature [14–16]. Adopting the TNM—1997 classification rather than the TNM—1987 caused a contraction of the N2 class, whose patients were partly recoded either as N1 or as N3. According to univariate analysis, male sex, age ≥ 70 years, diffuse type histology, more advanced depth of tumor invasion, or more distant node metastasis (TNM—1987) were negative prognostic factors. Shifting from TNM—1987 to TNM—1997 classification allowed us to identify a small group of high risk patients (N3), apparently without affecting the prognosis in the remaining classes, particularly in N1 and N2 patients.

A visual comparison between the prognostic significance of the two classifications is given in Figure 1, reporting Kaplan-Meier survival curves. It can be appreciated that the survival probability of N3 patients fell steeply to zero by the 14th month of follow-up.

The joint distribution of the patients, according to the two N classifications, is reported in Table 1. The two classifications are not superimposed. Indeed, whereas most of the N1 patients (81.8%) according to the old classification remained in the N1 class of the new classification, two-thirds of the N2 patients were coded differently by the new classification.

The preliminary evaluation of the new TNM system in the present series is reported in Table 3. It can be appreciated that the risk of death increased fourfold already in patients with just one or two positive nodes, did not increase further up to six lymph nodes, and started to increase markedly after a threshold of about seven positive nodes. Thus according to the present series the cutoffs adopted by the new TNM system appeared to reflect changes in survival.

A further insight into the prognostic significance of the new and old N classifications is given in Table 4, which reports the results of multivariate survival analysis. Among the risk factors considered, depth of tumor invasion, age, and nodal involvement (coded either as the distance or as the number of metastatic nodes) significantly affected survival. The multivariate analysis confirmed the poor prognosis of the N3 group of the new TNM system who presented the largest relative risk. Diffuse histology appeared to be a negative prognostic factor when taking into account the site of nodal involvement, but this effect disappeared when the number of positive nodes was considered. This discrepancy is due to the fact that cancer with diffuse histology tended to give rise to a larger number of positive nodes, whereas the sites involved by both histologic types of cancer are approximately the same. Indeed, diffuse histology was similarly represented in the N1 and N2 categories of the TNM—1987 system (47.7% and 56.6%, respectively), whereas it was more common in advanced classes of the TNM—1997 (38.3%, 74.1%, and 80.0% of the patients with N1, N2, and N3, respectively). The combined prognostic significance of the two pN classifications is presented in Table 5. The risk of death increased both with the distance and the number of metastatic nodes (TNM—1997). As a consequence, a remarkable heterogeneity in survival emerged within the tiers of the old TNM and within categories of the new TNM.

Discussion

The main findings of the present study are that (1) in gastric cancer patients undergoing curative resection, correspondence between the new TNM and old TNM classifications is rather low; (2) the site and number of positive lymph nodes are independent prognostic factors in gastric cancer patients; and (3) when the site and number of positive nodes are combined to form a new variable, both appeared to be important from a prognostic point of view.

There were marked differences between the old and new TNM classifications, not only because the TNM—1997 introduced a new category with advanced nodal involvement and poor prognosis (N3) but also because nearly half of the patients in the N2 category of the TNM—1987 were allotted to the N1 category by TNM—1997.

Multivariate survival analysis identified nodal involvement as an independent prognostic factor, whether considering the number or the site of the positive nodes. In the present study we could not evaluate simultaneously the effect of the site and the number of positive nodes on survival, as these two variables were highly collinear [17]. However, when the two variables were combined to form a new variable, both the site and the number of positive nodes were important from a prognostic point of view.

The TNM—1997 simplifies the N classification that is now directly in charge of the pathologist, and it is independent of the preparation and information on the location given by surgeons. Moreover, especially after en bloc resection, the new classification can avoid errors due to the difficulty of assigning the lymph nodes into the correct tier. However, the TNM—1997 seems to be less helpful for surgeons when compared with the TNM—1987, in which the assessment of lymphatic spread is based on its anatomic extension.

The meaning of the N3 category of the new classification remains controversial. On one hand, the N3 category identifies a group of high risk patients with no survivors after 13 months; on the other hand, it presents a prognosis even worse than that for patients with metastasis to the paraaortic nodes, which are regarded as distant metastases. Up to few years ago, the nodal involvement in this area was deemed incurable [18], but the results recently reported by Oriental surgeons after D4 lymphadenectomy (i.e., with complete dissection of the paraaortic nodes) have cast doubts on this statement. These studies revealed that the incidence of metastasis to the paraaortic nodes is higher than expected, ranging from 8% to 20% in patients who have gastric cancer with serosal invasion [19–23] and that 13% to 20% of

Table 4. Relative risks of death from gastric cancer after adjusting for all other variables.

Variable	Old TNM—1987[a]		New TNM—1997[a]	
	Relative risk adjusted for all other variables[a]	p^a	Relative risk adjusted for all other variables[a]	p
Sex (women vs. men)	0.72 (0.37–1.42)	0.33	0.72 (0.37–1.41)	0.33
Age (SD = 11.9 years)	1.42 (1.03–1.95)	0.029	1.38 (1.0–1.90)	0.049
Site				
Middle third versus upper third	0.63 (0.28–1.42)		0.84 (0.39–1.81)	
Lower third versus upper third	1.33 (0.70–2.53)	0.12	1.37 (0.74–2.54)	0.36
Histology (diffuse vs. intestinal)	1.86 (1.08–3.20)	0.024	1.38 (0.76–2.52)	0.29
Depth of tumor invasion				
T2 vs. T1	2.04 (0.60–6.88)		2.10 (0.62–7.11)	
T3 vs. T1	6.10 (2.05–18.13)	< 0.001	4.36 (1.42–13.31)	< 0.001
T4 vs. T1	17.73 (4.49–69.96)		16.43 (4.08–66.28)	
Nodal involvement				
N1 vs. N0	3.06 (0.95–9.84)			
N2 vs. N0	6.39 (2.10–19.48)	< 0.001		
M1a (N3–N4) vs. N0	7.76 (2.13–28.27)			
Nodal involvement				
N1 (1–6 positive nodes) vs. N0			3.84 (1.24–11.92)	
N2 (7–15 positive nodes) vs. N0			7.28 (2.17–24.45)	
N3 ($\geq$ 16 positive nodes) vs. N0			35.14 (8.62–143.2)	< 0.001
M1a (N3–N4) vs. N0			10.31 (2.78–38.17)	

Values in parentheses are 95% confidence intervals.
[a]Relative risks and p values were derived from Cox regression analysis; calculation of the relative risk for continuous variables was based on an increase in the value of 1 SD.

Table 5. Relative risk of death from gastric cancer according to the joint distribution of site and number of positive nodes.

	New TNM (1997)			
Old TNM (1987)	N1 (1–6 positive nodes)	N2 (7–15 positive nodes)	N3 ($\geq$ 16 positive nodes)	M1a
N1 vs. N0	3.27 (0.98–10.89)	5.03 (1.20–21.16)		
N2 vs. N0	4.26 (1.25–14.60)	8.70 (2.49–30.36)	32.9 (8.06–136.3)	
M1a vs. N0				9.28 (2.48–34.79)

Relative risks were derived from Cox regression model.
Numbers in parentheses are 95% confidence intervals.

patients with nodal deposits in this area survive more than 5 years after superextended node dissection [19, 22, 24]. Also in the present investigation, in which the use of D4 lymphadenectomy was extensive (67/175, 38.3%) the 3-year survival rate of N4 positive cases was 16%.

Conclusions

Both anatomic location and number of node metastases are important predictors of survival in gastric cancer patients. Caution should be used when comparing series classified according to the new TNM with series coded according to the old TNM, as the two classifications group patients in different ways. We believe that further studies enrolling a larger number of patients are necessary to determine if a combined classification based on the number of metastatic nodes in the different tiers could be useful.

Résumé

Fond du problème: La classification pN actuel du cancer gastrique est basée sur la distance entre les ganglions métastatiques et la tumeur primitive (TNM—1987). L'UICC (Union Internationale contre le Cancer) a récemment proposé une nouvelle classification basée sur le nombre de ganglion atteints (TNM—1997). Cette étude prospective a comme but de vérifier si les deux systèmes: 1) attribuent un rang équivalent à chaque patient, et 2) fournissent une information pronostique comparable. Méthodes: On a utilisé un modèle de Cox pour évaluer la signification pronostique de la distance et le nombre de ganglions envahis, en contrôlant pour le sexe, l'âge, le site, l'histologie et la profondeur d'invasion chez 175 patients ayant eu une chirurgie à visée curative pour cancer gastrique entre mars 1988 et octobre 1997. Résultats: Parmi les patients classés N1 et N2 selon la TNM—1987, 81,8% (36/44) et 35,8% (19/53),

respectivement, ont été classés N1 et N2 par la nouvelle classification. La probabilité de survie des catégories N1 et N2 était similaire dans les deux classifications. La catégorie N2 de la classification TNM—1987 comportait également 10 cas avec >15 ganglions envahis (catégorie N3 de la classification TNM 1997), ce qui présentait une mortalité très excessive (RR = 35.14 par rapport au N0). Quand le site et le nombre de ganglions envahis ont été pris ensembles, tous les deux apparaissaient comme facteurs pronostiques importants. Conclusion: Le site anatomique et le nombre de ganglions envahis sont des facteurs prédictifs dans la survie des patients ayant un cancer gastrique. Il faut faire attention lorsque l'on remplace l'ancienne classification par la nouvelle, car elle regroupe les patients d'une manière différente.

Resumen

Actualmente, la clasificación pN del cáncer gástrico se basa en la distancia existente entre el tumor primario y los nódulos metastásicos (TNM—1987). La Unión Internacional contra el Cáncer (UICC) ha propuesto una nueva clasificación basada en el número de ganglios afectados (TNM—1997). Este estudio prospectivo tiene como objetivos fundamentales verificar: 1) si la estadificación asignada a cada paciente es similar entre ambas clasificaciones y 2) averiguar si la información pronóstica es semejante. Se utilizó el modelo de regresión de Cox para valorar la significación pronóstica tanto de la distancia como del número de nódulos metastásicos positivos, controlándose además el sexo, edad, localización, tipo histológico y capacidad invasiva del tumor. El estudio se realizó en 175 pacientes sometidos a cirugía gástrica radical (curativa) por cáncer, intervenidos entre marzo de 1988 y octubre de 1997. Resultados: Entre los pacientes codificados como N1 y N2, de acuerdo con la clasificación TNM—1987, 81,8% (36/44) y 35,8% (19/53) fueron estadificados como N1 y N2 por la nueva clasificación. Las posibilidades de supervivencia en los estadios N1 y N2 fueron similares en ambas clasificaciones. En el grado N2 de la clasificación TNM—1987 se detectaron 10 casos con más de 15 nódulos positivos, que corresponderían al estadio N3 de la clasificación TNM—1997 y cuya mortalidad es muy superior a los N0 (RR = 35.14). Si se combinan en una nueva variable la localización y el número de nódulos positivos, se obtendría una mayor certeza pronóstica. Conclusión: Tanto la localización anatómica, como el número de nódulos metastásicos, desempeñan un importante papel en el pronóstico "ad vitam" de los pacientes con cáncer gástrico. La sustitución de la vieja por la nueva clasificación TNM, ha de realizarse con cautela, ya que la estadificación de los pacientes es diferente.

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