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DISEASES OF THE ESOPHAGUS

Original article

Comparison of the prognostic value of the 6th and 7th editions of the Union for International Cancer Control TNM staging system in patients with lower esophageal cancer undergoing neoadjuvant chemotherapy followed by surgery

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SUMMARY. **Carcinoma of the esophagus is classified according to the Union for International Cancer Control (UICC) TNM staging system. The 7th edition of the UICC TNM staging system was published in 2009. This is the first study to compare the prognostic value of the TNM 6th and 7th editions in patients with esophageal carcinoma treated with chemotherapy followed by surgery. Two hundred forty-three patients with esophageal carcinoma were retrospectively selected from two referral centers. All patients received chemotherapy before surgery. Histopathologic data from the resection specimens were retrieved and restaged according to the TNM 7th edition. Disease-specific survival curves were plotted for depth of tumor invasion (ypT), lymph node status (ypN), and ypTNM stage and then compared. Median follow-up after surgery was 2.5 years (range 0.2–9 years). Survival analysis using the log-rank method revealed that there was a significant difference in survival between ypT4 disease and ypT3 disease ($P = 0.003$), but no difference between ypT0, ypT1, ypT2, and ypT3 categories irrespective of TNM edition used. Survival probability was significantly different between ypN0 and ypN1 ($P = 0.001$ for TNM 6th and 7th edition), as well as ypN2 and ypN3 (TNM 7th edition, $P = 0.004$), but not between ypN1 and ypN2 (TNM 7th edition, $P = 0.89$). Neither the TNM 6th nor 7th edition T staging provides accurate survival probability stratification. However, the advantage of the 7th edition is the introduction of a third tier in survival stratification for patients with nodal involvement.**

KEY WORDS: **esophageal cancer, neoadjuvant chemotherapy, TNM staging.**

INTRODUCTION

The TNM classification is the globally accepted gold standard not only to describe the anatomic extent of cancer with the aim of aiding the clinician in planning treatment strategies but also to give an indication of patient prognosis and assist in evaluating the results of treatment.[1] Historically, esophageal cancer staging in the UK has adopted the Union for International Cancer Control (UICC) TNM system. The previous edition (6th) that came to effect in 2002 was neither data-driven nor harmonized with stomach cancer.[2] Furthermore, the growing body of literature regarding other factors associated with survival in patients with esophageal cancer was not accounted for by the 6th edition.[3,4]

At the request of the UICC, the 7th edition of the TNM staging system was introduced in 2009. Thirteen institutions from five countries submitted data to construct a database of 4627 patients treated by surgery alone to develop the new edition of the TNM system for esophageal cancer. The data,

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Disclosure: The authors have no commercial interests to disclose.
Synopsis: Comparison of the prognostic value of the UICC TNM 6th and 7th edition in patients with esophageal carcinoma treated with chemotherapy followed by surgery. TNM 7th edition introduces a third tier in survival stratification for patients with lymph node involvement.

analytic methods, and stage groupings for the 7th edition of the UICC cancer staging system have been reported recently.[5]

In the UK, the majority of patients with locally advanced esophageal cancer undergo neoadjuvant chemotherapy prior to surgery.[6] Thus, there is a need to evaluate the prognostic value of TNM 7th edition in this group of patients. This is the first study to determine the prognostic value of the recently introduced 7th edition of the UICC TNM staging system in a cohort of patients undergoing chemotherapy followed by surgery for esophageal cancer.

MATERIALS AND METHODS

This study was approved by the Leeds (West) and South Manchester Research Ethics committees.

Patients

The Leeds Teaching Hospitals National Health Service (NHS) Trust and the University Hospital of South Manchester are specialist referral centers for esophageal cancer management in the UK. Only patients who underwent esophagectomy after two cycles of 5-fluorouracil and cisplatin combination chemotherapy for resectable distal esophageal cancer were included. Patients were initially diagnosed through endoscopy and staging computed tomography (CT) scan of the thorax and abdomen. Endoscopic ultrasound (EUS) and positron emission tomography (PET) were not routinely used. Surgical procedures were carried out with curative intent and included a 2-field lymphadenectomy. The data extended from 1995 to 2008 for the University Hospital of South Manchester and 2001 to 2009 for the Leeds Teaching Hospitals NHS Trust. Patients were excluded if there was no residual tumor present (ypT0 ypN0) in the resected specimen.

A clinical database was established as part of this study. The following information was extracted from the pathology report: depth of invasion (ypT category), number of lymph nodes retrieved, and number of positive lymph nodes (ypN category), as well as histological tumor type. Patients with distant metastases (ypM1) were excluded from the study.

TNM staging

Depth of tumor invasion (ypT category) was classified into one of the following groups: intramucosal including lamina muscularis mucosae, submucosal, muscularis propria, adventitia, and serosal involvement. The pathologic nodal stage (ypN category) was determined on the basis of the presence or absence of involved lymph nodes for TNM 6th edition and then restaged using the number of positive nodes according to TNM 7th edition. ypTNM stage groupings were calculated for both TNM editions.

Follow-up

Patients were routinely seen at 6 weeks following discharge after surgery and then reviewed in clinic at regular intervals. The North Yorkshire Cancer Registry and Information Service database and clinical records were used to obtain information on cause of death.

Statistical analyses

The SPSS 16.0 software package (SPSS, Chicago, IL, USA) was used for statistical analysis. For each TNM edition, the relationship between ypT, ypN, and ypTNM stage categories with cancer specific survival was estimated using the Kaplan–Meier method.[7] Survival time was calculated from the date of surgery to the time of death or last date of follow-up, and compared between groups using the log-rank test. Prognostic relevance was also investigated using a multivariate Cox regression analysis including ypT, ypN, age, and gender in the model. *P*-values of less than 0.05 were considered statistically significant.

RESULTS

Patient demographics

In total, 243 patients were included in the study, 50 from the University Hospital of South Manchester and 193 from Leeds Teaching Hospitals NHS Trust. One hundred eighty-six (77%) patients were male, and 57 (23%) were female. The median age of the patient cohort was 61 years, ranging from 35 to 79 years. One hundred ninety-two (79%) cancers were classified as adenocarcinoma, 47 (19%) as squamous cell carcinoma, and 4 (2%) as adenosquamous cancers. The median number of lymph nodes retrieved from the resection specimen was 30, ranging from 3 to 104 nodes. The median number of positive nodes was 2, ranging from 0 to 63 nodes. Median follow-up time after surgery for all patients was 1.4 years (range 0–9 years); for those still alive at the end of the study period, it was 2.5 years (range 0.2–9 years). The number of patients in each of the ypT and ypN categories, and ypTNM stage according to TNM 6th and 7th edition are shown in Tables 1 and 2, respectively. The migration of numbers from the 6th to the 7th editions of TNM is shown in Figure 1.

Relationship of ypT, ypN, and ypTNM stage with patient cancer-specific survival

Survival curves with the number of patients at risk for ypT category, ypN category, and ypTNM stage

Table 1 Survival comparison for the ypT, ypN, and ypTNM stage categories according to TNM 6th edition

	No. of patients (n = 243) (%)	P-value
ypT category		0.001
ypT1	22 (9)	–
ypT2	40 (16)	0.52
ypT3	171 (70)	0.12
ypT4	10 (5)	0.003
ypN category		<0.001
ypN0	73 (30)	–
ypN1	170 (70)	<0.001
ypTNM stage		<0.001
I	11 (5)	–
IIA	61 (25)	0.27
IIB	33 (14)	0.02
III	138 (56)	0.03

–, No P value as this is the reference category.

according to TNM 6th and 7th edition are shown in Figures 2–4, respectively. There was a significant difference in the survival probability for the overall ypT category, ypN category, and ypTNM stage irrespective of TNM edition (see Tables 1 and 2).

We then compared each ypT, ypN, and ypTNM stage category with the category preceding it (e.g. ypT2 compared with ypT1, ypT3 compared with ypT2, and so forth). For ypT, there was no significant survival difference between categories when using either TNM edition except for ypT4 compared with ypT3 (P = 0.003, Table 1). For ypN, there was a significant difference between ypN0 and ypN1 for both TNM 6th and 7th edition (Tables 1 and 2). With TNM 7th edition, there was a significantly worse survival probability for ypN3 compared with ypN2 (P = 0.004) but not ypN2 compared with ypN1 (Table 2). For ypTNM stage, there was a significant

Table 2 Survival comparison for the ypT, ypN, and ypTNM stage categories according to TNM 7th edition

	No. of patients (n = 243) (%)	P-value
ypT category		0.002
ypT1a	7	–
ypT1b	15	0.39
ypT2	40	0.34
ypT3	171	0.12
ypT4a/b	10	0.003
ypN category		<0.001
ypN0	73	–
ypN1	64	<0.001
ypN2	52	0.89
ypN3	54	0.004
ypTNM stage		<0.001
IA	11	–
IB	18	0.47
IIA	43	0.84
IIB	17	0.06
IIIA	56	0.72
IIIB	40	0.36
IIIC	58	0.02

–, No P value as this is the reference category.

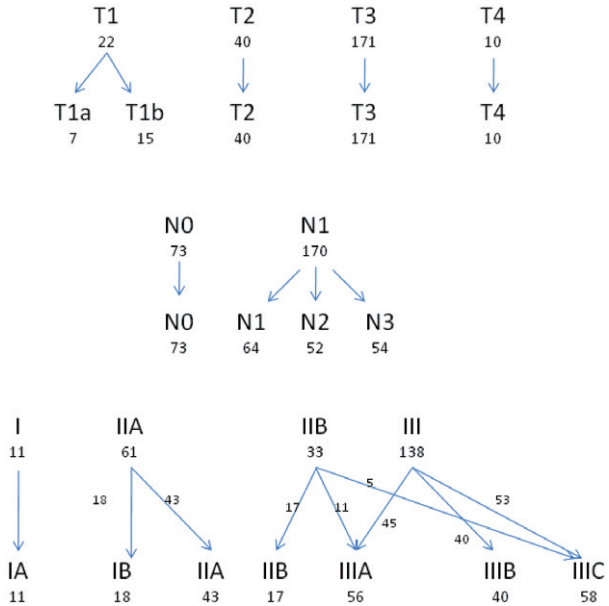

Fig. 1 Number of cases migrating between ypT, ypN, and ypTNM stages in TNM 6th edition (top row) and TNM 7th edition (bottom row).

difference between stage IIA and stage IIB, and also stage IIB and stage III when using TNM 6th edition (Table 1). With TNM 7th edition, however, there was only a significant difference between stage IIIB and stage IIIC (Table 2).

Multivariate Cox regression revealed that by using TNM 6th edition, both ypT and ypN were independent prognostic predictors of cancer-specific survival (hazard ratio (HR) 1.74, 95% confidence interval (CI) 1.13–2.68, P = 0.012; HR 5.34, 95% CI 2.42–11.79, P < 0.001). Using TNM 7th edition, only ypN was an independent prognostic predictor of cancer-specific survival (HR 1.87, 95% CI 1.47–2.38, P < 0.001). Age and gender were not related to patient survival.

DISCUSSION

The pathologic TNM stage after resection is currently the gold standard method for prognosis prediction in cancer patients. The UICC TNM 7th edition published in 2009[8] introduced a number of major changes to the staging of patients with esophageal cancer. In particular, the TNM 7th edition includes the subclassification of the TNM 6th edition T1 category into T1a and T1b, of the TNM 6th edition T4 category into T4a and T4b, the inclusion of lymph nodes previously classified as nonregional lymph nodes (pM1a) into the pN category, and the subclassification of pN according to the number of involved lymph nodes (pN1: 1–2 nodes; pN2: 3–6 nodes; and pN3: 7 or more nodes). Furthermore, new anatomic TNM stage groupings were introduced increasing the

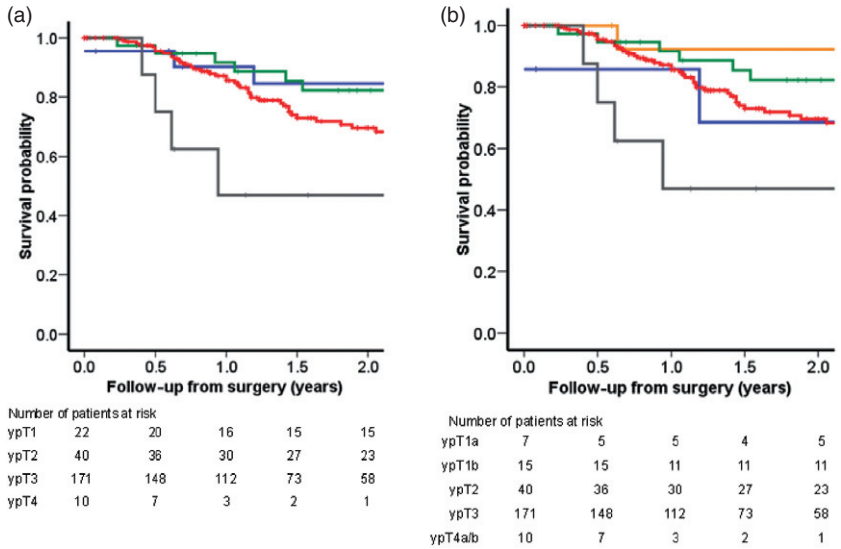

Fig. 2 Kaplan–Meier survival plots for ypT categories – (a) TNM 6th edition: (▁▔▁) ypT1, (▁▔▁) ypT2, (▁▔▁) ypT3, and (▁▔▁) ypT4; and (b) TNM 7th edition: (▁▔▁) ypT1a, (▁▔▁) ypT1b, (▁▔▁) ypT2, (▁▔▁) ypT3, and (▁▔▁) ypT4a/b.

number from four stages in TNM 6th edition to seven stages in TNM 7th edition.

The UICC TNM 7th edition staging system for esophageal cancer is based on the analysis of data from 4627 patients who were treated by surgical resection without preoperative and/or postoperative chemotherapy or chemoradiation.[2] In the UK, preoperative combination chemotherapy is the standard treatment given to patients with locally advanced esophageal cancer following the publication of results from the OE02 trial in 2002.[6] The current study is the first to evaluate whether postoperative staging using TNM 7th edition provides a better prognostic stratification compared with TNM 6th edition for patients who have undergone neoadjuvant chemotherapy prior to surgery for esophageal cancer.

The Kaplan–Meier survival analysis demonstrated that an increasing ypT, ypN, and ypTNM stage category was related to worse survival irrespective of TNM edition used. However, neither TNM 6th edition nor TNM 7th edition ypT category was able to stratify patients by survival. The only significant difference in survival was found between patients with ypT3 and those with ypT4 cancers in both TNM editions. Thus, only a very small number of patients (n = 10, 4%) with poorer survival can be identified using the ypT category alone. In our series, the survival of patients classified as ypT1a is similar to that

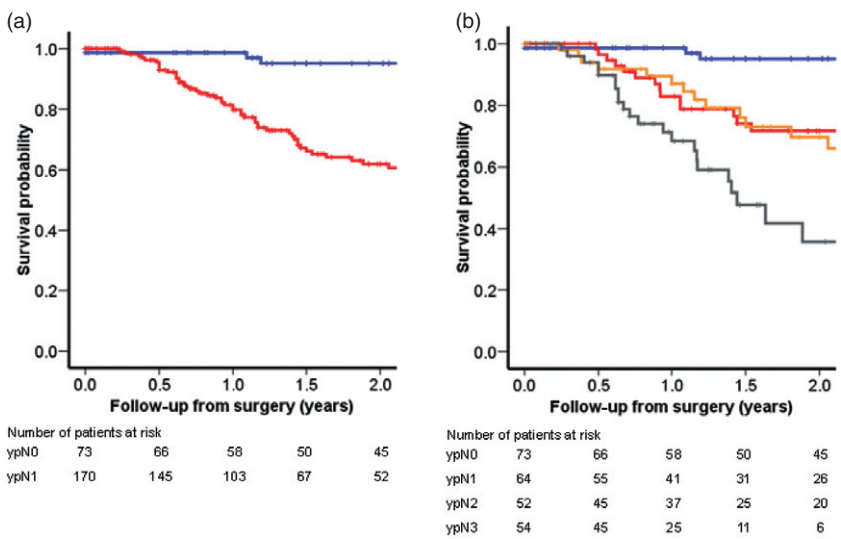

Fig. 3 Kaplan–Meier survival plots for ypN categories – (a) TNM 6th edition: (▁▔▁) ypN0 and (▁▔▁) ypN01; and (b) TNM 7th edition: (▁▔▁) ypN0, (▁▔▁) ypN1, (▁▔▁) ypN2, and (▁▔▁) ypN3.

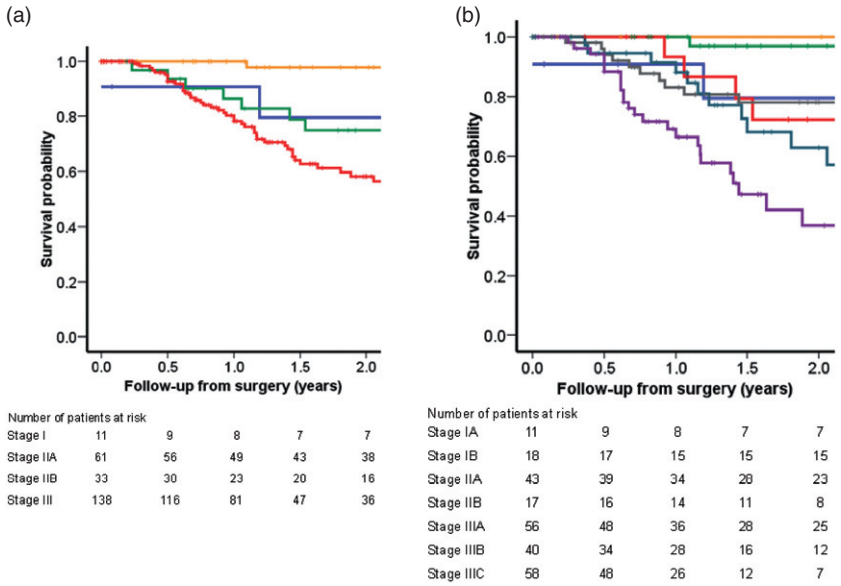

Fig. 4 Kaplan–Meier survival plots for ypTNM stage categories – (a) TNM 6th edition: (▁) I, (▁) IIA, (▁) IIB, and (▁) III; and (b) TNM 7th edition: (▁) IA, (▁) IB, (▁) IIA, (▁) IIB, (▁) IIIA, (▁) IIIB, and (▁) IIIC.

of ypT1b, which is most likely related to small numbers in the ypT1 category. We did not have any patients with ypT4b cancers and so cannot comment on the effect of this newly introduced category. Overall, there would appear to be no difference between the ypT category in TNM 6th edition and TNM 7th edition. Furthermore, the findings from the multivariate analysis that ypT by the TNM 6th edition and not TNM 7th edition was found to be independently prognostic need to be interpreted with caution because we feel that these results are likely to depend on the small number of cases in ypT1 and ypT4.

The two tier ypN category in TNM 6th edition (ypN0 vs. ypN1) stratified our patients into two groups with clearly distinct survival probability. Using TNM 7th edition ypN categories, there was a significant difference between ypN0 and ypN1, as well as between ypN2 and ypN3, but no survival difference was seen between ypN1 and ypN2. This suggests that there are only three groups of patients with differing survival probability in our study cohort, those with no lymph node metastasis (ypN0), those with one to six positive nodes (ypN1 and ypN2), and those with more than six positive nodes (ypN3). It is unclear why there is no significant survival difference between ypN1 and ypN2.

The ypTNM stage groupings (TNM 6th edition) discriminated between stages IIa, IIb, and III patients but only between stage IIIB and IIIC in the seven tier TNM 7th edition system. The survival curves in Figure 4b demonstrate a lack of monotonicity with regard to staging, and this may reflect the low numbers in the early-stage categories. Increasing the number of categories will always lead to a reduction of power for statistical analysis, and this could be one reason for less discriminatory power in the TNM 7th edition stage groupings. Alternatively, the statistical differences that were identified could well be related to the change in the nodal status between these stage categories. A much larger study would be needed to investigate the monotonicity of the new stage groupings in relation to survival for those undergoing neoadjuvant chemotherapy in order to confirm that these groupings are still valid for such patients.

In TNM 6th edition, one of the main differences between stages IIa and IIb is the presence of nodal metastases in IIb. Similarly, in TNM 7th edition, all patients with a high nodal burden (more than six positive nodes, ypN3) are included in stage IIIC irrespective of their ypT category. The importance of the lymph node status for patient survival was also demonstrated in the multivariate analysis, where the ypN category was an independent predictor of patient's prognosis in TNM 6th and 7th edition. These results are in concordance with several other studies in esophageal cancer patients treated with chemoradiation or chemotherapy before surgery that have reported ypN, but not ypT or ypTNM, stage as an independent prognostic marker using TNM 6th edition.[9–16]

The classification by TNM 7th edition is evidence-based[2] in contrast with previous TNM editions for esophageal cancer. However, these data are derived from patients treated with surgery alone. Evidence is now accumulating that a different staging system might be necessary to accurately stratify patient by prognosis after preoperative chemotherapy. In this context, it has been shown that the relationship between depth of invasion and lymph node status is

different after preoperative chemoradiotherapy compared with surgery alone.[13] There are already ypT-ypN combinations that do not exist in surgery alone, cases such as ypT0 (no primary tumor left after chemotherapy) combined with ypN1. In such circumstances, it is impossible to predict a patient's prognosis against the current TNM staging system. We deliberately excluded such cases from the current study, as we wanted to compare the prognostic value of the different ypTNM stage groupings. Our study and those from others show that depth of invasion (ypT category) has little prognostic value in patients after preoperative chemotherapy. This might be related to the observation that tumor cells may persist in small clusters anywhere in the wall of the esophagus and therefore no longer showing continuous growth from the lumen into the depth of the wall, as would be expected in chemo-naïve patients. Whether treatment response is an independent predictor of survival is still controversial.[9,12,14,17,18] In addition, a very recent study suggested that the size of the residual foci of tumor rather than depth of invasion *per se* may have greater prognostic significance.[19]

The current study has some limitations to consider when interpreting the results. This is a retrospective analysis, and the surgical procedures have most likely been performed in a non-standardized manner by different surgeons in two different hospitals. Furthermore, although PET and EUS were not routinely used during the study period, patients have not been matched by staging modality used. Finally, the available follow-up time was limited to 2 years, which may have influenced our ability to find survival differences for patients with early-stage tumors.

CONCLUSIONS

In conclusion, our results confirm that compared with TNM 6th edition, the UICC TNM 7th edition staging system does yield additional prognostic information with regard to ypN groupings in patients undergoing neoadjuvant chemotherapy, followed by surgery for esophageal cancer. This retrospective study is the first step in the evaluation of TNM 7th edition but clearly needs external validation by other centers. Our results are in agreement with previous studies demonstrating the advantages of the TNM 7th edition in patients having surgery alone[20,21] and in patients undergoing neoadjuvant chemoradiotherapy followed by surgery.[22]

Overall, however, the predictive value of the T, N, and TNM stage categories is limited in patients following chemotherapy. Our results highlight once more the importance of pathologic nodal status rather than the depth of tumor invasion as the key determinant of outcome in this patient group. The widespread use of neoadjuvant chemotherapy or chemoradiation in patients with advanced esophageal cancer in the Western world creates an urgent demand for a modified staging system to guide clinical treatment decisions. Our study has emphasized that the prognosis of these patients cannot be adequately determined by the current UICC TNM staging system.

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