# DISEASES OF THE ESOPHAGUS

**Original article**

# The number of lymph node metastases influences survival and International Union Against Cancer tumor–node–metastasis classification for esophageal squamous cell carcinoma

H-L. Zhang,[1,3] L-Q. Chen,[2,3] R-L. Liu,[1] Y-T. Shi,[1] M. He,[3] X-L. Meng,[3] S-X. Bai,[3] Y-M. Ping[3]

[1]*Department of Thoracic Surgery, Second Hospital of Hebei Medical University,* [3]*Department of Thoracic Surgery, Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, and* [2]*Department of Thoracic and Cardiovascular Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan, China*

*SUMMARY.* **To study the influence of the number of metastatic lymph nodes (LNs) on survival and International Union Against Cancer tumor–node–metastasis (TNM) classification for esophageal carcinoma. The clinicopathological data on 1146 patients with esophageal squamous cell carcinoma who had undergone an esophagectomy were retrospectively studied. Survival was analyzed by the Kaplan–Meier method. By subclassifying the nodes (N) category according to the number of metastatic LNs as: $N_0$ for no LN metastases; $N_{1(1)}$ for only one positive node; and $N_{1(2)}$ for $\geq 2$ positive nodes. TNM staging was refined as stage $II_a$ ($T_{2-3}N_0M_0$), stage $II_b$ ($T_1N_1M_0$ and $T_2N_{1(1)}M_0$), stage $IIIa$ ($T_2N_{1(2)}M_0$ and $T_3N_{1(1)}M_0$), and stage $III_b$ ($T_3N_{1(2)}M_0$ and $T_4N_{any}M_0$), and the survival was analyzed. LN metastases was found in 380 of 1146 (33.2%) treated esophageal cancer patients. In 4270 LNs harvested, metastases was detected in 807 (18.9%). The 5-year survival rates of the patients with 0, 1, and $\geq 2$ positive nodes were 59.8, 33.4, and 9.4%, respectively. There was statistically significant difference among these three groups. The 5-year survival of the patients in stages $T_2N_1M_0$ and $T_3N_1M_0$ was significantly higher in the $N_{1(1)}$ group than in the $N_{1(2)}$ group (41.5 *vs* 24.1%, and 31.2 *vs* 6.8%, $P < 0.001$). The 5-year survival rates of the patients in refined stage $II_a$, $II_b$, $III_a$, and $III_b$ were 57.1, 42.2, 28.6, and 8.5%, with significant difference existing in each stage groups. The number of positive LNs significantly influenced survival of the patients with esophageal cancer. Three grade classification (0, 1, $\geq 2$ positive nodes) could quite well demonstrate the effect of the number of LN metastases and the survival. The refined TNM classification based on the number of LN metastases could better reflect the prognosis of esophageal cancer. Our results offer a strong rationale for refining the International Union Against Cancer TNM classification for esophageal carcinoma.**

*KEY WORDS*: **esophageal cancer, lymph node metastasis, prognosis, survival analysis, TNM classification.**

## INTRODUCTION

In 2002, the 6th edition with the latest recommendations for classification of cancers was released by the International Union Against Cancer (UICC). This included the staging classification for esophageal cancer.[1] One important objective of the tumor–node–metastasis (TNM) staging is to give an as accurate as

possible indication of prognosis.[2] For the classification of esophageal cancer, however, there is an ongoing debate about the revision of the current guidelines, driven by surgeons who think that it does not stratify patients appropriately for prognosis.[3–8]

Esophageal cancer is the seventh most frequent cancer worldwide[9,10] and the fourth most common malignancy in China,[11] and it is the leading cause of cancer death in Hebei Province.[12] The death rate for squamous cell carcinoma of the esophagus in southern areas of Hebei Province in China has been reported to be the highest in the world at 199 cases per 100 000 of population.[13] In our previous study on the prognostic factors for resected esophageal cancer analyzed by the Cox proportional hazard model, the lymph node (LN) metastases has been identified as

Address correspondence to: Dr He-Lin Zhang, MD, PhD, Department of Thoracic Surgery, Second Hospital of Hebei Medical University, No. 215, W Heping Road, Shijiazhuang, Hebei 050000, China. E-mail: zhanghelin@hotmail.com; and Dr Long-Qi Chen, MD, PhD, Department of Thoracic & Cardiovascular Surgery, West China Hospital of Sichuan University, No. 37, Guoxue Avenue, Chengdu, Sichaun 610041, China. E-mail: drchenlq@gmail.com

the most important prognostic factor, which was in accordance with most of other observers.[14] Recently, the influence of the number of LN metastases on survival has attracted more and more attention.[4–8,15–22] Based on our complete clinicopathologic and following data on 1146 patients of squamous cell carcinoma of the thoracic esophagus undergoing simple esophagectomy with more than 10 years follow-up, the effect of the number of LN metastases on survival and TNM staging for esophageal carcinoma was assessed.

## MATERIAL AND METHODS

### Clinical data

From 1985 to 1990, 1146 patients with squamous cell carcinoma (SCC) of thoracic esophagus underwent esophagectomy without adjuvant therapy. Their complete clinicopathological and follow-up data was collected. More detail clinicopathological characteristics of the 1146 patients are listed in Table 1.

The survival time was defined as the interval between the operation and the final follow-up or death, and was recorded in months. Death from diseases other than esophageal cancer was considered as lost.

### Statistical analysis

All cases were staged according to the UICC Esophageal Cancer TNM Classification, 6th edition (2002) and were input in a computerized database. The survival curves were computed separately for patients within the different node (N) categories using the Kaplan–Meier method. Survival among groups was compared using the log-rank test. A two-sided $P$-value less than 0.05 was considered statistically significant. The statistical analysis was performed by using the SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

## RESULTS

Follow-up was until March 1, 2005 or until death if earlier. Median follow-up for the entire cohort was 39 months (range 6–234). The 5-year and 10-year follow-up rates were 94.5 and 92.4%, respectively.

### The number of LN metastases and the overall survival

LN metastases were documented in 380 of 1146 patients, with a rate of 33.2%. There were totally 4270 LNs harvested, of them 807 nodes were metastatic, with a degree of metastases of 18.9%. The 3, 5, and 10 years survival rates were 56.2, 47.1, and 42.2%,

**Table 1**  Characteristics of 1146 patients with esophageal cancer

| Variable | No. patients | % of 1146 |
|---|---|---|
| Sex | | |
| Male | 741 | 65.7 |
| Female | 405 | 35.3 |
| Age, years (25–73, median 53 years) | | |
| <40 | 71 | 6.2 |
| 40–59 | 861 | 75.1 |
| ≥60 | 214 | 18.7 |
| Location of tumor | | |
| Uoper third | 14 | 1.2 |
| Middle third | 881 | 76.9 |
| Lower third | 247 | 21.6 |
| Multiple | 4 | 0.3 |
| Depth of tumor invasion | | |
| Tis | 14 | 1.2 |
| $T_1$ | 40 | 3.6 |
| $T_2$ | 311 | 27.1 |
| $T_3$ | 775 | 67.6 |
| $T_4$ | 6 | 0.5 |
| Tumor–node–metastasis (TNM) staging | | |
| $T_{is}N_0M_0$ | 14 | 1.2 |
| $T_1N_0M_0$ | 32 | 2.8 |
| $T_2N_0M_0$ | 231 | 20.2 |
| $T_3N_0M_0$ | 486 | 42.4 |
| $T_1N_1M_0$ | 8 | 0.7 |
| $T_2N_1M_0$ | 80 | 7.0 |
| $T_3N_1M_0$ | 287 | 25.0 |
| $T_4N.M_0$ | 6 | 0.5 |
| $T.N.M_1$ | 2 | 0.2 |
| Length of tumor (cm) | | |
| <3 cm | 109 | 9.5 |
| 3–5 cm | 439 | 38.3 |
| 5–7 cm | 459 | 40.1 |
| ≥7 cm | 139 | 12.1 |
| Macropathologic type* | | |
| Medullary | 870 | 75.9 |
| Fungoid | 80 | 7.0 |
| Ucreative | 95 | 8.3 |
| Constrictive | 26 | 2.3 |
| Intraluminal | 21 | 1.8 |
| Superficial cancer | 54 | 4.7 |
| Grade of differentiation | | |
| Well + moderate (G1–G2) | 1090 | 95.1 |
| Poor (G3) | 56 | 4.9 |
| Number of lymph node metastases | | |
| 0 | 766 | 66.8 |
| 1 | 180 | 15.7 |
| 2 | 101 | 8.8 |
| 3 | 43 | 3.8 |
| ≥4 | 56 | 4.9 |
| Degree of lymph node metastases (%) | | |
| 0 | 766 | 66.8 |
| 0–50 | 230 | 20.1 |
| 50–75 | 150 | 13.1 |

respectively. Moreover, a significant difference in the 5 years survival between patients without or with LN metastases was observed (59.8% $vs$ 20.6%, $\chi^2 = 154.30$, $P < 0.001$).

### The influence of the number of LNs spreading on survival

To investigate the impact of the number of involved LNs on the prognosis of esophageal cancer, the survival was compared among esophageal cancer patients with different number of LN metastases.

**Table 2**   The number of lymph node (LN) metastases and survival

| Node classification | No. of cases | Survival (%) | |
|---|---|---|---|
| | | 5-year | 10-year |
| | 1146 | 47.13 | 42.18 |
| Lymph node metastases (yes/no) | | | |
| 0 | 766 | 59.79 | 53.94 |
| 1 | 380 | 20.64 | 17.45* |
| Number of LN metastases (five grades) | | | |
| 0 | 766 | 59.79 | 53.94 |
| 1 | 180 | 33.38 | 26.87 |
| 2 | 101 | 14.28 | 14.28 |
| 3 | 43 | 6.26 | 6.26 |
| $\geq 4$ | 56 | 2.98 | 2.98** |
| Number of LN metastases (three grades) | | | |
| 0 | 766 | 59.79 | 53.94 |
| 1 | 180 | 33.38 | 26.87*** |
| $\geq 2$ | 200 | 9.35 | 9.35**** |

*$P = 0.000$ (compared between 0 and 1 subgroups); **$P = 0.145$ (compared among with 2, 3, $\geq 4$ subgroups); ***$P = 0.000$ (compared between 0 and 1 subgroups); ****$P = 0.000$ (compared between 1 and $\geq 2$ with 1 subgroups).

Patients were grouped as 0, 1, 2, 3, and $\geq 4$ positive nodes. Their survival experiences were described by Kaplan–Meier's method and analyzed with log-rank test. On general, significant difference on survival existed among groups ($\chi^2 = 190.52$, $P < 0.001$). However, similar survival was observed among patients with 2, 3, and $\geq 4$ positive nodes ($\chi^2 = 3.87$, $P = 0.145$) (Table 2). Therefore, these three groups were merged together and the grouping was optimized to 0, 1, and $\geq 2$ nodes lymph metastases. The re-analysis showed significant difference on survival exist between each groups ($\chi^2 = 186.28$ and $30.81$; $P < 0.001$) (Table 2).

### The influence of the number of LNs spreading on the UICC-TNM staging for esophageal carcinoma

The number of LNs metastases could reflect the prognosis of patients with esophageal carcinoma after esophagectomy. The subclassification of the N category as 0, 1, and $\geq 2$ involved nodes could better describe the relationship between the LN metastases and prognosis. To investigate if the TNM staging of esophageal carcinoma is affected by the number of LN spreading, this system was redefined according to the number of LN metastases. According to the current UICC-TNM classification (6th edition, 2002),[1] the stage IIa esophageal cancers consist of $T_2N_0M_0$, and $T_3N_0M_0$; stage IIb cancers consist of $T_1N_1M_0$ and $T_2N_1M_0$, whereas stage III cancers include $T_3N_1M_0$ and $T_4N_{any}M_0$. Their survival were described by Kaplan–Meier's curves (Fig. 1). By the log-rank test, there existed significant differences in survival among these three stages of patients ($\chi^2 = 133.59$, $P = 0.000$) (Table 3). Obviously, only stages
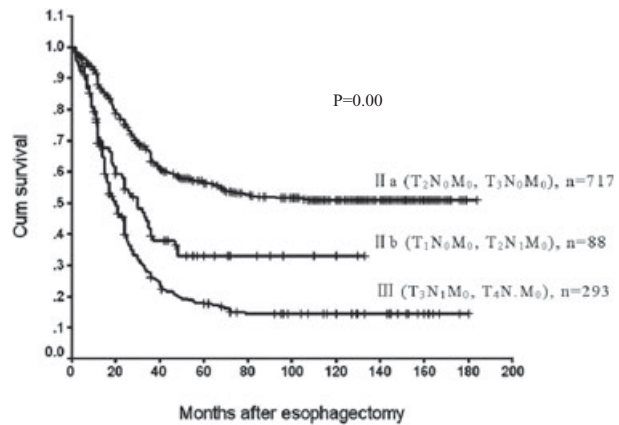
**Fig. 1**   Survival curves for stages IIa, IIb, and III by the current International Union Against Cancer classification. N = node; M = metastasis; T = tumor.

IIb and III esophageal cancers affected by the regional LN metastases, and they were redefined based on the number of LN metastases.

N1 category was subclassified into $N_{1(1)}$ with only one positive node and $N_{1(2)}$ with two or more positive nodes documented. In $T_2N_1M_0$, the 5-year survival between $T_2N_{1(1)}M_0$ and $T_2N_{1(2)}M_0$ tumors was significantly different ($\chi^2 = 4.28$, $P = 0.036$). Similar result was also observed in $T_3N_1M_0$ tumors, where the survival experience was significantly different between $T_3N_{1(1)}M_0$ and $T_3N_{1(2)}M_0$ ($\chi^2 = 24.57$, $P = 0.0000$). However, no survival difference was observed between $T_2N_{1(2)}M_0$ and $T_3N_{1(1)}M_0$ tumors ($\chi^2 = 3.58$, $P = 0.059$). Moreover, the survival of group $T_3N_{1(1)}M_0$ was better than group $T_2N_{1(2)}M_0$. There was a diverse composition and overlay in survival between group $T_2N_1M_0$ and $T_3N_1M_0$ (Table 4). The survival curves for stage $T_2N_0M_0$, $T_3N_0M_0$, $T_2N_{1(1)}M_0$, $T_2N_{1(2)}M_0$, $T_3N_{1(1)}M_0$, and $T_3N_{1(2)}M_0$ were described in Figure 2.

Now that there existed a diverse and overlaid composition of UICC stage $T_1N_1M_0$ and $T_3N_1M_0$ tumors, a refining to current TNM staging criteria according to the number of LN metastases was proposed as (new staging): stage IIa ($T_2N_0M_0$ and $T_3N_0M_0$); stage IIb ($T_1N_1M_0$ and $T_2N_{1(1)}M_0$); stage IIIa ($T_2N_{1(2)}M_0$ and $T_3N_{1(1)}M_0$); and stage IIIb ($T_3N_{1(2)}M_0$ and $T_4N-M_0$). By survival analysis (Kaplan–Meier and log-rank), the 5-year survival rates for refined stages IIa, IIb, IIIa,

**Table 3**   Current International Union Against Cancer tumor–node–metastasis (TNM) staging (II, III) and survival

| TNM staging | No. of cases | Survival (%) | |
|---|---|---|---|
| | | 5 years | 10 years |
| IIa: $T_2N_0M_0$, $T_3N_0M_0$ | 717 | 57.06 | 50.94 |
| IIb: $T_1N_1M_0$, $T_2N_1M_0$ | 88 | 32.64 | 32.64* |
| III: $T_3N_1M_0$, $T_4N_{any}M_0$ | 293 | 18.12 | 14.52** |

*$P = 0.000$ (compared between stages IIa and IIb subgroups); **$P = 0.000$ (compared between stages IIb and III subgroups).

**Table 4** The number of lymph node metastases and survival in stages $T_2N_1M_0$ and $T_3N_1M_0$

| Stages | | No. of cases | Survival (%) | |
|---|---|---|---|---|
| | | | 5 years | 10 years |
| $T_2N_1M_0$ | $T_2N_{1(1)}M_0$ | 44 | 41.49 | 41.49 |
| | $T_2N_{1(2)}M_0$ | 36 | 24.12 | 20.10* |
| $T_3N_1M_0$ | $T_3N_{1(1)}M_0$ | 131 | 31.12 | 22.38** |
| | $T_3N_{1(2)}M_0$ | 156 | 6.77 | 6.77*** |

\*$P = 0.036$ (compared between $T_2N_{1(1)}M_0$ and $T_2N_{1(2)}M_0$ subgroups); \*\*$P = 0.059$ (compared between $T_2N_{1(2)}M_0$ and $T_3N_{1(1)}M_0$ subgroups); \*\*\*$P = 0.000$ (compared between $T_3N_{1(1)}M_0$ and $T_3N_{1(2)}M_0$ subgroups). N = node; M = metastasis; T = tumor.

**Table 5** Refine current International Union Against Cancer tumor–node–metastasis (TNM) staging (II, III) and survival

| TNM staging | No. of cases | Survival (%) | |
|---|---|---|---|
| | | 5 years | 10 years |
| Stage IIa: $T_2N_0M_0$, $T_3N_0M_0$ | 717 | 57.06 | 50.94 |
| Stage IIb: $T_1N_1M_0$, $T_2N_{1(1)}M_0$ | 52 | 42.15 | 42.15* |
| Stage IIIa: $T_2N_{1(2)}M_0$, $T_3N_{1(1)}M_0$ | 167 | 28.57 | 21.58* |
| Stage IIIb: $T_3N_{1(2)}M_0$, $T_4N_{any}M_0$ | 162 | 8.52 | 8.52* |

\*$P = 0.000$ (compared between stages IIa and IIb subgroups; stages IIb and IIIa subgroups; stages IIIa and IIIb subgroups).

and IIIb were 57.06, 42.15, 28.57, and 8.52%, respectively. The survivals for the overall group, between stages IIa and IIB, IIa and IIa, IIIa and IIIb, were all statistically significant ($\chi^2 = 159.38$, 18.26, 25.86, and 23.31, respectively, $P = 0.000$) (Fig. 3, Table 5).
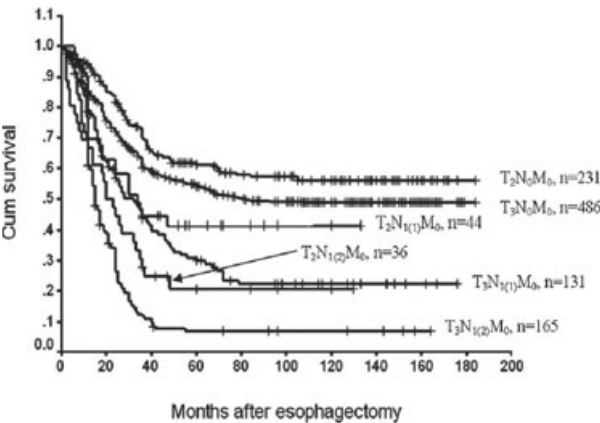


**Fig. 2** Survival curves for all stages by the current International Union Against Cancer classification. N = node; M = metastasis; T = tumor.
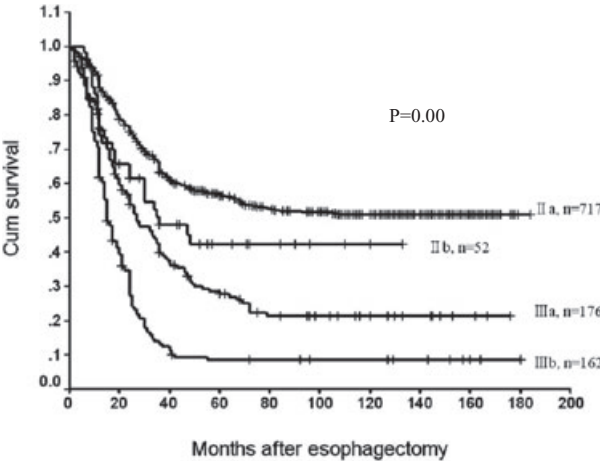


**Fig. 3** Survival curves for stages II and III by the proposed refined International Union Against Cancer classification.

## DISCUSSION

An accurate staging classification for cancer, according to guidelines that are internationally accepted among surgeons, oncologists, and other physicians, is of crucial importance. Not only does it provide an indication of the patient's prognosis, but it also aids the clinician in the planning of treatment, assists in the evaluation of the results of treatment, and facilitates the exchange of information between different centers.[2]

Esophageal carcinoma is one of most frequently seen life-threatening malignancies worldwide. It ranks the fifth both in incidence and mortality of cancer in men.[9,10] LN status is a critical determinant of the prognosis and management of esophageal carcinoma; albeit, the current staging system classifies patients into only two groups, $N_0$ vs $N_1$ diseases, based on whether regional LNs are free of disease or are involved by cancer. Recently, the influence of the number of metastatic LNs on survival for esophageal carcinoma has drawn more and more attention. Most of the reports suggested a negative correlation between the number of LN metastases and survival time.[5,15–21] Using our representative data from 1146 cases of surgically resected esophageal carcinoma, we found that the number of LNs metastases could reflect the prognosis of patients with esophageal carcinoma after esophagectomy. Hence we subclassified the N category according to the number of LN metastases and assessed its influence on survival of esophageal carcinoma. A potential limitation of the use the degree of LNs metastases as a prognostic index is that this factor is inherently confounded by the number of removed LNs. This is particularly a problem in the case of esophageal cancer because there is no standard procedure about the number of LNs to be removed during operations.

Our results demonstrated that the number of LN metastases was negatively correlated with the survival time of esophageal carcinoma. The 5-year survival rates in esophageal carcinoma patients with 0, 1, 2, 3, and ≥4 nodes were 59.79, 33.38, 14.28, 6.26, and 2.98%, respectively. Overall there existed significant difference, whereas no significant survival differences

were observed among those with 2, 3, and $\geq 4$ metastatic LNs. Tachibana *et al.*[19] found in their patients with thoracic esophageal carcinoma that if there was only a single LN metastasis, a better prognosis was observed after radical resection, which was similar to those without LN involvement; although a worse survival could be expected if there were more metastatic LNs documented. A study on 233 esophageal carcinoma patients by Korst and colleagues[5] revealed that when subgrouping their patients according to the number of LN metastases in five grades (0, 1, 2, 3, and $\geq 4$), there was no survival differences among patients with one, two, and three involved LNs ($P = 0.54$). However, when stratifying them by 3 (0, 1–3, and $\geq 4$ positive nodes), a significant survival difference was observed in between each grade ($P < 0.001$). Investigations from Bollschweiler[16] and Kimura[20] draw a similar conclusion. Rice[4] and Wijnhoven[22] classified the LN involvement as $N_0$ (no LN involved), $N_1$ (1–2 LN metastases), and $N_2$ (3 or more LN metastases); they found significant difference in survival between each subgroup. Wang *et al.*[23] also observed a worse 5-year survival in patients with more than four positive LNs identified, although statistical significance was not obtained when compared with those who had four or fewer metastatic LN. In current study, patients were classified into three subgroups according to the number of LN metastases (0, 1, and $\geq 2$); their 5-year survival rates were 59.79, 33.38, and 9.35%, respectively, with a significant difference existed in between each subgroup. It demonstrates that it is suitable to subclassify the N category according to the number of LN involved as 0 ($N_0$), 1 ($N_{1(1)}$), and $\geq 2$ ($N_{1(2)}$). This proposed that a three-grade classification could more accurately reflect patients' prognosis. Most studies have also recommended three-node groupings,[4,5,15,16,20] whereas some recommended four and others two groupings.

In 1997, UICC started to include the number of LN metastases into their 5th edition of the gastric cancer staging system. Thereafter, although there are increasing observations that investigated the influences of number of LN metastases on survival of esophageal carcinoma,[4–8,15–22] it was still not included in the most recent 6th edition (2002) of UICC cancer staging for esophageal carcinoma.[1] Based on the clinicopathological and follow-up data on 1146 patients with esophageal squamous cell carcinoma who underwent a curative intent esophagectomy, the UICC-TNM staging for esophageal carcinoma was refined as the proposed N category.

As the classification in TNM staging for esophageal carcinoma (UICC, 2002), stages 0, I, and IIa were all LN negative. Therefore the current refinement mainly focused on stages IIb and III diseases. The 5-year survival rates for stages IIa, IIb, and III were statistically significant difference. However, looking at the 5-year survival rates in patients with

**Table 6** Contrast of proposed and current International Union Against Cancer (UICC) staging (II and III)

| Current UICC staging | Tumor–node–metastasis classification† | Proposed staging |
|---|---|---|
| IIa | $T_2N_0M_0$ | IIa |
| IIa | $T_3N_0M_0$ | IIa |
| IIb | $T_1N_1M_0$ | IIb |
| IIb | $T_2N_{1(1)}M_0$ | IIb |
| IIb | $T_2N_{1(2)}M_0$ | IIIa |
| III | $T_3N_{1(1)}M_0$ | IIIa |
| III | $T_3N_{1(2)}M_0$ | IIIb |
| III | $T_4N_{any}M_0$ | IIIb |

†$N_{1(1)}$: 1 positive node, $N_{1(2)}$: $\geq 2$ positive nodes.

a single or $\geq 2$ positive nodes at stages $T_2N_{1(1)}M_0$ *vs* $T_2N_{1(2)}M_0$, and $T_3N_{1(1)}M_0$ *vs* $_3N_{1(2)}M_0$ (41.49 *vs* 12%, and 31.12 *vs* 6.77%), there existed significant different prognosis in each subgroup. This indicated a diverse grouping of stages $T_2N_1M_0$ and $T_3N_1M_0$. Meanwhile, the 5-year survival in stage $T_2N_{1(2)}M_0$ (24.12%) was lower than that in stage $T_3N_{1(1)}M_0$, an interplay between stages $T_2N_1M_0$ and $T_3N_1M_0$. Therefore, we refined stages II and III according to the number of LN metastases as follows: stages IIa ($T_2N_0M_0$, $T_3N_0M_0$); IIb ($T_1N_1M_0$, $T_2N_{1(1)}M_0$); IIIa ($T_2N_{1(2)}M_0$, $T_3N_{1(1)}M_0$); and IIIb ($T_3N_{1(2)}M_0$, $T_4N_{any}M_0$) (Table 5). The 5-year survival for refined stages IIa, IIb, IIIa, and IIIb were 57.06, 42.15, 28.57, and 8.52%, respectively. Statistically significant differences in survival were obtained in overall and each subgroup. Therefore, the proposed modification of TNM staging based on the number of metastatic LNs could better predict patients' prognosis (Table 6). This finding might account for apparent discrepancies between our proposed refinement of staging and that of Rice *et al.*,[4] who subclassified their node-positive patients as N1 (1 or 2 metastatic nodes) and N2 (3 or more metastatic nodes) and also demonstrated significant different survival rate; but the number of LN metastases ($N_1$, $N_2$) does not have to be considered in their stages II and III refined stage groupings.

In conclusion, the first large series investigation on the influences of the number of LN metastases on the survival and TNM staging for esophageal carcinoma based on over 1000 cases demonstrates: (i) the number of LN metastases markedly affects the prognosis of esophageal carcinoma – the subclassification of the N category by three grades (0, 1, and $\geq 2$) is optimal and could accurately describe the association between the number of LN metastases and survival; (ii) the proposed refinement of TNM staging (stages 0, I, IIa, IIb, IIIa, IIIb, and IV) could better reflect the prognosis of patients with esophageal carcinoma undergoing esophagectomy; (iii) current study provides evidence for making the new edition of UICC-TNM staging system for esophageal carcinoma.

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