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ORIGINAL ARTICLE

Should All Stage N3b Patients with Advanced Gastric Cancer Be Considered Equivalent? A 30-Year Single Center Study

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Abstract

Purpose To investigate the survival of stage N3b patients with advanced gastric cancer (AGC) after radical surgery and to evaluate the TNM staging of subgroups of stage N3b patients.

Methods We reviewed the data of 222 stage N3b patients with AGC who underwent D2/D3 radical surgery. Depending on the number of metastatic lymph nodes (MLNs), we divided N3b patients into several groups and compared the survival differences among them. We found that survival of patients with 16–20 MLNs was better than that of patients with ≥ 21 MLNs. Therefore, we divided the N3b patients into two subgroups and defined patients with 16–21 MLNs as N3b1 and patients with ≥ 21 MLNs as N3b2. Then, we compared survival differences between the two groups and their subgroups. Patients who underwent palliative surgery served as the reference group. In addition, we selected stage IIIB, IIIC, and IV patients from the same database to properly re-classify the N3b subgroups in the TNM staging system.

Results Survival differed significantly between the new N3b1and N3b2 groups and between the new N3b1 group and the palliative group. However, the survival of the new N3b2 group was similar to that of the palliative group. Comparisons of survival according to T staging revealed similarities between the following groups: (1) stages T2–3N3b1 and IIIB, (2) stages T4N3b1 and IIIC, and (3) stages T2–4N3b2 and IV.

Conclusions All stage N3b patients with AGC should not be considered equivalent. A significant difference in survival was observed between stage N3b1 and N3b2 patients after radical surgery, while the survival of stage N3b2 patients was similar to that of patients who undergo palliative surgery. We recommend re-classifying stage T2–3N3b1 as TNM stage IIIB, stage T4N3b1 as stage IIIC, and T2–4N3b2 as stage IV.

Keywords Advanced gastric cancer · Stage N3b · Metastatic lymph nodes

Background

Although the incidence of gastric cancer is declining, it remains the second leading cause of cancer-related mortality worldwide.[1–3] In China, approximately 400,000 new cases occur annually, accounting for 42% of global gastric cancer cases.[4] Lymph node metastasis is an important factor that affects the prognosis of gastric cancer patients.[5–7] In the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system, stage N3 was redefined as N3a (7–15 metastatic lymph nodes, MLNs) and stage N3b (> 15MLNs). Although many studies[8] have addressed lymph node metastasis in advanced gastric cancer (AGC), they have primarily focused on stage N0–N3a and rarely examined stage N3b patients. KIM SH[9] showed that differences in survival existed among stage N3b patients. However, in that study, a specific analysis of stage N3b disease and its subgroups was not performed.[9] To investigate the differences in survival among stage N3b patients, we conducted a retrospective study of the clinicopathological data of 222 stage N3b patients with AGC.

Zhe Zhang and Jin-yu Huang contributed equally to this work.

Synopsis We found significant differences among stage N3b patients with advanced gastric cancer (AGC); therefore, we divided these patients into new subgroups. By comparing these patients with several reference groups, the new subgroups were appropriately classified by the TNM staging system.

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Methods

Gastric cancer patients who underwent surgery at the Department of Surgical Oncology, First Affiliated Hospital of China Medical University, from January 1980 to March 2010 were entered into a prospectively maintained database. All stages described in this study are those of the UICC/AJCCTNM staging criteria (seventh edition). The inclusion criteria were as follows: (1) pathological diagnosis of adenocarcinoma with complete pathological data and (2) patients confirmed as having stage T2–4N3b disease after radical resection. The exclusion criteria were as follows: (1) patients with remnant gastric cancer and (2) patients who died within 1 month after surgery. The final study population included 222 patients. Patients did not receive neoadjuvant chemotherapy before surgery; however, they received conventional adjuvant chemotherapy for 4–6 weeks after surgery. The medications primarily consisted of platinum-based agents and fluorouracil.

The patients were followed up with telephone calls, letters, and outpatient reviews. Death was defined as the end of follow-up, and the final follow-up evaluation was performed on December 31, 2010 (mean follow-up, 23.99 ± 28.77 months).

A total of 222 patients with five progressively increasing MLNs were divided into groups as follows: group 1, 16–20 MLNs; group 2, 21–25 MLNs; group 3, 26–30 MLNs; group 4, 31–40 MLNs; group 5, 41–50 MLNs; and group 6, ≥ 51 MLNs (when too few patient cases were found, patients with ten progressively increasing MLNs were included). According to these results, stage N3b patients were divided into two subgroups, N3b1 and N3b2, depending on the number of MLNs. The control group consisted of 427 patients who underwent palliative surgery during the same period. These patients were selected as follows: (1) M0 stage patients; and (2a) positive margin proven by pathology after resection, (2b) patients who underwent palliative resection, or (2c) patients who underwent exploratory or diversion surgery. We intended to directly compare the survival of patients with numerous MLNs (≥ 21 MLNs) who underwent extended lymph node dissection with that of patients who underwent palliative resection or exploratory and diversion surgery alone to relieve obstructive symptoms. In addition, 1132 N0 patients, 723 N1 patients, 373 N2 patients, and 479 N3a patients were included in the reference groups.

Because few stage T2N3b patients were included in our database, we combined them with the T3N3b group (in the subsequent study, we did not examine stage T2 patients in particular). Stage N3b patients were divided into only two subgroups (T2–3 and T4) according to T staging. The survival rates were compared with those of palliative surgery patients with these two classifications.

According to the UICC/AJCCTNM staging criteria (seventh edition), T2–4N3b patients were classified as stages IIIB and IIIC. Therefore, we selected 416, 226, and 987 stage IIIB, IIIC, and IV patients, respectively, from the database who were treated during the same period as the reference groups. Although we were using the eighth edition of the UICC/AJCC TNM staging criteria, there had been no major changes to gastric cancer staging since the seventh edition. In the seventh edition, stage N3 was divided into stage N3a and N3b; however, this was not included in the TNM staging system, and the eighth edition resolved this problem. The changes in stage N3 between the seventh and eighth edition were compared. In the eighth edition, stage N3a had few changes: T4N3a was re-classified as IIIB (in the seventh edition, T4N3a was classified as IIIC); for stage N3b, T1N3b and T2N3b were re-classified as stage IIIB, T3N3b was re-classified as IIIC (in the seventh edition, T1N3b, T2N3b, and T3N3b had been classified as IIB, IIIA, and IIIB, respectively), and no changes were made to T4N3b, which was re-classified as IIIC. We compared the survival rates of these three groups with those of the T2–3N3b1, T4N3b1, T2–3N3b2, and T4N3b2 groups to properly re-classify the N3b subgroups into the TNM staging system.

All specimens were processed according to the UICC/AJCCTNM staging criteria (seventh edition). All lymph node biopsy sections were independently analyzed by two pathologists. The pathological examination methods, diagnostic criteria, and lymph node grouping principles of all specimens were performed according to the Japanese gastric cancer treatment protocol. The lymph nodes were removed from fresh specimens according to the anatomical position. Hematoxylin and eosin staining was used to detect metastasis.

SPSS 21.0 statistical software was used for data analysis. Survival rates were calculated using Kaplan-Meier analysis. The log-rank test was used for single-factor analysis. Significant variables were included in the multivariate factor analysis, and a value of $p < 0.05$ was considered statistically significant.

Results

A significant difference was observed between the reference group and the N3b group, as shown in Fig. 1 ($p = 0.000$). The median survival of stage N3b patients ($n = 222$, average age = 57.71 years, 73 women and 149 men) was 14 months. The 5-year survival rate was 7.6%, and the 10-year survival rate was 3.7% (Fig. 1). The number of patients in each group and median survival times were as follows: group 1, $n = 97$, 19 months; group 2, $n = 46$, 14 months; group 3, $n = 36$, 12 months; group 4, $n = 25$, 13 months; group 5, $n = 11$, 12.5 months; and group 6, $n = 7$, 8 months (Fig. 2a). Among the 8901 lymph nodes that we retrieved from the 222 stage N3b patients, 5675 lymph nodes showed metastasis, resulting in a lymph node metastasis rate of 63.75%. The maximum number of MLNs was 118 among all patients, and this patient's survival time was 17 months.

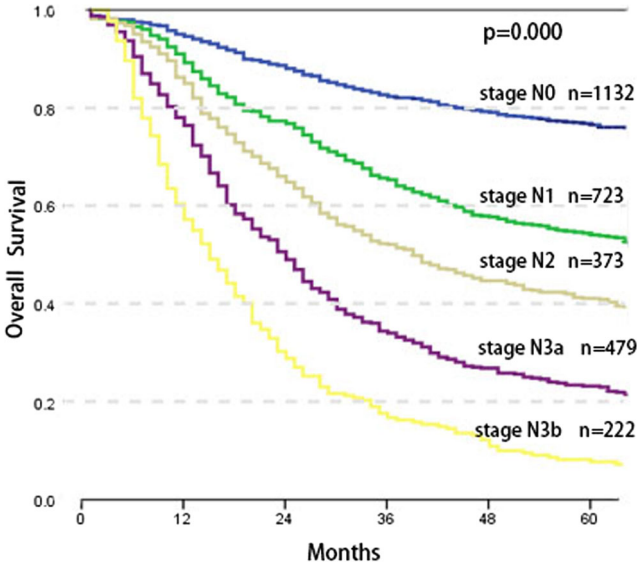

Fig. 1 Overall survival curves of stage N0, N1, N2, N3a, and N3b patients ($p = 0.000$)

The differences in survival among the six groups were statistically significant ($p = 0.025$) (Fig. 2b). Notably, the survival rate of group 1 was significantly better than that of the other groups ($p = 0.004$), and no significant difference in survival was found among groups 2–6 ($p = 0.948$) (Fig. 2b). Therefore, we selected 20 MLNs as the cut-off value for dividing the 222 patients into subgroups N3b1 (16–20 MLNs) and N3b2 (≥ 21 MLNs).

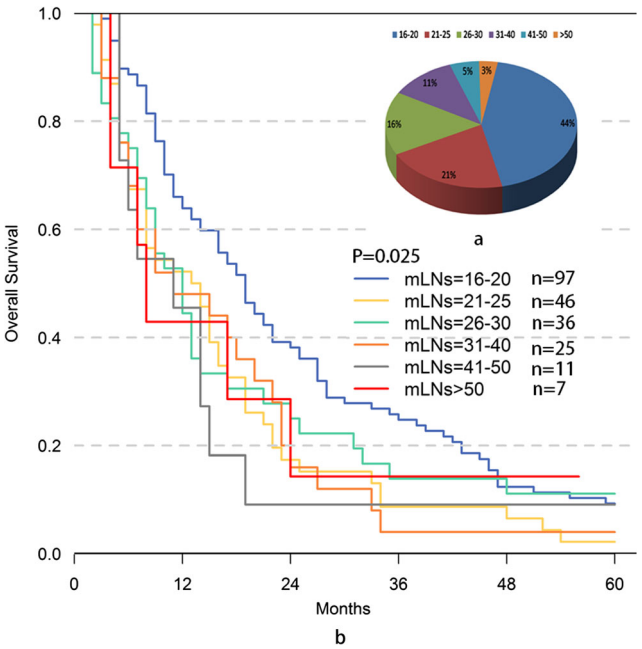

Fig. 2 (a) Distribution of 222 stage N3b AGC patients according to the number of MLNs. (b) Survival curves of six groups ($p = 0.025$). Group 1: 16–20 MLNs, group 2: 21–25 MLNs, group 3: 26–30 MLNs, group 4: 31–40 MLNs, group 5: 41–50 MLNs, and group 6: ≥ 51 MLNs. The p value between group 1 and groups 2–5 is 0.004. The p value among groups 2–5 is 0.948

We analyzed the associations among variables, including gender, age, tumor location and size, pathological and histological type, lymphovascular invasion, Borrmann type, depth of invasion, and the number of MLNs (Table 1). Individual variables that significantly influenced the prognosis of patients with stage N3b cancer included the Borrmann type ($p = 0.002$) and the number of MLNs ($p = 0.004$). We then included these variables in the multivariate analysis, which revealed that the Borrmann type ($p = 0.034$) and number of MLNs (0.041) were independent factors for predicting the prognosis of stage N3b patients (Table 2).

Significant differences were observed among the survival curves of the N3b1, N3b2, and palliative groups ($p = 0.001$).

Table 1 The clinical pathological data of the 222 N3b patients

Clinical pathological factors	Cases (%) (222 (100))	5-year OS (100%)	p value
Gender			0.809
Male	149 (67.1)	9.7	
Female	73 (32.9)	6.8	
Age (years)			0.885
≤ 60	128 (57.7)	6.3	
> 60	94 (42.3)	12.2	
Location			0.182
Upper	19 (8.5)	10.5	
Middle	35 (15.8)	4.7	
Lower	134 (60.4)	6.7	
Entire	34 (15.3)	8.8	
Size (cm)			0.596
< 5	59 (23.9)	5.2	
≥ 5	163 (76.1)	8.5	
Borrmann type			0.002
Borrmann 1, 2, and 3	171 (77.0)	8.7	
Borrmann 4 and 5	51 (23.0)	3.9	
Differentiation degree[a]			0.690
Differentiated	95 (42.8)	3.2	
Undifferentiated	127 (57.2)	11.0	
Lymphovascular invasion			0.675
Negative	167 (75.2)	8.3	
Positive	55 (24.8)	5.5	
Depth of invasion			0.151
T2	13 (5.9)	7.7	
T3	81 (36.5)	8.6	
T4a	121 (54.5)	6.5	
T4b	7 (3.1)	14.3	
Number of MLNs			0.004
16–20	97 (43.7)	9.3	
≥ 21	125 (56.3)	6.4	

[a] Differentiated types include high and medium differentiated papillary adenocarcinoma and tubular adenocarcinoma; undifferentiated types include low differentiated adenocarcinoma, signet ring cell carcinoma, mucous adenocarcinoma, and undifferentiated carcinoma

Table 2 Multifactorial analysis

Clinical pathological factors	RR	95%CI	*p* value
Borrmann type			0.034
Borrmann 1, 2, and 3	–	–	
Borrmann 4	1.445	1.029–2.208	
Number of MLNs			0.041
16–20	–	–	
≥ 21	1.351	1.012–1.804	

The 3-year overall survival (OS) rate of the N3b1 group was 24.7%, which was much better than those of the N3b2 (9.6%) and palliative groups (13.8%) ($p = 0.004$, $p = 0.001$). However, the survival rates of the N3b2 and palliative groups were similar ($p = 0.601$) (Fig. 3a). The p value was 0.090 among the survival curves of the T2–3N3b1, T2–3N3b2, and palliative groups. Although the p value was not statistically significant, a common trend was observed in our findings. The survival rate of the T2–3N3b1 group was much better than those of the T2–3N3b2 and palliative groups ($p = 0.000$ and $p = 0.000$, respectively), while the T2–3N3b2 and palliative groups exhibited similar survival rates ($p = 0.926$) (Fig. 3b). At the T4 level, the survival of T4N3b2 patients was similar to that of patients who underwent palliative surgery ($p = 0.984$) (Fig. 3c).

Next, we found similarities between the survival curves of stage T2–3N3b1 and IIIB ($p = 0.639$) patients as well as

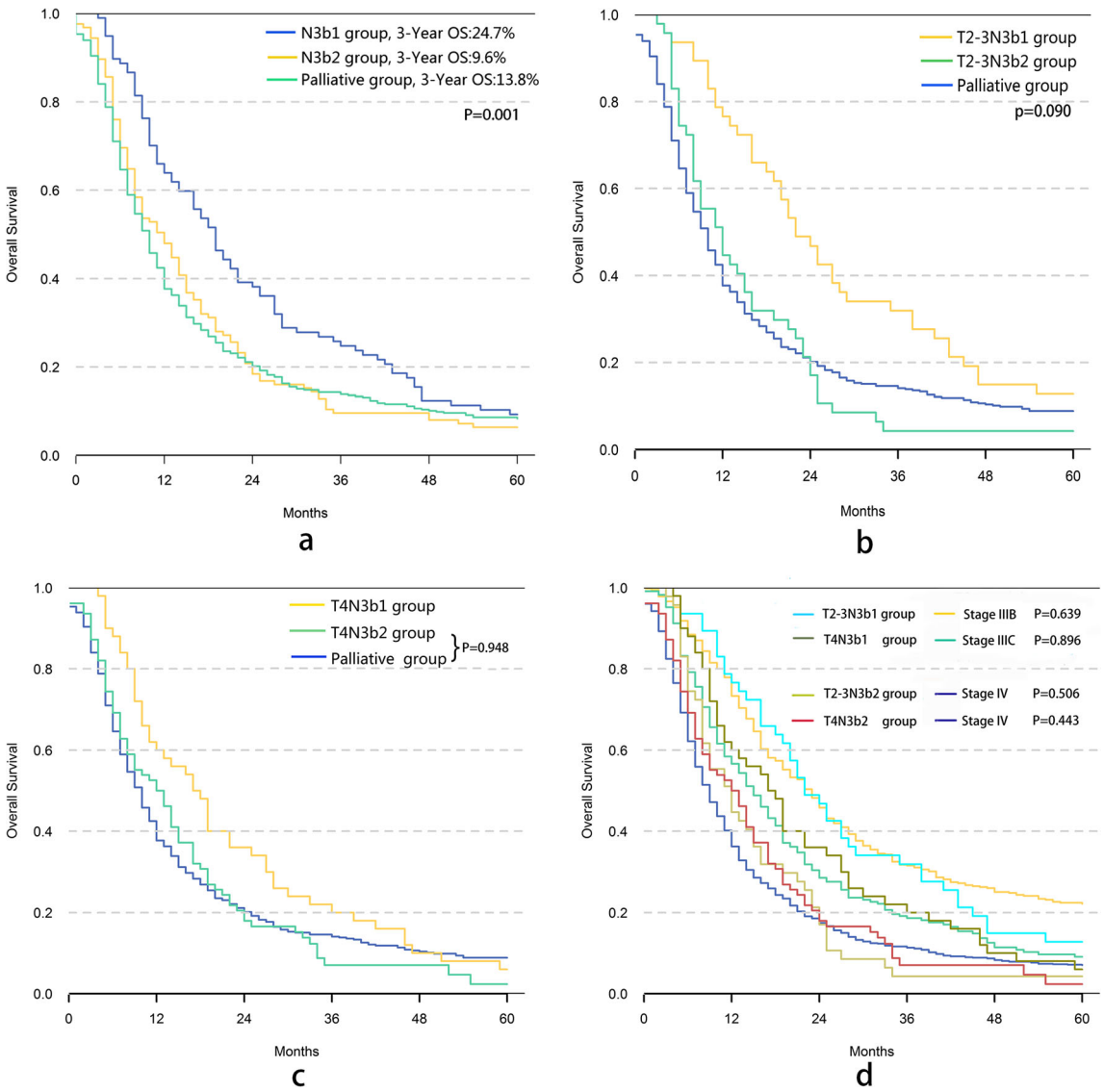

Fig. 3 **a** Comparison of the survival curves among patients in the N3b1, N3b2, and palliative groups. **b** Comparison of the survival curves among patients in the T2–3N3b1, T2–3N3b2, and palliative groups. **c** Comparison of the survival curves among patients in the T4N3b1, T4N3b2, and palliative groups. **d** Comparison of the survival curves among patients in the T2–3N3b1, T2–3N3b2, T4N3b1, T4N3b2, stage IIIB, stage IIIC, and stage IV groups

between stage T4N3b1 and IIIC patients ($p = 0.896$). Furthermore, the survival rates of stage T2–3N3b2 and T4N3b2 patients were similar to those of the stage IV group ($p = 0.506$ and $p = 0.443$, respectively) (Fig. 3d).

Discussion

A large body of evidence shows that the number of MLNs in gastric cancer patients is an important factor for predicting the prognosis.[9] The number of MLNs and the transfer ratio are foci of discussion.[10–13] Nevertheless, few studies have focused on patients with large numbers of MLNs after radical resection, particularly patients with stage N3b AGC.

Evidence conflicts regarding whether enlarged lymph node dissection is beneficial.[14–16] For example, a 15-year follow-up study demonstrated that D2 surgery could reduce the probability of local recurrence and prolong survival time compared to D1 surgery.[17] However, that study did not specifically address stage N3b patients with numerous MLNs. Another study[18] referred to the indication that D2+ dissection should include N3b subgroups, although an analysis of N3b patients was not performed. The authors believed that stage N3b patients exhibited late-stage disease, with potential peritoneal implantation and distant metastasis. Although extended lymph node dissection can reduce the probability of local recurrence, the potential for peritoneal implantation and distant recurrence could also be a primary cause of death. Therefore, it is necessary to evaluate the actual benefit of extended lymph node dissection conferred upon stage N3b patients.

In the present study, the median survival of 222 stage N3b patients was 14 months, and the 3-year and 5-year survival rates were 16.2% and 7.6%, respectively. In contrast, another study[19] reported that the 5-year survival rate of stage N3b patients was 28%, which is higher than our result. In addition, a study[20] showed that the 5-year survival rate of stage N3b patients was 10.2%, which is similar to our result.

Multivariate analysis indicated that the Borrmann type and number of MLNs were independent prognostic factors for stage N3b patients, which is consistent with the findings of published studies.[19–21]

The seventh edition of the UICC/AJCC staging guidelines divided stage N3 into stage N3a (7–15MLNs) and stage N3b (≥ 16 MLNs). Nevertheless, some scholars have found significant differences in survival among stage N3b patients. SH KIM[9] reported that, in stage IIIC patients, when the number of MLN was ≥ 29, the 5-year OS was similar to that of stage IV patients. Similarly, in stage IIIB patients, when the number of MLN was ≥ 28, the 5-year OS was similar to that of stage IV patients. In a study[8] evaluating the seventh edition of the AJCC/TNM staging system, Sun et al. classified T2N3b as stage IIIB, T3N3b as stage IIIC, and T4N3b as stage IV. The two studies above showed that N3b patients cannot be generalized and that stage N3b patients cannot be simply classified as stage IIIC or IV. To more accurately understand the progression of stage N3b patients and to better adjust the treatment strategy, we believe that it is necessary to subdivide stage N3b and to re-classify its subgroups according to the TNM staging system. Here, we selected 20 MLNs as the cut-off point (16–20, ≥ 21) to divide N3b patients into N3b1 and N3b2 subgroups. Figure 3a–c show that, in general, or at the T2–4 level, the survival of stage N3b2 patients was similar to that of patients who underwent diversion, exploration, and palliative resection. Thus, we conclude that stage N3b2 patients (≥ 21 MLNs) cannot significantly benefit from extended lymphadenectomy.

We included stage IIIB, IIIC, and IV patients to properly classify the N3b subgroups in the TNM staging system. Figure 3d shows that the survival curve of stage T2–3N3b1 patients was similar to that of stage IIIB patients, and the survival curve of T4N3b1 patients was similar to that of stage IIIC patients ($p = 0.896$). The survival curves of stage T2–3N3b2 and T4N3b2 patients were similar to that of stage IV patients ($p = 0.506$ and $p = 0.443$, respectively). Accordingly, we recommend classifying T2–3N3b1 patients as TNM stage IIIB, T4N3b1 patients as stage IIIC, and T2–4N3b2 patients as stage IV.

The survival rates of stage N3b patients will decrease as the number of MLNs increases. The survival rates were significantly different between patients with 16–20 MLNs and ≥ 21 MLNs. Depending on the number of MLNs and T staging, we divided stage N3b patients into T2–3N3b1, T2–3N3b2, T4N3b1, and T4N3b2 subgroups. We found that the survival benefit conferred upon stage N3b2 patients with a large quantity of MLNs was not significant after expanded lymphadenectomy. The findings also indicate that it is necessary to appropriately re-classify N3b patients in the TNM staging system.

In conclusion, all stage N3b patients with AGC should not be considered equivalent. We recommend dividing stage N3b patients with AGC into two subgroups according to the number of MLNs as follows: new stage N3b1 (16–20MLNs) and new stage N3b2 (≥ 21 MLNs). The survival benefit conferred upon stage T2–4N3b2 patients who underwent extended lymph node dissection was not substantial. Therefore, we believe that such patients should be treated as those with stage IV. We further recommend re-classifying new stage T2–3N3b1 patients as stage IIIB, new stage T4N3b1 patients as stage IIIC, and T2–4N3b2 patients as stage IV.

Limitations

The limitation of this study was its small sample size; only 222 stage N3b patients who underwent radical resection were analyzed. Further studies with larger sample sizes are therefore required to validate our findings. In addition, our study

covered a long span of time. Science and technology have progressed substantially over the past 30 years, including the diagnosis and treatment of diseases. These limitations may have some effects on our results.

Authors' Contributions Conception of the work: Hui-mian Xu.

Acquisition, analysis, interpretation of data: Zhe Zhang, Jin-yu Huang, Peng-liang Wang.

Drafting and critical revision of the manuscript for important intellectual content: Zhe Zhang, Wen-bin Hou, Song-cheng Yin.

Final approval: Zhe Zhang, Jin-yu Huang.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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