Int J Clin Exp Pathol 2017;10(4):4794-4800
www.ijcep.com /ISSN:1936-2625/IJCEP0048289

Original Article

More than 16 lymphatic metastasis (pN3b) of resectable gastric cancer (GC) associated with inferior prognosis of patients: a large sample single-center retrospective study

Lu-Chuan Chen*, Sheng-Hong Wei*, Zai-Sheng Ye*, Jun Xiao*, Yi Zeng, Zhen-Meng Lin, Yi Wang, Xiao-Ling Chen

*Department of Gastrointestinal Surgery, Fujian Province Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou 350001, Fujian Province, China. *Equal contributors.*

Received January 6, 2017; Accepted February 20, 2017; Epub April 1, 2017; Published April 15, 2017

Abstract: *Background*: The revision of pN classification of sub-stage $pTxN_3M_0$ within 7th TNM staging seems obscure. The purpose of this study was to establish whether stage $pTxN_{3b}M_0$ is associated with the inferior prognosis than stage $pTxN_{3a}M_0$. *Methods:* About 591 GC patients with stage $pTxN_3M_0$, who received radical gastrectomy, were reviewed retrospectively. All the cases were evaluated taken into account their clinicopathological features and surgical outcomes between the stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$ sub-groups. In the analysis of the overall cumulative probability of survival, the Kaplan-Meier method was accustomed. Their differences were calculated through the log-rank test. The Cox multiple factors analysis was carried out using the logistic regression method.*Results:* Among stage $pTxN_{3b}M_0$ group, it was noteworthy higher in poor differentiated degree, nerve invasion, and vessel carcinoma embolus, T4a plus T4b sub-group and IIIC stage. The 5-year overall survival rate (OS) for stage $pTxN_3M_0$ stage was 26.43%, and sub-group of stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$ were 33.73% and 13.59%, respectively. Multivariate survival analysis showed that TNM stage (OR = 1.854), and N stage (OR = 1.665) were significant prognostic factors for stage $pTxN_3M_0$ GC (all $P < 0.05$). Further analysis showed that BMI (OR = 0.905) was an independent protective factor, while differentiated degree (OR = 1.575), vessel carcinoma embolus (OR = 1.775) (all $P < 0.05$) were risk factor for stage $pTxN_{3b}M_0$ group. *Conclusion:* Number of lymph node(LN) dissection, categorized by stage $pTxN_{3b}M_0$ could be relevant to a more accurate prediction of an inferior survival outcome for the GC patients. Furthermore, studies of postoperative adjuvant therapies may take stage $pTxN_{3b}M_0$ status of each patient into consideration to evaluate the treatment effect.

Keywords: Gastric cancer, TNM-UICC classification, lymph node metastasis, N3 stage

Introduction

Gastric cancer (GC) is deemed to be a widespread and complex multi-factorial disease [1-3]. Surgical resection is the sole curative modality for GC, and D_2 dissection is a standard procedure for patients with GC in China [4-6]. Surgical resection is the sole curative modality for GC, and D_2 dissection is a standard procedure for patients with GC in China [7-9].

Nodal status is the strongest predictor of the prognosis of GC patients, and the treatment strategy against metastatic lymph nodes is the most important clinical issue [10, 11]. However, development of an appropriate LN staging system for GC has been controversial, involving frequent changes in proposed amending the TNM classification system [12-14]. The N classification used in the 7th edition of the AJCC/TNM classification required careful consideration and discussion. According to the 7th edition NCCN guidelines, stage $pTxN_3M_0$ was divided into stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$, but this sub-classification is not required for the final staging, which may cause serious problems in underestimating the GC severity.

In our experience, patients with stage $pTxN_{3b}M_0$ tumors seemed like a poor prognosis than stage $pTxN_{3a}M_0$. To enable such consideration,

Table 1. Demographic data of the 591 patients with GC who underwent gastrectomy

Characteristic	N3a (N = 366)		N3b (N = 225)		P
Age (years)	58.29±12.45		57.42±12.06		
Mean ± SD	59 (21-82)		58 (22-83)		
Gender					
Female	102	27.87%	75	33.33%	0.159
Male	264	72.13%	150	66.67%	
Family history					
Y	35	9.56%	21	9.33%	0.926
N	331	90.443%	204	90.67%	
HP infection status					
Y	28	7.65%	18	8.00%	0.878
N	338	92.35%	207	92.00%	
BMI					
Less than 18.5	52	14.21%	28	12.44%	0.103
18.5-24.99	268	73.22%	156	69.33%	
More than 25	46	12.57%	43	19.11%	
Differentiated degree					
Well	121	33.06%	44	19.56%	0.000*
Poor	245	66.94%	181	80.44%	
Borrmann types					
I to II	16	4.37%	4	1.78%	0.090
III to IV	350	95.63%	221	98.22%	
T stage					
T1b	1	.27%	-	-	0.004*
T2	18	4.92%	3	1.33%	
T3	55	15.03%	19	8.44%	
T4a	270	73.77%	181	80.44%	
T4b	22	6.01%	22	9.78%	
TNM stage					
IIB	1	.27%	-	-	0.019*
IIIA	17	4.64%	3	1.33%	
IIIB	45	12.30%	16	7.11%	
IIIC	303	82.79%	206	91.56%	
Nerve invasion					
Y	132	36.07%	107	47.56%	0.006*
N	234	63.93%	118	52.44%	
Vessel carcinoma embolus					
Y	231	63.11%	183	81.33%	0.000*
N	135	36.89%	42	18.67%	

BMI: Body Mass Index. SD: standard deviation. Y: yes, N: not, *: P < 0.05.

we sub-classified stage $pTxN_3M_0$ into stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$. The aim of this study was to investigatethe effectiveness of the 7th edition of the TNM staging system focusing on stage $pTxN_3M_0$ GCs.

Patients and methods

Patients

From January 2000 to December 2010, a retrospective analysis was conducted of 1,050 consecutive patients with advanced GC who underwent D_2 lymphadenectomy, at the Department of gastrointestinal surgery, Fujian tumor hospital. All of the surgery was operated by Lu-Chuan Chen. Among them, 591 patients were diagnosed with stage $pTxN_3M_0$ GC according to the 7th edition of the UICC/TNM classification. Data from these patients were entered into a prospectively maintained database.

The inclusion criteria were as follows: 1. advanced GC; 2. adenocarcinoma confirmed byhistopathology; 3. physical fitness suitable for surgery; 4. D_2 lymphadenectomy; and 5. no prior history ofany type of adjunctive therapy. The exclusion criteriawere as follows: 1. older than 80 years of age; 2. previous or concomitant other cancer; 3. previous orconcomitant gastrectomy for benign disease; 4. previous chemotherapy or radiotherapy; 5. esophageal involvement; or 6. distant metastatic disease; 7. non-curative resection, 8. multiple primary malignancies, 9. remnant GC, 10. 15 retrieved lymph nodes, and 11. mortality within 30 days after surgery.

All of the above patients were followed up by posting letters or by telephone interviews. The last follow-up was 1 January 2016. The cardiopathy logical and follow-up findings were collected and recorded in the database. All subjects gave written informed consent to the study protocol, which was approved by the Ethical Committees of Fujian Provincial Tumor Hospital.

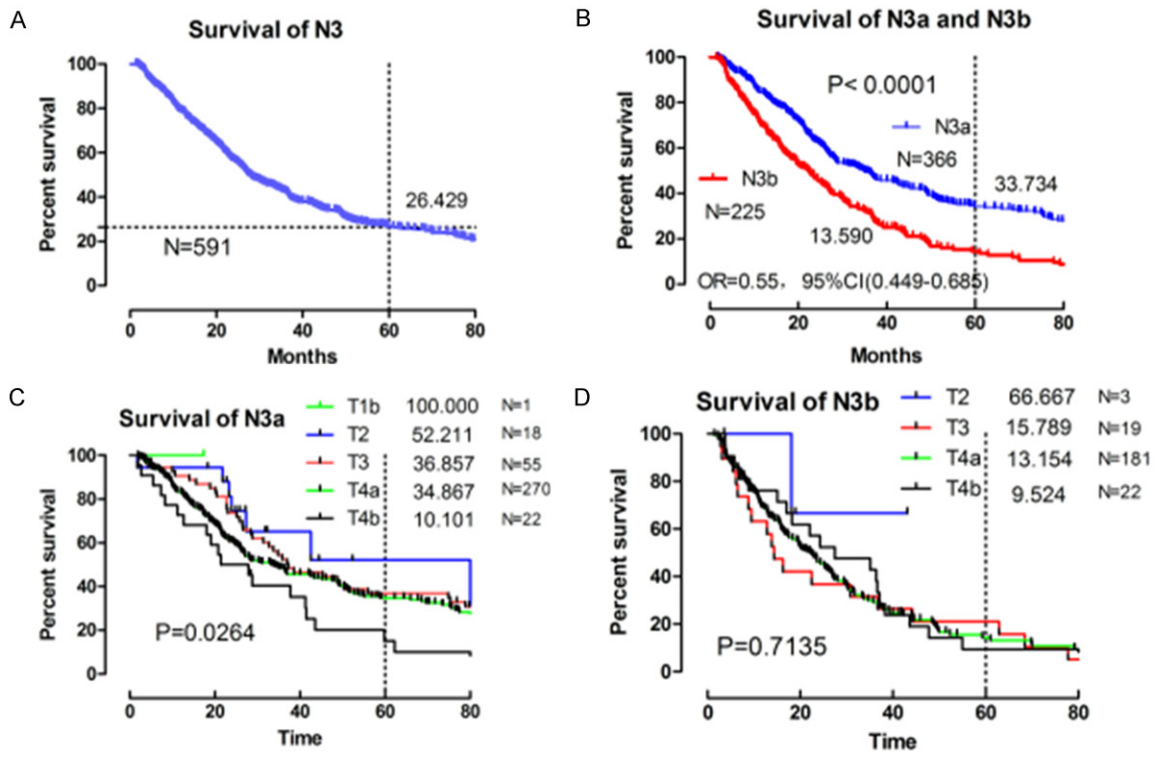

Figure 1. Survival analysis of stage $pTxN_3M_0$ GC patients who undergoing curative intent surgery. A: Survival of all patients with $pTxN_3M_0$, B: Survival of stage $pTxN_{3a}M_0$ versus stage $pTxN_{3b}M_0$ statuses, C: Survival of T category among $pTxN_{3a}M_0$ group, D: Survival of T category among $pTxN_{3b}M_0$ group. The *P* values for the survival comparison were determined by the log-rank test.

All patients with stage $pTxN_3M_0$ status were noted with adequate lymphadenectomy according to pathologic examination. They were further classified into stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$ groups for analysis.

Surgery

All patients in the study underwent standard total ordistal gastrectomy, being dependent on the location and macroscopic appearance of the primary tumor (**Table 1**). In the present study, distal gastrectomies were performed principally for tumors located in the lower third of the stomach. For tumors in the middlethird, either distal or total gastrectomies were performed, depending on the direction of tumor invasion. Total gastrectomies were used for tumors in the upper third of the stomach and those occupying the entire stomach. The strategy for LN dissections was determined using a standardized technique accordingto the guidelines of the 14th edition of the Japanese Classification of Gastric Cancer and Gastric Cancer Treatment Guidelines edited by the Japanese Gastric Cancer Association [15].

Clinicopathological characteristics

The clinicopathological findings, including depth of tumor invasion and LN metastases, were utilized to stage tumors according to the 7th edition of the International Union Against Cancer classification system. LNs were dissected and described according to the Japanese Classification of Gastric Carcinoma, which was also used to classify the location, histological type, and lymphatic invasion of tumors. The gross appearance of each tumor was classified using Borrmann's classification. According to this classification, tumors can bedivided into superficial tumors, well-defined tumors, and ill-defined tumors. Furthermore, they can beclassified as well-defined tumors (polypoid orfungating type, Borrmann's type I) and circumscribed excavating type (Borrmann's type II). Theill-defined tumors are ulcerated and infiltratingtype (Borrmann's type III) and diffusely thickened type (Borrmann's type IV).

Statistical analysis

Statistical analyses were conducted using Statistical Product for Social Sciences (SPSS)

Table 2. Multivariate analysis for stage $pTxN_3M_0$ GC patients with D_2 resection

	B	SE	Wald	df	Sig.	Exp (B)	95.0% CI	
							Lower	Upper
Family history	0.481	0.516	0.871	1	0.351	1.618	0.589	4.444
HP infection status	0.152	0.195	0.611	1	0.435	1.165	0.795	1.706
BMI	0.021	0.086	0.058	1	0.810	1.021	0.862	1.209
Gender	-0.053	0.111	0.231	1	0.631	0.948	0.764	1.178
Differentiated types	0.041	0.081	0.254	1	0.615	1.042	0.889	1.221
Location	0.102	0.057	3.200	1	0.074	1.107	0.990	1.237
Classification	0.074	0.106	0.484	1	0.487	1.077	0.874	1.326
Histological type	0.316	0.486	0.319	1	0.568	1.218	0.598	3.187
TNM Stage	0.617	0.089	47.775	1	0.000*	1.854	1.556	2.209
T Stage	-0.217	0.110	3.883	1	0.069	0.805	0.648	1.099
N Stage	0.510	0.110	21.538	1	0.000*	1.665	1.343	2.066
Nerves invaded	0.004	0.115	0.001	1	0.975	1.004	0.802	1.256
Vessel carcinoma embolus	-0.070	0.117	0.358	1	0.550	0.932	0.742	1.173

BMI: Body Mass Index. *: P < 0.05.

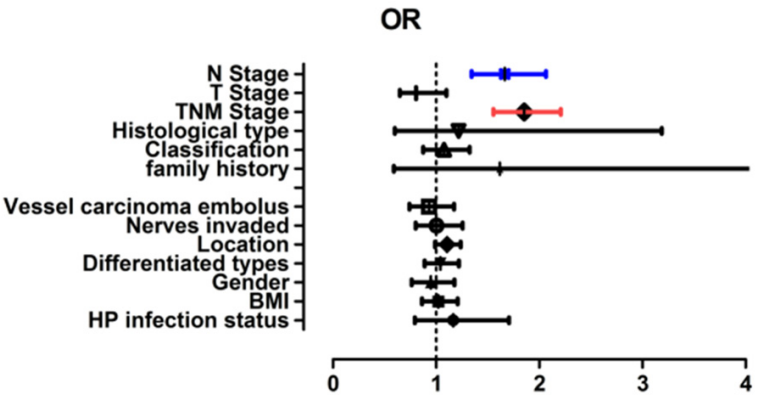

Figure 2. Multivariate analysis for stage $pTxN_3M_0$ GC patients with D_2 resection.

19.0 software (SPSS, Inc., Chicago, IL, USA). The distribution of baseline characteristics was compared by using either Fisher's exact test orthe chi-square test. Significant factors were extracted for further analysis, which was conducted by using the logistic regression method. The overall cumulative probability of survival was calculated by the Kaplan-Meier method, and differences were assessed by using the log-rank test. The Cox multiple factors analysis was carried out using the logistic regression method. A *P* value less than 0.05 was considered to be statistically significant.

Results

Clinicopathological characteristics

A total of 591 patients with stage $pTxN_3M_0$ GC underwent surgery. **Table 1** summarizes their demographic and clinicopathological features. No difference in these characteristics, including age, gender, BMI, Borrmann type, family history, HP infection status, was observed between patients with $pTxN_{3a}M_0$ and $pTxN_{3b}M_0$ GC (all P > 0.05).

Differences in staging according to the 7th editions of the TNM system are given in **Table 1**. Among patients with $pTxN_{3b}M_0$ group, a slightly higher percentage was found in poor differentiated degree (80.44% vs 66.94%), nerve invasion (47.56% vs 36.07%), and vessel carcinoma embolus (81.33% vs 63.11%) (all P > 0.05) yet without statistical differences. For T stage, a mildly rate grew up in T4 sub-group in stage $pTxN_{3b}M_0$ group than stage $pTxN_{3a}M_0$ group (90.22% vs 79.78%, P > 0.05). As for TNM stage, a merely higher percentage was noted in IIIC stage in stage $pTxN_{3b}M_0$ group than stage $pTxN_{3a}M_0$ group (91.56% vs 82.79%, P > 0.05).

Survival analysis

The 5-year overall survival rate (OS) of stage $pTxN_3M_0$ was 26.43% (**Figure 1A**). When GC patients in the stage $pTxN_{3a}M_0$ category be subclassified into stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$, a markedly worse prognosis was found in stage $pTxN_{3b}M_0$ group than in stage $pTxN_{3a}M_0$ group (13.59% vs 33.73%, P < 0.05, **Figure 1B**).

Table 3. Multivariate analysis of overall survival in stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$ GC

	N3a				N3b			
	Sig.	Exp (B)	95.0% CI		Sig.	Exp (B)	95.0% CI	
			Lower	Upper			Lower	Upper
Family history	0.522	1.399	0.500	3.909	0.512	1.191	0.501	2.019
HP infection status	0.140	1.669	0.822	2.124	0.769	0.910	0.486	1.704
BMI	0.255	1.143	0.908	1.437	0.041*	0.905	0.707	0.930
Gender	0.663	0.938	0.704	1.250	0.249	0.813	0.572	1.156
Differentiated degree	0.413	0.902	0.704	1.155	0.004*	1.575	1.213	3.149
Location	0.718	1.190	0.930	1.374	0.755	0.971	0.806	1.169
Classification	0.051	1.308	0.999	1.712	0.257	1.131	0.914	1.400
Histological type	0.578	1.318	0.498	3.487	0.459	1.427	0.557	3.651
TNM Stage	0.094	0.212	0.034	1.303	0.478	0.849	0.541	1.333
T Stage	0.666	1.063	0.806	1.402	0.177	0.752	0.497	1.137
Vessel carcinoma embolus	0.000*	1.875	1.494	2.354	0.000*	1.775	1.318	2.391
Nerves invaded	0.549	0.911	0.671	1.236	0.301	1.200	0.850	1.694

BMI: Body Mass Index. *: $P < 0.05$.

According to T stage, the 5-year OS for pT_{1b}, pT_2, pT_3, pT_{4a}, and pT_{4b} among stage $pTxN_{3a}M_0$ group were 100%, 52.21%, 36.86%, 34.87% and 10.10%, respectively ($P < 0.05$, **Figure 1C**). The corresponding data in stage $pTxN_{3b}M_0$ group were 66.67%, 15.79%, 13.15%, and 9.52%, respectively for pT_2, pT_3, pT_{4a}, and pT_{4b} groups ($P > 0.05$, **Figure 1D**).

Multivariate analysis

Multivariate survival analysis showed that TNM stage (OR = 1.854), N stage (OR = 1.665) were significant prognostic factors for stage $pTxN_3M_0$ GC (all $P < 0.05$, **Table 2**; **Figure 2A**). In the-stage $pTxN_{3a}M_0$ sub-group, vessel carcinoma embolus (OR = 1.875) was an independent hazard factor, besides, amongstage $pTxN_{3b}M_0$ group, BMI (OR = 0.905) was an independent protective factor, while differentiated degree (OR = 1.575), vessel carcinoma embolus (OR = 1.775) were risk factor calculated by multivariate analysis (all $P < 0.05$, **Table 3**; **Figure 2B** and **2C**).

Discussion

In this study, we explored the patterns of a subset of stage $pTxN_3M_0$ GC patients who underwent gastrectomy with D_2 lymph adenectomy at a single institution with long-term follow-up, concentrating primarily on prognosis status. Instage $pTxN_{3b}M_0$ group, a tendency towards higher was observed in deprived differentiated degree (80.44% vs 66.94%), nerve invasion (47.56% vs 36.07%), and vessel carcinoma embolus (81.33% vs 63.11%). Interestingly, when combined T category into consideration, a slightly higher percentage inresponse to T_4 sub-group in stage $pTxN_{3b}M_0$ group than stage $pTxN_{3a}M_0$ group (90.22% vs 79.78%). As for TNM stage, the percentage of IIIC stage did not differ, but stage $pTxN_{3b}M_0$ subgroup tended to be higher (91.56% vs 82.79%). The data above showed worse baseline conditions among stage $pTxN_{3b}M_0$ group.

The 7th edition NCCN guidelines have failed to distinguish the OS between stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$ groups. Our results showed that the 5-year OS of all patients with pN_3 stage was 26.43% calculated by the Kaplan-Meier. Additional analysis illustrated that a significantly decreased by OS was pointed out in stage $pTxN_{3b}M_0$ compared with stage $pTxN_{3a}M_0$ (13.59% vs 33.73%, $P < 0.05$). The data above explained that prognosis of stage $pTxN_{3b}M_0$ was inferior, supporting those of previous investigators in recent years. Such as Jun [16] reported that a 5-year OS was 46% for stage $pTxN_{3a}M_0$ and 28% for stage $pTxN_{3b}M_0$ stage. In addition, Chae [17] indicated that the 5-year OS was 23.1% and 5.4% for stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$ GC patients, respectively. Furthermore, Chen [18] pointed out that a 5-year OS was 29% for stage $pTxN_{3a}M_0$ and 19% for stage $pTxN_{3b}M_0$ stage. What is more, Yeh [19] also emphasized the illogicality of a 5-year OS was 35.5% for stage $pTxN_{3a}M_0$ and 10.2% for stage $pTxN_{3b}M_0$ stage. The reason for stage $pTxN_{3b}M_0$

sub-group showed an inferior OS might be tied toin adequate baseline conditions.

According to T stage, the 5-year OS for pT_{1b}, pT_2, pT_3, pT_{4a}, and pT_{4b} among stage $pTxN_{3a}M_0$ group was 100%, 52.21%, 36.86%, 34.87% and 10.10%, respectively, showing a significantly different ($P < 0.05$). On the other hand, among stage $pTxN_{3b}M_0$ group for pT_2, pT_3, pT_{4a}, and pT_{4b} was 66.67%, 15.79%, 13.15%, and 9.52%, respectively ($P > 0.05$). This data showed that the 7th edition of the TNM classification system is not utilized for distinguishing prognosis from pT_2, pT_3, pT_{4a}, and pT_{4b} stage effectively in stage $pTxN_{3b}M_0$ subgroup.

Nodal status is the strongest predictor of theprognosis of GC patients. Multivariate survival analysis showed that the N stage was significant prognostic factors for stage $pTxN_3M_0$ gastric cancer (OR = 1.665). When sub-categorized as stage $pTxN_{3a}M_0$ and stage $pTxN_{3b}M_0$, vessel carcinoma embolus was an independent hazard factor in both stage $pTxN_{3a}M_0$ (OR = 1.875) and stage $pTxN_{3b}M_0$ (OR = 1.775) subgroups. In addition to this, in consideration of worse baseline conditions among stage $pTxN_{3b}M_0$ group, differentiated degree (OR = 1.575) was a hazard factor while BMI (OR = 0.905) was an independent protective factor in stage $pTxN_{3b}M_0$ subgroup.

Although our results might support the proposed modifying seventh AJCC/TNM staging system for GC, there were several limitations inherent in this study. Firstly, this study was designed as a large sample retrospective study, clinical biased could potentially occur. In addition, our follow-up was done by telephone, and recall bias was existed. What is more, the precise evaluationof LN metastasis is the most important guarantee for theprediction of the prognosis of GC patients. However, manyfactors have potentially significant influences on the evaluationof LN metastasis in GC, including the surgery performed, pathological examination, immune condition, and anatomic variation.

In conclusion, categorized bystage $pTxN_{3b}M_0$ could play a role ina more accurate prediction of an inferior survival outcomefor the GC patients. Studies of postoperative adjuvant therapies may take stage $pTxN_{3b}M_0$ status of each patient into consideration to evaluate thetreatment effect rather than just stratifying patients based on AJCC staging system in future.

Acknowledgements

Domestic support from (1) The Young People Fund of Fujian Province Health Department (No.2014-2-8). (2) Fujian Provincial Natural Science Fund Subject (No.2016J01436). (3) The Guide Project of the Science and Technology office of Fujian Province(No. 2017Y0022).

Disclosure of conflict of interest

None.

Authors' contribution

Design of the study and approval of the final version: CLC. Data collection and analysis: YZ, ZML, YW. Contributed reagents/materials/analysis tools: SHW, ZSY. Critical revision: CLC. Writing of the manuscript: XJ.

Address correspondence to: Lu-Chuan Chen, Department of Gastrointestinal Surgery, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou 350001, Fujian Province, China. Tel: (86)-591-83660063; Fax: (86)-591-83660063; E-mail: luchuanchen@sina.com

References

[1] Hawk ET, Limburg PJ and Viner JL. Epidemiology and prevention of colorectal cancer. Surg Clin North Am 2002; 82: 905-941.

[2] Takezaki T, Gao CM, Ding JH, Liu TK, Li MS and Tajima K. Comparative study of lifestyles of residents in high and low risk areas for gastric cancer in Jiangsu province, China; with special reference to allium vegetables. J Epidemiol 1999; 9: 297-305.

[3] Stoicov C, Saffari R, Cai X, Hasyagar C and Houghton J. Molecular biology of gastric cancer: helicobacter infection and gastric adenocarcinoma: bacterial and host factors responsible for altered growth signaling. Gene 2004; 341: 1-17.

[4] Sun XD, Mu R, Zhou YS, Dai XD, Zhang SW, Huangfu XM, Sun J, Li LD, Lu FZ and Qiao YL. [Analysis of mortality rate of stomach cancer and its trend in twenty years in China]. Zhonghua Zhong Liu Za Zhi 2004; 26: 4-9.

[5] Tsubono Y and Hisamichi S. Screening for gastric cancer in Japan. Gastric Cancer 2000; 3: 9-18.

[6] Roukos DH and Kappas AM. Perspectives in the treatment of gastric cancer. Nat Clin Pract Oncol 2005; 2: 98-107.

[7] Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, Lui WY and Whang-Peng J. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006; 7: 309-315.
[8] Songun I, Putter H, Kranenbarg EM, Sasako M and van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11: 439-449.
[9] Degiuli M, Sasako M, Ponti A and Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. Br J Cancer 2004; 90: 1727-1732.
[10] Hartgrink HH, Jansen EP, van Grieken NC and van de Velde CJ. Gastric cancer. Lancet 2009; 374: 477-490.
[11] Kawaguchi T, Komatsu S, Ichikawa D, Kosuga T, Kubota T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H and Otsuji E. Clinical significance and prognostic impact of the total diameter of enlarged lymph nodes on preoperative multidetector computed tomography in patients with gastric cancer. J Gastroenterol Hepatol 2015; 30: 1603-1609.
[12] Klein Kranenbarg E, Hermans J, van Krieken JH and van de Velde CJ. Evaluation of the 5th edition of the TNM classification for gastric cancer: improved prognostic value. Br J Cancer 2001; 84: 64-71.
[13] Katai H, Yoshimura K, Maruyama K, Sasako M and Sano T. Evaluation of the New international union against cancer TNM staging for gastric carcinoma. Cancer 2000; 88: 1796-1800.
[14] Yamashita K, Sakuramoto S, Kikuchi S, Katada N, Kobayashi N and Watanabe M. Validation of staging systems for gastric cancer. Gastric Cancer 2008; 11: 111-118.
[15] Sano T. [Evaluation of the gastric cancer treatment guidelines of the Japanese Gastric Cancer Association]. Gan To Kagaku Ryoho 2010; 37: 582-586.
[16] Jun KH, Lee JS, Kim JH, Kim JJ, Chin HM and Park SM. The rationality of N3 classification in the 7th edition of the International Union Against Cancer TNM staging system for gastric adenocarcinomas: a case-control study. Int J Surg 2014; 12: 893-896.
[17] Chae S, Lee A and Lee JH. The effectiveness of the new (7th) UICC N classification in the prognosis evaluation of gastric cancer patients: a comparative study between the 5th/6th and 7th UICC N classification. Gastric Cancer 2011; 14: 166-171.
[18] Chen HN, Chen XZ, Zhang WH, Chen XL, Yang K, Liu JP, Zhang B, Chen ZX, Chen JP, Zhou ZG and Hu JK. Necessity of harvesting at least 25 lymph nodes in patients with stage N2-N3 resectable gastric cancer: a 10-year, single-institution cohort study. Medicine (Baltimore) 2015; 94: e620.
[19] Yeh CN, Wang SY, Hsu JT, Chiang KC, Cheng CT, Tsai CY, Liu YY, Liao CH, Liu KH and Yeh TS. N3 subclassification incorporated into the final pathologic staging of gastric cancer: a modified system based on current AJCC staging. Medicine (Baltimore) 2015; 94: e575.