

Comparison of the 8th union for international cancer control lymph node staging system for gastric cancer with two other lymph node staging systems

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Received March 13, 2018; Accepted October 4, 2018

DOI: 10.3892/ol.2018.9694

Abstract. The log odds of positive lymph nodes (LODDS) and the metastatic lymph node ratio (MLR) staging systems have previously been demonstrated to exhibit advantages compared with the tumor-node-metastasis (TNM) staging system in predicting the prognosis of gastric cancer. The current study compared the prognostic significance of the newest Union for International Cancer Control Node classification with the LODDS and MLR staging systems. From September 2010 to December 2012, all medical records for patients with gastric cancer at the Third Affiliated Hospital of Soochow University were retrospectively analyzed and the clinicopathologic characteristics were reviewed. Cut-off points were selected to divide the patients with gastric cancer into different groups. Univariate and multivariate analyses were performed to identify the prognostic risk factors for gastric cancer. The Harrell's concordance index (C-index) was adopted to compare the prognostic value of the three staging systems. A total of 877 patients with gastric cancer who met the inclusion criteria were analyzed in the current study. The patients were classified according to the three MLR subgroups as follows: MLR0 (MLR=0), MLR1 (0<MLR≤0.28) and MLR2 (0.28<MLR<1). The patients were classified according to the LODDS subgroups as follows: LODDS1 (LODDS≤-0.5), LODDS2 (-0.5<LODDS≤0), LODDS3 (0<LODDS≤0.5) and LODDS4 (LODDS>0.5). Based on multivariate analysis, LODDS, MLR and pathological node (pN) stage could significantly predict

survival rates of patients with gastric cancer. According to the C-index, the LODDS staging system more accurately predicted the 5-year overall survival for patients with gastric cancer compared with the other two staging systems. In summary, the current study has identified that LODDS may be superior to the MLR and pN staging systems in predicting the prognosis of patients with gastric cancer. However MLR may exhibit advantages compared with LODDS for patients who have undergone adequate lymphadenectomies.

Introduction

Gastric cancer is the fourth most common cancer type worldwide, with >93,000 new cases diagnosed every year, and is the second leading cause of cancer-associated cases of mortality, following lung cancer with 700,000 deaths each year (1,2). Gastric cancer is considered to be prevalent in east Asia, particularly in China (3). Currently, primary tumor resection with lymphadenectomy is the main surgical treatment for resectable gastric cancer; however, most cases of gastric cancer are diagnosed in the advanced stage as the symptoms of early stage disease are often atypical (4).

The 8th edition of the tumor-node-metastasis (TNM) staging system (5), established by the American Joint Committee on Cancer and the Union for International Cancer Control (UICC), is the most commonly used system for predicting the prognosis of gastric cancer (6). The 8th edition TNM staging system is considered to be an objective and reliable method for predicting the prognosis of patients with gastric cancer (7), however, the requirement of at least 15 retrieved lymph nodes (LNs) limits the use of this system in clinical practice (8). Furthermore, stage migration may occur if a low number of LNs are retrieved, which may underestimate the severity of the disease (9).

Previously, a number of new methods for predicting the prognosis of gastric cancer have been proposed. The metastatic lymph node ratio (MLR) is used as a supplement to the TNM staging system and is defined as the ratio of metastatic LNs to the total number of retrieved LNs (10). Several previous studies have demonstrated that MLR has advantages compared with the UICC pathological node (pN) staging system in predicting

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Key words: gastric cancer, metastatic lymph node ratio, log odds of positive lymph nodes, prognosis, staging system

the prognosis of gastric cancer (11-14). Another prognostic parameter, the log odds of positive LNs (LODDS), is defined as the log of the ratio of positive LNs to negative LNs (15). A number of studies have indicated that the prognostic value of LODDS is superior to the MLR and pN systems (15-17). The current study evaluated the prognostic significance of the LODDS and MLR staging systems compared with the 8th UICC pN staging system.

Materials and methods

Patients. Between September 2010 and December 2012, all medical records for patients with gastric cancer treated at the Third Affiliated Hospital of Soochow University (Changzhou, China) were retrospectively analyzed. The inclusion criterion was adenocarcinoma R0 resection with D2 LN dissection. Patients with M0 and M1 statuses were excluded from the study. Patients who had received neoadjuvant chemotherapy or radiotherapy were also excluded due to the possibility of incorrect staging. Specific data are presented in Fig. 1. Clinicopathologic characteristics, including age, sex, tumor size, tumor location, tumor differentiation, tumor depth (pT stage), pN stage and TNM stage, were reviewed. Follow-up was conducted by telephone calls, e-mails and on-site visits. Informed written consent was received from all patients and the current study was approved by the Ethics Committee of The Third Affiliated Hospital of Soochow University.

Different LN categories. All included patients were staged using the 8th edition of the TNM staging system. The pN stage classification was performed as follows: N0, negative; N1, 1-2 positive LNs; N2, 3-6 positive LNs; N3a, 7-15 positive LNs; and N3b >15 positive LNs. Negative was used to mean no lymph node metastasis, while positive was used to mean lymph node metastasis. MLR was calculated as follows: $MLR = \text{metastatic LNs} / \text{retrieved LNs}$. The median MLR was selected as the cut-off value to divide the patients into three subgroups. The median MLR was 0.28, therefore the patients were classified into three subgroups as follows: MLR0 (MLR=0), MLR1 ($0 < MLR \leq 0.28$) and MLR2 ($0.28 < MLR < 1$). LODDS was calculated as follows: $LODDS = \log \left(\frac{pnod + 0.5}{nnod + 0.5} \right)$, where pnod is the number of positive LNs and nnod is the number of negative LNs. The LODDS cut-off value was determined by comparing the 5-year overall survival rate with an interval of 0.5. As presented in Table I, patients were classified into four subgroups based on their LODDS value, as follows: LODDS1 ($LODDS \leq -0.5$), LODDS2 ($-0.5 < LODDS \leq 0$), LODDS3 ($0 < LODDS \leq 0.5$) and LODDS4 ($LODDS > 0.5$).

Statistical analysis. All analyses were performed using SPSS (version 16.0; SPSS, Inc., Chicago, IL, USA) and R software (version 3.0.0; www.r-project.org). Kaplan-Meier analysis followed by a log-rank test was used to compare the survival between subgroups. Univariate and multivariate analyses were performed using a Cox proportional hazards model. The Harrell's concordance index (C-index) was used to compare the accuracy of the prognostic predictions of different staging systems. A higher C-index indicates a better predictive accuracy. $P < 0.05$ was considered to indicate a statistically significant difference.

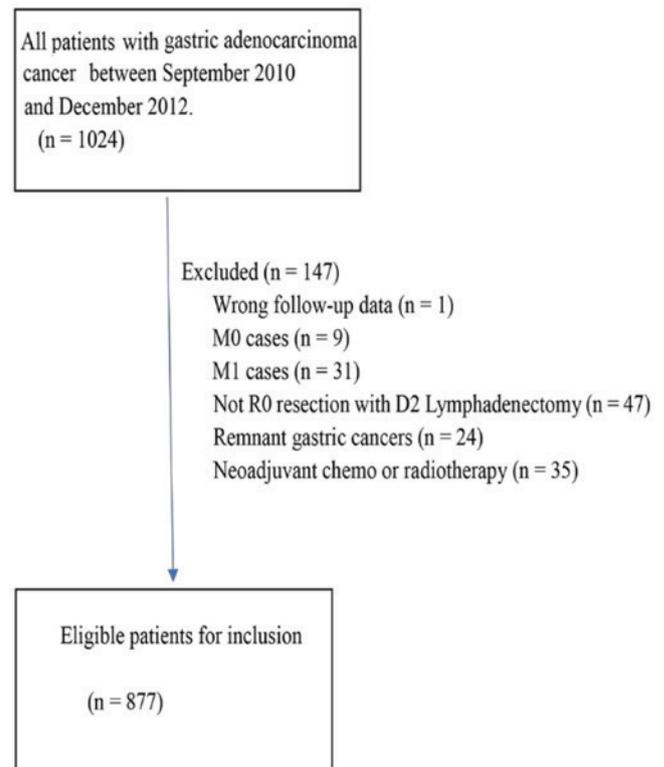


Figure 1. Inclusion criteria of the current study.

Results

Patient characteristics. A total of 877 patients with gastric cancer met the aforementioned criteria and were analyzed in the current study. The clinicopathological characteristics are presented in Table II. The number of patients ≤ 60 and > 60 years of age was 459 and 418, respectively. There were 605 male patients and 272 female patients. A total of 275 (31.4%) patients received postoperative chemotherapy. The majority of patients were in an advanced stage, with T3 and T4 patients accounting for 48.2 and 25.3%, respectively, and T1 and T2 patients accounting for 10.4 and 16.1%, respectively.

Analysis of prognostic factors and survival. As presented in Table III, risk factors were evaluated using univariate and multivariate analyses. Prognostic factors included age, sex, tumor location, tumor size, tumor differentiation, pT stage, pN stage, TNM stage, MLR and LODDS. Overall survival rates were shown for patients in different T subgroups (Fig. 2), N subgroups (Fig. 3), TNM subgroups (Fig. 4), MLR subgroups (Fig. 5) and LODDS subgroups (Fig. 6). Based on univariate analysis, pT stage, pN stage, tumor size, tumor differentiation, MLR, LODDS and TNM were identified as significant prognostic risk factors for gastric cancer. However, based on multivariate analysis, tumor size and pT stage were not identified as significant prognostic factors.

Comparison of prognostic value among the three systems. The C-index was used to compare the prognostic discrimination of the three staging systems. As demonstrated in Table IV, when all patients were included (LN ≥ 0), the C-index of the LODDS staging system was significantly higher compared

Table I. Overall survival rates according to the value of LODDS with an interval of 0.5.

LODDS value	No. of patients	5-year OS rate, %	^a P-value
LODDS≤-1.5	76	89.5	0.364
-1.5<LODDS≤-1.0	101	86.1	0.335
-1.0<LODDS≤-0.5	84	78.6	0.003
-0.5<LODDS≤0	160	59.4	<0.001
0<LODDS≤0.5	312	38.8	0.001
0.5<LODDS≤1.0	62	9.7	<0.001
1.0<LODDS≤1.5	36	11.1	0.298
LODDS>1.5	46	8.7	

LODDS, log odds of positive nodes; OS, overall survival. ^aCompared between adjacent subgroups (e.g., a subgroup row and its following subgroup row in the table).

Table II. Clinicopathological characteristics of 877 patients with gastric cancer.

Characteristic	No. (%)
Age, years	
≤60	459 (52.3)
>60	418 (47.7)
Sex	
Male	605 (69.0)
Female	272 (31.0)
Tumor location	
Upper	179 (20.4)
Middle	137 (15.6)
Lower	550 (62.7)
Entire	11 (1.3)
Tumor size, cm	
≤5	568 (64.8)
>5	309 (35.2)
Tumor differentiation	
Well	44 (5.0)
Moderately	317 (36.1)
Poorly	498 (56.8)
Undifferentiated	18 (2.1)
pT stage	
T1	91 (10.4)
T2	141 (16.1)
T3	423 (48.2)
T4a	211 (24.1)
T4b	11 (1.3)
pN stage	
N0	223 (25.4)
N1	175 (20.0)
N2	265 (30.2)
N3a	146 (16.6)
N3b	68 (7.8)

Table II. Continued.

Characteristic	No. (%)
TNM stage	
I	126 (14.4)
II	327 (37.3)
IIIA	183 (20.9)
IIIB	175 (20.0)
IIIC	66 (7.5)
MLR	
MLR0	223 (25.4)
MLR1	203 (23.1)
MLR2	451 (51.4)
LODDS	
LODDS1	261 (29.8)
LODDS2	160 (18.2)
LODDS3	312 (35.6)
LODDS4	144 (16.4)
Number of LN retrieved	
<15	404 (46.1)
≥15	473 (53.9)
Postoperative chemotherapy	
Yes	275 (31.4)
No	602 (68.6)

pT, tumor depth; pN, pathological node; TNM, tumor-node-metastasis; MLR, metastatic lymph node ratio; LODDS, log odds of positive nodes; LN, lymph nodes.

with the C-indexes of the MLR and pN staging systems (C-index=0.795, 0.790 and 0.779, respectively; P<0.001). The patients were divided into two groups according to the number of LNs retrieved. When the number of retrieved LNs was <15, the C-index of the LODDS staging system was significantly higher compared with that of the MLR and pN staging systems (C-index=0.792, 0.781 and 0.790, respectively; P<0.001). However, when the number of retrieved LNs was ≥15, the C-index of the MLR was significantly higher compared with the LODDS and pN staging systems (C-index=0.772, 0.780 and 0.698, respectively; P=0.001).

Discussion

The TNM system is widely used to offer guidance for the treatment of gastric cancer (7). The 8th edition of the TNM staging system for gastric cancer was released in 2016, replacing the 2009 7th edition (8). Compared with the previous edition, the 8th edition has no changes in the definition of T and N classifications. A noteworthy difference in the 8th edition system involves separate consideration of N3a and N3b in the TNM staging system, which has been demonstrated to achieve improved prognosis prediction in patients with stage III gastric cancer (5,6). A number of previous studies have indicated that the MLR is an improved method for evaluating the prognosis of patients with

Table III. Univariate and multivariate analyses of prognostic factors.

Parameter	No. of patients	5-year OS rate, %	Univariate analysis P-value	Multivariate analysis		
				HR	95% CI	P-value
Age, years			0.677			
≤60	459	56.2				
>60	418	46.2				
Sex			0.51			
Male	605	50.9				
Female	272	52.6				
Tumor location			0.374			
Upper	179	52				
Middle	137	51.8				
Lower	550	51.6				
Entire	11	27.3				
Tumor size, cm			0.001	1.983	0.942-3.011	0.094
≤5	568	61.3				
>5	309	33.3				
Tumor differentiation			0.003	1.335	1.022-1.844	0.029
Well	44	72.7				
Moderately	317	59				
Poorly	498	46				
Undifferentiated	18	16.7				
pT stage			0.039	1.892	0.933-2.984	0.556
T1	91	84.6				
T2	141	72.3				
T3	423	44.7				
T4	222	37.4				
pN stage			<0.001	2.012	1.113-2.868	<0.001
N0	223	80.3				
N1	175	64.6				
N2	265	38.9				
N3a	146	28.1				
N3b	68	22.1				
TNM stage			<0.001	2.343	1.572-3.125	0.006
II	126	87.3				
III	327	60.2				
IV	424	34				
MLR			<0.001	1.766	1.023-2.318	<0.001
MLR0	223	80.2				
MLR1	203	62.1				
MLR2	451	32.6				
LODDS			<0.001	1.875	1.101-2.877	<0.001
LODDS1	261	84.7				
LODDS2	160	59.4				
LODDS3	312	38.8				
LODDS4	144	9.7				

MLR, metastatic lymph node ratio; LODDS, log odds of positive nodes; OS, overall survival; HR, hazard ratio; CI, confidence interval; pT, tumor depth; pN, pathological node.

gastric cancer compared with the previous TNM staging system (18,19). In addition, the LODDS staging system

has been demonstrated to be superior in terms of accuracy compared with the MLR and TNM systems with regard to

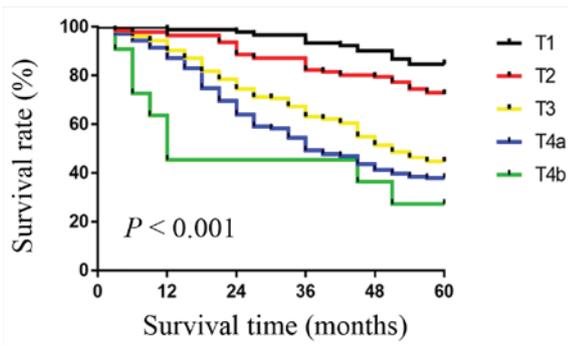


Figure 2. Overall survival rates for patients in different T subgroups. According to mixed analysis of the five groups, the 5-year survival rate was 84.6% for T1, 72.3% for T2, 44.7% for T3, 37.9% for T4a and 27.3% for T4b. $P < 0.001$. T, tumor depth.

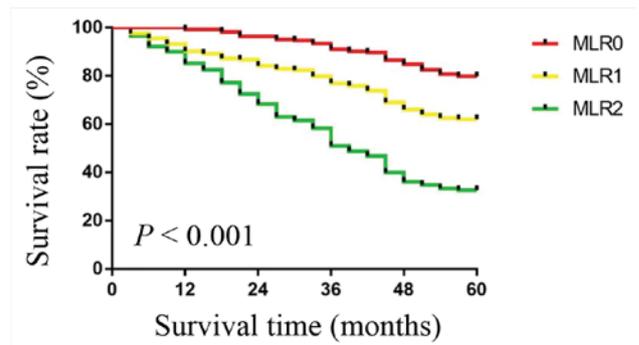


Figure 5. Overall survival rates for patients in different MLR subgroups. According to mixed analysis of the three groups, the 5-year survival rate was 80.2% for MLR0, 62.1% for MLR1 and 32.6% for MLR2. $P < 0.001$. MLR, metastatic lymph node ratio.

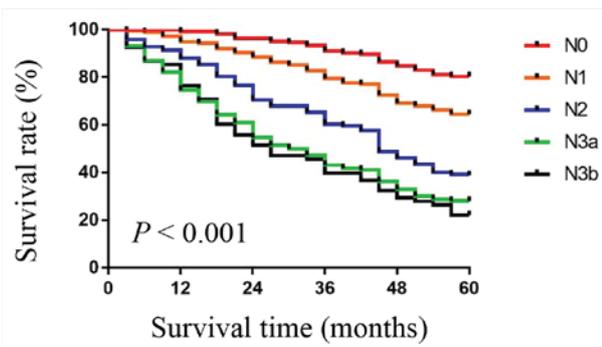


Figure 3. Overall survival rates for patients in different N subgroups. According to mixed analysis of the five groups, the 5-year survival rate was 80.3% for N0, 64.6% for N1, 38.9% for N2, 28.1% for N3a and 22.1% for N3b. $P < 0.001$. N, lymph node.

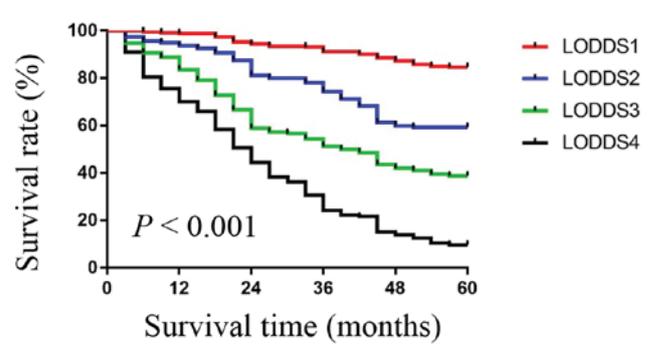


Figure 6. Overall survival rates for patients in different LODDS subgroups. According to mixed analysis of the four groups, the 5-year survival rate was 84.7% for LODDS1, 59.4% for LODDS2, 38.8% for LODDS3 and 9.7% for LODDS4. $P < 0.001$. LODDS, log odds of positive nodes.

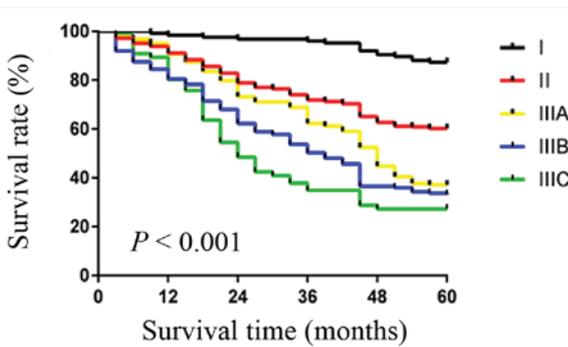


Figure 4. Overall survival rates for patients in different TNM subgroups. According to mixed analysis of the five groups, the 5-year survival rate was 87.3% for stage I, 60.2% for stage II, 37.2% for stage IIIA, 33.1% for stage IIIB and 27.3% for stage IIIC. $P < 0.001$. TNM, tumor-node-metastasis.

predicting survival (20-22). LN stage is considered to be the most important prognostic factor for patients with gastric cancer (14). In addition, clinicopathological characteristics are associated with prognosis (13).

In the current study, the LODDS, MLR and the 8th UICC pN staging systems were evaluated to compare prognostic prediction. A number of factors were responsible for making the current study novel. Firstly, the 8th UICC pN staging system was considered in the current study, which, to the best

our knowledge, has not been considered in previous studies. Secondly, the 8th pN, MLR and LODDS staging systems were all compared together while the majority of previous studies have only compared the UICC pN staging system with one other system. Finally, the current study divided the patients into two groups based on the number of retrieved LNs (< 15 or ≥ 15), which may increase the accuracy of determining the best system. The current study concluded that the LODDS staging system is superior to the MLR and TNM staging systems, particularly in patients with < 15 retrieved LNs.

Based on univariate and multivariate analysis, the MLR, LODDS and pN staging systems were all significantly associated with prognosis. Similar outcomes were identified in a number of previous studies. Jian-Hui *et al* (16) analyzed 935 patients undergoing radical surgery treatment and demonstrated that the three systems were all independent factors for overall survival based on multivariate analysis. Furthermore, this study concluded that LODDS was the superior staging system. Tóth *et al* (19) revealed that the LODDS staging system was the best predictor of prognosis when < 16 LNs were retrieved and the MLR should be applied in patients who underwent extended lymphadenectomies. Aurello *et al* (23) analyzed 177 patients and identified that the LODDS staging system, nodal ratio and pN are all prognostic factors based on multivariate analysis, and the LODDS staging system was capable of predicting survival

Table IV. Comparison of systems in predicting prognosis based on different numbers of retrieved LNs.

No. of LNs retrieved	No. of patients	System	C-index	95% CI	^a P-value
≥0	877	LODDS	0.795	0.568-1.421	<0.001
		MLR	0.790	0.512-1.344	
		pN staging	0.779	0.606-1.108	
<15	404	LODDS	0.792	0.433-1.246	<0.001
		MLR	0.781	0.446-1.298	
		pN staging	0.790	0.522-0.998	
≥15	473	LODDS	0.772	0.502-1.450	0.001
		MLR	0.780	0.476-0.966	
		pN staging	0.698	0.412-0.988	

MLR, metastatic lymph node ratio; LODDS, log odds of positive nodes; LN, lymph nodes; C-index, Harrell's concordance index; CI, confidence interval; TNM, tumor-node-metastasis. ^aCompared with the system with the highest C-index.

even when <15 LNs were harvested. These studies, in addition to the current study, all supported the hypothesis that LODDS can better minimize stage migration compared with the pN system, particularly when an insufficient number of LNs are retrieved (20).

There is no agreement regarding a cut-off value for MLR in patients with gastric cancer. Zeng *et al* (24) divided patients into four subgroups and used X-tile to determine the optimal cut-off value. Cut-off values can also be adopted based on commonly used values in previous studies. Tóth *et al* (19) categorized MLR with four subgroups according to previously published cut-off values. In addition, the median MLR may be used as the cut-off value (1,2). The current study selected the median MLR as the cut-off value and divided the patients into three subgroups. It was identified that patients with high MLRs had low 5-year overall survival rates, as reported by Ke *et al* (25) in an analysis of 370 patients who underwent R0 surgery. This method of LODDS classification is relatively consistent. The current study stratified LODDS at an interval of 0.5 and compared the overall survival between adjacent subgroups. This method has been adopted by a number of previous studies (15,19,26,27).

The current study compared the C-index of the LODDS, MLR and 8th UICC pN staging systems. The LODDS staging system demonstrated the largest C-index when all patients were included. The same result appeared in the group with <15 LNs retrieved. In the group with ≥15 LNs retrieved, the MLR demonstrated the largest C-index. The results were generally consistent with a study conducted in 2016, in which the LODDS staging system was revealed to be an independent prognostic factor and superior to the MLR and 7th UICC pN staging systems (15). Aurello *et al* (23) concluded that the success of the LODDS staging system was not associated with the number of LNs examined and revealed that LODDS could predict survival when <15 LNs were retrieved, which was verified by the current study.

In conclusion, the LODDS and MLR staging systems may be adopted as alternative pN staging systems to predict the prognosis of patients with gastric cancer. Both systems were identified to be superior compared with the 8th edition of the UICC pN staging system. The LODDS staging system exhibits

a higher prognostic accuracy compared with MLR when an inadequate number of LNs are retrieved, while MLR is applicable to predict prognosis in cases with adequate lymphadenectomies.

Acknowledgements

Not applicable.

Funding

The current study was supported by the Changzhou Municipal Scientific Research grant (grant no. CE20125020).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HC, ZT and YW wrote the manuscript and analyzed clinicopathologic data. ZY, QW, ZL and QL carried out the follow-up and collected the clinicopathologic data of patients. YW assisted HC and ZT to draft and revise the manuscript, and funded the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The current study was approved by the Ethics Committee of The Third Affiliated Hospital of Soochow University (Changzhou, Jiangsu, China). Informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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