

Risk factors for lymph node metastasis in gastric neuroendocrine tumor: a retrospective study

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Abstract

Background: Lymph node metastasis (LNM) plays a vital role in the determination of clinical outcome in patients with gastric neuroendocrine tumor (G-NET). Preoperative identification of LNM is helpful for intraoperative lymphadenectomy. This study aims to investigate risk factors for LNM in patients with G-NET.

Method: We performed a retrospective study involving 37 patients in non-LNM group and 82 patients in LNM group. Data of demographics, preoperative lab result, clinical pathological results, surgical management and postoperative situation were compared between groups. Significant parameters were subsequently entered into logistic regression for further analysis.

Results: Patients in LNM group exhibited older age ($p=0.011$), lower preoperative albumin (ALB) ($p=0.003$), higher carcinoembryonic antigen (CEA) ($p=0.020$), higher International normalized ratio ($p=0.034$), longer thrombin time ($p=0.018$), different tumor location ($p=0.005$), higher chromogranin A positive rate ($p=0.045$), and higher Ki-67 expression level ($p=0.002$). Logistic regression revealed ALB ($p=0.043$), CEA ($p=0.032$), tumor location ($p=0.013$) and Ki-67 ($p=0.041$) were independent risk factors for LNM in G-NET patients.

Conclusions: ALB, CEA, tumor location and Ki-67 expression level correlate with the risk of LNM in patients with G-NET.

Background

Gastric neuroendocrine tumors (G-NET) formed by heterogeneous neoplasms arising from secretory cells of diffuse neuroendocrine system in stomach, one of the most common pathogenic site. Though G-NET is rare with the 1 ~ 2/1,000,000 incidence which account for 6.9 ~ 8.7% of all digestive neuroendocrine neoplasms per year, its incidence is increasing during the last few decades worldwide.[1–4] Surgery serves as the main strategy for the management of G-NET to date.[5] Lymphadenectomy is required in patients with lymph node metastasis (LNM) for the purpose of recurrence and metastasis prevention. Moreover, compared with the metastasis rate of gastric adenocarcinoma, the G-NET lymph node metastasis rate is higher.[6] Of note, G-NETs and LNM diagnosis have become a challenging issue worthy our attention.

The World Health Organization (WHO) revised G grade in neuroendocrine tumors in 2010, in which G stands for grading according to mitotic count and Ki-67 index. The classifications and site-specific staging system are mainly based on clinical pathology and immunohistochemistry, which provides few information of lymph node metastasis. Evidence regarding the preoperative identification of LNM in neuroendocrine tumor is very limited in current literature. In this circumstance, we aim to explore independent risk factors for LNM in patients with G-NET.

Material And Methods

1. Patient selection

Between 2012 and 2019, all patients with G-NET that registered in Gastrointestinal Surgery of our hospital were recruited for qualification screening. The inclusion criteria were as follows: (1) definitive pathological diagnosis of G-NET; (2) the availability of pathological report; (3) absence of preoperative treatment including chemotherapy and radiotherapy.

2. Data collection

Data including demographics, preoperative lab result, clinical pathological results, surgical management and postoperative outcome were retrieved from the Electronic Medical Record System. Demographics included sex, age, underlying disease, past abdominal surgical history and chief complaint. Preoperative lab result consisted of white blood cell count, neutrophil cell count, lymphocyte count, monocyte count, hemoglobin, platelet, albumin (ALB), C-reactive protein (CRP) levels, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Onodera prognostic nutrition index (OPNI), fecal occult blood test, carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), CA125, CA199, CA242, CA724, international normalized ratio (INR), activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT). All these results were recorded from the last test before surgery. Clinical pathological results included lymph node metastasis, total number of resected lymph nodes, tumor size, tumor location, CD56, tumor proliferation index (Ki67), synaptophysin (Syn) and Chromogranin A (CgA). Surgical management included type of surgical procedure, duration of operation and intraoperative hemorrhage. Postoperative outcome consisted of postoperative hospitalization time, postoperative oral feeding time and postoperative complications. All enrolled patients were divided into LNM group or non-LNM group according to the postoperative pathological report.

3. Statistical analysis

All analyses were 2-tailed. The confidence interval was 5 ~ 95%, and p-values < 0.05 were defined as statistically significant. For continuous variables, data were presented as the mean \pm SD (standard deviation), and unpaired t-test with Welch's correction were applied for statistical analysis. For categorical variables, data were presented as frequency (percentage), and Chi-square test with Fisher's exact test were conducted for statistical analysis. Significant variables in univariate analysis were brought into binary logistic regression model for multivariate analysis. And the individual predict risk factors entered receiver operation characteristic (ROC) curve analysis. All statistical analysis were performed in SPSS software (version 23.0; IBM Inc., Chicago, IL) and MedCalc software (version 11.4.2; MedCalc Software, Ostend, Belgium)

Results

Between 2012 and 2019, a total of 122 patients with G-NET that received surgery in our department were enrolled into the study. According to the pathological report, 37 patients formed the non-LNM group, 82

patients formed the LNM group, and the other 3 patients were excluded due to the unavailability of lymph node information in pathological reports.

1. Demographics

Results of univariate analysis were listed in Table 1. Patients in LNM group were older than no LNM group ($p = 0.011$). However, the difference in gender, hypertension, diabetes, other underlying diseases, past abdominal surgical history and chief complaint between two groups were not significant.

Table 1
Demographics

	Non-LNM group	LNM group	P value
Male (n, %)	24(64.9%)	60(83.2%)	0.357
Age (Median \pm SD)	61.22 \pm 10.27	66.09 \pm 9.16	0.011*
Hypertension (n, %)	11(31.4%)	23(28.8%)	0.772
Diabetes (n, %)	2(5.7%)	8(10.0%)	0.696
Other background disease (n, %)	2(5.9%)	6(7.7%)	0.732
Past abdominal surgical history (n, %)	8(22.9%)	21(26.2%)	0.700
Chief complaint			0.410
Health examination/reexamination	2(5.7%)	4(5.0%)	-
Pain	20(57.1%)	35(43.8%)	-
Melena/ hematemesis	4(11.4%)	13(16.2%)	-
Abdominal fullness/ dysphagia/ discomfort	9(25.7%)	22(27.5%)	-
*Significant statistical difference. Standard deviation (SD)			

2. Preoperative lab test

As showed in Table 2, higher ALB level was observed in non-LNM group ($p = 0.003$), whereas higher INR ($p = 0.034$) longer TT ($p = 0.018$) and higher CEA level ($p = 0.020$) were observed in LNM group. The differences of routine preoperative blood test, tumor marker examination and residual items of other lab tests were not significant between two groups. It is worth noting that G grade was not dedicated to dividing two groups.

Table 2
Preoperative lab test

	Non-LNM group	LNM group	P value
WBCs (Median ± SD) 10 ⁹ /L	5.64 ± 1.55	6.35 ± 2.38	0.097
Neutrophils (Median ± SD) 10 ⁹ /L	3.53 ± 1.24	3.92 ± 2.13	0.307
Lymphocytes (Median ± SD) 10 ⁹ /L	1.56 ± 0.50	1.52 ± 0.61	0.749
Monocytes (Median ± SD) 10 ⁹ /L	0.69 ± 1.39	0.52 ± 0.75	0.412
Hb (Median ± SD) g/L	121.43 ± 26.31	114.01 ± 25.61	0.150
PLT (Median ± SD) 10 ⁹ /L	236.84 ± 85.12	228.91 ± 87.55	0.646
ALB (Median ± SD) g/L	39.93 ± 4.71	36.63 ± 5.69	0.003*
CRP (Median ± SD) mg/L	8.18 ± 14.88	16.70 ± 32.75	0.134
NLR (Median ± SD)	2.41 ± 0.88	3.00 ± 2.81	0.226
PLR (Median ± SD)	159.63 ± 58.80	165.78 ± 101.28	0.739
OPNI (Median ± SD)	46.03 ± 9.78	43.54 ± 8.54	0.166
Fecal occult blood test			0.428
- (n%)	28(75.7%)	56(68.3%)	-
+ (n%)	4(10.8%)	13(15.9%)	-
Unknown(n%)	5(13.5%)	13(15.9%)	-
AFP (Median ± SD) ng/ml	9.90 ± 27.94	5.30 ± 18.41	0.320
CEA (Median ± SD) ng/ml	2.41 ± 3.29	12.25 ± 23.78	0.020*
CA125 (Median ± SD) U/ml	23.84 ± 68.17	13.05 ± 15.03	0.203
CA199 (Median ± SD) U/ml	9.29 ± 7.14	27.82 ± 96.43	0.274
CA242 (Median ± SD) U/ml	4.05 ± 3.16	6.60 ± 9.92	0.213
CA724 (Median ± SD) U/ml	2.18 ± 3.56	6.88 ± 23.36	0.312
INR (Median ± SD)	1.01 ± 0.77	1.04 ± 0.78	0.034*
APPT (Median ± SD) s	26.41 ± 5.10	28.25 ± 5.30	0.081
PT (Median ± SD) s	17.66 ± 3.31	18.32 ± 1.85	0.171
TT (Median ± SD) s	11.53 ± 0.87	11.96 ± 0.94	0.018*

3. Oncological characteristics

The distributions of tumor locations were not similar between non-LNM and LNM groups ($p = 0.005$), although the tumor in both groups preferred cardia and fundus of stomach. Besides, higher Ki-67 index ($p = 0.002$) and higher CgA positive rate ($p = 0.045$) were found in LNM group. (Table 3)

Table 3
Oncological characteristics

	Non-LNM group	LNM group	P value
Tumor size	4.44 ± 3.81	5.37 ± 2.54	0.120
Tumor size classification			0.062
< 5 cm (n%)	27(73.0%)	45(54.9%)	-
≥ 5 cm (n%)	10(27.0%)	37(45.1%)	-
G grade			0.210
G1	3(8.3%)	5(6.1%)	-
G2	0(0.0%)	4(4.88%)	-
G3	22(61.1%)	59(72.0%)	-
NEC	11(30.6%)	14(17.1%)	-
Tumor location			0.005*
Cardia and fundus of stomach	16(43.2%)	46(56.3%)	-
Body of stomach	9(24.3%)	30(36.6%)	-
Pyloric antrum	7(18.9%)	5(6.5%)	-
Pyloric canal	5(13.5%)	1(1.2%)	-
CD56			0.177
-(n%)	9(27.3%)	15(21.9%)	-
+(n%)	12(36.4%)	32(46.4%)	-
++(n%)	8(24.2%)	7(10.1%)	-
+++ (n%)	4(12.1%)	15(21.7%)	-
Unknown	4(12.1%)	13(15.9%)	-
Ki67 (Median ± SD)	43.27%±27.59%	58.26%±21.61%	0.002*
Syn,			0.405
-(n%)	0	1(1.2%)	-
+(n%)	14(37.8%)	22(26.8%)	-
++(n%)	5(13.5%)	20(24.4%)	-
+++ (n%)	17(45.9%)	37(45.1%)	-

	Non-LNM group	LNM group	P value
Unknown	1(2.7%)	2(2.4%)	-
CgA			0.045*
-(n%)	9(24.4%)	22(26.8%)	-
+(n%)	14(37.8%)	31(37.8%)	-
++(n%)	0	11(13.4%)	-
+++ (n%)	13(35.1%)	15(18.3%)	-
Unknown	1(2.7%)	3(3.7%)	-

4. Short-turn outcomes

There was no statistical difference of surgical procedure, duration of operation, intraoperative hemorrhage, postoperative hospitalization time, postoperative oral feeding time and postoperative complications between two groups. (Table 4) Taken together, we mainly focus on predictable risk factors in this article.

Table 4
Surgical procedures and outcome

	Non-LNM group	LNM group	P value
Surgical procedure			0.119
Local resection	2(5.4%)	1	-
Distal gastrectomy	9(24.3%)	9(11.0%)	-
Proximal gastrectomy	6(16.2%)	13(15.9%)	-
Total gastrectomy	20(54.1%)	59(72.6%)	-
Duration of operation (Median \pm SD) min	225.97 \pm 84.84	239.83 \pm 71.07	0.367
Intraoperative hemorrhage (Median \pm SD)	338.57 \pm 541.93	260.13 \pm 259.23	0.303
Postoperative hospitalization time (Median \pm SD) day	14.97 \pm 10.16	13.49 \pm 5.44	0.311
postoperative oral feeding time (Median \pm SD)day	9.09 \pm 6.46	7.61 \pm 2.91	0.093
Postoperative complications (n,%)	1(2.7%)	1(1.2%)	0.509
Length of intense care unit stay (Median \pm SD) day	0.56 \pm 0.94	0.59 \pm 1.59	0.897

To exclude potential interaction between variables, binary logistic regression was further conducted. Significant variables identified in previous univariate analysis, including age, ALB, CEA, INR, TT, tumor location, Ki67 and CgA, were entered into the regression model. ALB ($p = 0.004$), CEA ($p < 0.001$), tumor location ($p = 0.006$) and Ki67 ($p = 0.041$) were statistically significant between non-LNM group and LNM group (Table 5). The ROC curve analysis exert the risk factors with a significant result (AUC = 0.779, 95% CI = 0.688 ~ 0.855, p value < 0.0001). (Figure.1)

Table 5
 Logistic regression analysis of risk factors for lymph node metastasis in G-NET.

	95% CI	OR	P value
ALB	0.789 ~ 0.996	0.887	0.043
CEA	1.009 ~ 1.228	1.113	0.032
Tumor location			0.013
Cardia and fundus of stomach	ref		
Body of stomach	0.585 ~ 81.856	6.920	0.125
Pyloric antrum	0.840 ~ 137.107	10.733	0.068
Pyloric canal	0.008 ~ 7.373	0.238	0.413
Ki-67	1.085 ~ 61.568	8.174	0.041

Table 6

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Pyloric canal	0.008 ~ 7.373	0.238	0.413
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Discussion

Here is a summary of our main findings in this study. By comparing G-NET patients with or without lymph node metastasis, we found that older age, preoperative lower albumin level, higher CEA level, higher INR, longer TT, higher Ki67 and CgA positive rate were associated with lymph node metastasis. Logistic regression identified that ALB, CEA, tumor location and Ki67 were risk factors for LNM in patients with G-NET. There has been an increasing incidence of G-NET in recent decades.[7] Surgical resection is the first-line recommendation for G-NET.[8] However, it is largely unknown how to determine the possibility of LNM

preoperatively. Here, our study has provided useful information that ALB, CEA and Ki67 as well as location of tumor are associated with the possibility of LNM in patients with G-NET.

As with other digestive NETs, our patients were divided into several groups as specified according to the WHO G grade classification system. Albeit G grade system has exerted the versatile negative prognostic factor in digestive NETs from pancreas and jejunum-ileum, its diagnosis value for determining the prognosis of patients with G-NET didn't live up to expectation.[9] Likewise, the lack of solid evidence situated on the G grade system effective on G-NET lymph node metastasis aroused our interest. However, resultant data retard the harnessing of G grade system to predict nodal metastasis. We sought to figure out risk factors with forecasted usage value to address this issue in this scenario.

Serum ALB level is an easily accessible laboratory indicator that reflects individual nutritional status. Previous study has demonstrated that albumin is a vital source of energy and amino acids for tumor cells, and it was increasingly absorbed by tumor cells owing to fast grow and active metabolism of tumors.[10] In addition, ALB is considered as an indicator of systemic inflammatory reaction in malignant tumors. G-NET potentially affects digestive and absorptive ability and is associated with systemic inflammatory response. Both of reasons lead to suppressed synthesis of ALB, which was found more severe in G-NET patients with LNM. [11] A study involving 207 patients with malignant tumors reported that patients with lower prognostic nutrition index exhibited higher lymph node metastasis rate. Another retrospective study recruited 136 patients found that lymph node invasion was significantly correlated with ALB level.[12] Moreover, a scoring system named Glasgow prognostic score based on inflammation (CRP and ALB) has been validated as a versatile predicting progress for gastric cancer[13].

CEA is associated with various types of cancer including gastric cancer and correlated with overall survival of patients. [14, 15]A study in China found that increased CEA level were associated with LNM in remnant gastric cancer.[16] Another study discovered that gastroenteropancreatic neuroendocrine neoplasm patients with elevated CEA, CA125 or CA19-9 exhibited worse overall survival.[17] Nevertheless, there were few data about the relationship between CEA and LNM in NET. Our study found that elevated CEA could serve as a predicting factor of LNM in G-NET.

There were few studies discussing the correlation between tumor location and LNM in G-NET. Liang J et al revealed that G-NET mainly located in esophagogastric junction, most of which were aggressive malignant.[18] To our knowledge, our findings are the first investigation towards tumor location and LNM in G-NET. Our study has highlighted the tumor distribution in stomach associated with LNM manifestation in this specific cohort of patients. As for clinicians, LNM is worthy of more concern facing the G-NET patient whose tumor located in cardia and fundus of stomach and body of stomach.

The nuclear antigen Ki67 structurally associated with chromatin helps determine tumor grade and prognosis. [19] Previous studies suggested a significant correlation between Ki-67 level and clinical outcome. BOO, Y. J. et al revealed that higher Ki67 (> 60%) was associated with aggressive G-NET.[20] Another study illustrated that higher Ki67 was not only associated with higher T stage ($p = 0.003$) but also tended to be associated with LNM ($p = 0.071$).[21] In consistent with previous reports, our study revealed

that higher Ki67 could serve as an independent predict factor for LNM in G-NET. In fact, when it comes to neuroendocrine tumors, Ki67 is the major prognostic factor and utilized in the novel grading system.[22]

We are aware of the limitations in our study. First, this is a single-center retrospective study that may lead to potential selection bias. Second, since the short-term outcomes between two groups was not significant and the follow-up data is not fully available, we did not compare long-term outcomes of G-NET patients in LNM and non-LNM group. Third, the rarity of G-NET and limited sample size hampers subgroup analysis such as distant metastasis compared to adjacent metastasis. In addition, molecular analysis was conducted in very few patients, which leads to failure of comparison of molecular features between LNM and non-LNM groups. Nevertheless, our study has provided a comprehensive exploration towards possible risk factors of lymph node metastasis in patients with G-NET to explore effective prediction for clinicians. (Figure.2) Future prospective studies are expected to provide more possibility in the identification of LNM in G-NET.

Conclusions

In conclusion, ALB, CEA, tumor location and Ki67 expression level correlate with the risk of LNM in patients with G-NET. Furthermore, multicenter prospective study are expected to validate our results in the future.

Declarations

Ethics approval and consent to participate

This study has been approved by the Ethics Committees of Nanjing Drum Tower Hospital. Informed consent is waived for this retrospective study by the Ethics Committees of Nanjing Drum Tower Hospital. We confirmed all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

All authors agree to publish.

Competing interests

All authors have no conflict of interest.

Availability of data and material

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

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Author Contributions

Wenxian Guan and Song Liu designed the research; Xianghui Li, Meng Wang and Xiaofeng Lu collected the data; Xianghui Li, Zhengyang Yang, Shichao Ai and Feng Sun performed the data analysis; Xianghui Li wrote the manuscript; Wenxian Guan and Song Liu reviewed the manuscript.

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Figures

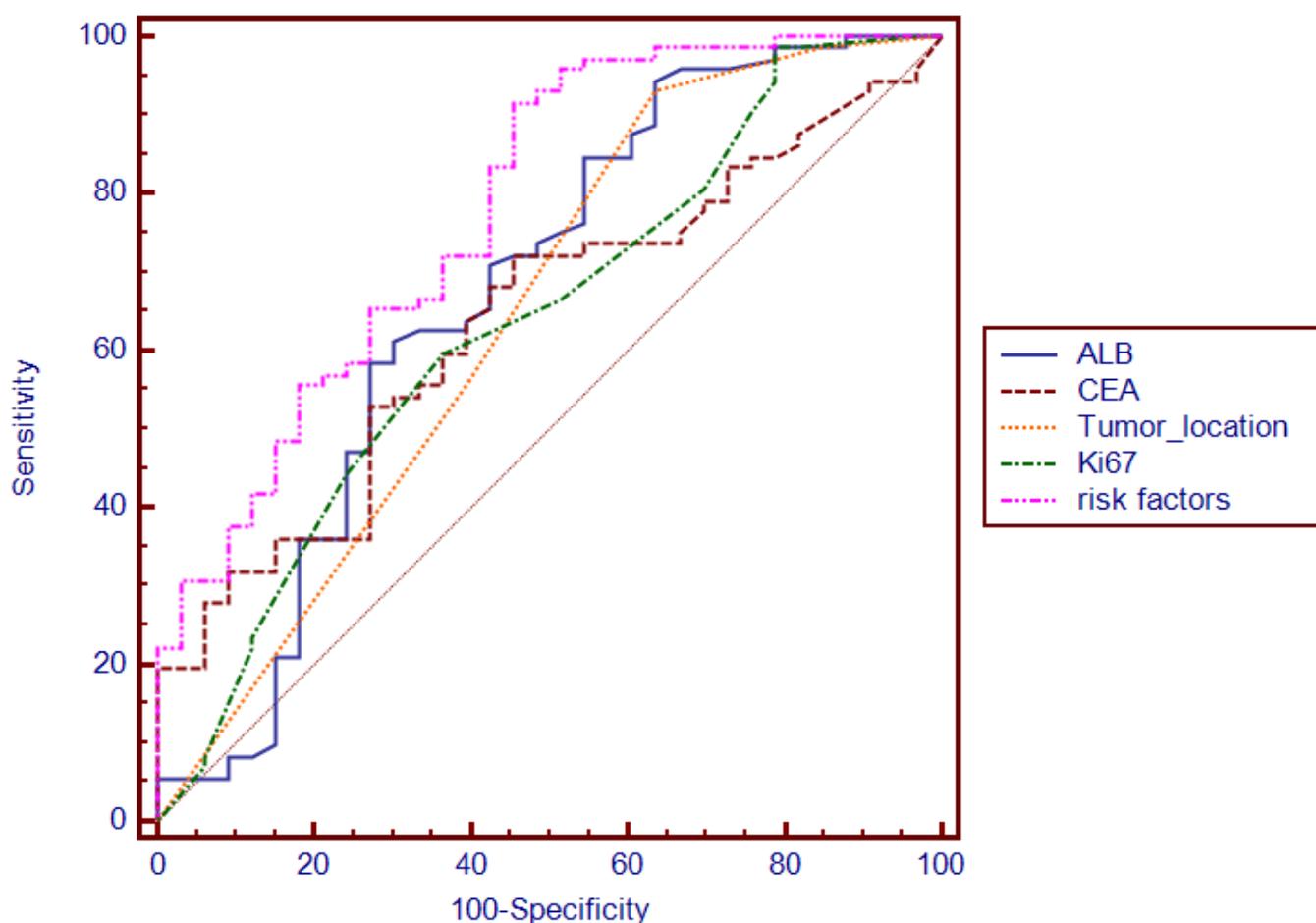


Figure 1

The ROC curve of ALB, CEA, Ki67, tumor site and the integrated diagnostics to lymph node metastasis. (ALB: AUC=0.707, 95% CI=0.616~0.787, p=0.0002; CEA: AUC=0.642, 95% CI=0.543~0.733, p=0.0101; Tumor location: AUC=0.618, 95% CI=0.524~0.705, p=0.0344; Ki67: AUC=0.657, 95% CI=0.564~0.742, p=0.0044; Risk factors: AUC=0.779, 95% CI=0.688~0.855, p<0.0001)

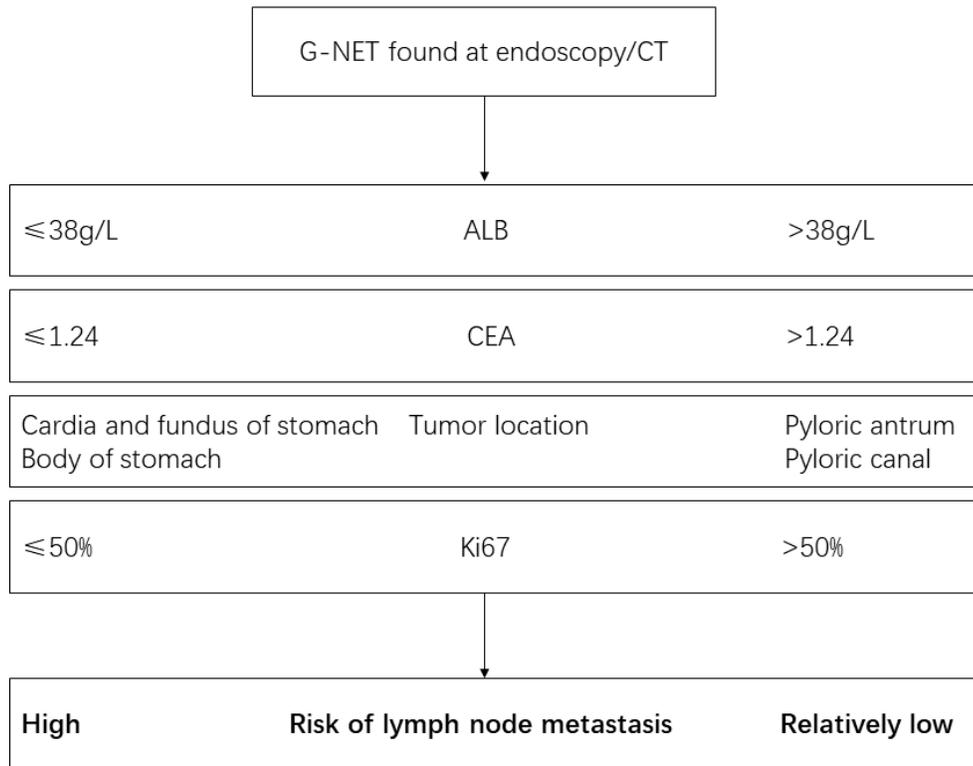


Figure 2

Proposed risk of lymph node metastasis approach to G-NET. The cut-off values were extracted from previous ROC curve analysis.