Clinicopathological and prognostic features of early gastric cancer patients after surgery: a retrospective study

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Research

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Abstract

Background: Despite the decline in the incidence of gastric cancer, the incidence of early gastric cancer has increased. Hence, understanding the clinicopathological and prognostic features of early gastric cancers could help us understand the development of gastric cancer and improve the prognosis of early gastric cancer.

Methods: A total of 244 patients diagnosed with early gastric cancer after surgery at Xiangya Hospital Central South University were retrospectively analyzed.

Results: General data showed that in patients with a mean age of 54.30 ± 10.68 years (M:F = 1.6:1), the median tumor size was 2.203 ± 1.245 cm. A total of 15.6% of patients had lymph node metastasis. By univariate analysis, the longest diameter of the tumor, T stage, total number of dissected lymph nodes, number of metastatic lymph nodes, metastatic-to-total dissected lymph node (LN) ratio, vascular invasion, NLRc, and MLRc were associated with disease-free survival; tumor size, invasive depths, vascular invasion, NLRc, MLRc, NWRc and LWRc were associated with lymph node metastasis. Additionally, the longest diameter of tumor and total number of dissected lymph nodes were independent factors for early gastric cancer patients; tumor size, invasive depths, vascular invasion and NLRc were independent risk factors for lymph node metastasis in EGC.

Conclusion: The longest diameter of the tumor and total number of dissected LNs were independent prognostic factors for EGC patients. Additionally, the longest diameter of the tumor, tumor invasive depths, vascular invasion and NLRc were the independent risk factors for lymph node metastasis in EGC patients.

Introduction

In recent years, the incidence rates of gastric cancer (GC) have been declining steadily worldwide[1]. However, GC is still the fifth most common malignant tumor and the third leading cause of cancer-related mortality globally, with an estimated 1,033,701 new cases and 782,654 deaths in 2018[2, 3]. This translates into a high fatality to new case rate of 75%, which is much higher than that of other prevalent solid cancers, including breast and prostate cancers[2]. The incidence of GC varies regionally, with approximately 70% occurring in Eastern Asia, Central and Eastern Europe and South America[4]. Approximately 50% of patients are diagnosed with advanced disease, with a 5-year cancer-specific survival rate lower than 30%[5]. However, the prognosis of GC markedly depends on the stage at diagnosis. In Western countries, including Europe and the United States, the 5-year survival rate does not exceed 25%[6], but in Japan, the 5-year cancer-specific survival rate is 90% with the diagnosis of early GC of up to 50%[7].

Similar to other common cancers, GC rarely occurs in children and young persons, with a peak incidence ranging from 55 to 80 years, and gastric cancer rates are twice as high in men as in women[8]. GC is divided into early gastric cancer (EGC) and advanced gastric cancer, with significant differences in

recurrence and cancer-related survival rates. EGC is defined as a carcinoma invading the mucosa and/or submucosa with or without lymph node metastases[9]. Despite a decline in the incidence of total gastric cancer and the aging of the population, the incidence of early gastric cancer has been steadily increasing since the late 1980s[10].

Recent studies on EGC data remain incomplete and conflicting; with the growing incidence of early gastric cancer, it is essential to focus on the clinical and prognostic features of early gastric cancer, as they are controversial. We retrospectively examined patients with early gastric cancer in our center, aiming to achieve a better understanding of clinicopathologic features, the development of gastric cancer and prognostic factors in early gastric cancer and to improve the outcomes of gastric cancer.

Patients And Methods

Patient selection

Data of patients who were diagnosed with EGC from January 2013 to December 2018 after surgery at Xiangya Hospital Central South University were collected through a pathology information system. The eligibility criteria in this study included (1) patients who were histopathologically diagnosed with early gastric cancer (carcinoma invading the mucosa and/or submucosa) after surgery; (2) no other synchronous malignant neoplasia; (3) no perioperative or postoperative chemotherapy or radiotherapy applied.

This retrospective study was supported by the Medical Ethical Committee of Xiangya Hospital, Central South University, and due to the retrospective nature of the study, informed consent was waived.

Data of routine blood collection

All patients' preoperative and postoperative peripheral routine blood tests were drawn within 7 days before the operation and 7 days after the operation. iNLR (initial preoperative neutrophil-to-lymphocyte ratio), iMLR(initial preoperative monocyte-to-lymphocyte ratio), iNWR (initial preoperative neutrophil-to-white blood cell ratio), iLWR (initial preoperative lymphocyte-to-white blood cell ratio), iPLR (initial preoperative platelet-to-lymphocyte ratio), iMWR (initial preoperative monocyte-to-white blood cell ratio), NLRc (postoperative change NLR), MLRc (postoperative change MLR), NWRc (postoperative change NWR), LWRc (postoperative change LWR), PLRc (postoperative change PLR), and MWRc (postoperative change MWR) were determined by ROC curve analysis.

Follow-up data

Patients who underwent surgery were followed every 3 months for the first 2 years, every 6 months between 2 and 5 years, and then every 12 months thereafter. We supplemented the follow-ups with our outpatient system or communicated with patients by telephone. We examined the postoperative EGC patients by chest scan, abdominal CT scan, magnetic resonance imaging (MRI) scan, abdominal ultrasound scan, endoscopy (including gastroscopy and colonoscopy) and positron emission

tomography-computerized tomography (PET-CT) (if necessary) to evaluate tumor recurrence and distant metastasis. All patients were monitored until October 1, 2019, or death. Metastatic recurrence revealed by imaging and death were regarded as the endpoint events.

X-tile and statistical analyses

Patient characteristics between each group were compared by chi-square test. The values for the iNLR, iMLR, iPLR, iNWR, iLWR, iMWR, NLRc, MLRc, PLRc, NWRc, LWRc, MWRc, longest diameter of the tumor, total number of dissected lymph nodes (LNs), number of metastatic LNs, and ratio of metastatic-to-total dissected LNs were determined by receiver operating characteristic (ROC) curve, based on the results of the ROC curve, X-tile analyses were conducted to assess the optimal cutoff values based on the integral optic density (IOD). The disease-free survival (DFS) and overall survival (OS) were calculated by the Kaplan–Meier method, and differences between Kaplan–Meier curves were investigated by the log-rank test. Significant predictors for survival identified by univariate analysis were further assessed by multivariate analysis using a multivariate Cox proportional hazards regression model (forward stepwise method, conditional likelihood ratio). The significant predictors for lymph node metastasis by univariate analysis were further assessed by logistic regression. Statistical analyses were performed using SPSS V22.0 (SPSS Inc., USA). P value was considered statistically significant below the 5% level.

Results

Clinicopathologic features for EGC patients

For our research, 244 patients were eventually enrolled as our study group (Fig. 1). As shown in Table 1, the EGC group comprised 149 males and 95 females, and the male-to-female ratio was approximately 1.6:1, with a mean age of 54.30 ± 10.68 years, ranging from 24 to 82 years. All patients underwent D2 lymphadenectomy and curative gastrectomy (68.9% underwent the open method and 31.3% underwent the laparoscopy method). Most EGC patients underwent Billroth II reconstruction (71.7%), the tumor was most commonly located in the antrum and pylorus (61.9%), and the average size of the longest diameter of the tumor was 22.03 ± 12.45 mm, ranging from 3 to 85 mm. The most common pathological features included moderate-poor differentiation (58.2%), T1b (50.4%), N0 (84.4%), non-perineurium invasion (99.2%), nonvascular invasion (90.6%), HER2-negative immunohistochemistry (81.6%) and TMN stage Ia (76.6%). More details are shown in Table 1.

Table 1
Characterization of the study group

Quality		N(%) or mean $\pm$ SD
Mean Age[years](range)		54.30 $\pm$ 10.68(24–82)
Gender	Male	149 (61.1%)
	Female	95 (38.9%)
Methods for operation	Open method	168(68.9%)
	Laparoscopic method	76 (31.3%)
Methods for reconstruction	Billroth I	36 (14.8%)
	Billroth II	175(71.7%)
	Roux-en-Y	33 (13.5%)
Localization	Cardia	6(2.5%)
	Fundus	21(8.6%)
	Body of stomach	66(27.0%)
	Antrum and pylorus	151(61.9%)
Tumor maximal dimension [mm] (range)		22.03 $\pm$ 12.45(3–85)
Tumor differentiation	Well	102(41.8%)
	Moderate-poor	142(58.2%)
T stage	Tis	17(7.0%)
	T1a	104(42.6%)
	T1b	123(50.4%)
N stage	N0	206(84.4%)
	N1	23(9.4%)
	N2	11(4.5%)
	N3a	4(1.6%)
Numbers of lymph nodes dissection		20.92 $\pm$ 7.53(4–51)
Metastatic numbers of lymph nodes dissection		0.45 $\pm$ 1.44(0–10)
Perineuronal invasion	Yes	2(0.08%)
	No	242(99.2%)
vascular invasion	Yes	23(9.4%)

Quality		N(%) or mean $\pm$ SD
Immunohistochemistry score for her-2	No	221(90.6%)
	0	199(81.6%)
	+	26(10.7%)
	++	14(5.7%)
	+++	5(2.0%)
TNM stage*	0	17(7.0%)
	Ia	187(76.6%)
	Ib	25(10.2%)
	IIa	11(4.5%)
	IIb	4(1.6%)
*according to the NCCN guidelines Gastric cancer(2019,Version 4)		

ROC analysis and X-tile analyses

The values of iNLR, NLRc, iMLR, MLRc, iPLR, PLRc, iNWR, NWRc, iLWR LWRc, iMWR and MWRc were calculated by using ROC curves. Results showed the areas under the ROC curve for NLRc and MLRc were 0.632 (95% CI: 0.519–0.744; P = 0.046) and 0.659 (95% CI: 0.549–0.768; P = 0.016), respectively (Table 2, Fig. 2a-e). Besides, NLRc = 7.80 and MLRc = 1.40 were the optimal cutoff points determined by the X-tile program (Fig. 3a-b).

Table 2
Area under the curve(AUC) identified by Disease-free Survival

Variable	Area	P value	95%CI
iNLR	0.510	0.882	0.380–0.639
iMLR	0.543	0.516	0.420–0.666
iPLR	0.571	0.281	0.448–0.695
iNWR	0.512	0.859	0.381–0.643
iLWR	0.484	0.806	0.359–0.609
iMWR	0.508	0.898	0.369–0.648
NLRc	0.632	0.046	0.519–0.744
MLRc	0.659	0.016	0.549–0.768
PLRc	0.536	0.589	0.399–0.672
NWRc	0.566	0.315	0.441–0.692
LWRc	0.611	0.085	0.489–0.734
MWRc	0.524	0.714	0.397–0.652
Tumor maximal dimension	0.712	0.001	0.617–0.808
Total LN dissection numbers	0.690	0.003	0.573–0.807
Metastatic LN dissection numbers	0.764	0.001	0.634–0.894
Metastatic-to-total LN dissection numbers ratio	0.770	0.001	0.639–0.901
CI: Confidence interval; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; NWR: neutrophil-to-white blood cell ratio; LWR: lymphocyte-to-white blood cell ratio; MWR: monocyte-to-white blood cell ratio;LN: lymph node;LN: lymph node.			

In addition, results also indicated that the areas under the ROC curve for the longest diameter of the tumor, total number of dissected LNs, number of metastatic LNs and ratio of metastatic-to-total dissected LNs were 0.712 (95% CI: 0.617–0.808; $P = 0.001$), 0.690 (95% CI: 0.573–0.807; $P = 0.003$), 0.764 (95% CI: 0.634–0.894; $P = 0.001$), and 0.770 (95% CI: 0.639–0.901; $P = 0.001$), respectively (Table 2, Fig. 2f-i). Moreover, the best cutoff values were 2.0 cm for the diameter of the tumor, 13 for the total number of dissected LNs, 1 for the number of metastatic LNs, and 6% for the ratio of metastatic-to-total dissected LNs determined by X-tile program (Fig. 3c-f).

Risk factors for lymph node(LN) metastasis in EGC patient

Since the LN metastasis plays a critical role for the selection of clinical treatment (EMR/ESD or surgery) in EGC patients, it is essential to identify the risk factors for LN metastasis in EGC patients. ROC curve

was conducted to calculate the best cutoff points of each viriate for the LN metastasis. Results showed that the optimal cutoff points of NLRc, MLRc, NWRc, LWRc, and tumor maximal dimension were 5.29, 0.49, 0.70, 0.13 and 1.9, respectively (Table S1, Figure S1). Next, we investigated the risk factors for lymph node metastasis according to univariate analysis. As shown in Table 3, tumor maximal dimension, T stage, vascular invasion, NLRc, MLRc, NWRc, and LWRc were associated with LN metastasis in EGC patients. Moreover, through multivariate analysis we found that tumor maximal dimension (≤ 1.9 / >1.9 cm) (RR:2.421, $p = 0.044$), T stage (Tis + T1a/T1b) (RR:3.807, $p = 0.004$), vascular invasion (yes/no) (RR:0.241, $p = 0.006$) and NLRc (≤ 5.29 / >5.29) (RR:8.500, $p = 0.010$) were the independent risk factors for LN metastasis in EGC patients (Table 4).

Table 3
Risk Factors for LN metastasis in EGC patients according to univariate analysis

Risk factors		LN-	LN+	95% CI	P value
Age(years)	≤60	129	28	0.234–1.156	0.104
	≥ 60	77	10		
Gender	Male	129	20	0.751–3.026	0.246
	Female	77	18		
Methods for operation	Open method	141	27	0.413–1.890	0.750
	Laparoscopic method	65	11		
Methods for reconstruction	Billroth I	33	3	-	0.310
	Billroth II	144	31		
	Roux-en-Y	29	4		
Localization	Cardia	5	1	-	0.752
	Fundus	18	3		
	Body of stomach	53	13		
	Antrum and pylorus	130	21		
Tumor maximal dimension [cm]	≤ 1.9	93	9	1.196–5.882	0.014
	>1.9	113	29		
Tumor differentiation	Well	91	12	0.820–3.583	0.149
	Moderate-poor	115	26		
T stage	Tis	17	0	-	0.005
	T1a	94	10		
	T1b	95	28		
Perineuronal invasion	Yes	1	1	0.011–2.950	0.178
	No	205	37		
vascular invasion	Yes	11	12	0.049–0.305	<0.001
	No	195	26		
Immunohistochemistry score (Her-2)	0	171	28	-	0.119
	+	18	8		
	++	12	2		

Risk factors		LN-	LN+	95% CI	P value
	+++	5	0		
NLRc	≤ 5.29	93	7	1.535–8.655	0.002
	>5.29	113	31		
MLRc	≤ 0.49	50	2	1.341–24.819	0.009
	>0.49	20	5		
NWRc	≤ 0.70	70	5	1.270–9.086	0.011
	>0.70	136	33		
NLRc	≤ 0.13	106	27	0.203–0.916	0.026
	>0.13	100	11		
LN: lymph node; EGC: early gastric cancer; EGC: early gastric cancer; cm: centimetre; LN: lymph node; NLRc: postoperative neutrophil-to-lymphocyte ratio change; MLRc: postoperative monocyte-to-lymphocyte ratio change; NWRc: postoperative neutrophil-to-white blood cell ratio change; LWRc: postoperative lymphocyte -to-white blood cell ratio change.					

Table 4
Risk Factors for LN metastasis in EGC patients according to multivariate analysis

Risk factors	B	SE	RR	95% CI	P value
Tumor maximal dimension (≤ 1.9 / >1.9 cm)	0.884	0.440	2.421	1.023–5.799	0.044
T stage(Tis + T1a/T1b)	1.337	0.464	3.807	1.533–9.452	0.004
vascular invasion(yes/no)	-1.423	0.515	0.241	0.088–0.661	0.006
NLRc(≤ 5.29 / >5.29)	2.140	0.826	8.500	1.683–42.914	0.010
MLRc (≤ 0.49 / >0.49)	1.178	0.828	3.246	0.642–16.453	0.154
MLRc (≤ 0.70 / >0.70)	0.286	0.661	1.331	0.364–4.865	0.665
MLRc (≤ 0.13 / >0.13)	1.347	0.699	3.844	0.978–15.117	0.054
LN: lymph node; EGC: early gastric cancer; EGC: early gastric cancer; cm: centimetre; LN: lymph node; NLRc: postoperative neutrophil-to-lymphocyte ratio change; MLRc: postoperative monocyte-to-lymphocyte ratio change; NWRc: postoperative neutrophil-to-white blood cell ratio change; LWRc: postoperative lymphocyte -to-white blood cell ratio change.					

Prognostic features for EGC

We further investigated the relationship between the clinicopathologic features and prognosis of EGC patients according to univariate analysis. As shown in Table 5, we found the longest diameter of the tumor > 2 cm, T1b, total number of dissected LNs ≤ 13 , number of metastatic LNs ≥ 1 , ratio of metastatic-to-total dissected LNs $\geq 6\%$, vascular invasion, NLRc > 7.80 , MLRc > 1.40 were both associated with

recurrence/metastasis and overall survival in EGC patients. Next, Cox proportional hazard models were performed to identify independent prognostic factors. Those identified as significant prognostic factors by univariate analysis were further assessed by a multivariate analysis. The multivariate analysis results showed that the longest diameter of the tumor ($\leq 2/ >2$ cm) (RR: 7.404, P = 0.001) and total number of dissected LNs ($\leq 13/ >13$) (RR: 0.289, P = 0.015) were independent risk factors for recurrence/metastasis in EGC patients (Table 6), otherwise, longest diameter of tumor ($\leq 2/ >2$ cm) (RR: 4.109, P = 0.033) was the independent risk factors for overall survival in EGC patients (Table 7). The DFS and OS for the significant prognostic factors identified by the multivariate analysis is presented in Fig. 5.

Table 5
Prognostic Factors in EGC patients according to univariate analysis

Prognostic factors		Number	DFS		OS	
			95% CI	P value	95% CI	P value
Age(years)	≤60	158	72.311–78.587	0.140	72.744–78.874	0.941
	≥ 60	86	64.002–74.879		70.292–78.258	
Gender	Male	149	69.120–75.992	0.700	72.373–77.898	0.263
	Female	95	69.057–78.181		69.625–78.659	
Methods for operation	Open method	168	69.457–75.631	0.738	72.109–77.252	0.424
	Laparoscopic method	76	65.962–78.996		67.532–79.906	
Methods for reconstruction	Billroth I	36	74.225–80.517	0.259	74.423–80.452	0.177
	Billroth II	175	68.084–75.918		70.645–77.748	
	Roux-en-Y	33	62.928–77.358		69.810–77.904	
Localization	Cardia	6	-	0.583	-	0.909
	Fundus	21	-		-	
	Body of stomach	66	-		-	
	Antrum and pylorus	151	-		-	
Tumor maximal dimension[cm]	≤ 2	140	75.813–80.586	0.001	76.621–80.909	0.004
	>2	104	60.953–71.988		65.094–74.938	
Tumor differentiation	Well	103	68.198–76.818	0.964	70.182–77.897	0.809
	Moderate-poor	141	70.358–77.545		72.973–79.132	

Prognostic factors		Number	DFS		OS	
			95% CI	P value	95% CI	P value
T stage	Tis + T1a	121	72.946–78.524	0.013	75.091–79.215	0.019
	T1b	123	65.677–75.136		68.529–77.093	
Total LN numbers	≤ 13	32	56.160–74.715	0.006	61.206–77.822	0.017
	≥ 13	212	71.386–76.631		73.116–77.687	
Metastatic LN numers	0	206	41.107–56.570	0.001	77.240–80.725	0.001
	≥ 1	38	39.656–49.126		46.925–63.573	
Metastatic-to-total LN ratio	≤ 6%	219	75.462–79.773	0.001	77.487–80.744	0.001
	≥ 6%	25	32.105–50.481		37.059–57.319	
Perineuronal invasion	Yes	2	-	0.656	-	0.682
	No	242	-		-	
vascular invasion	Yes	23	33.024–54.850	0.001	35.285–54.730	0.001
	No	221	73.715–78.722		76.566–80.299	
Immunohistochemistry score for Her-2	0	199	-	0.410	-	0.369
	+	26	-		-	
	++	14	-		-	
	+++	5	-		-	
NLRc	≤ 7.80	149	74.102–79.649	0.014	75.453–80.315	0.045
	≥ 7.80	95	60.067–71.073		64.168–73.808	
MLRc	≤ 1.40	219	72.776–78.148	0.002	74.550–79.242	0.014
	≥ 1.40	25	43.446–64.243		49.086–68.157	

Prognostic factors	Number	DFS		OS	
		95% CI	P value	95% CI	P value
EGC: early gastric cancer; DFS:disease-free survival; OS: overall survival; EGC: early gastric cancer; LN: lymph node; cm: centimetre; LN: lymph node; NLRc: postoperative neutrophil-to-lymphocyte ratio change; MLRc: postoperative monocyte-to-lymphocyte ratio change.					

Table 6
Prognostic Factors for DFS in EGC patients according to multivariate analysis

Prognostic factors	B	SE	RR	95% CI	P value
Tumor maximal dimension ($\leq 2/2$ cm)	2.002	0.604	7.404	2.265–24.196	0.001
T stage(Tis + T1a/T1b)	0.825	0.568	2.281	0.750–6.939	0.146
Total LN numbers ($\leq 13/13$)	-1.242	0.513	0.289	0.106–0.789	0.015
Metastatic LN numers($0/\geq 1$)	0.965	1.157	2.626	0.272–25.336	0.404
Metastatic-to-total LN ratio($\leq 6\%/6\%$)	0.970	1.149	2.637	0.277–25.077	0.399
vascular invasion(yes/no)	-0.517	0.571	0.596	0.195–1.824	0.365
NLRc($\leq 7.80/7.80$)	0.764	0.544	2.148	0.740–6.235	0.160
MLRc ($\leq 1.40/1.40$)	0.872	0.564	2.392	0.792–7.228	0.122
DFS: Disease-free survival, EGC: Early gastric cancer, CI: confidence interval, RR: relative risk, LN: lymph node, cm: centimetre, NLRc = postoperative neutrophil-to-lymphocyte ratio change, MLRc = postoperative monocyte-to-lymphocyte ratio change.					

Table 7
Prognostic Factors for OS in EGC patients according to multivariate analysis

Prognostic factors	B	SE	RR	95% CI	P value
Tumor maximal dimension ($\leq 2/$ ≥ 2 cm)	1.413	0.665	4.109	1.117–15.121	0.033
T stage(Tis + T1a/T1b)	0.601	0.738	1.825	0.429–7.759	0.415
Total LN numbers ($\leq 13/$ ≥ 13)	-0.952	0.606	0.386	0.118–1.266	0.116
Metastastic LN numers($0/$ ≥ 1)	-7.753	79.179	0.000	0.000-1.072E + 64	0.922
Metastastic-to-total LN ratio($\leq 6\%/$ $\geq 6\%$)	9.569	79.179	14315.765	0.000-3.570E + 71	0.904
vascular invasion(yes/no)	-1.090	0.703	0.336	0.085–1.333	0.121
NLRc($\leq 7.80/$ ≥ 7.80)	0.413	0.653	1.511	0.421–5.428	0.527
MLRc ($\leq 1.40/$ ≥ 1.40)	0.781	0.713	2.183	0.540–8.829	0.274
OS: overall survival, EGC: early gastric cancer, CI: confidence interval, RR: relative risk, LN: lymph node, cm: centimetre, NLRc = postoperative neutrophil-to-lymphocyte ratio change, MLRc = postoperative monocyte-to-lymphocyte ratio change.					

Discussion

Gastric cancer (GC) has been a critical health burden due to its high morbidity and mortality worldwide, with approximately 1,033,701 new cases and 782,654 deaths in 2018[2]. Gastric cancer can be divided into early gastric cancer (EGC) and advanced gastric cancer, with significant differences in prognosis. Moreover, despite the declining incidence of GC and due to the advancement of early diagnostic techniques and health examinations, the incidence of EGC seems to have steadily increased since the late 1980s[10–11]. Many studies have indicated clinicopathologic features, multiple genes and molecules in advanced gastric cancer; however, there are limited studies focusing on the clinicopathologic and prognostic features of EGC.

Our retrospective analysis of 244 patients with EGC found that the male-to-female ratio was 1.6:1, indicated that gastric cancer is a sex-related carcinoma regardless of whether early gastric cancer or overall gastric cancer patients were included, similar results were indicated by McGuire, S [8]. We further investigated the prognostic features in EGC and found no significant differences in age, sex, surgical methods, reconstruction methods, tumor location, tumor differentiation, perineurium invasion or immunohistochemistry score for HER2. As our previous study indicated that laparoscopic distal gastrectomy achieves the same degree of radicality and short-term prognosis as open distal gastrectomy[12], we now verified no significant difference between laparoscopic and open surgical methods in terms of long-term survival of GC patients. Additionally, we found that HER2 expression had

no prognostic influence in EGC. However, some retrospective studies have suggested that HER2 positivity is the second worst prognostic factor[13, 14], whereas other studies have suggested that HER2 status has no relationship with short- and long-term survival according to univariate and multivariate analyses[15].

We found that the longest diameter of the tumor ≥ 2 cm were the best cutoff points for the prognosis factor in our large-scale group of EGC patients. Furthermore, the longest diameter of the tumor ($\leq 2/ \geq 2$ cm) and total number of dissected LNs ($\leq 13/ \geq 13$) were independent risk factors for EGC patients according to multivariate analysis, with RRs of 7.404 ($P = 0.001$) and 0.289 ($P = 0.015$), respectively. Li Y reported that lesions of over 2 cm might be more likely to have lymph node metastasis in EGC[17]. Similar results have been verified by Li H et al.[18]. Our research is the first to identify the relationship between the longest diameter of the tumor and disease-free survival rate by using X-tile software and ROC curves.

The radical dissection of lymph nodes is a highly effective procedure in gastric cancer to improve the prognosis of GC and limit LN metastasis. Our study found that LN metastasis was 13.9% in EGC, which is higher than the LN metastasis rate of 2.5–8.6% in Japan[19]. In addition, NCCN guidelines indicated that the number of dissected LNs in GC should be greater than 15; due to the lower incidence of LN metastasis in EGC, lymphadenectomy is always applied with D1+, modified D2 or D2. However, Wu H et al, indicated that in EGC patients with unknown LN status, D2 dissection was the first choice, which could prolong the survival time for those patients[20]; a similar suggestion was given by Korean and Japanese investigators[21, 22]. Our research also showed that the number of dissected LNs lower than 13 was associated with a poor prognosis of EGC patients, and this might be because limited LN dissection might lead to residual cancer, increasing the risk of recurrence or metastasis.

Since lymph node metastasis remains a critical role in the therapeutic approach (EMR/ESD vs surgery) for EGC patients, it is important to identify the risk factors for EGC patients[23]. Our study demonstrated that longest diameter of the tumor ($\leq 1.9/ \geq 1.9$ cm), T stage ($T_{is} + T_{1a}/T_{1b}$), vascular invasion (yes/no), and NLRc ($\leq 5.29/ \geq 5.29$) were the independent risk factors for LN metastasis. Similarly, Japanese Gastric Cancer Association (JGCA) points that nonulcerated, well-differentiated and lesions diameter less than 2 cm are the indications for EMR/EDS approach in EGC patients[24]. Additionally, our study also found that the invasive depth of EGC(T stage) and vascular invasion were also associated with lymph node metastasis, Chu YN et al also found that submucosal invasion depth and LVI were the predictive factors for lymph node metastasis[25], hence, it is truly for the application of ultrasound gastroscope to identify the invasive depths in EGC patients, which could not only measured the lesion size, but also measured the invasive depths of EGC tumors[26]. In collaboration with previous studies, our research indicated that tumor size ≤ 1.9 cm, ultrasound gastroscope presents the non-submucosa invasion and non-vascular invasion might be the indications for ESD/EMR in EGC patients.

There are several limitations in our study. Due to the retrospective nature of the study, some information(such as H.pylori infection, E.B virus infection et, al.) could not be collected; therefore, the analysable risk factors for those patients are still limited, and more data should be considered and collected. In addition, our findings should be verified by large-scale, multiple-center cohort. Moreover, our

research retrospectively from 2013 to 2018, which might be affected by the developments of practices and surgical expertise in different surgeons. Furthermore, adequate interventions should be applied to improve the EGC prognosis as patients have such poor prognostic factors.

Conclusion

The longest diameter of the tumor and total number of dissected LNs were independent prognostic factors for EGC patients. Additionally, the longest diameter of the tumor, tumor invasive depths, vascular invasion and NLRc were the independent risk factors for lymph node metastasis in EGC patients.

Declarations

Ethics approval and consent to participate

The research was supported by the Medical Ethical Committee of Xiangya Hospital, Central South University (No. 202004082).

Consent for publication

Not applicable.

Availability of data and materials

The raw data underlying this paper are available upon request to the corresponding author due to ethical restrictions.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceived and designed the experiments: Liao G

Analyzed the data: Qi J. Performed the experiments: Qi J, Zhu C, Liu S, Liu W, Cai G.

Wrote the paper: Qi J, Liao G. All authors read and approved the final manuscript.

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Figures

Figure 1

The study profile of patients enrolled in our study.

Figure 2

Receiver operating characteristic (ROC) curves for predicting disease-free survival among 244 early gastric cancer patients. (a) Preoperative parameters of routine blood analysis showed no significant prediction of DFS; (b) partial postoperative parameters (including PLRc, NWRc, and MWRc) of routine blood analysis showed no significant prediction of DFS; (c-i) in addition, ROC curves of LWRc, NLRc, MLRc, the longest diameter of the tumor, total number of dissected lymph nodes, number of metastatic lymph nodes, and ratio of metastatic-to-total dissected lymph nodes were used to predict disease-free survival.

Figure 3

X-tile analysis of prognosis based on integral optic density (IOD). X-tile plots showing DFS among 244 EGC patients. (a-f) The data are stratified by NLRc, MLRc, the longest diameter of the tumor, total number of dissected lymph nodes, number of metastatic lymph nodes, and ratio of metastatic-to-total dissected lymph node.

Figure 4

Disease-free survival and overall survival for 244 early gastric cancer patients. The data are stratified (a-i) by the longest diameter of the tumor (≤ 2 cm vs > 2 cm), total number of dissected lymph nodes (≤ 13 vs > 13), number of metastatic lymph nodes (0 vs ≥ 1), ratio of metastatic-to-total dissected lymph nodes ($< 6\%$ vs $\geq 6\%$), T stage (Tis+T1a vs T1b), vascular invasion (yes vs no), NLRc (≤ 7.80 vs > 7.80), and MLRc (≤ 1.40 vs > 1.40) based on the univariate analyses.

Figure 5

Disease-free survival and overall survival for 244 early gastric cancer patients according to multivariate analysis. The data are stratified by (a) the longest diameter of the tumor (≤ 2 cm vs > 2 cm) for recurrence/metastasis in EGC patients; (b) total number of dissected lymph nodes (≤ 13 vs > 13) for recurrence/metastasis in EGC patients; (c) the longest diameter of the tumor (≤ 2 cm vs > 2 cm) for overall survival in EGC patients.

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