Gender and Age Differences in Risk Factors of Lymph Node Metastasis in Patients With Early Gastric Cancer and Analysis Prognosis of Early Gastric Cancer

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Research

Abstract

Objective

To explore the effects of gender and age differences in the risk factors for lymph node metastasis in patients and analysis prognosis of patients of early gastric cancer (EGC).

Methods

A total of 411 patients with EGC who underwent surgical treatment at the First Affiliated Hospital of Anhui Medical University from 2011 to 2017 were included in this study and grouped according to gender and age. Retrospective analysis of the effects of gender and age on tumor size, histological type, depth of invasion, and ulcer type was performed, and differences in the clinicopathological characteristics of lymphovascular invasion were noted. Follow-up of the postoperative recurrence and metastasis of the patients and analysis of their prognosis were finally conducted. All follow-ups ended in August 2020.

Result

The participants in this study ranged in age from 25 years to 85 years (average, 60.27 ± 10.77 years). A total of 57 (13.9%) of the patients showed lymph node metastasis. Females accounted for 25.5% (105/411) while males accounted for 74.5% (306/411) of the study population. Patients aged ≤60 years accounted for 55.5% (228/411) while patients aged >60 years accounted for 44.5% (183/411) of the study population. Univariate analysis of male patients showed that tumor size, depth of tumor invasion, ulcerative tumors, and lymphovascular invasion are related to lymph node metastasis ($P < 0.05$). Univariate analysis of female patients showed that tumor size, depth of tumor invasion, tumor histology, and lymphovascular invasion are related to lymph node metastasis ($P < 0.05$). Univariate analysis of patients aged ≤60 years showed that depth of tumor invasion, ulcerative tumors, and lymphovascular invasion are related to lymph node metastasis ($P < 0.05$). Univariate analysis of patients aged >60 years showed that depth of tumor invasion, ulcerative tumors, and lymphovascular invasion are related to lymph node metastasis ($P < 0.05$). Multivariate analysis of male patients, female patients, and patients aged ≤60 years showed that depth of tumor invasion is an independent risk factor for lymph node metastasis. Multivariate analysis of patients aged >60 years showed that depth of tumor invasion, ulcerative tumors, and lymphovascular invasion are independent risk factors for lymph node metastasis.

Conclusion

The risk factors for lymph node metastasis in patients with EGC differed according to gender and age. The results provide a reference for choosing suitable treatment options for these patients.

Introduction

Gastric cancer is one of the most common malignant tumors in the world. Among malignant cancers, gastric cancer ranks fifth in terms of incidence and third in terms of mortality. Thus, the disease seriously affects patients' lives and health[1]. In early gastric cancer (EGC), the tumor is confined to the mucosal or submucosal layer, and it is not limited to whether there is lymph node metastasis[2]. At present, the diagnosis rate of early gastric cancer (EGC) in China is less than 10%, which is much lower than the rates recorded in Japan (70%) and

South Korea (50%)[3, 4]. Previous reports indicated that the five-year survival rates of EGC without and with lymph node metastasis are 94.2% and 87.3%, respectively[5]. In view of the good prognosis of EGC, clarifying the prognostic factors related to the disease, especially the risk factors affecting lymph node metastasis, is an important endeavor. Studies have reported several risk factors for EGC lymph node metastasis, including depth of tumor invasion, tumor size, ulcerative tumors, and undifferentiated tumors[6-9]. However, reports on the effects of age and gender on the risk factors for EGC lymph node metastasis are limited. Endoscopic treatment is the standard treatment plan for EGC without lymph node metastasis[10, 11]. According to the guidelines for the diagnosis and treatment of gastric cancer in Japan, treatment of EGC by endoscopic resection is indicated when the depth of invasion is T1a, the tumor is of the non-ulcerative type, and the diameter of the tumor does not exceed 2 cm[12]. Clarifying the risk factors for EGC lymph node metastasis, particularly the effects of age and gender on these factors, can help clinicians develop optimal treatment plans for patients with EGC.

Materials And Methods

A total of 411 patients with EGC underwent radical surgical resection at the General Surgery Department of the First Affiliated Hospital of Anhui Medical University from 2011 to 2017. Radical surgery is defined as the complete removal of the tumor, no macroscopic residual tumor, no cancer cell invasion at the margins, and no evidence of distant metastasis. The patients were followed-up by professional medical staff via telephone, visitation, or reviews of their consultation records at the outpatient department. Patient survival time was considered as the time from diagnosis to the time of last contact or date of death or date of survival information collection. EGC patients were grouped according to age and gender, and the following risk factors for lymph node metastasis were assessed: (1) Tumor size: The longest diameter of the lesion was measured by pathology after surgery, and multiple tumors are calculated by the largest long diameter. Divided into ≤2 cm and >2 cm. (2) Tumors were divided into the ulcerative, ulcerative scarring, and non-ulcerative types. (3) With or without lymphovascular invasion. (4) Tumor differentiation was divided into differentiated (moderate–high and moderate differentiation) and undifferentiated (poor–moderate and poor differentiation, mixed, mucinous adenocarcinoma, and signet ring cell carcinoma). (5) Postoperative pathology: depth of invasion (mucosa and submucosa).

Statistical methods: The data were analyzed using SPSS version 21 statistical software. The chi-squared test (single-factor analysis) was used to analyze the risk factors for lymph node metastasis. Variables found to be related to lymph node metastasis during single-factor analysis ($P<0.05$) were included in binary logistic regression analysis. Survival data were analyzed by K-M and Cox survival regression analyses to determine the impact of the related risk factors on patient prognosis. P values were considered statistically significant at the level of <0.05.

Results

Analysis of the demographic and clinicopathological characteristics of ECG patients: A total of 411 patients were included in this retrospective study; 57 (13.9%) patients had postoperative pathological evidence of lymph node metastasis. The study population included 105 (25.5%) females, 16 of whom showed lymph node metastasis after surgery, and 306 (74.5%) males, 41 of whom showed lymph node metastasis after surgery. Among the 411 patients with EGC, 183 (44.5%) were aged ≤60 years, and 25 of them had lymph node

metastasis. The rest of the patients (228, 55.5%) were aged >60 years old, and 32 of them patients had lymph node metastasis.

Factor analysis of lymph node metastasis in EGC patients of different genders: Univariate analysis (Table 1) showed that lymph node metastasis in male EGC is related to tumor size, depth of tumor invasion, tumor ulceration, and lymphovascular invasion (P < 0.05). Lymph node metastasis in female EGC was related to tumor size, tumor invasion depth, tumor histological type, and lymphovascular invasion (P < 0.05). Factors with statistical significance were included in multivariate logistic regression analysis, and the results indicated that depth of tumor invasion is an independent risk factor for lymph node metastasis in male (p = 0.02, OR = 0.213, 95%CI: 0.079−0.575) and female (p = 0.033, OR = 10.524, 95%CI: 1.213−91.295) patients with EGC (Table 3).

Factor analysis of lymph node metastasis in EGC patients of different ages: Univariate analysis (Table 2) showed that lymph node metastasis of EGC patients aged ≤60 years is related to depth of tumor invasion, tumor ulceration, and lymphovascular invasion (P < 0.05). Lymph node metastasis of EGC patients aged >60 years was related to tumor size, tumor invasion depth, and lymphovascular invasion (P < 0.05). Factors with statistical significance were included in multiple logistic regression analysis, and results revealed that depth of tumor invasion (p = 0.04, OR = 20.008, 95%CI: 2.592−154.421) is an independent risk factor for lymph node metastasis in EGC patients aged ≤60 years. Moreover, tumor size (p = 0.012, OR = 3.094, 95%CI: 1.288−7.429), depth of tumor invasion (p = 0.019, OR = 3.408, 95%CI: 1.223−9.494), and lymphovascular invasion (p = 0.000, OR = 0.075, 95%CI: 0.018−0.311) are independent risk factors for lymph node metastasis in EGC patients aged >60 years (Table 4).

Survival analysis results of EGC patients: The whole group of 411 patients with EGC received complete follow-up. Cox survival regression analysis was applied to the factors affecting the prognosis of EGC, and results showed that lymph node metastasis (p = 0.043, OR = 1.960, 95%CI: 1.022−3.758), age (p = 0.000, OR = 0.289, 95%CI: 0.147−0.567), and vascular infiltration (p = 0.046, OR = 2.637, 95%CI: 1.016−6.845) are independent risk factors affecting patient prognosis (Table 5). The survival curve of the patients clearly showed that lymph node metastasis, vascular invasion, and age are independent risk factors affecting the prognosis of patients with EGC (Figures 1、2、3).

Discussion

Previous studies indicated that lymph node metastasis is one of the main factors affecting the prognosis of gastric cancer[13]. However reports on the effects of gender and age on the risk factors related to lymph node metastasis are scarce. Earlier studies showed that the lymph node metastasis rate of EGC is between 10% and 15%[14, 15]. The rate of lymph node metastasis in EGC patients in this study was 13.9%. Some studies indicate that the risk factors for lymph node metastasis in EGC include tumor invasion depth, tumor size, ulcerative tumors, and undifferentiated tumors[6-9]. Related reports also confirm that tumors measuring >2 cm are risk factors for EGC lymph node metastasis[16, 17]. However, these studies did not show differences in these factors in EGC patients according to age and gender. Our study found that when tumors > 2 cm are a risk factor for lymph node metastasis in both male and female patients.It is for EGC age ≤ 60 years,we also found that tumors measuring >2 cm are not a risk factor for patients with lymph node metastasis. Yusuke et al. found that ulcerative tumors are a risk factor for EGC lymph node metastasis[18]. Our study also confirmed this finding but noted differences according to age. Ulcerative tumors are only a risk factor for lymph node metastasis in male

patients and patients ≤60 years of age. Some researchers have found that undifferentiated tumors are a risk factor for EGC lymph node metastasis[19-21]. However, other reports indicate that the histological type of tumors is not an independent risk factor for EGC lymph node metastasis[22]. Our study found that undifferentiated tumors are a risk factor for lymph node metastasis only in female patients. Therefore, further research is necessary to explore whether undifferentiated tumors affect EGC lymph node metastasis. Earlier studies revealed that submucosal infiltration of tumors is the most predictive risk factor for EGC lymph node metastasis[23]. In the present study, the lymph node metastasis rates of patients with EGC showing intramucosal infiltration and submucosal infiltration were 2.3% and 22.5%, respectively, similar to the results of a large number of previous studies[24-26]. The aim of this study from the univariate and multivariate analysis also confirmed the different ages and different sex submucosal tumor infiltrating lymph node metastasis in EGC are risk factors, clinicians in the face of EGC patients submucosal invasion need to be more careful with. Some reports show that lymphovascular invasion is a risk factor for lymph node metastasis in EGC[27], similar to the results of our study. This finding suggests that lymphovascular invasion is a factor that cannot be ignored for EGC lymph node metastasis. Takatsu et al. showed that young patients with EGC are more likely to have lymph node metastasis than older patients and that age is an independent risk factor for lymph node metastasis[18]. However, some studies also show that age is not a risk factor for lymph node metastasis in EGC[28]. Our study did not find differences in lymph node metastasis between patients of different ages with EGC. Whether age is a risk factor for EGC lymph node metastasis requires further study. A number of researchers have found that female sex is an independent risk factor for lymph node metastasis in EGC. The estrogen signaling pathway in women affects the generation and development of breast cancer and endometrial cancer; it has also been shown to affect the occurrence and development of gastric cancer[6, 29, 30]. Our research did not find that gender affects the lymph node metastasis of EGC. Whether gender affects EGC lymph node metastasis must be assessed in other studies.

Our analysis showed that lymph node metastasis, age, and tumor invasion are the main prognostic factors for patients with EGC. Lymph nodes metastasis are one of the main prognostic factors for EGC[13], as confirmed in our current research and analysis. Age is an important prognostic factors for many cancers[31]. Song et al. demonstrated that the prognosis of gastric cancer varies with age and that the survival rate of young patients with gastric cancer is usually higher than that of elderly patients[32]. Our research confirms the findings of previous research, which may be attributed to two factors. First, younger patients may have better tolerance to surgery and subsequent chemotherapy than older patients. Second, younger patients may have better physical conditions and be able to recover faster than older patients. Some researchers have reported that submucosal infiltration is an independent prognostic factor for patients with EGC[33]; this finding is similar to the results of our research. Our study found that submucosal invasion is a risk factor for lymph node metastasis in patients of different genders and ages with EGC. Increases in depth of tumor invasion appear to increase the risk of lymph node metastasis in patients with EGC.

Endoscopic technology has developed rapidly in recent years, and today's endoscopic operations are low cost, safe, and have little impact on the quality of life of patients. However, lymph node metastasis is a contraindication to EMR（Endoscopic Mucosal Resection）and ESD（Endoscopic Submucosal Dissection）. In this case, additional radical surgery may be required resection and lymph node dissection. Therefore, clinicians must accurately assess the presence of lymph node metastasis prior to surgery to be able to select the best treatment plan for patients with EGC. Understanding the risk factors for lymph node metastasis in these patients is of great

guiding significance for clinical work. According to gastric cancer diagnosis and treatment guidelines in Japan, endoscopic resection is indicated for EGC treatment when the depth of invasion is T1a, the tumor is not ulcerated, and the diameter of the tumor does not exceed 2 cm[12]. These guidelines, however, do not consider differences in patients of different genders and ages with EGC. We found that the risk factors for lymph node metastasis in EGC differ according to patient gender and age. In view of these differences, our findings may serve as a reference for clinicians choosing treatment options for their patients. The results of our prognostic analysis suggest that age, lymph node metastasis, and tumor submucosal infiltration are the main prognostic factors for patients with EGC. While the current research presents a number of limitations and shortcomings, future research may be expected to provide patients with more reasonable treatment plans.

Declarations

Competing interests

The authors declare that they have no conflicts of interest

Consent for Publication

Written informed consent for publication was obtained from the patient.

Ethics approval and consent to participate

This study was approved by the Institutional Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University. And written informed consent was obtained from the patient.

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Author Contributions

Jingjing Wang and Tao Meng composed the manuscript and literature review; Ke Chen and Zhengguang Wang had final approval of the version to be published, and agreemento be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical considerations

This research was permitted by the Ethical Committee of the First Affiliated Hospital of Anhui Medical University.

Availability of data and materials

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

Acknowledgment

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Tables

Table1　Univariate analysis of positive lymph node metastasis in men and women with EGC

Characteristics	Male				Female			
	Number of cases	Lymph node metastasis	X^2	P	Number of cases	Lymph node metastasis	X^2	P
Age			0.001	0.978			0.026	0.871
≦60	120	16			61	9		
>60	186	25			44	7		
Tumor size			5.084	0.024			8.666	0.003
≦2cm	162	15			67	5		
>2cm	144	26			38	11		
Depth of invasion			–	0.000[a]			–	0.000[a]
Mucosa(T1a)	123	2			52	1		
Submucosa(T1b)	183	39			53	15		
Histology			0.570	0.450			–	0.047[a]
Differentiated-type	166	20			37	2		
Undifferentiated-type	140	21			68	14		
Ulcerative type			17.047	0.000			1.668	0.197
Yes	118	27			41	8		
No	188	14			74	8		
Lymphovascular invasion			19.348	0.000			5.954	0.015[a]
Yes	10	6			6	3		
No	296	35			99	86		

a:Fisher's excar probability method was used

Table2　Univariate analysis of positive lymph node metastasis in patients with EGC at different ages

Characteristics	≦60				>60			
	Number of cases	Lymph node metastasis	X^2	P	Number of cases	Lymph node metastasis	X^2	P
sex			0.093	0.761			0.159	0.690
Male	122	16			184	25		
Female	61	9			44	7		
Tumor size			2.497	0.114			10.348	0.01
≦2cm	107	11			124	9		
>2cm	76	14			104	23		
Depth of invasion			–	0.000[a]			–	0.000[a]
Mucosa(T1a)	81	0			94	3		
Submucosa(T1b)	102	25			134	29		
Histology			2.018	0.155			1.298	0.255
Differentiated-type	75	7			128	15		
Undifferentiated-type	108	18			100	17		
Ulcerative			7.745	0.005			7.010	0.08
Yes	71	16			87	19		
No	112	9			141	13		
Lymphovascular invasion			–	0.019[a]			15.720	0.001
Yes	5	3			11	5		
No	178	22			217	26		

a:Fisher's excar probability method was used

Table3：Analysis of lymph node metastasis according to sex using a logistic regression model

Characteristics	Male		Characteristics	Female	
	Odds ratio(95%CI)	P		Odds ratio(95%CI)	P
Ulcerative type			**Histology**		
Yes	1.768(0.865-3.617)	0.118	Differentiated-type	1	0.202
No	1		Undifferentiated-type	3.097(0.546-17.577)	
Depth of invasion			**Depth of invasion**		
Mucosa(T1a)	0.213(0.079-0.575)	0.02	Mucosa(T1a)	1	0.033
Submucosa(T1b)	1		Submucosa(T1b)	10.524(1.213-91.295)	
Lymphovascular invasion			**Lymphovascular invasion**		
Yes	6.957(1.719-28.166)	0.07	Yes	1	0.079
No	1		No	0.164(0.022-1.236)	
Tumor size			**Tumor size**		
≦2cm	0.602(0.297-1.220)	0.159	≦2cm	1	0.125
>2cm	1		>2cm	3.259(0.722-14.717)	

Table4　Analysis of lymph node metastasis using a logistic regression model according to age.

Characteristics	≦60		Characteristics	>60	
	Odds ratio(95%CI)	P		Odds ratio(95%CI)	P
Ulcerative type			Tumor size		
Yes	1	0.404	≦2cm	1	0.012
No	0.673(0.265-1.706)		>2cm	3.094(1.288-7.429)	
Depth of invasion			Depth of invasion		
Mucosa(T1a)	1	0.04	Mucosa(T1a)	1	0.019
Submucosa(T1b)	20.008(2.592-154.421)		Submucosa(T1b)	3.408(1.223-9.494)	
Lymphovascular invasion			Vascular invasion		
Yes	1	0.07	Yes	1	0.000
No	0.464(0.071-3.025)		No	0.075(0.018-0.311)	

Table5：Multivariate analysis of factors influencing survival using a cox proportional hazards model.

| Characteristics	Odds ratio(95%CI)	P
Age		
≦60	0.289（0.147-0.567）	0.000
>60	1	
Lymph node metastasis		
Yes	1.960（1.022-3.758）	0.043
No	1	
Lymphovascular invasion		
Yes	1	0.675
No	0.675（0.365-1.249）	
Sex		
Female	1.193（0.600-2.370）	0.614
Male	1	
Depth of invasion		
Mucosa(T1a)	1	0.046
Submucosa(T1b)	2.637（1.016-6.845）	
Histology		
Differentiated-type	1	0.362
Undifferentiated-type	1.293（0.744-2.245）	
Tumor size		
≦2cm	0.875（0.504-1.521）	0.637
>2cm	1	
Ulcerative type		
Yes	1	0.244
No	0.706（0.393-1.269）	

Figures
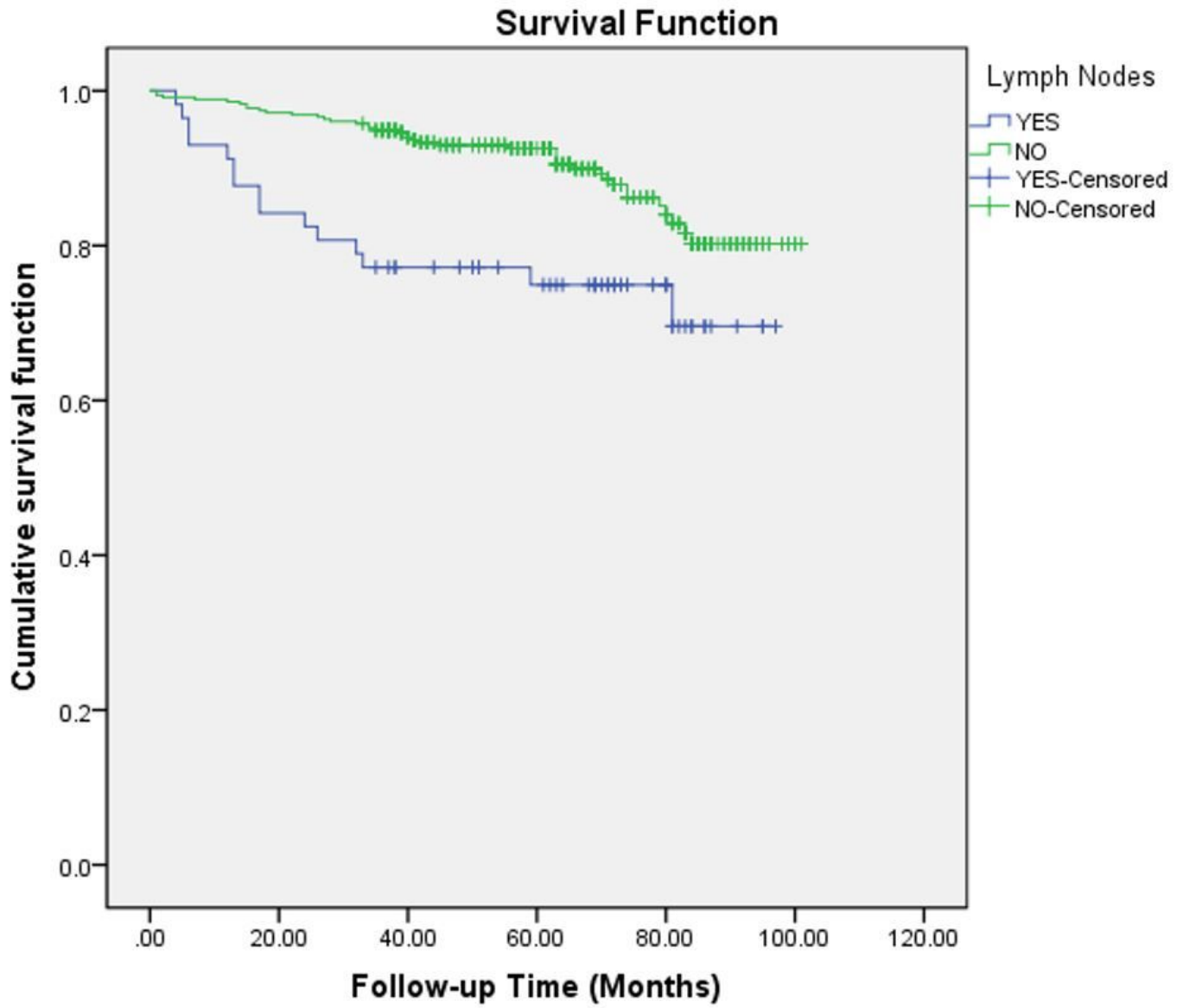
Figure 1

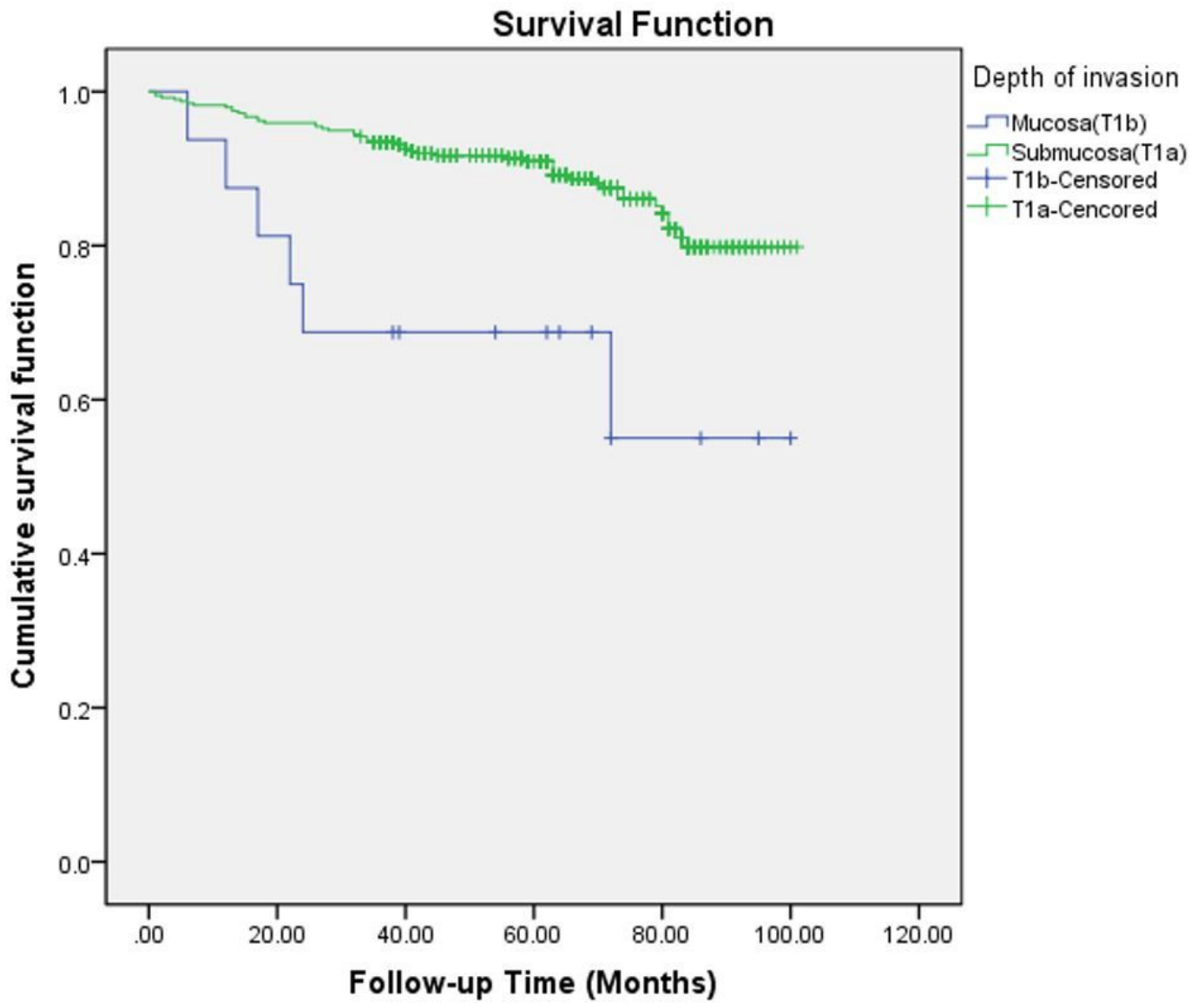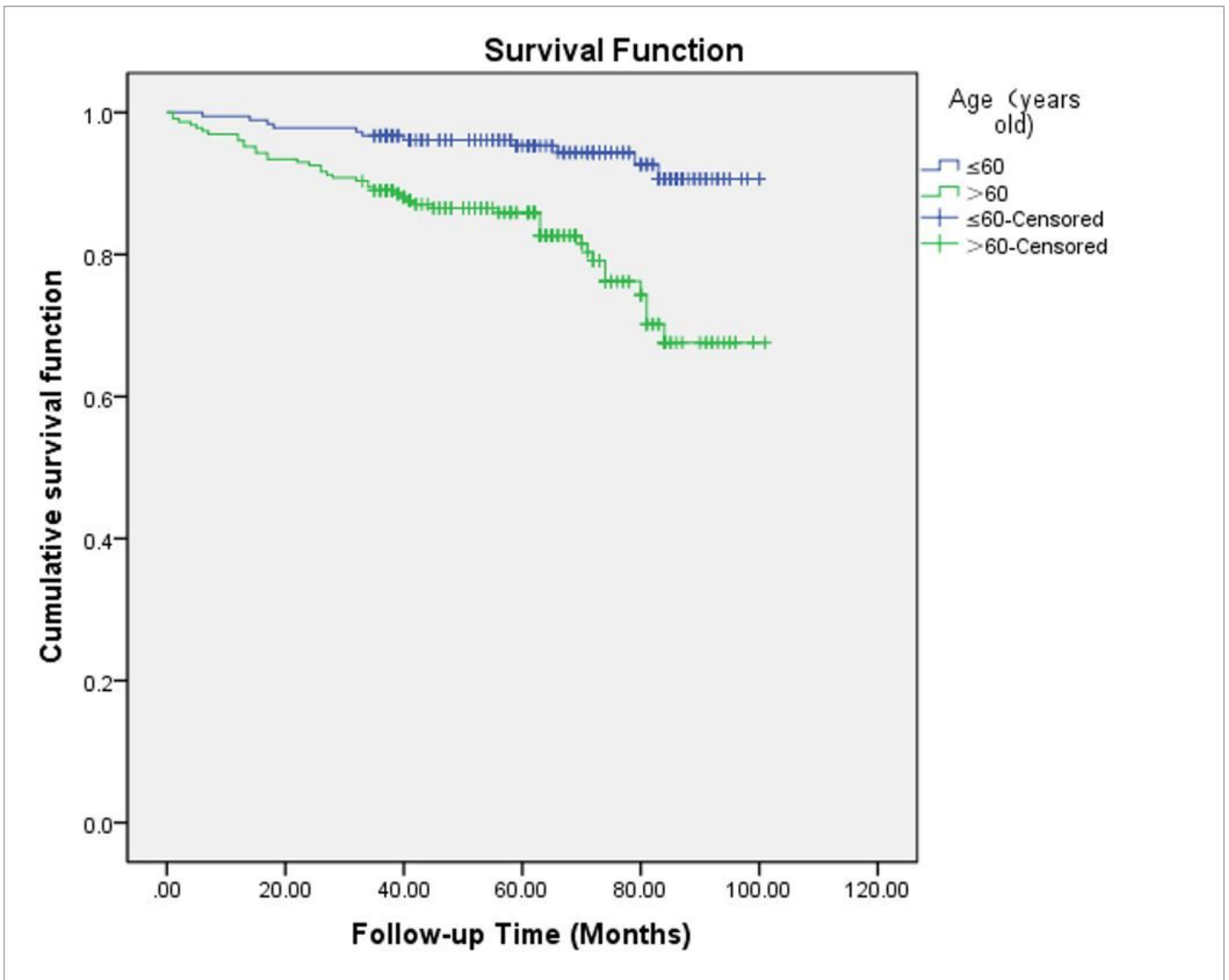Kaplan-Meier analysis of Lymph node metastasis

Figure 2

Kaplan-Meier analysis of Depth of invasion

Figure 3

Kaplan-Meier analysis of Age