Prognostic Significance of the Proximal Margin for Esophagogastric Junction Adenocarcinoma With Type II and III Tumors After Surgery

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Research article

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Abstract

Background

The incidence of esophagogastric junction adenocarcinoma (EJA) has increased in recent years, with surgical resection the main choice of treatment. The optimal length of the proximal margin for EJA is still under debate, and the impact of EJA survival and recurrence remains unclear. The aim of the present study was to investigate the influence of the optimal length of the proximal margin on EJA.

Methods

From January 2011 to December 2015, 131 patients who had EJA with type II tumors were included and retrospectively analyzed. All patients underwent radical R0 resection. The proximal margin was measured promptly after resection, and the frozen-section pathological examination was negative for the margin.

Results

There were 3 cases of Siewert type I EJA (2.9 %), 75 cases of Siewert type II EJA (57.9 %), and 53 cases (40.1%) of Siewert type III EJA. The median number of lymph nodes examined was 19 (range: 1–41), and the median number of positive lymph nodes was 2 (range: 0–18). Sixty-three patients underwent total gastrectomy (48.1%), and 68 underwent proximal gastrectomy (51.9%). The median follow-up time was 57.3 months: (range 1.9–174.1); 34 patients (26%) relapsed and 74 (56.5%) died. The 5-year overall survival rate of type II tumor patients was 68.2%, and that of type III tumor patients was 38.5% ($P = 0.02$). For patients with a proximal margin <2 cm, the median recurrence time was 41.6 months, whereas it was for 42.8 months for patients with proximal margin >2 cm (log–rank: 0.496). Our data analysis found that a proximal margin length of 2 cm was a prognostic variable for type II and type III tumors.

Conclusions

There are a number of factors associated with recurrence and overall survival at 5 years for patients who have EJA with type II and type III tumors, and a proximal margin >2 cm may indicate better prognosis.

Background

The incidence of esophagogastric junction adenocarcinoma (EJA) has increased in recent years, particularly in Western and Asian countries.[1–3] According to data from Japan, the incidence of EJA has increased by 7.3% from the 1960s to the beginning of the 21st century. [4] A single-center registration study of gastric cancer in China found that the proportion of esophageal–gastric junction (EGJ) cancer increased from 22.3% to 35.7% between 1988 and 2012.[5] According to the Siewert classification, there are three types of EJA: Siewert type I is defined as tumors located 1–5 cm above the esophagogastric junction, Siewert type II tumors are located at the upper I–2 cm below the esophagogastric junction, and Siewert type III tumors are located 2–5 cm below the esophagogastric junction.[6] According to the *AJCC*

Cancer Staging Manual, 8th edition, EJA is categorized and staged as esophageal cancer, as long as the tumor center is within 2 cm of the junction, regardless of whether it invades the esophagus. If it is not within 2 cm of the junction, the tumor is grouped and treated as stomach cancer, even if it has invaded the EGJ.[7] Currently, surgical resection is regarded as the cornerstone of curative treatment, although the introduction of neoadjuvant/adjuvant chemotherapy and radiotherapy and chemotherapy have been found to improve disease prognosis.[8] Due to the complexities of EJA tumor location, a consensus has yet to be reached on the best surgical strategy. The appropriate resection range of the esophagus and stomach, the scope and location of lymph node resection, and the best surgical method are still unclear.[9]

The optimal length of the proximal margin for EJA is also still under debate, with only a limited number of studies published on this. In their study, Barbour et al. showed that the proximal margin length might be associated with patient survival in type II–IV tumors, but not in type I tumors, and they found that if the length of the proximal margin was >3.8 cm, then the prognosis of type II+ tumor patients could be significantly improved.[10] However, Mine et al. found that, for patients who have EJA with type II or type III tumors, the length of the proximal margin exceeds 2 cm, which seems to be satisfactory.[11] The proximal margin length is key for R0 and R1 resection status, and thus for survival outcome.[12,13] Therefore, it is crucial to determine a safe operation range when performing surgery.

Methods

We conducted a retrospective, observational study. Based on the classification of the *AJCC Cancer Staging Manual*, 8th edition, patients diagnosed with EJA type II and type III tumors, treated with surgery between January 2011 and December 2015, were included in the present study, except patients with gastric cancer and/or those undergoing neoadjuvant therapy. The inclusion criteria were: (i) patients undergoing radical surgery, including radical proximal or total gastrectomy; (ii) a negative confirmation of the proximal margin; and (iii) type II and type III tumors without distant metastasis. Patients with incomplete medical information, those undergoing neoadjuvant therapy, those with malignant tumors in other locations, and those who had previously had exploratory or tumor-reduction surgeries were excluded. Fresh specimens were cut longitudinally immediately after resection. The sample was then stretched to the maximum extent and fixed to a plate. The surgeon then measured and recorded the length of the proximal edge. The proximal margin was sent for frozen-section pathological examination to confirm whether the proximal margin length was sufficient. If insufficient, further resection was performed until there was a negative confirmation of the proximal margin. All surgical procedures and the extent of lymph node clearance conformed to the Japanese Gastric Cancer Treatment Guidelines (Japanese Gastric Cancer Association 2011). All procedures were conducted in accordance with the Declaration of Helsinki, as revised in 2013[14].

Data on age, sex, Siewert type, extent of surgery, tumor size, proximal margin, T stage, clinical stage, lymphatic–vascular invasion, neural invasion, differentiation status, total lymph nodes, lymph node metastasis, mediastinal lymph node dissection, Lauren type, human epidermal growth factor 2 status,

adjuvant therapy, and relapse or recovery were collected. All patients underwent enhanced chest and abdominal computed tomography every 6 months after discharge to evaluate tumor recurrence and distant metastasis until October 2015. Follow-up was generally conducted through outpatient visits, email, and telephone interviews, and follow-up data were updated until November 1, 2015. The follow-up rate, median follow-up time (months), and overall survival results were included in the study. The main reason that patients could not be followed up was because they declined outpatient visits or changed their telephone numbers and addresses.

All variables were analyzed using descriptive statistics. The results are presented as percentages, means, and dispersion measures. We used the unadjusted Kaplan–Meier method for visualization of the survival curves, and the log–rank test to compare survival curves using SPSS version 22.0. Logistic regression analysis was used for survival identified by univariate analysis were further assessed by multivariate analysis. The *P*-value was considered to be statistically significant at the 5% level. To better define the surgical margin, we use the receiver–operator curve (ROC). Based on the Declaration of Helsinki and the general research health law.[14] Informed consent was not required for the present study, and patient confidentiality was assured.

We present the following article in accordance with the STROBE reporting checklist.

Results

In total, 168 patients diagnosed with EJA without neoadjuvant chemotherapy were included in the present study, according to our admission and discharge criteria. Thirty-seven patients were excluded; 4 had undergone exploration or tumor-reduction surgery, 10 were diagnosed with T1 tumors according to the final pathological report, and 23 had incomplete information (Figure 1). Finally, 131 patients were included: 100 men (76.3%) and 31 women (23.7%, male-to-female ratio 3.22:1), with a median age of 64 years (range: 38–86). Three patients (2.9%) had Siewert type I tumors, 75 (57.3%) had Siewert type II tumors, and 53 (40.1%) had Siewert type III tumors. For Siewert type I tumors, the median tumor size was 4.5 cm (range: 4–5.5 cm); for Siewert type II tumors, the median tumor size was 4 cm (range: 1–10 cm); and for Siewert type III tumors, the median tumor size was 6 cm (range: 2.5–10 cm). All patients underwent open or laparoscopic surgery. Sixty-three (48.1%) patients underwent total gastrectomy, and 68 (51.9%) underwent subtotal gastrectomy. The median number of lymph nodes examined was 19 (range: 1–41), and the median number of positive lymph nodes was 2 (range: 0–18). The median delay time of adjuvant therapy was 8 weeks (range: 4–13 weeks). Chemotherapy regimens included XELOX, CapeOx, FOLFOX, and capecitabine. The patient clinical characteristics are shown in Table 1.

The median length of the proximal margin was 1 cm (range: 0.5–2.5) in patients with Siewert type I tumors, 1 cm (range: 0.4–5) in Siewert type II tumors, and 1.2 cm (range: 0.4–5) in patients with Siewert type III tumors (Table 1). The impact of the proximal margin length on overall survival was analyzed. A proximal margin length of 2 cm was found to be a prognostic variable for patients with type II and type III

tumors in both the univariate (Kaplan–Meier method, $P = 0.02$) and multivariable analyses (hazard ratio: 2.00, 95% confidence interval: 0.54 –7.41, $P = 0.25$, Cox method) (Tables 2 and 3).

The length of the proximal edge in the surgical specimens and its relationship with recurrence and the 5-year overall survival rate, which is sorted by centimeters (from nearest to farthest), is shown in Figures 1 and 2.

In the univariate analysis, patients with poorly differentiated tumors ($P = 0.005$), late clinical stage ($P = 0{\cdot}008$), and neural invasion ($P = 0.044$) were at higher risk of recurrence. Patients with higher pT category tumors ($P = 0{\cdot}028$), more lymph node metastasis (P = 0·013), poorly differentiated tumors ($P = 0{\cdot}005$), proximal margins of ≤2 cm ($P = 0{\cdot}019$), late clinical stage ($P = 0.012$), and postsurgical recurrence had significantly worse survival (Table 2).

The median follow-up time was 57.3 months (range: 1.9–174.1); 34 patients (26%) relapsed and 74 patients (56.5%) died. The median overall survival time of patients with a tumor proximal margin of <2 cm was 55.5 months, and that of patients with a proximal margin of >2 cm was 68 months (log–rank: 0.019). The median recurrence time for patients with a proximal margin of <2 cm was 41.6 months, whereas it was 42.8 months for patients with a proximal margin of >2 cm (log–rank: 0.496) (Table 1).

In the multivariate analysis, only tumor differentiation status was found to be the prognostic factor for recurrence. The variables related to the 5-year overall survival rate were tumor infiltration (type II vs. III), proximal margin, tumor differentiation status, and recurrence. However, in the ROC analysis, we did not find that a definitive margin showed better tumor outcomes (Tables 3 and 4).

Type II tumor patients had a 5-year overall survival of 68.2%, and type III tumor patients had a 5-year overall survival of 38.5% ($P = 0.02$) (Figure 4).We observed an 18.2% recurrence in type II tumor patients, and a 27.5% recurrence in type III tumor patients ($P = 0.19$) (Figure 5). Patients with type II and type III tumors had a 5-year overall survival of 43.5%. The recurrence rate was 26%; 11 patients had local–regional relapse (32.4%), 23 (67.6%) had distant metastasis, 5 had relapse at 1 distant site (21.7%), 10 had relapse at 2 distant sites (43.5%), 6 had relapse at 3 distant sites (26.1%), and 2 patients had relapse at 4 or more sites (17.4%). No patients died post surgery.

Discussion

An increase in EJA has been observed globally in recent years, particularly in Western and Asian countries. According to previous literature, the most common tumor types are types II and III.[1–3,15,16] Our retrospective study showed a slight increase in the prevalence of EJA in our hospital (data not shown) during the past 10 years, which is similar to findings reported in the literature. Our data revealed that patients with EJA had poorer survival outcomes than patients with distal gastric cancer because of the different tumor characteristics.[17,18] The optimal length of the proximal margin for EJA is still under debate, and the impact of EJA survival and recurrence remains unclear. Compared with subtotal esophagectomy, the proximal margin of patients undergoing extended gastrectomy should be shorter.

Barbour et al. found that proximal margin length was a more significant prognostic factor in types II–IV tumors with N0–2 (P<0.01). However, the same cannot be said for patients with types II–IV N3 tumors (P = 0.48). A proximal length of 3.8 cm in resected specimens is considered an independent prognostic factor according to analyses limited to R0 or R1 resection. The proximal margin length was considered a prognostic factor between the esophagectomy group (5 cm) and the gastrectomy group (2 cm) and influenced the survival of patients with Siewert type I tumors.[10] Mine et al. found that, for patients with EJA with types II–IV tumors, a proximal margin length >2 cm seemed to be associated with better survival (P = 0.008). Type IV tumor patients are more likely to require neoadjuvant therapy. Thus, different surgical strategies can influence the proximal margin length. Barbour et al. performed used esophagectomy (69.7%), whereas Mine et al. exclusively used transhiatal extended gastrectomy.[10,11] Our research mainly focused on the effect of the proximal margin length on patients with EJA type II and III tumors, and we found that a gross proximal margin of >2 cm was an independent prognostic factor for patients with EJA type II and III tumors undergoing radical surgery. Gross proximal margin lengths of 1.5, 2.5, 3, and 3.5 cm had no statistically significant impact on survival. Patients with poor differentiation status seemed more prone to relapse and had a worse prognosis, according to our analysis, which was similar to previous literature.[10,11,17,18] However, Feng et al. and Ohe et al. found that a sufficient proximal margin was not an absolute factor related to survival and recurrence, and in the case of R0 resection, the distance between the free margin and tumor did not affect prognosis.[19,20] Squires et al. also demonstrated there are other pathological factors that affect survival other than the proximal margin.[21]

We observed a 26% (34/131) recurrence rate, and tumor differentiation status was found to be the only significant prognostic factor of recurrence. Most recurrences were distant (23/34, 67.6%), and local–regional recurrences were relatively lower (11/34, 32.4%). According to Patrão et al., tumor differentiation status, pT stage were the strongest prognostic factors for poor outcome and relapse.[22] In their study, the relapse rate was 61% (108/177), with only 9 (8.3%) isolated cases of local–regional relapse with symptoms, whereas the majority of cases (99/108, 91.7%) presented with distant metastasis. In their study, Suh et al. had a recurrence rate of 30% after excluding type I cancers; distant metastasis was found to be more prevalent (14%), and only 4.1–0.6% of patients had local–regional recurrence[23]. This could be due to only suspicious clinical or laboratory findings undergoing more advanced imaging examinations, such as computed tomography, magnetic resonance imaging, and gastrointestinal endoscopy, and thus many asymptomatic local recurrences are missed due to a lack of timely imaging examinations. Therefore, we may be underestimated and cannot reliably describe the overall local recurrence rate. Almost all recurrences are only diagnosed when there are symptoms, which could be at a relatively late stage, and could explain why the incidence of isolated local metastases was relatively lower. These results suggest that effective systemic treatment is important, and to a large extent, represents the unmet needs of EJA. If we consider that our study only covers type II and type III tumor patients during the 5-year follow-up period, our data are different from those reported in the literature to some extent.

Our specimens were cut longitudinally and lymph nodes were removed for pathological examination, stretched to the maximum extent, and placed on plates. The total length of the proximal edge was determined by vision and touch, and was measured and recorded by the surgeon. If insufficient and additional distal esophagus was removed, we measured the total length of the proximal edge. Because of shrinkage of the specimens, these measured lengths did not true reflect the corresponding *in situ* lengths before the conclusion of the operation. In 1986, Siu et al. found that esophageal specimens shrunk to approximately half their length after resection, and the upper margin was reduced to a greater extent than the lower edge (44% vs 54% of *in situ length*, respectively) after resection and before fxation.[18] Thus, based on their findings, a proximal margin of 2 cm would be 4 cm, and the cited minimal proximal margin ranging between 2 and 5 cm would be between 4 and 10 cm *in situ*.

Limitations

The present retrospective study had several limitations. First, we did not have accurate measurements of the proximal margin length due to shrinkage of the esophagus after resection, and due to the difference between observers; therefore, the lack of a centralized examination of pathological specimens may have led to deviation in the results. Second, the sample size used in the present study was small and was limited to a single institution; thus, more prospective studies are needed to verify our findings in the Chinese population. Finally, we did not evaluate the risk factors for the positive proximal margin, nor did we evaluate the effect of neoadjuvant therapy on the state of the proximal margin after resection.

Conclusion

There are a number of factors associated with recurrence and overall survival at 5 years for patients who have EJA with type II and type III tumors, and a proximal margin of >2 cm may indicate a better prognosis.

Abbreviations

esophagogastric junction adenocarcinoma (EJA)

American Joint Committee on Cancer(AJCC)

receiver–operator curve (ROC)

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Guangdong Provincial People's Hospital and was carried out in adherence with the Declaration of Helsinki [No. GDREC2016296H(R1)].

Consent for publication

Not applicable.

Availability of data and materials section

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table. 1 Population characteristics.

Variables	Scale	No. of patients
sex ratio(M:F)		100:31
Age(year)		64（38-86）
Siewert type	I	3（2.3）
	II	75（57.3）
	III	53（40.4）
Resection	Total gastrectomy	63（48.1）
	Subtotal gastrectomy	68（51.9）
Size(cm)		4.5（1-10）
Proximal margin(cm)		1.0（0.4-5.5）
Lauren type	intestinal	77（58.8）
	diffuse	54（41.2）
Differentiation status	Poor	67(51.1)
	Median-high	64（48.9）
Invasion	T2	22（16.8）
	T3	109（83.2）
Total lymph nodes		19（1-47）
Positive lymph nodes		2（0-18）
Mediastinal lymph node dissection	Yes	53(49.5)
	No	78(59.5)
Neural invasion	Yes	71（54.2）
	No	60（45.8）
Lymphatic–vascular invasion	Yes	69（52.7）
	No	62（47.3）
Adjuvant treatment	Yes	91（69.5）
	No	40（30.5）
HER-2 stastus	Positive	19（14.5）
	Negative	112（85.5）
Recurrence	Yes	34（26.0）

	No	97（74.0）
Clinical stage	I	1（0.8）
	II	29（22.1）
	III	73（55.7）
	IV	28（21.4）

Table.2 Univariate analysis of potential risk factors for T2-3 AEJ cancers

Variables	Scale	Survived 57 (%)	No survived 74 (%)	P value	Recurrence 34 (%)	No recurrence 97 (%)	P value
Gender	Male	44 (77.2)	56 (75.7)	0.989	27 (79.4)	73 (75.3)	0.618
	Female	13 (22.8)	18 (24.3)		7 (20.6)	24 (24.7)	
Age	<65	24(42.1)	29 (39.2)	0.259	13(38.2)	40(41.2)	0.941
	≥65	33 (57.9)	45 (60.8)		21 (61.8)	57 (58.8)	
Siewert type	I	2(3.5)	1 (1.4)	0.682	1(2.9)	2 (2.1)	0.769
	II	30 (52.6)	45(60.8)		20 (58.8)	55 (56.7)	
	III	25 (43.9)	28 (37.8)		13 (38.2)	40 (41.2)	
Resection	Total gastrectomy	30 (52.6)	33 (44.6)	0.409	15 (44.1)	48 (49.5)	0.606
	Subtotal gastrectomy	27 (47.4)	41(55.4)		19 (55.9)	49 (50.5)	
Size	<4 cm	27(47.4)	27 (36.5)	0.359	12 (35.3)	42 (43.3)	0.388
	≥4 cm	30 (52.6)	47(63.5)		22(64.7)	55 (56.7)	
Proximal margin	<2.0cm	42(73.7	67(90.5)	0.019	28(82.4)	81(83.5)	0.497
	≥2.0cm	15 (16.8)	7 (9.5)		6(17.6)	16(16.5)	
Lauren type	intestinal	40 (70.2)	37 (50.0)	0.075	19 (55.9)	58 (59.8)	0.581
	diffuse	17 (29.8)	37 (50.0)		15(44.1)	39 (40.2)	
Differentiation status	Poor	21 (36.8)	46(62.2)	0.005	23(67.6)	44 (45.4)	0.010
	Median-high	36(63.2)	28(37.8)		11(32.4)	53(54.6)	
Invasion	T2	15 (16.8)	7 (9.5)	0.028	4 (11.8)	18(18.6)	0.194
	T3	42 (73.7)	67 (90.5)		30 (88.2)	79(81.4)	

Total lymph nodes	<16	24(42.1)	26(35.1)	0.803	14 (41.2)	36 (37.1)	0.865
	≥16	33(57.9)	48(64.9)		20 (58.8)	61 (62.9)	
Positive lymph nodes	<5	44(77.2)	42(56.8)	0.013	21(61.8)	65(67.0)	0.159
	≥5	13 (22.8)	32 (43.2)		13 (38.2)	32(33.0)	
Mediastinal Lymph node dissection	Yes	21(36.8)	32 (43.2)	0.622	19 (55.9)	34(35.1)	0.056
	No	36(63.2)	42 (56.8)		15(44.1)	63(64.9)	
Neural membrame	Yes	29 (50.9)	42 (56.8)	0.342	23 (67.6)	48 (49.5)	0.044
	No	28(49.1)	32 (43.2)		11 (32.4)	49(50.5)	
Vascular thrombus	Yes	27(47.4)	42 (56.8)	0.135	21(61.8)	49(50.5)	0.059
	No	30 (52.6)	32 (43.2)		13 (38.2)	48 (49.5)	
	I	1 (1.8)	0(0.00)	0.012	0(0.0)	1 (1.0)	0.008
	II	19 (33.3)	10(13.5)		4(11.8)	25 (25.8)	
	III	28(49.1)	45 60.8)		21 (61.8)	52 (53.6)	
	IV	9 (15.8)	19(25.7)		9(26.5)	19(19.6)	
Adjuvant treatment	Yes	39 (68.4)	52 (70.3)	0.517	25(73.5)	66 (68.0)	0.480
	No	18(31.6)	22 (29.7)		9(26.5)	31(32.0)	
HER-2	positive	9 (15.8)	10 (13.5)	0.727	7 (20.6)	12(12.4)	0.392
	negtive	48(84.2)	64 (86.5)		27 (79.4)	85 (87.6)	
Recurrence	Yes	8 (14.0)	26(35.1)	0.001	N/A	N/A	
	No	49(86.0)	48 (64.9)		N/A	N/A	

Table.3 Cox regression of the factors associated with 5-OS

	B	Hazard ratio(95% CI)	P
Proximal margin	-0.935	0.393(0.179-0.86)	0.019
Recurrence	0.717	2.048(1.254-3.343)	0.004
Differentiation status	-0.489	0.614(0.379-0.992)	0.046

Table .4 Cox regression of the factors associated with recurrence

	B	Hazard ratio(95% CI)	P
Differentiation status	0.744	2.105(1.008-4.395)	0.048

Figures

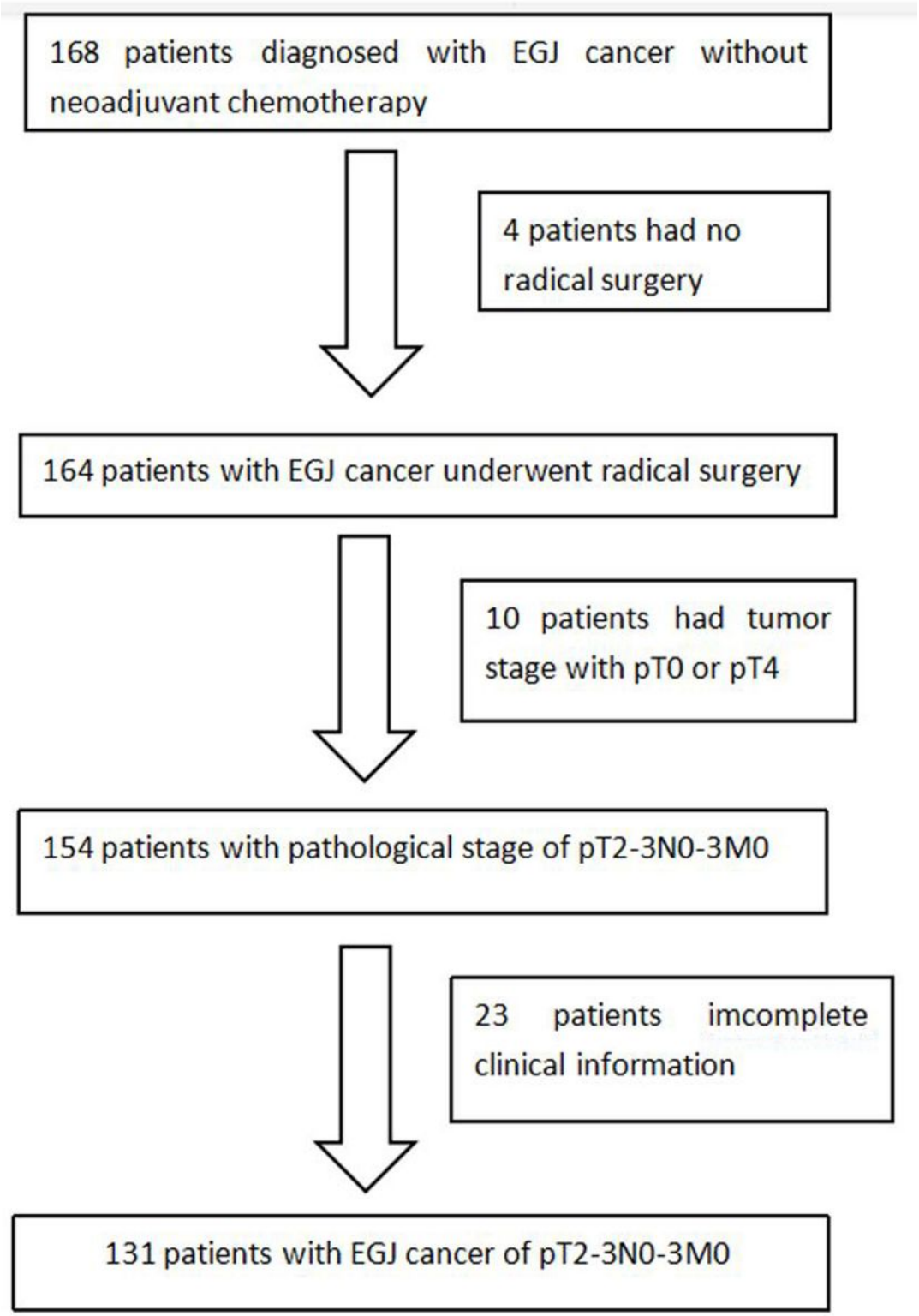
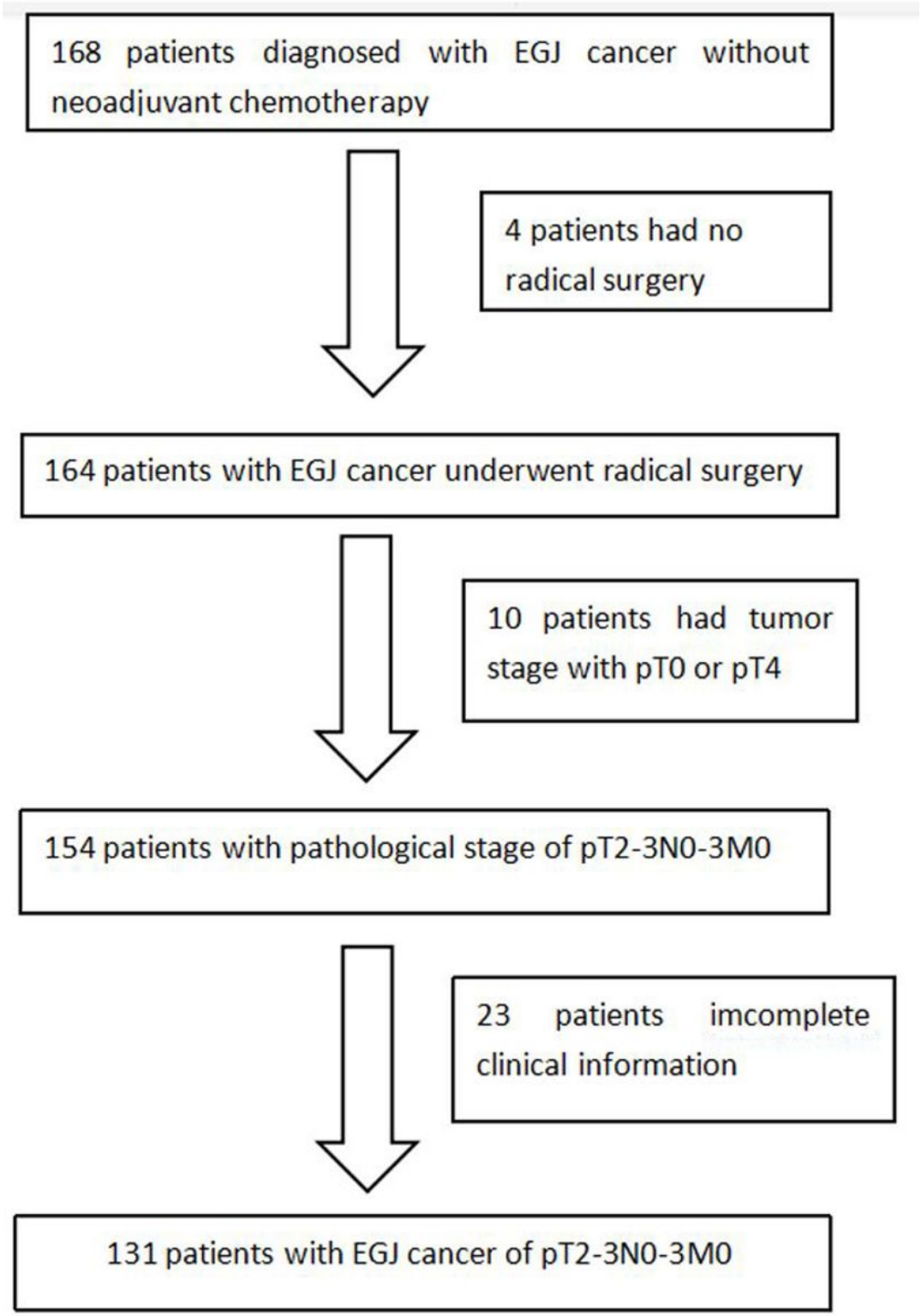


Figure 1

CONSORT diagram showing patient selection for the study according to inclusion criteria.



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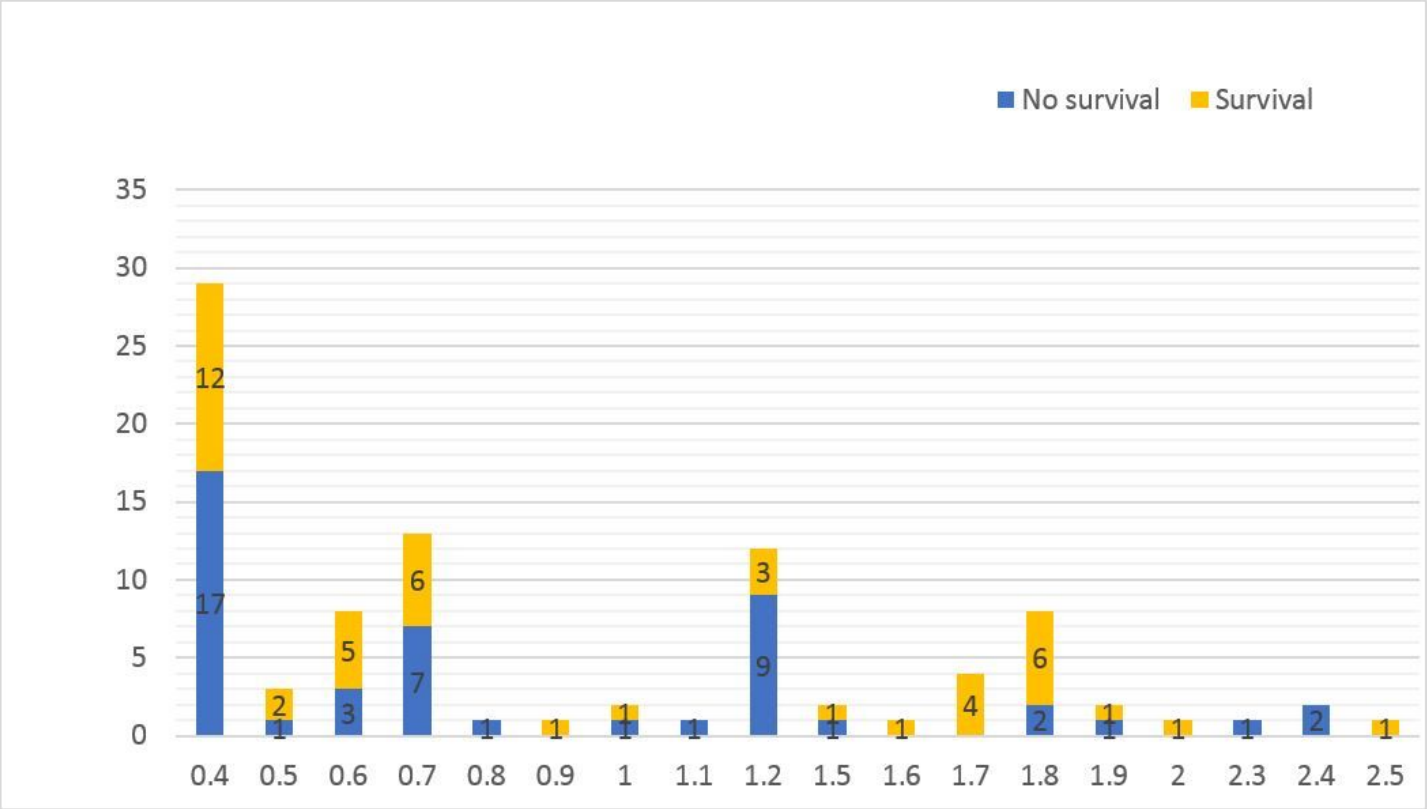
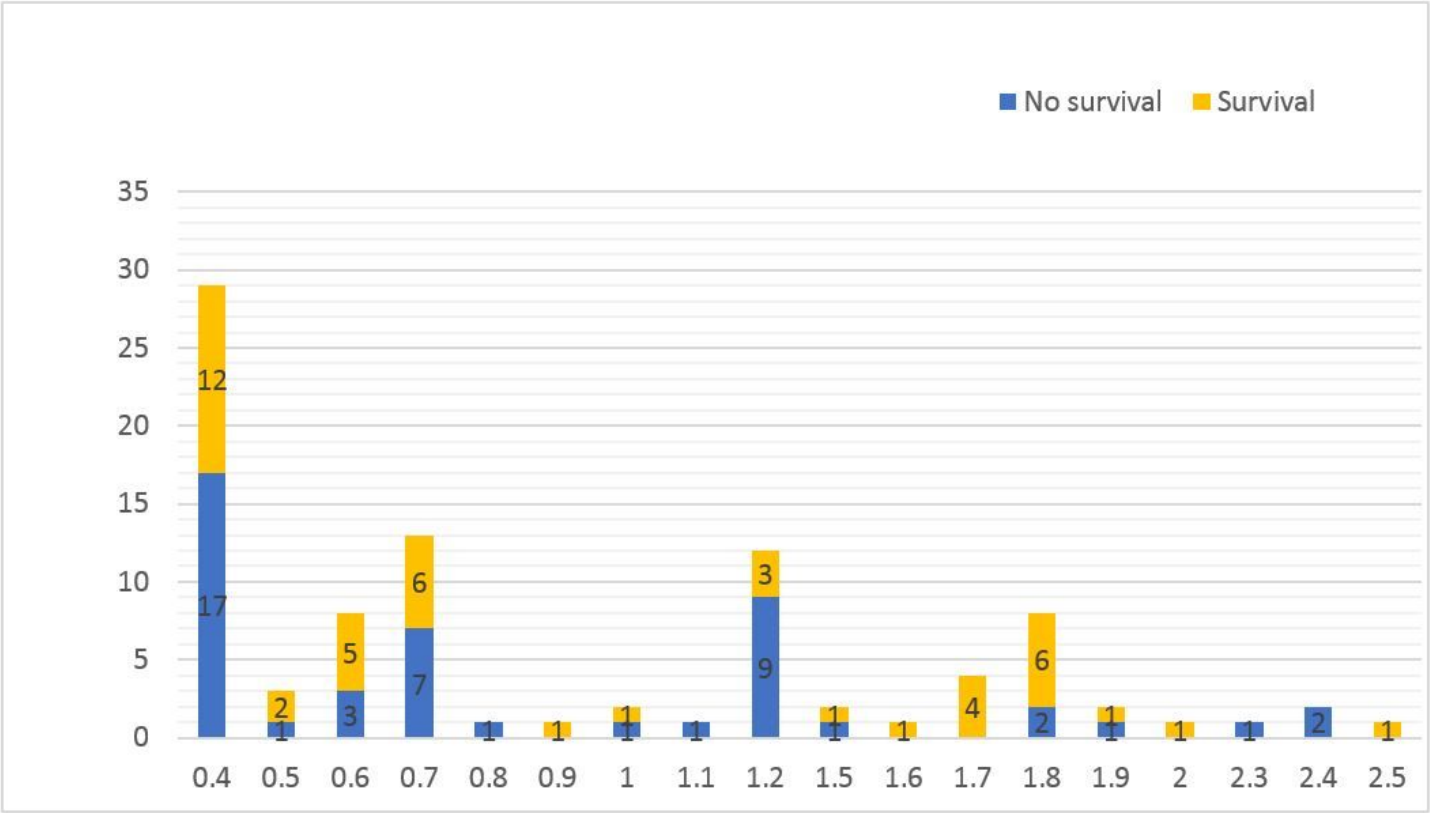


Figure 2

The length of proximal margin in the surgical specimen and its relationship with 5-year overall survival rate , sorted by cm from nearest to farthest.



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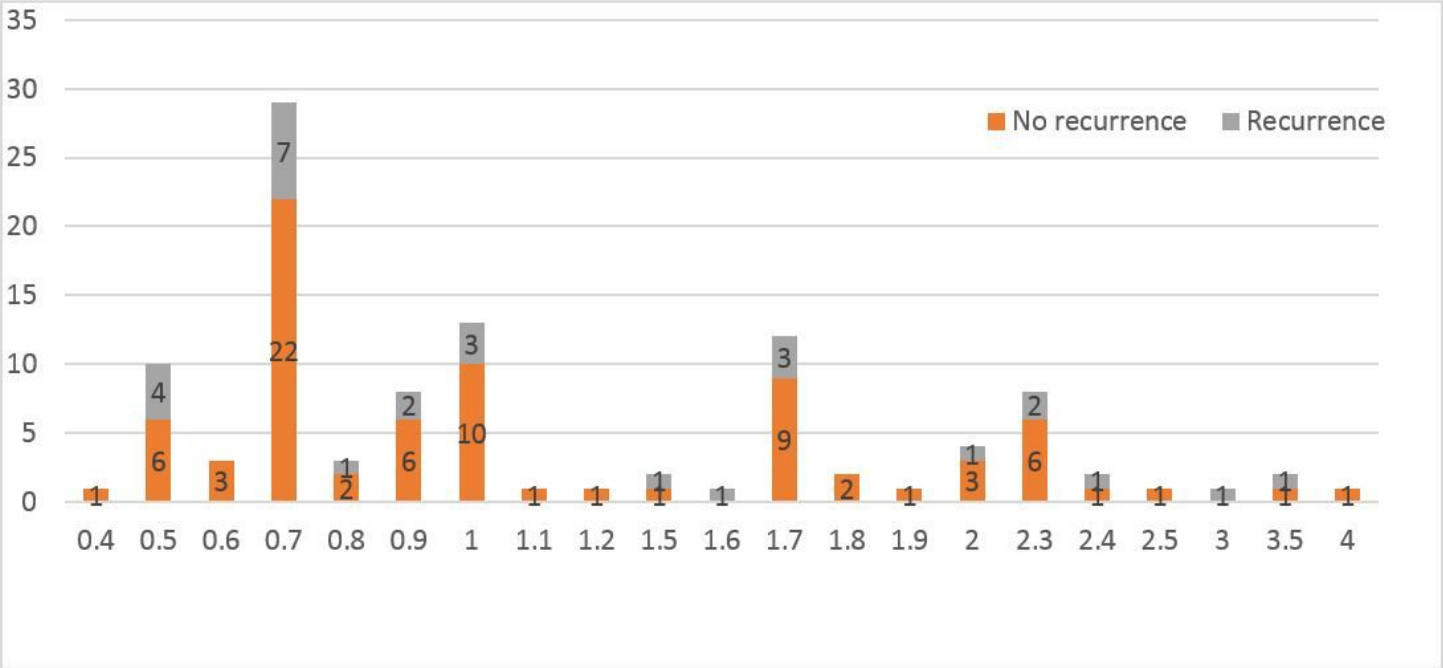
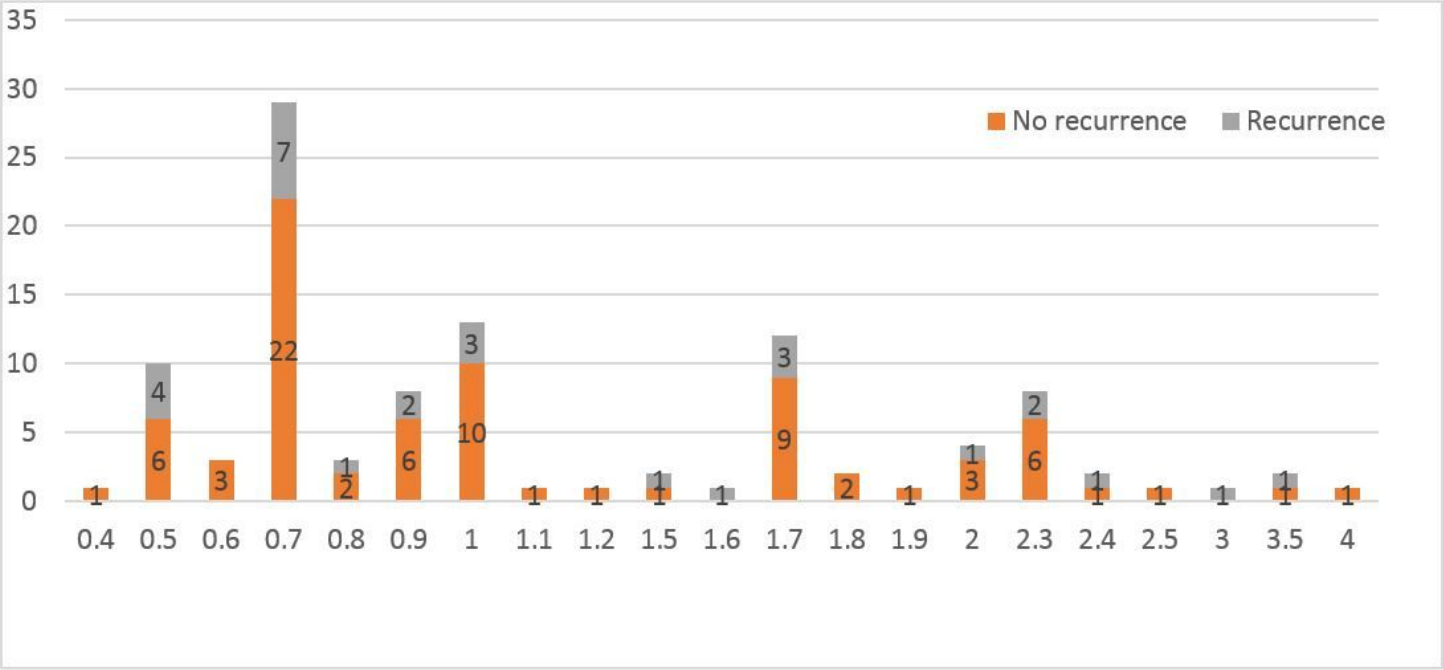


Figure 3

The length of proximal margin in the surgical specimen and its relationship with recurrence , sorted by cm from nearest to farthest.



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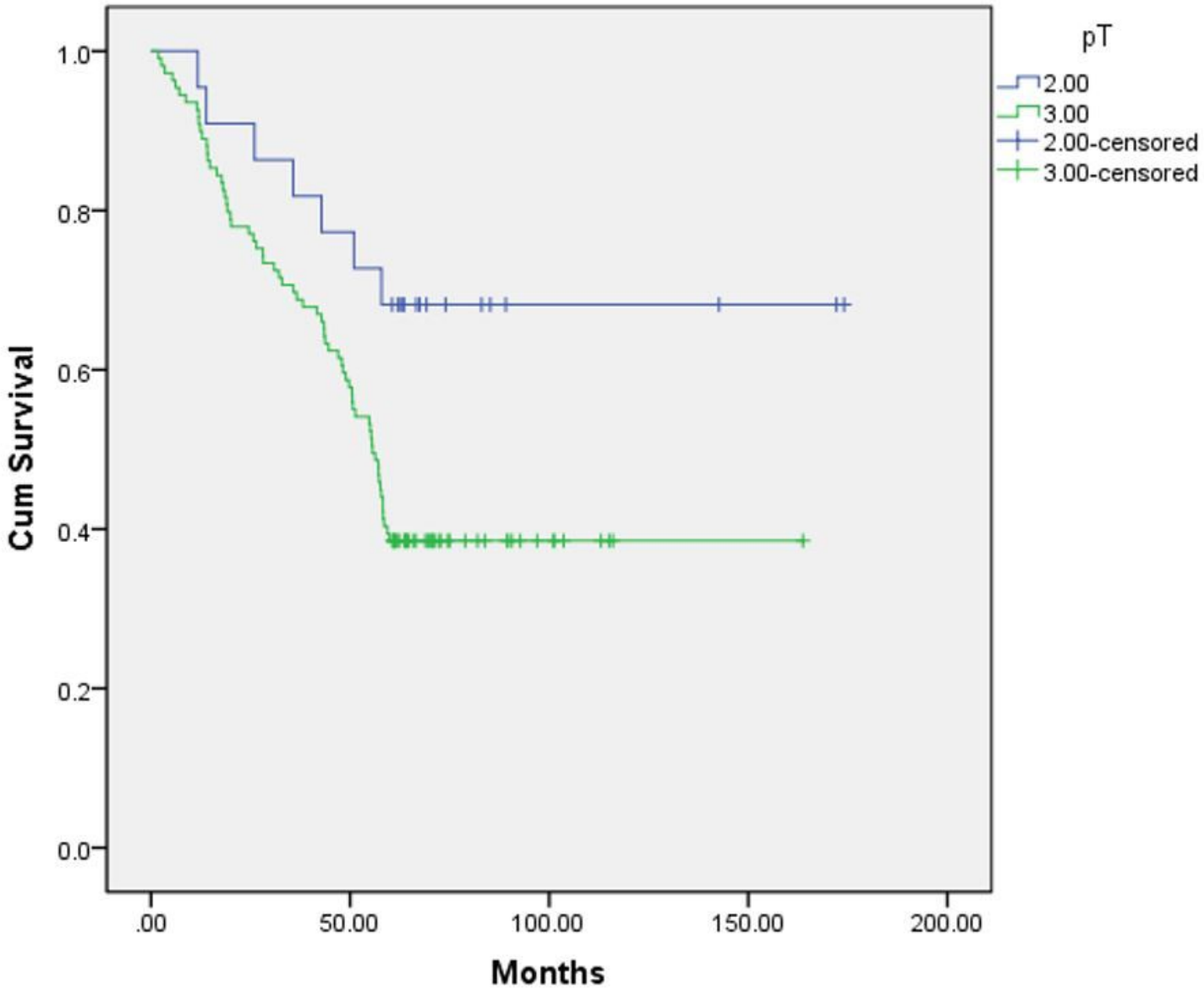
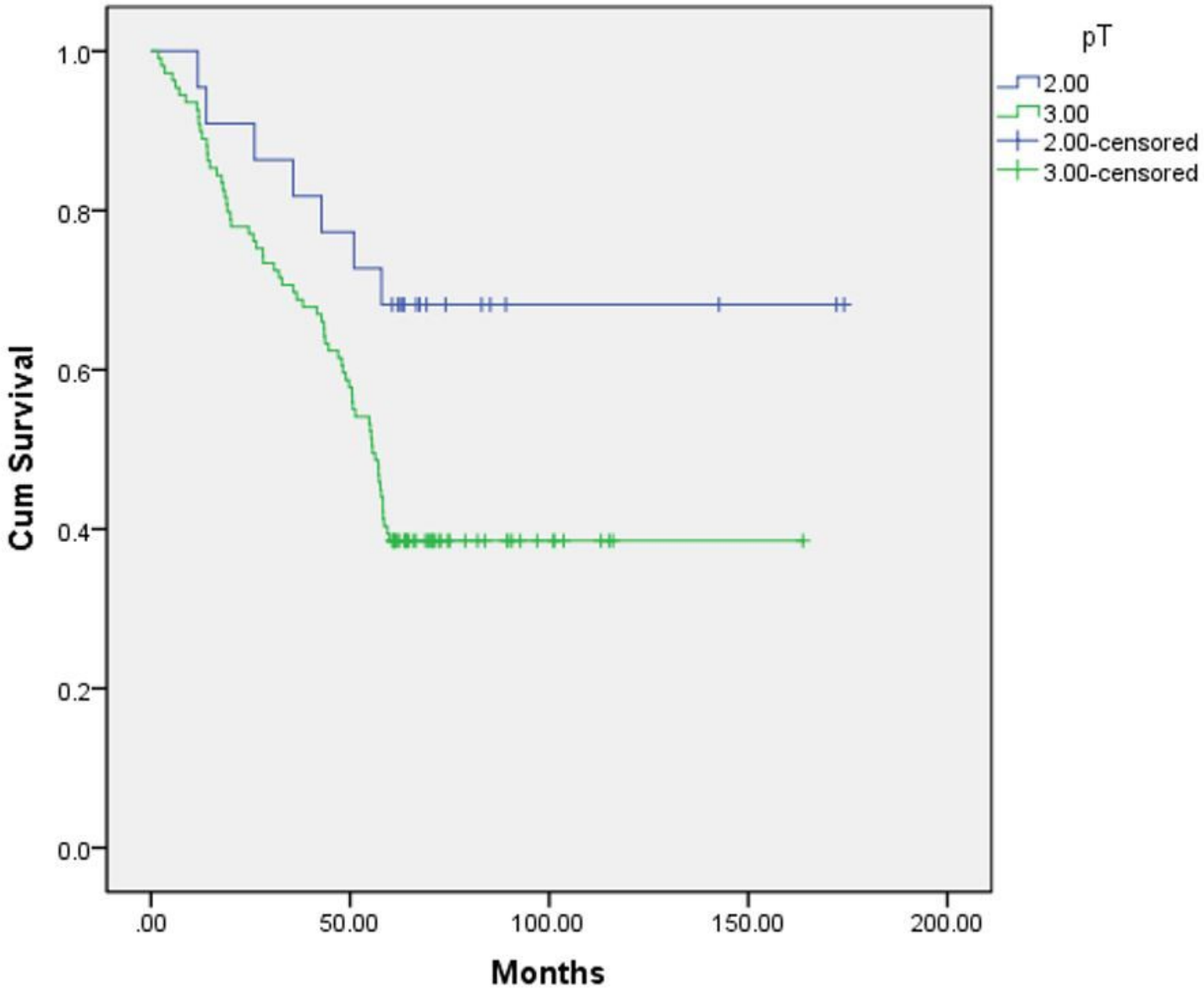


Figure 4

Illustration of the survival curves based on the T stage of AEG patients. The 5-year OS rate for the T2 and T3group was 68.2% and38.5%, respectively.



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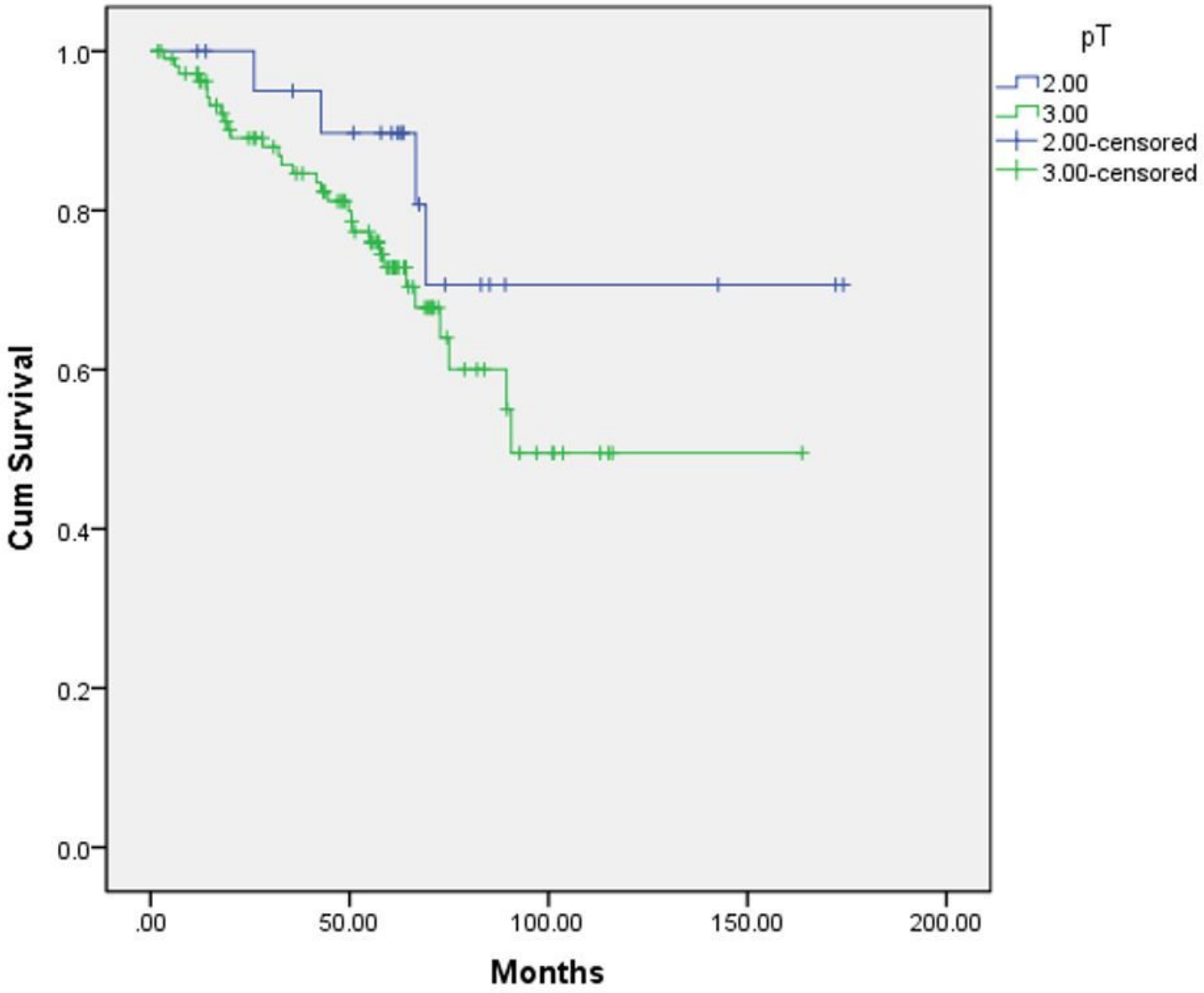
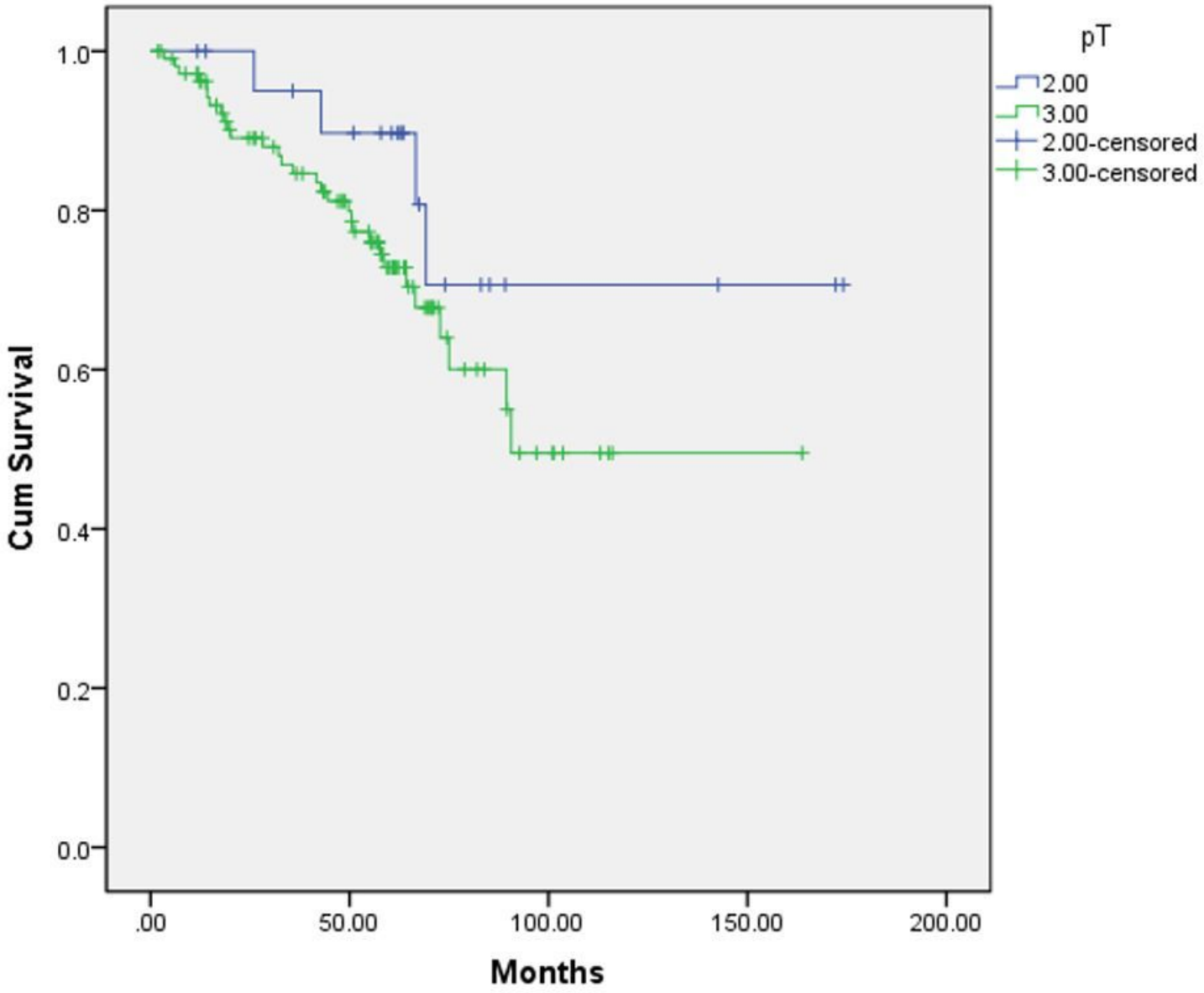


Figure 5

Illustration of the survival curves based on the T stage of the AEG patients. The 5-year recurrence rate for the T2 and T3 was 18.2% and 27.5%, respectively.



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