Long-term outcomes and prognostic factor analysis of resected Siewert type II adenocarcinoma of esophagogastric junction in China: a seven-year study

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Abstract

BACKGROUND

The incidence rate of adenocarcinoma of esophagogastric junction (AEG) was significantly increased over the past two decades. Surgery remians the only way to cure. Indeed, there are currently few studies on Chinese AEG patients. The purpose of this study was to retrospectively analyze the survival and prognostic factors of AEG patients in our center.

METHODS

Between January 2008 and September 2014, 249 AEG patients who underwent radical resection were enrolled in this retrospective study, including 196 males and 53 females, with a median age of 64 (range 31–82). Prognostic factors were assessed with Log-rank test, Cox univariate and multivariate analysis.

RESULTS

The 5-year survival rate of all patients was 49%. The median survival time of all enrolled patients was 70.1 months. Pathology type, intraoperative blood transfusion, tumor size, adjuvant chemotherapy, hospital stay days, serum CA199, CA125, CA242 and CEA, pTNM stage, lymphovascular or perineuronal invasion, and the ratio of positive to negative lymph nodes (PNLNR) were significant associated with overall survival when analyzed with univariate analysis.

CONCLUSIONS

Our study found that intraoperative blood transfusion, tumor size, adjuvant chemotherapy, serum CEA and PNLNR, postoperative hospital stays were independent risk factors.

Background

Adenocarcinoma of esophagogastric junction (AEG) was reported to account for about 5–8%[1, 2] of all esophageal cancers in china, and 35.7% of gastric cancers and lower esophageal cancers worldwide[3]. Many population-based studies have showed that the incidence rate of AEG was significantly increased over the past two decades, both in the West countries and in East Asian[4–6]. The reported seven-fold increase in morbidity of AEG [7], which is a more substantial increase than other malignancies, led to a steady increase in mortality from 2–15/100,000 patients[8].

Surgical resection is the main curable treatment for AEG. Unlike gastric cancer, which treated by standard surgical resection plus D2 lymph nodes resection, surgery of AEG is still controversial in many ways, especially for Siewert type II AEG. AEG surgical treatment includes primary tumor removal, lymph node

dissection and reconstruction of the digestive tract. Regional lymph node metastasis is the most common metastasis method of AEG. Studies have found that the lymph node metastasis rate of AEG is 76.3%, much higher than that of distal gastric adenocarcinoma (67.4%)[9]. At the meantime, the distribution of lymph node metastasis in different Siewet subtypes was different, resulting in several different surgical approaches[10, 11] and there are still remain controversies on N staging of AJCC TNM staging system[12]. Other controversial issues include laparoscopic surgery or open surgery, and whether R0 resectable AEG should undergo neoadjuvant chemoradiotherapy.

Based on the above problems, although Siewet classified AEG in 2000, there are still lots of problems exists it clinical practice. As to china, squamous cell carcinoma remains to be the predominant pathological type of esophageal cancer. Therefore, esophageal adenocarcinoma was rarely investigated among Chinese patients. Our study aimed to explore the long outcome of resected AEG Chinese patients and analysis related prognostic factors.

Methods

Patients

From January 2008 to September 2014, there were 420 cases in which curative R0 resection was performed for esophagogastric junction cancers. Data of 420 patients were collected, the inclusion criteria are, (I) patients with pathologically and immunohistochemically diagnosed AEG; (II) patients underwent radical resection and without distant metastasis; (III) patients with Siewert type II AEG. The exclusion criteria are: (I) patients without complete data for analysis; (II) patients with neuroendocrine or other non-adenocarcinoma pathologic types; (III) patients with Siewert type I or III AEG. Among all collected patients, 249 cases had complete clinical data and confirmed postoperative pathology as adenocarcinoma, and meet all inclusion and exclusion creteria.

Data of demographic, comorbidity, pathologic details, surgical approach, blood infusion, hospital stay days, adjuvant therapy and survival time were collected and subsequently analyzed. Among the characteristics, hospital stay days was classified according to whether the patient was hospitalized for more than 10 days or not; the tumor size was classified according whether tumor size was more than 4 cm or not; the tumor pathology was subdivided whether there was lymphovascular invasion or perineuranol invasion. Because the number of lymph nodes dissected varies greatly from different patients, we specifically defined the ratio of positive to negative lymph nodes in all dissected lymph nodes to further differentiate the prognostic differential population, defined as PNLNR (positive lymph nodes/ negative lymph nodes rate).

All postoperative patients in our center are followed up regularly. In general, the frequency of follow-up is every 3 months for the first 2 years, then every 6 months for the following 3 years, and annually thereafter. Telephone follow-up was conducted at irregular intervals. The retrospective study was in

accordance with the ethical standards of the Ethic Committee of Zhejiang Cancer Hospital and received Institutional Review Board approval. No informed consent is needed for this study.

Surgical approaches selection

A reasonable surgical route should include tumor resection, lymph node dissection, surgical margin and safety. The alternative AEG surgical approaches include left thoracotomy, Ivor-Leiws, McKeown, transhiatal or abdominal-transhiatal approach. The selection of surgical approaches referred to the NCCN guidelines for Esophageal and Esophagogastirc Junction Cancers, NCCN guidelines for Gastric Cancer and Chinese expert consensus on the surgical treatment for adenocarcinoma of esophagogastric junction. Preoperative staging was referred to the eighth edition of TNM staging system, and preoperative classification was referred to the Siewert type.

In general, abdominal- transhiatal approach preferred for those with esophageal involvement distance < 3 cm, and thoracotomy approach for those with esophageal involvement distance ≥ 3 cm.

Statistical analyses

All statistical calculations were performed by the IBM SPSS Statistics (Version 19.0; IBM Corp., New York, USA). Chart making was performed by the GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA). The overall survival (OS) was calculated from the surgery date to the date of death due to any cause. Data of patients lost to follow-up were censored at the date of the last observation. The Cox proportional hazards model was used to determine the univariate and multivariate hazards ratios for the study parameters. Pearson product- moment correlation analysis was used to measure the relationship between the two variables. For all tests, $P < 0.05$ was defined as statistically significant.

Results

Characteristics of patients

The baseline characteristics of patients are shown in Table 1. There were 196 males and 53 females in the population. The median age of all enrolled patients is 64y, range 31-82y. The details of pathology outcome showed that most patients (72.3%) had pure adenocarcinoma, and the remaining patients had mixed adenocarcinoma with signet ring or mucinous. There were 165 patients with tumors diameters larger than 4cm, and 84 patients with tumor diameters less than or equal to 4cm. Among then, 127 patients had lymphovascular invasion, and 154 patients had perineuronal invasion. Pathological differentiation showed that only 2 patients were G1, G2 accounts for 36.9%, and G3 remain the largest part, accounting for 62.2%.

Among the dissected lymph nodes, 70 patients had no positive lymph nodes, and 32 patients with PNLNR greater than 1, and 147 with PNLNR less than 1. Accoding to TNM stage, there were 23 patients defined as stage I, 45 patients stage II, 94 patients stage III and 87 patients stage IV.

In terms of surgery, there were a total of 3 types of surgical approaches, including 73 cases of left thoracotomy surgery, 1 case of Ivor Lewis surgery, and 175 cases of Transhiatal surgery. Total gastrectomy was performed in 115 patients, and proximal gastrectomy was performed in 134 patients. During surgery, a small part of patients (n=18) received intraoperative blood transfusion. After surgery, 53.4% patients stayed in the hospital more than 10 days, and 46.6% patients stayed less than or equal to 10 days. Long hospital stay is mainly due to postoperative complications, postoperative nutritional status and several other reasons. As to adjuvant chemotherapy, there were 100 patients received adjuvant chemotherapy, and the main chemotherapy regimens were SOX (S-1 and oxaliplatin) and XELOX (capitabin and oxaliplatin).

Survival data and prognostic factors

We conducted our last follow-up in October 2019 by telephone, outpatient or inpatient department visit. The median follow-up time was about 75 months. At the last follow-up, 111 patients are still alive. 1-year, 3-year and 5-year survival rate of all enrolled patients were72%, 59%, and 49%, respectively. The median survival time (mOS) of these patients was 70.1 months (95% CI 53.6-86.6m). Female patients had significant longer survival time than male patients (NA vs. 62.4m). Patients with pure adenocarcinoma had significant longer survival time than mixed pathology patients (85.4 vs. 42.5m). Patients with perineuronal invasion (NA vs. 48.1) or lymphovascular invasion (NA vs. 40.9) had shorter survival time. received blood transfusion (12.4 vs. 81.8) had shorter survival time (Figure 1). Patients received adjuvant chemotherapy (61.7 vs. 93.4) had longer survival time. The median survival time of no lymph node metastasis patients had not reached, while the median survival time of N2 and N3 patients was 64.5m and 24.0m, respectively. As to PNLNR, the mOS of patients with PNLNR≤ 1 was 10.3m, and patients with PNLNR>1 was 1.9m (Figure 2). The mOS of patients whose tumor size more than 4cm had also unreached, while mOS of those tumor size less than or equal to 4cm was 43.8m (Figure 3). pTNM stage was also significant related to survival time. Patients with elevated CA199, CEA, CA242 and AFP had shorter survival time (Table 2). Only 1 of 249 patients died within 30 days after surgery .

Prognostic factors including age, gender, pathology, tumor size, type of surgical approach, serum tumor biomarkers, and blood transfusion. Both univariate and multivariate analyses were applied (Table 2 and Table 3). Among the factors related to survival in univariate analyses, there were 16 factors had significant statistical differences, including gender, pathology, intraoperative blood transfusion, surgical approaches selection, and several serum tumor biomarkers. While factors including type of gastric resection, tumor differentiation, elevated serum AFP and serum ferritin had no significant differences. Then, the multivariate analysis was conducted to identify the predictive indicators for a good prognosis using the parameters which P value less than 0.5 by the univariate analysis. Multivariate analysis showed that intraoperative blood transfusion, tumor size more than 4cm, no adjuvant chemotherapy, higher positive/negative lymph node rate, perineuronal invasion and elevated serum CEA before surgery, stay more than 10 days in hospital after surgery are independent risk factors in resected Siewert type II AEG patients.

Discussion

A number of various surgical approaches are available for Siewert type II AEG patients. With the increasing use of surgery under the laparoscopic or thoracoscopic, the surgical options have become more diversified. Various surgical approaches may lead to varies numbers of dissected lymph nodes, and surgical approaches are strongly associated with prognosis.

Previous studies have suggested that the incidence of espiratory-related complications was noted higher in the thoracotomy group than in the transhiatal group[13–15]. In this study, only 1 patient underwent Ivor Lewis surgery. There was no significant difference in postoperative hospital stay between Left thoracotomy group and Transhiatal group, with a median postoperative hospital stay of 11 days for both groups. But survival was longer in the Transhiatal group than in the thoracotomy group, which was consistent with previous similar studies[13]. Although no convicting theory so far can explain the difference between left thoracotomy and transhiatal, left thoracotomy is considered to be more invasive and have a lower survival benefit. Which may due to the basis of the much higher morbidity after thoracotomy, more and more researches concluded that transhiatal would be better for Siewert type 2 AEG patients.

In previous retrospective studies, perioperative blood transfusions were associated with poor prognosis after surgery for cancer, and were a major independent risk factor for postoperative bacterial infection[16, 17]. Patients receiving intraoperative blood transfusion often have anemia before operation or large intraoperative blood loss during surgery. This study found that the prognosis of patients receiving intraoperative blood transfusion was poor. In this respect, laparoscopic surgery may be more advantageous as a minimally invasive surgery procedure.

When the number of positive lymph node metastases was included in the univariate analysis, it was concluded that patients with different lymph node stages had significant survival differences, but in multiple factors analysis, it does not draw the number of lymph node metastasis were independent risk factors of this conclusion. However, the ratio of positive lymph nodes than negative lymph nodes (PNLNR) acquired significant differences in both univariate and multivariate analysis. This may be because the number of lymph nodes dissected by different surgeries varies a lot, and mere comparison of positive lymph nodes cannot accurately assess the prognosis of patients, while PNLNR is a better predictor of prognosis.

As is known, tumor size is a key factor affecting prognosis, and previous articles used tumor diameter of 4 cm as the dividing line to analyze prognosis[18]. In this study, it was found that tumor size affected prognosis more than T stage and pTNM stage, and patients with tumor size more than 4 cm also with poor prognosis. Moreover, adjuvant study is quite important for resected AEG patients. Oxaliplatin- based systemic chemotherapy has brought significant survival benefits. Elevated serum CEA and perineuronal invasion in pathology were also prognostic factors, which reminds us to conduct thorough preoperative detection, including serum tumor biomarker, and conduct detailed pathological reports.

As our study is a single-center retrospective research, we could not avoid some biases from the incomplete patient data and homogeneous surgical operations. Because of incomplete information on the time of recurrence, we did not conduct statistics on the median time of recurrence and did not analyze the factors affecting recurrence. And our study was unable to record all complications in detail, therefore, we can only indirectly reflect the influence of patient recovery on prognosis from the length of hospital stay. A larger study, preferably a randomized control trial in multiple centers, is needed to regulate the way of Siewert type II AEG patients surgical option.

Conclusions

Intraoperative blood transfusion, tumor size, adjuvant chemotherapy, PNLNR, perineuronal invasion and serum CEA, hospital stay after surgery are independent risk factors in resected Siewert type II AEG patients. Transhiatal approach seemed to bring longer survival time than left thoracotomy. And PNLNR is a better prognosis factor than pure N stage.

Abbreviations

AEG
adenocarcinoma of esophagogastric junction
PNLNR
ratio of positive to negative lymph nodes
OS
overall survival

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Research and Education Department of the Zhejiang Cancer Hospital. And consent was not required by ehics committee since its a retrospective study.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Feng YD designed the research, collected the data and wrote the paper; Chen QX designed the research and supervised the report; Zhang HY contributed to the statistical analysis; Jiang YH, Zhao Q, Liu JS supervised the report. All authors read and approved the final manuscript.

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Tables

Table 1 clinical characteristics of 249 patients

Characteristics	Case No. (%)
Gender	
Male	196 (78.7)
Female	53 (21.3)
Age	
Range	31-82
Median	64
Type of pathology	
Adenocarcinoma	180 (72.3)
Adenocarcinoma with partial signet ring or mucinous	69 (27.7)
Intraoperative blood transfusion	
Yes	231 (92.8)
No	18 (7.2)
Tumor size	
>4 cm	165 (66.3)
≤4 cm	84 (33.7)
pTNM stage	
I	23 (9.2)
II	45 (18.1)
III	94 (37.8)
IV	87 (34.9)
Differentiation	
G1	2 (0.8)
G2	92 (36.9)
G3	155 (62.2)
Lymphovascular invasion	
Yes	127 (51)
No	122 (49)
Perineuronal invasion	
Yes	154 (61.8)
No	95 (38.2)
Adjuvant chemotherapy	
Yes	100 (40.2)
No	149 (59.8)
Number of metastatic lymph nodes	
Median (range)	3 (0-38)
PNLNR	32 (12.9)
>1	70 (28.1)
=0	147 (59)
≤ 1	
Postoperative hospital stays	133 (53.4)
>10 d	116 (46.6)
≤ 10 d	
Type of gastric resection	
Total gastrectomy	115 (46.2)
Proximal gastrectomy	134 (53.8)
Surgical approach	
Left thoracotomy	73 (29.3)
Ivor Lewis	1
Transhiatal	175 (70.3)

PNLNR; positive lymph nodes/ negative lymph nodes rate

Table2 univariate analysis of survival after surgery

es	MST (month)	Univariate analysis		P-value
		HR	95% CI	
(male vs. female)	62.4 vs. NA	1.608	1.019-2.539	0.039
gy (adeno vs. mix)	85.4 vs. 42.5	0.632	0.442-	0.011
ansfusion (no vs. yes)	12.4 vs. 81.8	0.262	0.903	<0.001
l approaches (left thoracotomy vs. tal)	42.5 vs. 87.6	1.569	0.156-0.440	<0.001
size (≤4cm vs. >4cm)	NA vs. 43.8	0.410	1.110-	<0.001
t chemotherapy (no vs. yes)	61.7 vs. 93.4	1.477	2.218	0.027
rative hospital stays (≤10d vs. >10d)	59.9 vs. 99.7	0.806		0.012
gastric resection (total vs. proximal)	73.5 vs. 64.5	0.960	0.274-	0.630
			0.616	<0.001
	NA	0.403	1.042-	
	10.3	0.772	2.094	
	1.9	1	0.680-	
ronal invasion (no vs. yes)	NA vs. 48.1	0.454	0.956	<0.001
vascular invasion (no vs. yes)	NA vs. 40.9	0.448	0.811-	<0.001
tiation	80 vs. 73 vs.		1.135	0.851
tage	63			<0.001
		0.253	0.298-	
	97.4	0.265	0.543	
	99.7	0.364	0.613-	
	119.56	1	0.972	
CA199 (U/ml) (<37 vs. ≥37)	24.5	0.784	1	0.008
CEA (ng/ml) (<5 vs. ≥5)	93.4 vs. 31.7	0.740	0.310-	<0.001
CA242 (U/ml) (<20 vs. ≥20)	80.0 vs. 26.3	0.746	0.664	0.010
CA125 (U/ml) (<35 vs. ≥35)	73.0 vs. 12.0	0.605	0.317-	0.004
AFP (ng/ml) (<10 vs. ≥10)	71.4 vs. 70.1	1.067	0.634	0.706
CA724 (U/ml) (<6.9 vs. ≥6.9)	80.3 vs. 51.1	0.862		0.117
erritin (ng/ml) (<274.66 vs. ≥274.66)	70.1 vs. 80.0	0.952		0.745
			0.121-	
			0.526	
			0.155-	
			0.451	
			0.248-	
			0.533	
			1	
			0.654-	
			0.939	
			0.623-	
			0.878	
			0.596-	
			0.934	
			0.423-	
			0.866	
			0.761-	
			1.496	
			0.715-	
			1.039	
			0.708-	
			1.280	

Table 3 multiple cox regression analysis of survival after surgery

Variables	Multivariate analysis		P-value
	HR	95%CI	
Gender (male vs. female)	1.250	0.981-1.593	0.071
Pathology (adeno vs. mix)	1.066	0.864-1.314	0.550
Blood transfusion (no vs. yes)	0.630	0.471-0.843	0.002
Surgical approaches (left thoracotomy vs. transhiatal)	1.365	0.935-1.995	0.107
Tumor size (≤4cm vs. >4cm)			
Postoperative hospital stays (≤10d vs. >10d)	0.728	0.582-0.912	0.006
PNLNR (>1)	0.833	0.694-0.999	0.048
PNLNR (=0)	1	1	<0.001
PNLNR (≤ 1)	0.561	0.268-1.175	0.126
Perineuronal invasion (no vs. yes)	0.773	0.507-1.180	0.233
Lymphovascular invasion (no vs. yes)	0.727	0.574-0.922	0.008
pTNM stage IV	0.899	0.721-1.121	0.346
stage III	1	1	0.171
stage II	1.166	0.541-2.512	0.694
stage I	0.868	0.442-1.707	0.682
Serum CA199 (U/ml) (<37 vs. ≥37)	0.764	0.426-1.369	0.366
Serum CEA (ng/ml) (<5 vs. ≥5)	0.986	0.784-1.239	0.902
Serum CA242 (U/ml) (<20 vs. ≥20)	0.768	0.623-0.947	0.014
Serum CA125 (U/ml) (<35 vs. ≥35)	0.934	0.707-1.233	0.629
Adjuvant chemotherapy (no vs. yes)	0.739	0.490-1.114	0.148
	1.478	1.214-1.800	<0.001

Figures

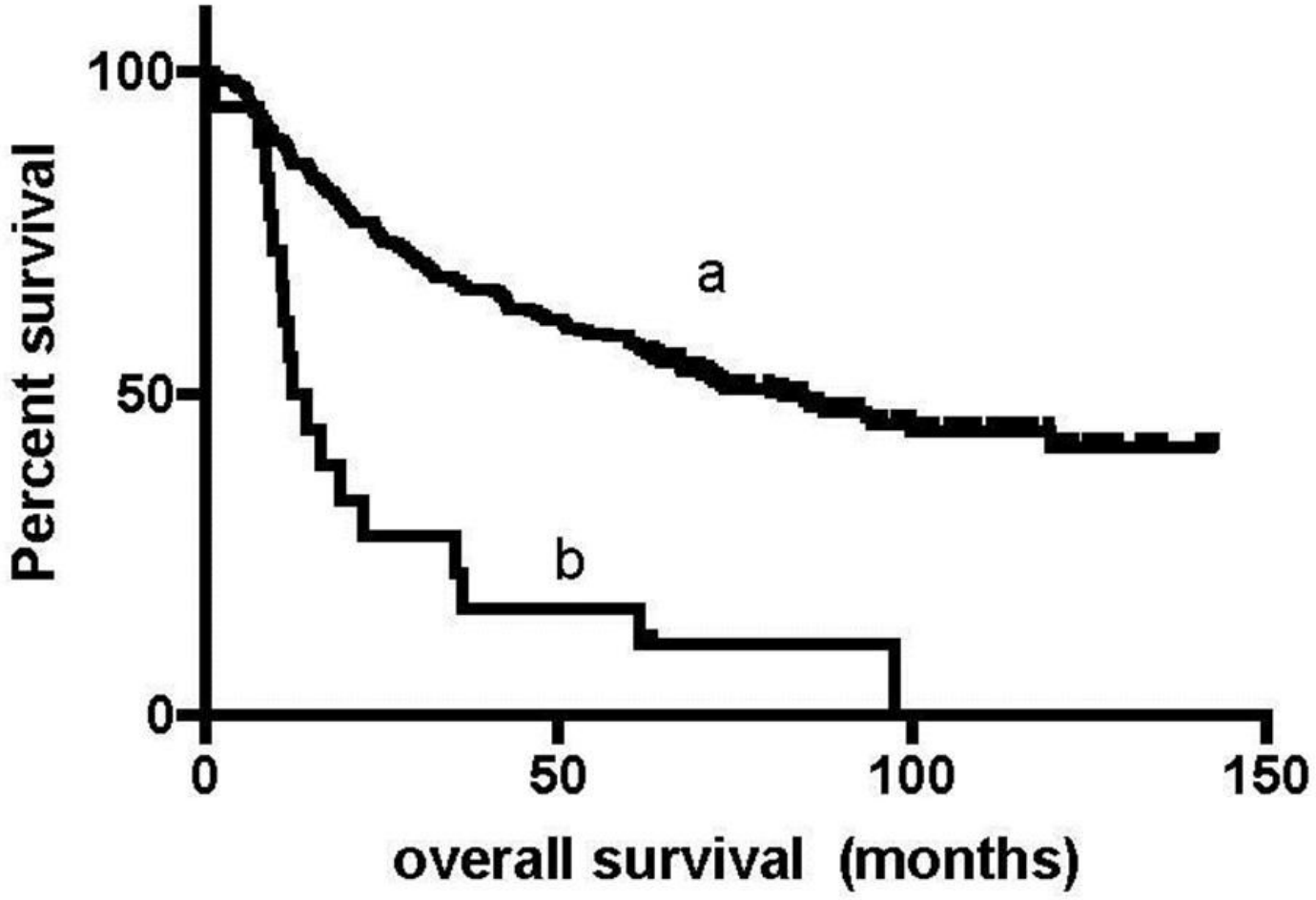

Figure 1

The mOS of patients without intraoperative blood transfusion is 81.8m (a) and patients with intraoperative blood transfusion is 12.4m (b), $p<0.001$.

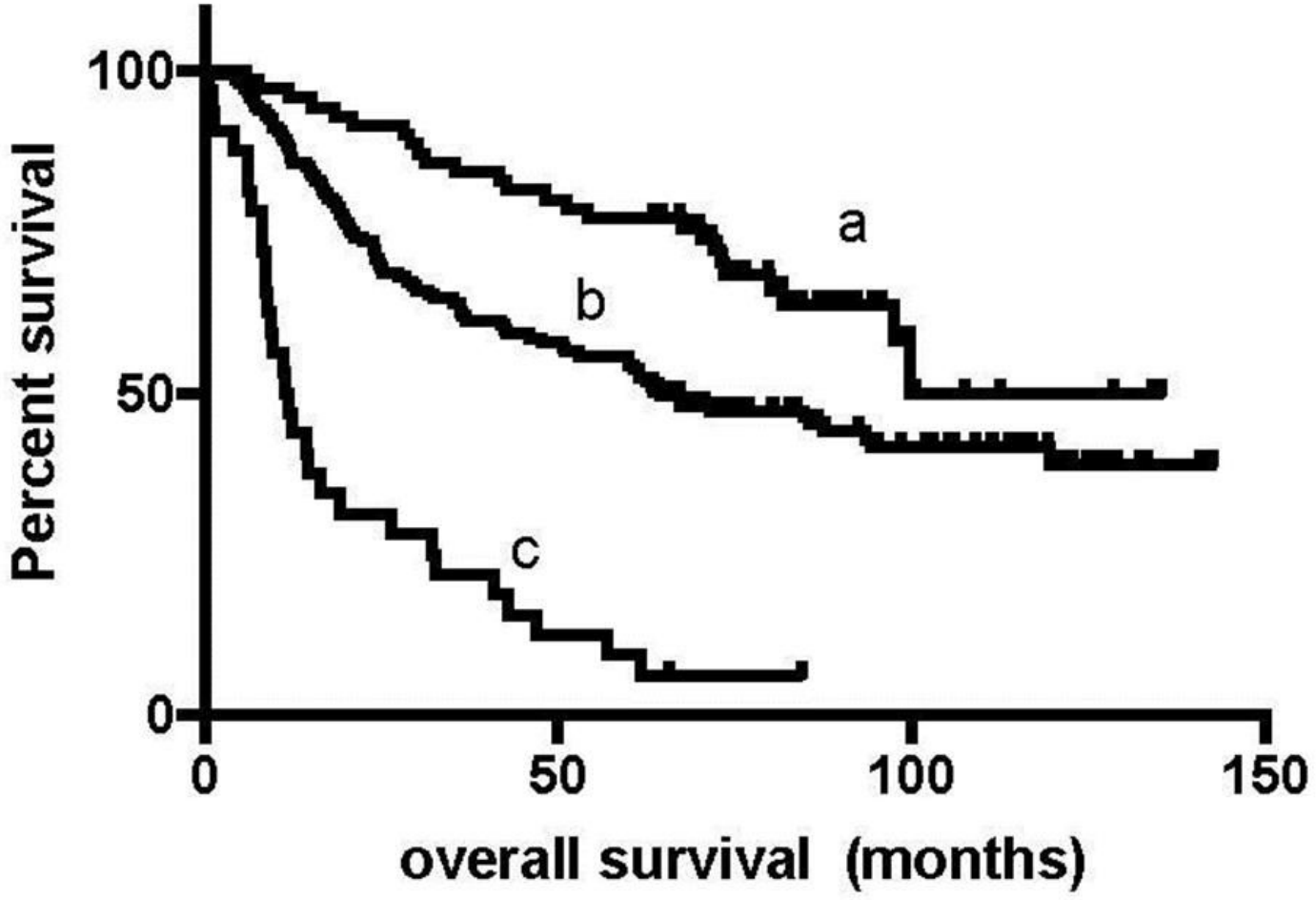

Figure 2

The mOS of patients with PNLNR>1 was 1.9m (c), paitents with PNLNR≤ 1 (b) was 10.3m, and patients with PNLNR=0 had not reached (a), p<0.001.

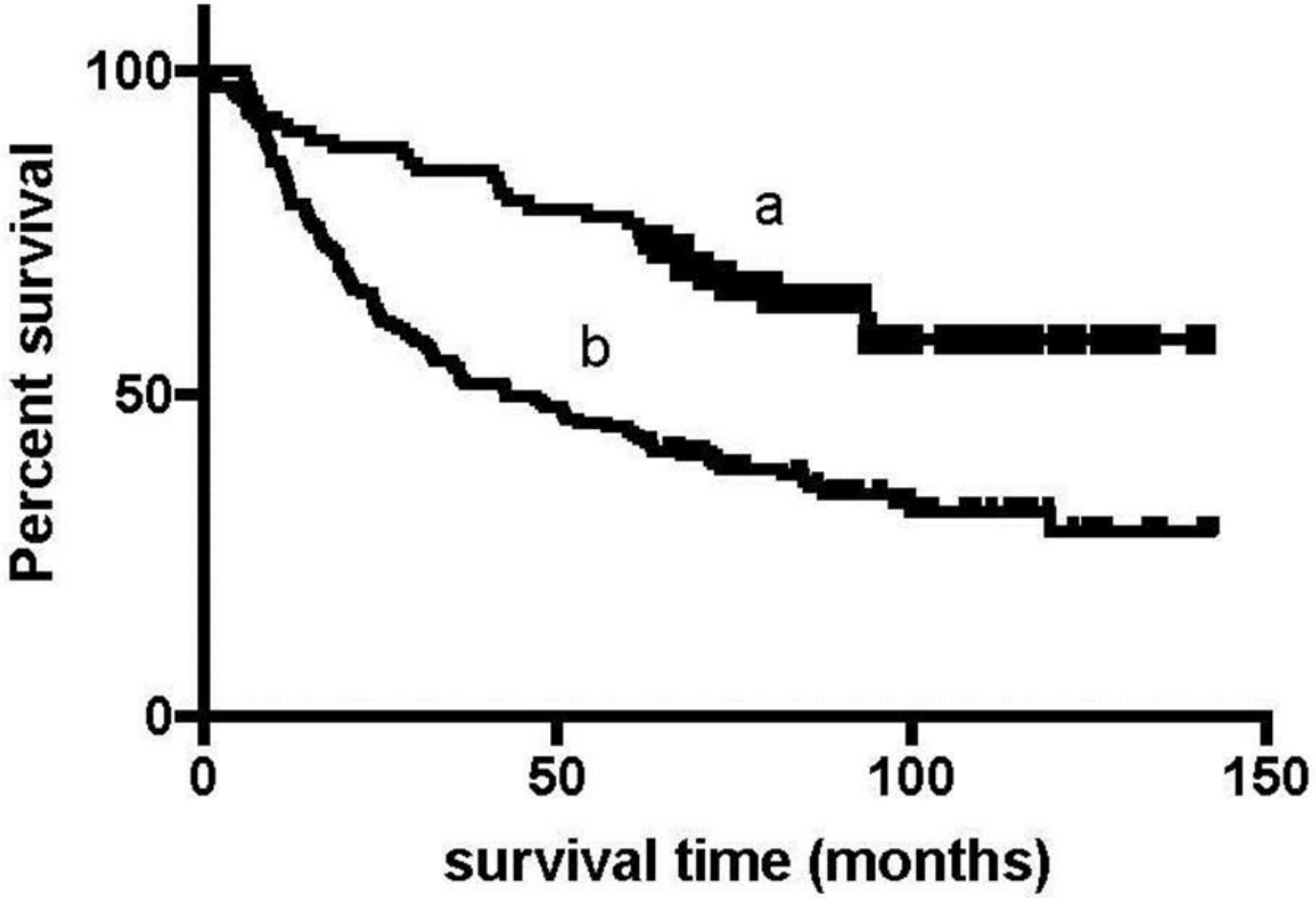

Figure 3

The median overall survival (mOS) of patients with tumor diameter more than 4cm had not reached (a), and mOS of tumor diameter less or equal to 4cm was 43.8m (b), $p<0.001$.