Long-term clinicopathological prognosis on 609 cases after gastrectomy: A 10-year follow up single-institutional retrospective analysis

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Research

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Abstract

Objective: This retrospective study focused on relevant factors about gastric cancer patients who underwent gastrectomy after 10 years, which showed great significance of prolonging survival time of gastric cancer patients.

Methods: 609 gastric cancer patients after surgery were recruited from January, 2005 to December, 2007. They were perfectly followed and their clinicopathological data were collected. Univariate analysis was performed using Log-rank test in order to compare survival rates between or among groups. The outcomes with statistical significance ($P < 0.05$) were screened out. Cox regression model was employed for survival multivariate analysis. Forward stepwise LR analysis was used to screen the factors influencing survival qualities of relevant patients after surgery.

Results: Univariate analysis indicated that prognosis was correlated with age, pT stage, pN stage, pM stage, tumor size, location, type of gastrectomy, degree of differentiation, vascular invasion, nerve invasion, radical treatment, chemotherapy, radiotherapy, pTNM stage and BMI ($P \leq 0.05$). Multivariate analysis showed that pT stage, pN stage, pM stage, degree of differentiation, vascular invasion, nerve invasion, radical treatment, chemotherapy, radiotherapy, pTNM stage were independent prognostic factors of GC patients ($P \leq 0.05$).

Conclusions: The 10-year survival rates of gastric cancer patients are primarily determined by tumor progression. Appropriate treatment can improve prognosis of patients. Early diagnosis of gastric cancer and prompt implementation of radical surgery and adjuvant chemotherapy are essential for increasing survival rates. This study provides a promising direction for future basic researches.

Introduction

Gastric cancer (GC) is one of the most prevalent malignancies worldwide, whose incidence ranks the fifth only to lung cancer, breast cancer, colorectal cancer and prostate cancer based on GLOBOCAN published in 2018[1]. Approximately one third of worldwide cases of GC took place in China. Chinese date of malignancy registration showed that the incidence of GC ranks the second in new cases and the third in cases whose deaths were caused by malignancies [2]. As the major treatment method, surgery is considered as the sole way to cure GC. However, clinical surveys have demonstrated that long-term efficacy of gastrectomy can be uncertain. There are many studies at home and abroad with the purpose of exploring factors that influence prognosis. Shortcomings also exist, including absence of 10-year followed-up surveys, lack of adequate samples and incompleteness of prognostic factors. In order to compensate for the disadvantages of current studies, the authors collected 609 GC patients with complete followed-up information who underwent surgery from 2005 to 2007 in General Hospital of the People's Liberation Army of China. The data were retrospectively analyzed. Relevant results were statistically analyzed according to clinicopathological characteristics and post-surgery adjuvant

chemoradiotherapy. It can provide reference for clinical judgment of prognosis and reasonable selection of treatment regimens.

Materials And Methods

1. Patients

All of 609 recruited patients, diagnosed as having GC by pathological examination, underwent GC surgery from January, 2005 to December, 2007 in General Hospital of the People's Liberation Army of China, including 454 men and 155 women, whose ages ranged from 23 to 83 years old. Their followed-up information were completed. Data in case history were recorded in detail. The clinicopathological information included age, sex, pT stage, pN stage, pM stage, tumor size, location, type of gastrectomy, degree of differentiation, the amount of dissected lymph nodes, vascular invasion, nerve invasion, radical treatment, selected approach and therapeutic number of chemoradiotherapy, pTNM stage and body mass index (BMI). Also, patients whose death were not due to GC were excluded in this study.

2. Follow-up

The patients were followed through telephone interview or review in outpatient clinic. The follow-up surveys were implemented every 3 months within 2 years after the end of treatment, every 6 months within 3 to 5 years and every year after 5 years, the end point of which was until December 25, 2017. The overall survival time should be from the day after surgery to the outcome or the end of survey. The follow-up of these patients were from less than 1 month to 155 months. All the cases included were followed.

3. Statistical analysis

SPSS (version 22.0) software was used for the statistical analysis. Univariate analysis employed Kaplan-Meier method to calculate survival rate, survival rate curve, and median survival time. Log-rank test was used to compare survival rates between or among groups. The target variables with statistical significance were screened out in univariate analysis. Statistically significant multi-category variables were transformed into two-category dummy variables. Cox regression analysis was employed to perform survival multivariate analysis. The authors then summarized these results and explored outcomes that markedly affected the prognosis. Finally, the correlations between survival time and outcomes were found. The significance level was $P=0.05$.

Results

Overall survival: there had been 159 in 609 patients still alive until the end point of follow-up. The longest survival time reached 155 months while the shortest survival time was 1 month. The median survival time was 48 months. The 5-year and 10-year survival rates were 44.8% and 26.1%, respectively. Overall survival curves are shown in Figure.1

Univariate analysis:

609 patients were divided into groups according to clinicopathological characteristics. Kaplan-Meier method was used to calculate the cumulative 5-year and 10-year survival rates. Otherwise, the difference among groups were shown by Log-rank test. Univariate analysis indicated that prognosis was statistically associated with age, pT stage, pN stage, pM stage, tumor size, location, type of gastrectomy, degree of differentiation, vascular invasion, nerve invasion, radical treatment, chemotherapy, radiotherapy, pTNM stage, BMI ($P \leq 0.05$). However, prognosis was not proved significantly correlated with sex and number of dissected lymph nodes ($p \geq 0.05$). (Table.1)

Table1. Clinicopathological material and 10-year survival rate of 609 patients

Clinicopathological material	Median survival time—months—	n	5-year survival (%)	10-year survival (%)	Log Rank c^2	P
Sex					1.682	0.195
Male	45	454	44.3	24.4		
Female	55	155	46.5	31		
Age(years)					10.286	0.001
≤65	54	400	47.8	30.5		
>65	38	209	39.2	17.7		
pT stage					64.233	0.000
T1a	110	55	85.5	47.3		
T1b	—	26	84.6	57.7		
T2	111	54	79.6	42.6		
T3	44	181	39.2	22.1		
T4a	26	144	31.9	19.4		
T4b	23	134	29.9	17.9		
pN stage					122.899	0.000
N0	100	219	66.7	40.2		
N1	86	90	55.6	34.4		
N2	31	131	36.6	19.1		
N3a	22	103	20.4	10.7		
N3b	9	28	10.7	3.6		
pM stage					113.131	0.000
M0	60	529	50.1	29.1		
M1	9	63	6.3	3.2		
Tumor diameter (cm)					33.144	0.000
≤5	88	307	57.3	33.6		
>5	24	270	32.2	19.3		
Tumor location					29.836	0.000
Upper one-third	40	232	38.8	22		
Middle one-third	51	95	49.5	30.5		
Lower one-third	84	235	54	31.9		
more	16	46	17.4	6.5		
Surgical procedure					37.090	0.000
Proximal	50	228	44.7	27.2		
Distal	91	248	57.7	33.9		
Total	17	93	24.7	12.9		
Differentiation					15.486	0.000
Non or Low	31	210	37.6	19.5		
Mid or Well	76	293	52.9	32.1		
Harvest lymph nodes					0.054	0.816
<15	56	356	48	27.2		
≥15	49	201	45.3	27.9		
Lymphovascular invasion					29.655	0.000
Yes	23	102	22.5	14.7		
No	74	459	52.5	30.3		
Nerve invasion					7.695	0.006
Yes	22	30	23.3	13.3		
No	56	530	48.5	28.3		
Radical surgery					104.713	0.000
YES	57	552	48.4	28.8		
NO	9	57	10.5	0.0		
Chemotherapy					16.032	0.025
No chemotherapy	45	249	45.4	24.5		

One time	32	31	38.7	29		
Two times	22	32	31.3	12.5		
Three times	52	47	44.7	29.8		
Four times	45	28	42.9	32.1		
Five times	74	20	55	35		
Six times	91	95	60	38.9		
≥Six times	50	61	42.6	23		
Radiotherapy					9.725	0.002
Yes	25	49	26.5	10.2		
No	54	529	47.4	28.2		
pTNM stage					203.948	0.000
IA	111	71	84.5	47.9		
IB	105	42	71.4	45.2		
IIA	109	52	67.3	40.4		
IIB	86	73	57.5	35.6		
IIIA	42	68	44.1	20.6		
IIIB	36	133	37.6	21.8		
IIIC	21	92	19.6	12.0		
IV	9	70	5.7	2.9		
Body mass index (kg/m ²)					5.101	0.024
<25	43	441	42.6	23.8		
≥25	60	168	50.6	32.1		

Multivariate Cox regression analysis:

In order to adjust the relationships among variables and remove confounding factors, the outcomes with statistical significance in univariate analysis were included into Cox proportional hazards regression models. Forward stepwise LR method was employed in multivariate analysis. PTNM stage, separated with pT, pN and pM, was included in the other regression model analysis since TNM stage should be dependent on the tumor, the number of involved regional lymph nodes and metastasis. Moreover, polytomous variables were included as dummy variables. The system encoded dummy variables in the way that the last dummy variable served as the baseline level. The results showed that these outcomes were independent prognostic factors of GC patients after surgery, including age, pT stage, pN stage, pM stage, degree of differentiation, vascular invasion, nerve invasion, radical treatment, chemotherapy, radiotherapy and pTNM stage (All $P \leq 0.05$, Table.2). Survival curves are respectively shown in Figure.2, Figure 3 and Figure 4.

Table 2. Multivariate analysis of the factors affecting the prognosis of 609 patients

Variables	Cox proportional hazard model A			Cox proportional hazard model B		
	Hazard radio	95% confidential interval	p- value	Hazard radio	95% confidential interval	P- value
Age(years)			0.000			0.000
≤65 vs. >65	0.559	0.436-0.716	0.000	0.585	0.456-0.751	0.000
pT stage			0.000			
T1a vs. T4b	0.409	0.224-0.749	0.004			
T1b vs. T4b	0.389	0.184-0.822	0.013			
T2 vs. T4b	0.483	0.302-0.774	0.002			
T3 vs. T4b	0.821	0.593-1.135	0.135			
T4a vs. T4b	1.049	0.757-1.455	0.773			
pN stage			0.000			
N0 vs. N3b	0.162	0.090-0.291	0.000			
N1 vs. N3b	0.189	0.102-0.350	0.000			
N2 vs. N3b	0.312	0.178-0.545	0.000			
N3a vs. N3b	0.480	0.270-0.852	0.000			
pM stage			0.022			
M0 vs. M1	0.522	0.299-0.911	0.022			
Differentiation			0.004			0.007
Non/Low vs. Mid/Well	1.433	0.119-1.837	0.004	1.400	1.094-1.792	0.007
Lymphovascular invasion			0.093			0.003
Yes vs. No			0.093	0.641	0.475-0.864	0.003
Nerve invasion			0.030			0.010
Yes vs. No	0.593	0.370-0.951	0.030	0.552	0.351-0.867	0.010
Radical surgery			0.001			0.002
Yes vs. No	2.765	1.491-5.126	0.001	2.619	1.408-4.871	0.002
Chemotherapy			0.000			0.005
Non vs. ≤ 6 times	1.607	1.077-2.396	0.020	1.657	1.098-2.500	0.016
1 time vs. ≤6 times	1.558	0.877-2.767	0.131	1.574	0.871-2.845	0.133
2 times vs. ≤6 times	1.653	0.963-2.837	0.068	1.606	0.939-2.747	0.084
3 times vs. ≤6 times	1.076	0.640-1.810	0.783	1.079	0.636-1.830	0.779
4 times vs. ≤6 times	0.816	0.439-1.518	0.521	1.033	0.557-1.913	0.919
5 times vs. ≤6 times	0.739	0.336-1.625	0.452	0.807	0.365-1.782	0.595
6 times vs. ≤6 times	0.642	0.403-1.021	0.061	0.824	0.520-1.305	0.409
Radiotherapy			0.002			0.003
Yes vs. No	0.530	0.355-0.791	0.002	0.540	0.362-0.806	0.003
pTNM stage						0.000
IA vs. IV				0.129	0.063-0.266	0.000
IB vs. IV				0.184	0.091-0.372	0.000
IIA vs. IV				0.199	0.099-0.401	0.000
IIB vs. IV				0.257	0.132-0.498	0.000
IIIA vs. IV				0.379	0.199-0.724	0.003

IIIB vs. IV	0.391	0.215-0.713	0.002
IIIC vs. IV	0.742	0.408-1.348	0.327

Discussion

The incidence of GC presents decreasing tendency worldwide while Chinese incidence is still situated ahead of all kinds of malignancies, the mortality of which ranks the first in China [3]. This dilemma can be attributed to underdevelopment of economy, leading to difficulty in screening a variety of malignancies. Most patients will not get final diagnosis until advanced stage. Therefore, it is crucial to appropriately select comprehensive treatment regimens for improving rates of clinical cure and long-term survival. The factors that influence prognosis of GC are definitely complicated. It is generally acknowledged that prognosis is closely associated with clinicopathological stage, depth of tumor invasion, lymphatic metastasis, radical treatment, etc. Nevertheless, there still exist arguments on the roles of tumor size, location, type of gastrectomy, sex, age, postoperative chemoradiotherapy in GC prognosis.

Studies have reported inconsistent results about relationship between age and prognosis [4–5], which may result from the absence of unified criterion of age groups. The elderly are identified as old people who are more than 65 years old by World Health Organization (WHO). In this study, the elderly accounted for 34.3% (209/609). Univariate and multivariate analysis both demonstrated that age was significantly correlated with GC prognosis ($P \leq 0.05$), which was consistent with results of former studies [6]. Survival curves showed that long-term survival rates of patients who were over 65 years old were obviously lower than the ones of patients who were below 65 years old. This result might be partially due to deterioration of physical condition and increasing incidence of complications in the elderly.

The depth of tumor invasion, lymphatic metastasis and distant metastasis of tumor can objectively reflect tumor biological behaviors and progression degrees. In terms of the depth of tumor invasion, analysis of survival curves in this study indicated that prognosis was better in the cases that tumor tissues were limited to mucosa, submucosa or muscularis. Once subserosa was involved, survival rates apparently declined. Prognosis showed the worst condition in the case that tumor invaded serosa or outside. This comparison suggested that muscularis of gastric wall could play an important role in the prevention of tumor invasion, which also provided clear directions in basic researches. Multivariate analysis showed that the depth of tumor invasion could serve as an independent prognostic factor. This conclusion was consistent with Orman's study [7].

Lymphatic metastasis and distant metastasis both reflect biological characteristics of tumor. It still remains weakness for surgeons to deal with metastasis. The two characteristics can significantly decline the surgical effects and prognosis. This study demonstrated that lymphatic metastasis and distant metastasis were also independent prognostic factors of GC. Prognosis would be worse as stages became more advanced. The median survival of N0 and N3b stages were 100 months and 9 months, which of M0

and M1 stages were 60 months and 9 months, respectively. The 10-year survival rates of M0 and M1 stages were 29.1% and 3.2%, respectively. This strong correlation owned consistence with relevant studies [8]. Orman and his colleagues indicated that tumor had the chances of metastasizing to lymph nodes with increasing depth of tumor invasion, decreasing survival rates of GC patients. It proved that tumor could invade tissues near lymphatic vessels, damage integrity of vessel walls, and flow into lymphatic vessels. This process is dominantly dependent on a variety of adherence factors and proteinase in response to lymphatic vessel walls. If basic researches can elucidate concrete mechanisms and find the access to blocking targeted key molecules, malignant process may be reversed. It will establish obstacles for lymphatic and distant metastasis, even when tumor invades more deep. The survival rates will naturally become free from tumors. This logical method is displayed as the thinking of "Precision Medicine".

pTNM stage was proved as an important independent prognostic factor of GC patients [9]. This study found that 10-year cumulative survival rates apparently decreased with more advanced stages. Univariate and multivariate analysis indicated that pTNM systematic stage could serve as an important and independent prognostic factor. The same conclusion was drawn in studies of western and developing countries [10–11]. 10-year survival rates of IA and IV stages were respectively 47.9% and 2.9%. 10-year survival rate was generally low in this study because of a small proportion of patients at early stage. Most patients were diagnosed as GC at advanced stage. Therefore, it is concluded that prognosis is greatly dependent on GC clinical stage. Thus, surgery at early stage can promote prognosis.

There are abundant blood vessels, lymphatic vessels and nerves in the gastric wall layer from mucosa to serosa. The more deep tumors invade gastric wall, the more chances tumor cells will have to spread to vicinity of tumors through vessels and nerves, resulting in lymphatic and hematogenous metastasis. This is the major way of GC metastasis [12]. Scartozzi and his colleagues collected 734 patients who had undergone radical cancer gastrectomy at advanced stage and found that vessel and nerve invasion were independent prognostic factors of influencing recurrence and long-term survival of GC patients [13]. Univariate and multivariate analysis in this study both demonstrated that lymph node metastasis was an independent prognostic factor. Consequently, vessel and nerve invasion are determined to play important roles in tumor metastasis.

Tumors are likely to recur for GC patients, especially those at advanced stage, because of macroscopically invisible remnants in surgical areas even when the visible tumors are clearly dissected. Postoperative chemoradiotherapy is an effective approach to killing remaining tumor cells. It was reported that increasing survival rates of GC patients after surgery were mainly attributed to the improved capability of postoperative chemotherapy [14]. Two large clinical randomized controlled trials proved that postoperative chemotherapy could contribute to better prognosis than surgery alone [15–16]. However, there are no studies about the relationship between numbers of chemotherapy and prognosis. Univariate and multivariate analysis in this study showed that postoperative chemotherapy was an independent prognostic factor. According to survival curves, survival rates of six cycles of chemotherapy were the highest, and the ones of over 6 cycles were statistically lower ($p = 0.028$). This difference proved that 6

cycles of chemotherapy was the best choice in the condition that patients could have good physical endurance. Over 6 cycles of chemotherapy is regarded as a kind of overtreatment and cannot improve survival rates. Patients who underwent 2 cycles of chemotherapy had the lowest 10-year survival, reasons of which may be concluded as three aspects: a) sample errors can be huge based on small number of patients who underwent 2 cycles of chemotherapy; b) the compliance of chemotherapy can be not optimal; c) it is widely accepted that weak patients cannot tolerate more cycles of chemotherapy. The influence of physical weakness on survival is much bigger than the one of numbers of chemotherapeutic cycles.

Conventional radiotherapy had mostly served as palliative treatment in GC until New England Journal published a study of Macdonald in 2001. Since this event, radiotherapy, as a kind of adjuvant therapy, has received wide attention in multidisciplinary treatment [17]. However, the application of radiotherapy in GC owns less clinical studies and acceptance than other kinds of tumors, because there have been long-term conventional concept and different features in GC treatment between China and western countries. Univariate and multivariate analysis in this study showed postoperative radiotherapy was an independent prognostic factor. However, 10-year survival rates of patients who underwent radiotherapy were lower than those who did not receive radiotherapy, which might be attributed to degrees of tumor differentiation. The influence of poor differentiation on prognosis is much severer than the one of radiotherapy. Mohsen and his colleagues drew the similar conclusion that survival rates of patients who received radiotherapy and did not receive radiotherapy were 9% and 19%, respectively ($P = 0.59$). There was no statistical difference between them [18]. Otherwise, univariate and multivariate analysis both indicated that the degree of differentiation and radical treatment were two independent prognostic factors of GC, consistent with previous studies [19–20].

Univariate analysis showed that sex was not an independent prognostic factor of GC, which was keeping with previous studies [20–21]. We indicated that prognosis was associated with tumor size, location, type of gastrectomy and BMI. Survival curves was shown in Fig. 5. Whereas multivariate analysis showed that these outcomes were not independent prognostic factors in GC, inconsistent with some studies [7, 20, 21]. The type of gastrectomy mainly depends on tumor location and size in clinical practice. It can take on relative distributions of patients in subgroups. Therefore, the conclusion about tumor size, location, type of gastrectomy is the same as other studies. There still exist controversies about the relationship between BMI and prognosis [23]. Some scholars claimed that high BMI led to more difficult surgery, higher chances of complications, more residual involved lymph nodes, higher rates of recurrence and metastasis [24]. In this way, high BMI can decrease survival rates of GC patients. Some other scholars claimed that the surgical and adjuvant therapeutic duration of patients with high BMI was better than the ones with low BMI. Dystrophic patients, which is also called patients with abnormally low BMI, were easy to suffer systemic inflammation. This physiopathological process could promote malignant biological behaviors [25]. It seems that high BMI may increase survival rates of patients. However, opposite results may be partly due to different races, different regions, different numbers of samples and mutual effects of prognostic factors. The correct conclusion needs further studies.

Figure.5 The survival curves of tumor size, location, type of gastrectomy and BMI

pT stage, pN stage, pM stage, vascular invasion, nerve invasion, pTNM stage were all proved associated with tumor progression among independent prognostic factors of GC. Survival curves of these factors, especially pT stage, obviously showed dissociative phenomena. T2 and T3 curves were extremely dissociative in pT stage, which proved that when tumor cells penetrated muscularis and entered subserosa, the prognosis of patients sharply deteriorated. This result suggested that the microenvironment of subserosa could induce plasticity of tumor cells. Mutual effects of tumor cells and microenvironment of subserosa made the former shifted to more aggressive cell colonies. Nevertheless, basic studies are confined to mucosa microenvironment [26]. It is reported that Periostin, an extracellular matrix molecule, was closely associated with the genesis, progression and prognosis of GC [27]. The author's previous basic studies found that Periostin could interfere with tumor plasticity through induction of stem-like potential, promoting malignant biological behaviors of tumor cells. This study strongly indicated that the molecules that acted as essential roles of GC were probably located in subserosa. It is not clear that whether Periostin took the leading position of plasticity of tumor cells. The exploration of concrete molecular mechanisms and confirmation of key molecules will provide more reliable theoretical proof for monitoring the processes of GC and choose individualized treatment regimens in future basic studies.

This study will provide not only references for diagnosis, treatment, and evaluation of GC prognosis, but also an access to future basic studies through clinical phenomena and problems. This amazing advancement will lead the direction of basic medicine and assist to overcome clinical challenges more specifically, which is also displayed as the thinking of "Precision Medicine". The process is exactly the authentic value of basic studies.

Conclusion

Univariate and multivariate analysis in this study both showed that age, pT stage, pN stage, pM stage, degree of differentiation, vascular invasion, nerve invasion, radical treatment, chemotherapy, radiotherapy, pTNM stage were independent prognostic factors of GC prognosis ($P \leq 0.05$). pT stage, pN stage, pM stage, vascular invasion, nerve invasion, pTNM stage were directly correlated with tumor progression. The 10-year survival rate of GC patients mainly depends on the progression of dissected tumor tissues. The more advanced the tumor progression is, the lower 10-year survival rates will be. Radical treatment, chemotherapy and radiotherapy belong to treatment types. Reasonable treatment types can improve prognosis to some extent. Age and degree of differentiation are respectively classified as properties of patients and tumors, both of which exert considerable impacts on prognosis. However, these two properties, as uncontrollable factors, are beyond artificial prevention and interference. In summary, the 10-year survival rates are determined by degrees of tumor progression, treatment types and properties of patients and tumors. The effective approaches to fighting with GC are early diagnosis, prompt radical treatment and adjuvant chemotherapy. They are crucial for increasing survival rates after gastrectomy.

Finally, this study provides a promising access to establishing a bridge between basic and clinical studies.

Abbreviations

GC: gastric cancer; BMI: body mass index.

Declarations

Ethical Approval and consent to participate section The study protocol was approved by the Ethics Committee of Chinese PLA general hospital and the study compliance with the Helsinki Declaration. Written informed consent was obtained from all of the patients. **Availability of data and materials** Access to the database can be obtained from the corresponding author on a reasonable request. **Consent for publication** Not applicable.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

All authors made substantial contributions to the intellectual content of this paper. Bo Wei and Lin Chen constructed this research as the co-corresponding author. Guoxiao Liu and Hao Cui contributed equally to this work as the co-first author. Wang Zhang and Bo Cao collected and summarized original data. Guoxiao Liu wrote this paper and translated by Bo Cao. Guoxiao Liu and Hao Cui were in charge of revising manuscript. Zhida Chen, Ting Cong, Hao Cui and Huan Deng performed follow-up by telephone.

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Figures

Figure 1

Overall survival curve of 609 patients

Figure 2

Kaplan–Meier estimates of cumulative survival according to different pT(a) ,pN(b), pM(c) , pTNM(d) stage based on 8th AJCC Cancer Staging Manual and differentiation level(e).

Figure 3

Kaplan–Meier estimates of cumulative survival according to lymphovascular invasion or not (a) and nerve invasion or not (b).

Figure 4

Kaplan–Meier estimates of cumulative survival according to different treatment like surgery(a) , chemotherapy(b) and radiotherapy(c).

Figure 5

The survival curves of tumor size(a), location(b), type of gastrectomy(c) and BMI(d)