Long-term outcomes of gastric cancer in a single small center: a retrospective analysis

Ji Yoon Jeong

Inje University Busan Paik Hospital

Kwang Hee Kim

Inje University Busan Paik Hospital

Sang Hyuk Seo (✉ sshgs@paik.ac.kr)

Inje University Busan Paik Hospital <https://orcid.org/0000-0002-7534-9421>

Min Sung An

Inje University Busan Paik Hospital

HyungJoo Baik

Inje University Busan Paik Hospital

Yo-Han Park

Inje University Busan Paik Hospital

Sang Hyun Kang

Inje University Busan Paik Hospital

Jin Soo Kim

Inje University Haeundae Paik Hospital

Ki Hoon Kim

Inje University Haeundae Paik Hospital

Sang Hoon Oh

Inje University Seoul Paik Hospital

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Abstract

Background

The aim of this study is to evaluate the long-term outcomes and short-term outcomes of gastric cancer patients who underwent surgical treatment in a small-sized single center by one surgeon.

Methods

We retrospectively reviewed the medical records of 950 patients who underwent surgical treatment for gastric cancer between January 2000 and January 2010 at Dong-rae Paik Hospital, Inje University College of Medicine, Busan, Korea. A total of 820 patients were included and analyzed. We divided the time period into 2 groups: 2000–2005 (period 1) and 2006–2010 (period 2). Since all the surgeries were performed by one surgeon, we were able to analyze the changes in long-term outcomes as the individual surgeon volume accumulated.

Results

The mean follow-up period was 78.26 months. The overall survival and relapse-free survival rates of all patients were 84.6%, and 86.5%, respectively; the postoperative morbidity and mortality rates were 12% and 0.36%, respectively. The relapse-free survival rate was higher in period 2 than in period 1 (82.9% versus 90.2%, $p = 0.002$)

Conclusions

Our study showed that the short-term outcomes and long-term outcomes of gastric cancer treatment in a small-sized hospital were comparable to those in large-sized hospitals. Accumulated individual surgeon volume was related to a high relapse-free survival rate.

Background

Numerous developments have been made in surgical techniques and adjuvant chemotherapy for gastric cancer. However, gastric cancer remains the fourth most common cause of cancer-related death worldwide (1). Its treatment requires a complex surgical procedure and multidisciplinary treatment, but high mortality and relapse rates are important problems that need to be overcome.

To improve the quality of gastric cancer treatment, studies concerning volume-outcome relationships have been ongoing since 1990. It has been reported that hospital volume has a positive relationship with clinical outcome (2, 3). Based on these studies, Western countries, such as the United States, England,

Australia, the Netherlands, and Sweden, started a policy for the centralization of cancer treatment in high-volume centers (4–8).

Surgeon volume is another important factor (9, 10), and there is a controversy over whether hospital volume or surgeon volume is more important. However, there are a limited number of studies concerning the relationship between individual surgeon volume and long-term outcomes of gastric cancer.

The aim of our study is to evaluate the short-term outcomes and long-term outcomes of gastric cancer patients who underwent surgical treatment in a small-sized single center in a local region. Based on our experience, we analyzed the changes in outcomes as the individual surgeon volume accumulated.

Materials And Methods

Patients

We retrospectively reviewed the medical records of 950 patients who underwent surgical treatment for gastric cancer between January 2000 and January 2010 at Dong-rae Paik Hospital, Inje University College of Medicine, Busan, Korea. Among the 950 patients, we excluded patients who underwent neoadjuvant chemotherapy ($n = 2$), patients who were diagnosed with stage VI cancer ($n = 98$), patients who had a postoperative biopsy that revealed a remnant tumor ($n = 17$), patients who underwent completion gastrectomy due to recurrent gastric cancer ($n = 7$), patients who were diagnosed with double primary cancer from other organs ($n = 3$), and patients who died within 50 days after surgery ($n = 3$). After exclusion, 820 patients over the age of 19 were included in the analysis. The patients' clinicopathologic characteristics, treatment methods, and treatment outcomes including short-term and long-term outcomes were analyzed (Fig. 1).

Clinical outcomes

For gastric cancer staging, the 7th American Joint Committee on Cancer(AJCC) TNM staging system was used. Other clinicopathologic characteristics were evaluated according to the Japanese classification for gastric cancer (11). Postoperative morbidity was defined by the Clavien-Dindo classification with any grade within 50 days after surgery, and major complications were defined as complications graded higher than grade 3 in Clavien-Dindo classification (12). Postoperative mortality was defined as death from any cause within 50 days after surgery.

Patients with stage Ia cancer did not undergo out postoperative adjuvant chemotherapy. For some stage Ib and stage II patients, oral fluorouracil was administered. Other stage II and most stage III patients received a platinum-based regimen, an MMC combined regimen or oral S-1 chemotherapy.

We followed patients from the operation day to December 31, 2013. All patients' physical examinations were checked every two months, and chest X-rays, tumor markers, and abdominal computed tomography scans were performed every 6 months. Esophagogastroduodenoscopy was performed every year. If we

lost the patients' to follow-up, we collected data regarding survival or cause of death from the National Statistical Office of Korea. Overall survival was calculated from the date of the operation to the date of cancer-related death or the last follow-up. Disease recurrence was identified by imaging findings or biopsy-proven recurrent gastric cancer.

Since all the surgeries were performed by one individual surgeon, we were able to analyze the changes in long-term outcomes as the individual surgeon volume accumulated. Therefore, we divided the time period into 2 groups: 2000–2005 (period 1, n = 407) and 2006–2010 (period 2, n = 413). Subgroup analysis was performed between the two groups.

The research protocols were approved by the IRB of our institute. (IRB no 19–0189)

Statistical analysis

SPSS version 25 (SPSS, Chicago, IL) was used for statistical analysis. Independent sample t-tests and Mann-Whitney tests were used for continuous variables. A Chi-square test and linear-by-linear association were used to analyze categorical data. The Kaplan-Meier estimator was used to analyze survival curves, while the log-rank test was used to compare the survival distributions (or rates) of corresponding groups. A p-value of less than 0.05 was considered statistically significant for all cases.

Results

Clinicopathologic characteristics

The demographics of the patients and the clinicopathologic characteristics overall and in period 1 (P1) and period 2 (P2) are shown in Table 1. The mean age was 58.8 years, and BMI was 22.7. BMI was higher in P2 than P1 (22.4 vs 22.9, $p = 0.041$). There were no changes in tumor location between the two periods. The distribution of T stage was different in both periods (P1 vs P2, T1: T2: T3: T4, 59.8%: 10.4%: 27.2%: 2.7% vs 56.5%: 10.1%: 30.7%: 2.7%, $p = 0.042$), but the distribution of N stage and the total stage had no significant difference (P1 vs P2, N1: N2: N3, 64.9%: 11.1%: 10.3% vs 68.0%: 9.7%: 8.2%, $p = 0.544$) (P1 vs P2, stage1: stage2: stage3, 60.4%: 21.9%: 21.9% vs 66.8%: 13.8%: 19.4%, $p = 0.117$).

Histopathologically, less perineural invasion (PNI) and lymphatic invasion (LVI) was detected in P2 than in P1 (P1 vs P2, PNI positive: PNI negative, 3.9%: 96.1% vs 6.6%: 93.4%, $p < 0.001$) (P1 vs P2, LVI positive: LVI negative, 12.4%: 87.6% vs 17.4%: 82.6%, $p < 0.001$).

Short-term treatment outcomes

Table 2 shows short-term treatment outcomes of 820 patients, 741 underwent gastrectomy with an open method (90.4%), and 79 underwent laparoscopic-assisted distal gastrectomy (LADG) (9.6%). There was a higher rate of LADG in P2 than in P1 (P1 vs P2, 1.2% vs 17.9%, $p < 0.001$). There was no difference in the extent of resection in either period (P1 vs P2, subtotal: total: other, 80.7%: 18.9%: 0.4% vs 81.3%: 18.2%: 0.5%, $p = 0.743$). Three patients underwent other types of gastrectomies: two proximal gastrectomies, and one gastric wedge resection.

The distribution of lymph node dissection was different in both periods (P1 vs P2, D1: D1+: D2, 4.4%: 44.1%: 51.5% vs 0.5%: 44.5%: 55.0%, $p < 0.001$). More lymph nodes were harvested in P2 than P1 (27.2 vs 41.4, $p < 0.001$).

There was a shorter hospital stay in P2 than in P1 (18.0 vs 14.6, $p < 0.001$). A total of 660 patients underwent postoperative adjuvant chemotherapy either orally or intravenously (IV) (80.5%). The distribution of adjuvant chemotherapy was different in both periods (P1 vs P2, none: oral: IV, 15.2%: 44.7%: 40.0% vs 23.7%: 63.0%: 13.3%, $p < 0.001$).

The total postoperative morbidity rate was 11.9%, and the major complication rate was 4.1%. The postoperative morbidity rate was not significantly different between the two periods (P1 vs P2, 12.3% vs 12.0%, $p = 0.751$). The major complication rate was also not significantly different between the two periods (P1 vs P2, 3.9% vs 4.4%, $p = 0.942$). Although we did not include mortality in the statistical analysis, 3 cases of mortality were recorded within 50 days after surgery (postoperative mortality rate = 0.36%). The first case was a 68-year-old male, who died of acute myocardial infarction on postoperative day (POD) 17. The second case was a 70-year-old female, who died of spontaneous intracranial hemorrhage on POD 11. The third case was a 72-year-old male, who died of acute respiratory distress syndrome on POD 32.

Long-term treatment outcomes

The mean follow-up period was 78.26 months. The 5-year overall survival rate and relapse-free survival rate of all patients were 84.6% and 86.5%, respectively. The 5-year overall survival rate and relapse-free survival rate for each stage were 97.8% and 97.8% for stage I, 82.6% and 86.2% for stage II, and 43.4% and 49.7% for stage III, respectively (Fig. 2). We identified 111 cases of recurrence among 820 patients. Thirty-one patients experienced liver recurrence (27.9%), 27 had distant lymph nodes (24.3%), 24 had peritoneum recurrence (21.6%), 16 had bone recurrence (14.4%), and 29 had local recurrence (26.1%). Forty-one patients (36.9%) had multiple metastases in at least two different organs.

The relapse-free survival rate was higher in P2 than in P1 (P1 vs P2, 82.9% vs 90.2%, $p = 0.002$). The overall survival rate was higher in P2 than in P1, but there was no significant difference (P1 vs P2, 78.1% vs 80.3%, $p = 0.713$) (Fig. 3).

Multivariate analysis

In multivariate analysis, the independent factors affecting overall survival were T stage, N stage, tumor location, VNI, and LVI (Table 3). The independent factors affecting the relapse-free survival were T stage, N stage, venous invasion (VNI), PNI, and LVI (Table 4).

Discussion

Studies regarding volume outcomes are ongoing. There is no consensus regarding whether hospital volume or surgeon volume affects the long-term outcomes of cancer treatment, but Birkmeyer et al

reported lower operative mortality and a better survival rate in high-volume hospitals with selected cancer resection (13). For gastric cancer, Coupland et al reported lower short-term and long-term mortality in rates high-volume hospitals for esophageal and gastric cancer (7). Thus, based on the evidence, the centralization of gastric cancer treatment in high-volume centers is performed, as well as in South Korea. However, others report no positive effect of volume (14–18). There are a limited number of studies concerning the relationship between individual surgeon volume and long-term outcomes of gastric cancer.

Regarding the size of the hospital in terms of the number of beds, Dong-rae Paik Hospital is a small-sized hospital with a total of 220 beds, 14 medical departments including internal medicine and surgery, and 10 beds in the intensive care unit. Our study analyzed the outcomes of 10 years of gastric cancer treatment performed in this hospital, and when these 10 years were divided into two periods, P2 showed the outcome of accumulated surgeon volume compared to P1 since all the surgeries were performed by one surgeon. Our study offers a result of the relationship between individual surgeon volume and long-term outcomes of gastric cancer.

Compared with studies conducted in large-sized hospitals with more than 1000 beds, Hyung et al. reviewed 5374 patients who underwent gastric cancer surgery from 1989 to 1999. The 5-year overall survival rate was 94.2% for stage I cancer, 73.4% for stage II, and 44.7% for stage III. The postoperative overall mortality rate was 0.7% (19). Park et al. reviewed 933 patients from 1997 to 2001 and reported a 5-year overall survival rate of 96% for stage Ia, 92% for stage Ib, 72% for stage II, 54% for stage IIIa, and 34% for stage IIIb. The total postoperative morbidity rate was 3.9% and the postoperative mortality rate was 0.6% (20). In our study, the total postoperative morbidity and major complication rates, as well as the postoperative mortality rate, were 11.9%, 4.1%, and 0.36%, respectively. For the long-term results, the 5-year overall survival rate at each stage was 97.8% for stage I, 82.6% for stage II, and 43.4% for stage III. Our results were comparable with those of large-sized hospitals.

Given the changes between the two periods, less PNI and LVI were detected in P2 than in P1. This lower detection of PNI and LVI may be related to the difference in the distribution of T stage (21). PNI has been regarded as an independent prognostic factor for overall survival and relapse-free survival in other studies (22–24), as well as LVI (25). In our multivariate analysis, T stage, N stage, VNI, PNI, and LVI were independent factors related to relapse-free survival, which corresponded to previous studies (20, 24–26). Although those factors may have influenced relapse-free survival over the entire period, it is difficult to determine that those factors had a significant effect on the reduction in relapse-free survival between the two periods. BMI was higher in P2 than in P1, and some studies report that BMI could be an independent factor for long-term survival after surgical treatment for gastric cancer (27, 28). In our study, the average BMI difference between the two periods was only 0.5, and Voglino et al. suggested that BMI does not affect postoperative complications or long-term survival (29).

Since LADG was first introduced by Kitano in 1994, LADG for early gastric cancer has increased in South Korea (30, 31). Dong-rae Paik Hospital began implementing LADG in 2003 and the rate of LADG rose to

18% in P2. This led to a shortening of hospital stay (32). At the beginning of LADG implementation, extended D2 lymph node dissection was not a standard procedure. Therefore, the proportion of D1 lymph node dissection seems to have been increased as LADG increased. Although LADG started mainly in P2, You et al. reported that the short-term outcomes of LADG for gastric cancer by a trained beginner surgeon were comparable with those of open surgery performed by an experienced surgeon (33), which was also seen in our study. There was a significant difference between the two periods in terms of the number of harvested lymph nodes (27.2 vs 41.4, $p < 0.001$). This seems to be the contribution of the development in pathology and the replacement of pathologists, rather than an increase in the number of lymph nodes actually harvested.

Mamidanna et al. reported that postoperative morbidity and mortality decreased as the surgeon volume increased (9), but in our study, there was no significant difference in postoperative morbidity or major complications as the individual surgeon volume accumulated.

There was no significant difference in the overall survival rate between the two periods, but the relapse-free survival rate was higher in P2 than in P1. Park et al. analyzed 12 years of gastric cancer treatment in a single center and reported that increasing the early detection of gastric cancer increased the overall survival rate (20). However, in our study, there was no difference in the distribution of the total stage between the two periods. We presumed that accumulated surgeon volume was associated with lower relapse-free survival rates in P2.

In South Korea, the standardization of management and assessment of treatment are being performed based on hospital volume as well (34). However, regarding these efforts, hospital size, not volume, tends to be the major factor for Koreans in terms of hospital selection, which led to large-sized and capital concentration despite gastric cancer occurring evenly in all geographical areas in Korea. This led to the distortion of the medical delivery system and delay of surgical treatment (16). In our study, even in the small-sized hospital, the well-trained surgeon showed good results in gastric cancer treatment, and as the surgeon volume accumulated over time, the long-term outcomes improved. It is hard to say that the accumulated surgeon volume directly affects long-term outcomes, but it seems to have been combined with the improvement in surgical skills and technical development as well as the introduction of adjuvant chemotherapy. Nevertheless, our study may have implications for the current Korean social atmosphere. Rather than focusing on the expansion of hospital size for attracting patients, improving the quality of treatment through the training of experienced surgeons and the intensive management of patients should be considered.

Our study has some limitations. First, this study was a retrospective study in a single center, in which there may have been information bias due to errors in information collection. Second, this study was not a head-to-head comparison study but a single-arm study with reviewing of other articles that did not include standardization or control of patients; in addition, the definition of terms was different. Third, the last follow-up was 2013, and the follow-up duration was shorter in P2 than in P1. Because there were patients lost to follow-up, Dong-rae Paik Hospital was absorbed into another hospital. Fourth, although

there is a consensus for adjuvant chemotherapy based on oral S-1 or capecitabine plus oxaliplatin in advanced gastric cancer after gastrectomy recently (35, 36), standardization of adjuvant chemotherapy for gastric cancer was not established before 2010. The lack of evidence-based adjuvant chemotherapy in our study did not provide information on how long-term outcomes were affected.

Conclusions

Our study showed that the short-term outcomes and long-term outcomes of gastric cancer treatment in a small-sized hospital were comparable to those of large-sized hospitals. Although short-term outcomes did not improve as surgeon volume accumulated, accumulated individual surgeon volume was related to a high relapse-free survival rate. Surgeon volume should be considered more valuable than the size of the hospital in terms of gastric cancer treatment.

Abbreviations

IV: Intravenous, LN: Lymph node, LADG: Laparoscopic-assisted distal gastrectomy, HR: Hazard ratio, CI: Confidence interval, BMI: Body mass index, PNI: Perineural invasion, LVI: Lymphatic invasion, VNI: Venous invasion, P1: period 1 (2000-2005), P2: period 2 (2006-2010)

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Busan Paik Hospital, Inje University, Busan, Republic of Korea (IRB no 19-0189)

Consent for publication

Not applicable

Availability of data and materials

The data used and/or analyzed 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

SHS contributed to the study conception and design. JYJ and KHK contributed to the development of methodology. KHK and JSK contributed to the acquisition of data. HJB contributed to the analysis and interpretation of data. JYJ and KHK contributed equally to the writing, review, and/or revision of the manuscript as 1st author. SHO contributed to the administrative, technical, or material support. SHS contributed to the study supervision. MSA, SHK, and YHP had other relevant contributions to the study. All authors read and approved the final manuscript.

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Tables

Table 1. Demographics of the patients' clinicopathologic characteristics

		Total Period N=820(%)	Period 1 N=407(%)	Period 2 N=413(%)	p-value
Age		58.8±11.04	58.34±10.75	59.30±11.30	0.215
Sex	Male	544(66.3)	269(66.1)	275(66.6)	0.881
	Female	276(33.7)	138(33.9)	138(33.4)	
BMI (kg/m ²)		22.71±3.13	22.49±3.01	22.93±3.24	0.041
Tumor location	Low	493(60.3)	239(58.7)	254(61.8)	0.848
	Middle	193(23.6)	104(25.6)	89(21.7)	
	Upper	125(15.3)	63(12.5)	62(15.1)	
	Whole	7(0.9)	1(0.2)	6(1.5)	
T stage	T1	490(59.8)	230(56.5)	260(63.0)	0.042
	T2	85(10.4)	41(10.1)	44(10.7)	
	T3	223(27.2)	125(30.7)	98(23.7)	
	T4	22(2.7)	11(2.7)	11(2.7)	
N stage	N0	545(66.5)	264(64.9)	281(68.0)	0.544
	N1	85(10.4)	45(11.1)	40(9.7)	
	N2	76(9.3)	42(10.3)	34(8.2)	
	N3	114(13.9)	56(13.8)	58(14.0)	
Stage	Stage 1	522(63.7)	246(60.4)	276(66.8)	0.117
	Stage 2	129(15.7)	72(21.9)	57(13.8)	
	Stage 3	169(20.6)	89(21.9)	80(19.4)	
Histology	Differentiated	459(56.5)	234(58.4)	225(54.6)	0.440
	Undifferentiated	350(43.1)	163(40.6)	187(45.4)	
	Other	4(0.5)	4(1.0)	0(0)	
VNI	Yes	34(4.1)	19(4.7)	15(3.6)	0.457
	No	786(95.9)	388(95.3)	398(96.4)	
PNI	Yes	32(3.9)	27(6.6)	5(1.2)	<0.001
	No	788(96.1)	380(93.4)	408(98.8)	
LVI	Yes	102(12.4)	71(17.4)	31(7.5)	<0.001
	No	718(87.6)	336(82.6)	382(92.5)	

BMI Body mass index, VNI Venous invasion, PNI Perineural invasion, LVI Lymphatic invasion

Table 2. Short-term treatment outcomes of patients

		Total Period N=820(%)	Period 1 N=407(%)	Period 2 N=413(%)	p-value
Operation method	Open	741(90.4)	402(98.8)	339(82.1)	<0.001
	LADG	79(9.6)	5(1.2)	74(17.9)	
Resection extent	Subtotal	662(80.7)	331(81.3)	331(80.1)	0.743
	Total	155(18.9)	74(18.2)	81(19.6)	
	Other	3(0.4)	2(0.5)	1(0.2)	
LN dissection level	D1	36(4.4)	2(0.5)	34(8.2)	<0.001
	D1+	362(44.1)	181(44.5)	181(43.8)	
	D2	422(51.5)	224(55.0)	198(47.9)	
Harvested LN		34.40±16.44	27.21±12.07	41.48±17.10	<0.001
Adjuvant chemotherapy	None	160(19.5)	62(15.2)	98(23.7)	<0.001
	Oral	442(53.9)	182(44.7)	260(63.0)	
	IV	218(26.6)	163(40.0)	55(13.3)	
Hospital stay		16.32±12.54	18.04±14.68	14.61±9.70	<0.001
Postoperative morbidity*	G1-2	64(7.8)	34(8.4)	30(7.3)	0.942
	G3-4	34(4.1)	16(3.9)	18(4.4)	
	None	722(88.0)	357(87.7)	365(88.4)	

LN Lymph node, LADG Laparoscopic-assisted distal gastrectomy

*Postoperative morbidity classified by Clavien-Dindo classification

Table 3. Univariate and multivariate analyses of risk factors for overall survival

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Period	1.127 (0.762-1.668)	0.549		
Age	1.013 (0.997-1.030)	0.110		
BMI (kg/m ²)	0.987 (0.932-1.045)	0.649		
T stage				
T1 vs T2	3.991 (1.523-10.458)	0.005	3.832 (1.788-8.213)	0.001
T1 vs T3	5.696 (1.674-19.376)	0.005	6.490 (3.330-12.650)	0.000
T1 vs T4	9.937 (2.578-38.303)	0.001	12.802 (5.396-30.373)	0.000
N stage				
N0 vs N1	1.670 (0.777-3.590)	0.189	1.724 (0.895-3.319)	0.103
N0 vs N2	1.326 (0.345-5.091)	0.681	2.239 (1.193-4.200)	0.012
N0 vs N3	1.856 (0.464-7.426)	0.382	3.516 (1.937-6.381)	0.000
Stage				
stage 1 vs stage 2	1.007 (0.293-3.462)	0.991		
stage 1 vs stage 3	1.965 (0.261-14.796)	0.512		
Tumor location				
Low vs Middle	0.635 (0.374-1.077)	0.092	0.618 (0.367-1.041)	0.071
Low vs Upper	1.338 (0.873-2.050)	0.182	1.336 (0.885-2.018)	0.168
Low vs Whole	2.841 (0.980-8.232)	0.054	2.508 (0.931-6.760)	0.069
Histology				
Diff vs Undiff	1.324 (0.914-1.916)	0.138		
Diff vs Unknown	1.839 (0.424-7.983)	0.416		
VNI	1.966 (1.094-3.535)	0.024	1.948 (1.113-3.410)	0.020
PNI	0.793 (0.436-1.442)	0.447		
LVI	2.570 (1.697-3.890)	0.000	2.394 (1.641-3.465)	0.000

HR Hazard ratio, CI Confidence interval, BMI Body mass index, Diff Differentiated, Undiff Undifferentiated, VNI Venous invasion, PNI Perineural invasion, LVI Lymphatic invasion,

Table 4. Univariate and multivariate analyses of risk factors for relapse-free survival

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Period	0.845 (0.528-1.353)	0.483		
Age	0.997 (0.978-1.016)	0.739		
BMI (kg/m ²)	1.013 (0.950-1.080)	0.688		
T stage				
T1 vs T2	3.708 (1.036-13.267)	0.044	3.072 (1.127-8.377)	0.028
T1 vs T3	8.703 (1.808-41.896)	0.007	7.471 (3.274-17.050)	0.000
T1 vs T4	17.147 (3.098-94.908)	0.001	14.548 (5.508-38.427)	0.000
N stage				
N0 vs N1	2.168 (0.871-5.396)	0.096	2.137 (0.972-4.696)	0.059
N0 vs N2	2.182 (0.483-9.869)	0.311	2.705 (1.290-5.674)	0.008
N0 vs N3	2.996 (0.640-14.028)	0.164	3.803 (1.872-7.727)	0.000
Stage				
stage 1 vs stage 2	0.774 (0.158-3.794)	0.752		
stage 1 vs stage 3	1.128 (0.102-12.442)	0.922		
Tumor location				
Low vs Middle	0.818 (0.466-1.438)	0.486		
Low vs Upper	0.778 (0.458-1.322)	0.353		
Low vs Whole	2.215 (0.687-7.138)	0.183		
Histology				
Diff vs Undiff	0.984 (0.644-1.504)	0.940		
Diff vs Unknown	2.073 (0.468-9.192)	0.337		
VNI	2.743 (1.472-5.113)	0.001	2.415 (1.378-4.232)	0.002
PNI	1.604 (0.899-2.862)	0.110	1.877 (1.125-3.131)	0.016
LVI	1.966 (1.235-3.130)	0.004	2.249 (1.469-3.442)	0.000

HR Hazard ratio, *CI* Confidence interval, *BMI* Body mass index, *Diff* Differentiated, *Undiff* Undifferentiated, *VNI* Venous invasion, *PNI* Perineural invasion, *LVI* Lymphatic invasion,

Figures

Figure 1

Flow chart of the patients

Figure 2

(a) 5-year overall survival of Kaplan-Meier curves for each stage (b) 5-year relapse-free survival of Kaplan-Meier curves for each stage

Figure 3

(a) 5-year overall survival of patients in period 1 and period 2 (b) 5-year relapse-free survival of patients in period 1 and period 2