

Impact of postoperative complications on long-term survival after radical resection for gastric cancer

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Abstract

AIM: To investigate the potential impact of complications in gastric cancer patients who survive the initial postoperative period.

METHODS: Between January 1, 2005 and December 31, 2006, 432 patients who received curative gastrectomy with D2 lymph node dissection for gastric cancer at our department were studied. Associations between clinicopathological factors [age, sex, American Society of Anesthesiologists grade, body mass index, tumor-node-metastases (TNM) stage and tumor grade], including postoperative complications (defined as any deviation from an uneventful postoperative course within 30 d of the operation and survival rates) and treatment-specific factors (blood transfusion, neoadjuvant therapy and duration of surgery). Patients were divided into 2 groups: with ($n = 54$) or without ($n = 378$) complications. Survival curves were compared between the groups, and univariate and multivariate models were conducted to identify independent prognostic factors.

RESULTS: Among the 432 patients evaluated, 61 complications occurred affecting 54 patients (12.50%).

Complications included anastomotic leakages, gastric motility disorders, anastomotic block, wound infections, intra-abdominal abscesses, infectious diarrhea, bleeding, bowel obstructions, arrhythmias, angina pectoris, pneumonia, atelectasis, thrombosis, unexplained fever, delirium, ocular fungal infection and multiple organ failure. American Society of Anesthesiologists grade, body mass index, combined organ resection and median duration of operation were associated with higher postoperative complications. The 1-, 3- and 5-year survival rates were 83.3%, 53.2% and 37.5%, respectively. In the univariate analysis, the size of lesions, TNM stage, blood transfusion, lymphovascular invasion, perineural invasion, neoadjuvant chemotherapy, and postoperative complications were significant predictors of overall survival. In the multivariate analysis, only TNM stage and the presence of complications remained significant predictors of reduced survival.

CONCLUSION: The occurrence of in-hospital postoperative complications was an independent predictor of worse 5-year overall survival rate after radical resection of gastric cancer.

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Key words: Gastric cancer; Perioperative complication; Surgical resection; Complications

Core tip: The concept of perioperative complications as a risk factor for survival is well known in gastric cancer, however, the potential impact of complications for patients who survive the initial postoperative period has not been determined. We showed that the occurrence of in-hospital postoperative complications is an independent predictor of worse 5-year overall survival after radical resection of gastric cancer. In 432 patients evaluated, 61 complications occurred affecting 54 patients (12.50%). American Society of Anesthesiologists grade, body mass index, combined organ resection and median duration of operation were associated with higher post-

operative complications. The 1-, 3- and 5-year survival rates were 83.3%, 53.2% and 37.5%, respectively.

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INTRODUCTION

Globally, gastric cancer ranks fourth and fifth in males and females, respectively, in terms of incidence, and ranks third and fifth in males and females, respectively, in terms of mortality^[1]. China is classified as a high incidence area for gastric cancer. Stomach cancer has the third highest incidence and is the second leading cause of death among all cancers^[2]. Surgery is the cornerstone in the treatment of gastric cancer. Although postoperative complications after surgical resection of gastric cancer are common, the potential long-term impact of these complications for patients who survive the initial postoperative period is not well understood. Western countries have published complication rates ranging from 35% to 46%, and mortality rates from 4% to 16% after D2 lymph node dissection^[3-5]. Major complications include anastomotic leakage, intra-abdominal bleeding, intra-abdominal abscess, intestinal obstruction and wound infection. Previous investigations focused on the immediate effect of postoperative complications and their impact on acute perioperative course and length of hospital stay. The concept of perioperative complications as a risk factor for survival is well known in other cancer surgery, such as esophageal, colorectal cancer liver metastases, hilar cholangiocarcinoma and colorectal cancer^[6-9]. To date, few studies have determined the potential impact of early surgical complications on long-term survival for patients with gastric cancer. The aim of this study was to assess the impact of prognostic factors, in particular perioperative complications, on the long-term survival of patients undergoing radical resection for gastric cancer.

MATERIALS AND METHODS

Patients

Patients' medical records and clinicopathological data during the period from January 1, 2005 to December 31, 2006 were studied retrospectively at the Department of Gastrointestinal Surgery, First Clinic Medical School of Yangzhou University, Yangzhou, China. Patients' inclusion criteria were: (1) All patients in the study had histologically confirmed gastric adenocarcinoma and received curative gastrectomy with D2 lymph node dissection; (2) Information regarding postoperative complications and mortality was available for each patient studied. As

a result, 432 patients were eligible for analysis. All these patients were followed up for a minimum of 60 mo after gastric resection. These 432 patients comprised 263 men (60.88%) and 169 women (39.12%). Their median age was 64 years (range, 28-83 years). The follow-up of patients after surgery was 5 years. Numbers of subtotal and total gastric resection were 186 and 246, respectively, and gastrointestinal reconstruction comprised 82 Billroth I, 68 Billroth II and 282 Roux-en-Y anastomoses. This research was in compliance with the Helsinki Declaration and was approved by the ethics committee of the First Clinic Medical School of Yangzhou University. The main characteristics of 432 people included study are summarized in Table 1.

Assessment of complications

Complications were defined as any deviation from an uneventful postoperative course within 30 d of the operation. A recently published standardized complication classification system (Clavien-Dindo classification) was used to grade postoperative complications^[10]. Briefly, grade I complications include any deviation from the normal postoperative course not needing specific treatment, as well as wound infections treated topically at the bedside. Grade II complications can be treated solely by drugs, blood transfusion, physiotherapy and nutritional support. Grade III complications require interventional or surgical treatment, without (IIIa) or with (IIIb) general anesthesia. Grade IV complications are life-threatening complications requiring intensive-care unit management (IVa, single organ dysfunction; IVb, multiple organ dysfunction). Grade V represents death of the patient. In the present study, if a patient had more than 1 complication, the grade used for analysis was defined by the highest-ranked complication.

Follow-up

Complete follow-up was available for all study patients. Follow-up was calculated from the date of surgery. Follow-up data were obtained by phone, letter, and the outpatient clinical database. The end of the follow-up period was 5 years after surgery.

Statistical analysis

The impact of clinicopathological and therapy-related variables with a potential influence on a postoperative complication were investigated. For this purpose, patients with postoperative complications were compared with those who recovered normally. The two groups were compared by univariate analysis with respect to clinicopathological factors [age, sex, American Society of Anesthesiologists (ASA) grade, body mass index (BMI), tumor-node-metastases (TNM) stage and tumor grade] and treatment-specific (blood transfusion, neoadjuvant therapy and duration of surgery) variables. For the outcome analysis, the patients were divided into two groups: those with complications and those with no postoperative complications. To investigate the impact of such complications on postoperative

Table 1 Intergroup comparison of epidemiological and treatment-related variables in 432 patients

Variable	Postoperative complications (<i>n</i> = 54)	No postoperative complications (<i>n</i> = 378)	<i>P</i> value
Age (yr), median (range)	60 (28-80)	59 (23-76)	0.516 ¹
Sex			0.236 ²
Male	37	226	
Female	17	152	
ASA grade			0.000 ²
I	24	341	
II	18	33	
III	11	4	
IV	1	0	
Body mass index (kg/m ²)			0.040 ²
< 28	42	332	
≥ 28	12	46	
TNM stage			0.358 ²
I	5	49	
II	9	94	
III	28	174	
IV	12	61	
Tumor size (cm), mean (range)	4.9 (2.0-12.0)	4.7 (0.5-12.0)	0.338 ¹
Combined organ resection			0.000 ²
No	35	346	
Yes	19	32	
Neoadjuvant therapy			0.126 ²
No	50	366	
Yes	4	12	
Median (range) duration of operation (min)	220 (175-310)	195 (160-300)	0.000 ¹

¹*t* test; ²Pearson χ^2 . ASA: American Society of Anesthesiologists; TNM: Tumor-node-metastases.

outcome, the two groups were compared using Kaplan-Meier survival curves. Postoperative complications are listed in Table 2. Assessment of the oncological relevance of the complication was based on an analysis of the two groups of patients. The 5-year survival rates were first subjected to univariate analysis, followed by multivariate analysis. Three patients who died within 30 d after surgery were excluded from the survival analysis.

RESULTS

Complications

Sixty-one complications occurred, affecting 54 patients (12.50%). Complications were graded into seven categories according to their severity. The details are given in Table 2. Ten patients suffered from gastric resection-related complications. Thirteen patients experienced infectious complications. Eight patients had bleeding complications and six had bowel obstructions. Five patients developed cardiac complications. Eleven patients had pulmonary complications. Two had thrombosis and six patients had other complications. Three patients died during hospitalization within 5 to 26 d after the initial gastrectomy, representing an in-hospital mortality of 0.69%. Two patients died as a result of postoperative sepsis and multiple organ failure. One died from acute respiratory distress syndrome.

Table 2 Post-operative complication types, frequencies and severities

Variables	Number
Gastric resection-related complications	
Anastomotic leakages	5
Gastric motility disorders	4
Anastomotic block	1
Infectious complications	
Wound infection	7
Intra-abdominal abscess	5
Infectious diarrhea	1
Bleeding complications	
Anastomotic bleeding	2
Intra-abdominal bleeding	5
Subcutaneous hematoma surrounding drainage tubes	1
Bowel obstructions	6
Pulmonary complications	
Pneumonia	10
Atelectasis	1
Cardiac complications	
Arrhythmia	4
Angina pectoris	1
Thrombosis	
Deep venous thrombosis	1
Portal venous thrombosis	1
Other complications	
Delirium	2
Unexpected fever	2
Ocular fungal infection	1
Multiple-organ failure	1
Incidence and severity (Clavien-Dindo grade)	
I	8
II	35
IIIa	11
IIIb	2
IVa	1
IVb	1
V	3

Risk factors for post-operative complication

The variables age, sex, ASA grade, BMI, TNM stage, mean tumor size, combined organ resection, neoadjuvant therapy and median duration of operation were investigated by Pearson χ^2 test or by *t* test. Only ASA grade, BMI, combined organ resection and median duration of operation had an independent impact on the occurrence of complications ($P < 0.05$).

Survival

The 1-, 3- and 5-year survival rates were 83.3%, 53.2% and 37.5%, respectively. In the univariate analysis, survival was not influenced by gender, age or BMI. In contrast, the size of the lesions, TNM stage, blood transfusion, lymphovascular invasion, perineural invasion, neoadjuvant chemotherapy and postoperative complications were significant predictors of overall survival (Table 3). In the multivariate analysis, perineural invasion, the size of the lesions, blood transfusion, lymphovascular invasion and neoadjuvant chemotherapy were no longer predictive factors for reduced survival. However, the TNM stage and the presence of complications remained significant predictors of reduced survival (Table 4).

Table 3 Univariate survival analysis of gastric cancer patients according to various clinicopathological variables and complications

Variable	Patients	5-yr survival	Log rank χ^2 test	P value
Gender			2.847	0.092
Male	262	34.00%		
Female	167	43.70%		
Age (yr)			1.157	0.282
≤ 60	230	40.00%		
> 60	199	35.20%		
BMI (kg/m ²)			0.018	0.893
≤ 26	278	38.50%		
> 26	151	36.40%		
Size of lesions (cm)			8.130	0.004
< 5	269	42.00%		
≥ 5	160	30.60%		
TNM stage			60.453	0.000
I	54	72.20%		
II	101	54.90%		
III	202	28.70%		
IV	72	12.70%		
Blood transfusion			4.982	0.026
Yes	74	27.00%		
No	355	40.00%		
Lymphovascular invasion			4.673	0.031
Yes	69	21.70%		
No	360	40.80%		
Perineural invasion			5.237	0.022
Yes	36	25.00%		
No	393	38.90%		
Neoadjuvant chemotherapy			7.124	0.008
No	411	38.60%		
Yes	18	16.70%		
Complications			25.946	0.000
Yes	51	21.80%		
No	378	39.90%		

BMI: Body mass index; TNM: Tumor-node-metastases.

DISCUSSION

In the surgical approach for early and selective advanced gastric cancer, gastrectomy with D2 lymphadenectomy is justified^[11,12]. Local tumor control and long-term oncological survival are dependent on the quality of the surgical treatment and the surgeon's case-load^[13]. The occurrence of postoperative complications is higher in inexperienced hands, and there is a considerable difference in early surgical outcomes among centers^[14,15]. Overall survival rate is higher at specialized centers. Therefore, it may be stated that gastric cancer surgery is safe at specialized centers. The postoperative complications at our institution were in the acceptable range: most patients had a smooth recovery and postoperative mortality was not high.

In this study, ASA grade, BMI, combined organ resection and duration of operation were greater in the postoperative complications group than in the no complications group. These findings are in agreement with recent reports showing similar predictors of postoperative complications. ASA grade was reported to affect surgical complications^[1], but this was not consistent with prior studies reported by Kawamura *et al.*^[16]. A negative effect of BMI on perioperative complications of gastrectomy has also been reported^[17,18]; elevated BMI was signifi-

Table 4 Predictors of survival: Multivariate analysis

Risk factor	HR (95%CI)	P value
Size of lesions	1.2 (0.9-1.5)	0.156
TNM stage	1.6 (1.4-1.9)	0.000
Blood transfusion	0.9 (0.5-1.4)	0.752
Lymphovascular invasion	1.0 (0.6-1.6)	0.841
Perineural invasion	0.7 (0.4-1.0)	0.107
Neoadjuvant chemotherapy	1.5 (0.8-2.5)	0.134
Post-operative complications	2.5 (1.8-3.6)	0.000

Cox regression analysis of patient survival. TNM: Tumor-node-metastases.

cantly associated with increased weight of the stomach extirpated *en bloc* with omentum and perigastric lymph nodes, which was found to increase operative times. Additional organ resection in surgical therapy for gastric cancer has been associated with increased complications and perioperative mortality in pursuit of a D2 lymphadenectomy^[19,20]. A large retrospective study from Japan found no survival difference when patients undergoing gastrectomy alone were compared to patients with additional organ resection, however, the complication rate was greater^[21]. The duration of operation was greater in the postoperative complications group than in the no complications group. Patients with advanced TNM stage, combined organ resection and elevated BMI always require a longer operation time than others.

Although this is the first study to identify the independent impact of postoperative complications among patients undergoing surgery for gastric cancer, other investigators have explored the potential relationship between postoperative complications and long-term survival beyond the initial perioperative period in other malignancies. In an analysis of 197 colorectal cancer liver metastases patients, Schiesser *et al.*^[22] reported 30% perioperative complications, and the median survival time of patients with perioperative complications was 3.2 years, compared to 4.4 years in those patients without complications. Similar results were reported for hilar cholangiocarcinoma^[8]. Given these findings, it is logical to fully explore the potential impact of in-hospital, postoperative complications on long-term cancer survival. Mechanisms currently under discussion include more serious immunosuppression and more obvious inflammation associated with postoperative complications. Generally, postoperative complications have been suggested to lead to an extended period of immunosuppression, which permits residual tumor cells to proliferate and survive in the host. One example supporting this hypothesis is based, in part, on the finding that in several other malignancies, perioperative blood transfusions correlated with negative immunomodulatory effects and earlier cancer recurrence^[23,24]. Our findings could be explained in a similar manner. Infective complications are the most common complications, including intra-abdominal abscesses, wound infections, pneumonia, infectious diarrhea and anastomotic leakage, which can also cause abdominal infection. Several studies have demonstrated a correlation

between long-term outcomes after curative resections of solid tumors and postoperative infection and sepsis^[7,25-27]. Infection and sepsis potentiate proinflammatory cytokine cascades, including tumor necrosis factor- α and interleukins 1, 6 and 8. These immune modulators can affect the function and regulation of natural killer cells, cytotoxic T-lymphocytes and antigen-presenting cells^[28-30]. Hypothetically, micrometastases may progress rapidly during brief and prolonged periods of relative immunosuppression resulting from postoperative complications. Besides, both sepsis and blood transfusion may stimulate vascular endothelial growth factor release, which is one of the most potent stimulators of metastatic growth^[31,32]. This combination of transfusion and sepsis may stimulate cancer recurrence^[33].

Our results show a clear association between postoperative complications and long-term survival for patients undergoing resection for gastric cancer. The study highlights the significance not only of appropriate patient selection and surgical technique, but also serves to emphasize the potential impact that postoperative monitoring and hospital care can have on long-term outcomes. Performance of a safe operation with minimal blood loss, careful lymphadenectomy and gastrointestinal reconstruction are important for reducing post-operative complications. Avoidance of complications improves long-term survival.

In summary, our study aimed to evaluate the impact of complications on survival for patients who received radical surgery for gastric cancer. We found that the occurrence of in-hospital postoperative complications was an independent predictor of worse 5-year overall survival rate after radical resection of gastric cancer.

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COMMENTS

Background

The concept of perioperative complications as a risk factor for survival is well known in gastric cancer, however, the potential impact of complications for patients who survive the initial postoperative period has not been determined. This article studies the potential impact of complications on patients who survive the initial postoperative period.

Research frontiers

Perioperative complications are an important factor after surgery. Currently, many experts have focused on lymphatic metastasis for survival; however, perioperative complications have not been unequivocally addressed. In this study, the authors demonstrate that the occurrence of in-hospital postoperative complications was an independent predictor of worse 5-year overall survival rate after radical resection of gastric cancer.

Innovations and breakthroughs

Between January 1, 2005 and December 31, 2006, 432 patients who received curative gastrectomy with D2 lymph node dissection were studied. Associations between clinicopathological factors, including postoperative complications and survival, were studied using univariate and multivariate models.

Applications

To understand survival during the initial postoperative period of gastric cancer, this article studied the potential impact of complications for patients who survive the initial postoperative period. In the univariate analysis, size of lesions, tumor-node-metastases (TNM) stage, blood transfusion, lymphovascular invasion, perineural invasion, neoadjuvant chemotherapy and postoperative complications were significant predictors of overall survival. In the multivariate analysis, only TNM stage and the presence of complications remained significant predictors of reduced survival.

Peer review

The article provides a detailed description of the survival impact of postoperative complications. This data is valuable for the treatment of gastric malignancy.

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