

Risk factors of esophagojejunal anastomosis leakage after total gastrectomy

Ezofagojejuninės jungties nesandarumo išsivystymo rizikos veiksniai po gastrektomijos

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Background/Aim

Esophagojejunal anastomotic leakage (EJAL) after total gastrectomy is one of the most frequent life-threatening complications. The rate of EJAL after total gastrectomy is about 2–11% worldwide. The aim of this study was to identify the independent prognostic risk factors that may predict EJAL progression for patients after total gastrectomy.

Materials and methods

This retrospective study analyzed medical records of 175 patients. All these patients had undergone radical gastrectomy due to gastric cancer. The analyzed factors were: age, gender, American Society of Anaesthesiologists (ASA) functional class, splenectomy, anastomosis technique, operative time, cancer stage, the number of dissected lymph nodes, the number of metastatic lymph nodes, resection margins. White blood cells count, C reactive protein (CRP) value, body temperature, drain output were calculated in the early postoperative period.

Results

The average age of the patients was 63.2 ± 11.5 years. The EJAL rate was found to be 6.3%. The mortality rate among patients who developed EJAL was 9%. Postoperative laboratory and clinical findings significantly related to EJAL were the average temperature of 4 postoperative days >37.2 °C ($p = 0.018$), postoperative white blood cell count $>16.7 \times 10^9/l$ ($p = 0.031$), postoperative CRP level >160 mg/l ($p = 0.001$) and operative time >248 min ($p = 0.009$), although the binary logistic regression analysis revealed that none of these variables can be used as statistically significant predictors for EJAL.

Conclusions

The esophagojejunal anastomotic leakage rate of 6.3% was found among patients undergoing radical gastrectomy due to gastric carcinoma. Mortality rate in case of EJAL increases up to 9%. In our study, we didn't find any independent predictors for EJAL.

Key words: gastrectomy, esophagojejunal anastomosis leakage, risk factors

Įvadas

Ezofagojejuninės jungties nesandarumas (EJN) po gastrektomijos yra viena iš didžiausių grėsmę gyvybei keliančių komplikacijų. Mokslinių tyrimų duomenimis, EJN dažnis svyruoja nuo 2 iki 11 %. Darbo tikslas – nustatyti rizikos veiksnius, darančius įtaką ezofagojejuninės jungties nesandarumo vystymuisi po gastrektomijos dėl skrandžio vėžio, ir prognozuoti jų įtaką EJN išsivystymui.

Ligoniai ir metodai

Retrospektyviai ištirta 175 pacientų medicininė dokumentacija. Tirtiems pacientams 2006–2010 metais atlikta gastrektomija dėl skrandžio vėžio. Analizuoti veiksniai: amžius, lytis, Amerikos anesteziologų asociacijos (ASA) funkcinė klasė, splenektomija, jungties susiuvimo būdas, operacijos trukmė, naviko stadija, operacijos metu pašalintų limfmazgių skaičius, limfmazgių su metastazėmis skaičius, rezekciniai kraštai. Ankstyvuojų pooperaciniu laikotarpiu vertinta leukocitų kiekis, C reaktyviojo baltymo (CRB) koncentracija kraujyje, pooperacinė temperatūra, sekrecija pro drenus.

Rezultatai

Tirtų pacientų amžiaus vidurkis 63,2±11,5 metų. Vyrų 50,6 %, moterų 49,4 %. EJN dažnis 6,3 %. Turėjusių EJN pacientų mirtingumas siekė 9 %. Nustatyti rizikos veiksniai, statistiškai patikimai susiję su EJN išsivystymu. Jų reikšmės patikslintos randant ROC kreivės lūžio taškus: 4 parų vidutinė temperatūra 37,15°C (p=0,018), maksimalios leukocitų (11,7×10⁹/l, p=0,031) ir C reaktyviojo baltymo reikšmės (159,95 mg/l, p=0,001), operacijos trukmė 247,5 min (p=0,009). Tačiau binarinė logistinė regresija parodė, kad šie kriterijai negali būti statistiškai patikimi prognoziniai EJN vystymosi veiksniai.

Išvados

Ezofagojejuninės jungties nesandarumo dažnis po gastrektomijos dėl skrandžio vėžio yra 6,3%, šią komplikaciją turėjusių pacientų mirštamumas – 9%. Savo tyrime neradome prognostiškai reikšmingų rizikos veiksnių.

Reikšminiai žodžiai: gastrektomija, ezofagojejuninės jungties nesandarumas, rizikos veiksniai

Introduction

Gastric cancer remains the main cause of death of about 800 000 patients worldwide every year [1]. Surgical removal of the tumor by lymphadenectomy is the only curative treatment of gastric cancer [2]. Although recent improvements in surgical techniques and perioperative management have resulted in a marked decrease in morbidity and mortality rates after gastric surgery, some postoperative complications are still present. The postoperative complications not only lead to a longer in-hospital stay or delay the start of adjuvant therapy; they are also recognized as independent prognostic factors [3].

Anastomotic leakage is one of the most serious complications after gastric surgery; it is associated with a high mortality rate [4]. Safe and stable formation of esophagojejunostomy is one of the major concerns among gastric surgeons. With some experience along the learning curve and the wide spread of mechanical stapling devices, the incidence of esophagojejunal anastomotic leakage (EJAL) has been reduced [5]. However, absolute prevention of anastomosis leakages remains challenging, and the reported incidences of EJAL vary between 2 and 11% [5–9].

In this retrospective study, we tried to find out the possible causes of EJAL in detail. We analyzed the patient-related, operation-related and early postoperative period related factors which can predict EJAL. The presented data were collected from a single surgery center (upper gastrointestinal surgery unit) in which a unified approach to gastric cancer surgery had been established.

Materials and methods

The records of a series of 175 patients who underwent radical gastrectomy and esophagojejunal anastomosis formation at the Clinic of Surgery of Lithuanian University of Health Sciences hospital from January 2006 to December 2010 were retrospectively analyzed. Gastric carcinoma had been histologically confirmed in all cases. None of the patients had neoadjuvant therapy. Gastrectomy with D2 lymphadenectomy had been performed as a standard procedure.

The Roux-en-Y anastomosis method had been used for intestinal reconstruction in all cases. Esophagojejunostomy had been performed in an end-to-side manner with either circular stapling devices (Ethicon Endo-Surgery, Inc.) or manually applying two-layer interrupted

sutures. In some cases, after performing anastomosis with a circular stapling device, one layer of interrupted sutures had been performed additionally. The selection of the anastomosis technique was left to the discretion of the surgical team. The size of the stapling device for esophagojejunal anastomosis was 25 mm for the majority of patients. However, 21 mm or 28 mm circular staplers were used when a narrow or large esophagus had been detected.

Splenectomy was performed only in cases when the lesion had directly invaded the organ. A water-soluble contrast medium was used to confirm the anastomotic leakage radiologically. A radiology study was not performed routinely but was always carried out when anastomotic leakage was suspected.

In order to analyze the potential risk factors, all patients were divided into two groups: the group with EJAL and the group without EJAL. The patient- and operation-related factors included age, gender, the American Society of Anesthesiologists (ASA) functional class, splenectomy performed, anastomosis technique, operative time, cancer T stage, the number of dissected lymph nodes, the number of metastatic lymph nodes, resection margins. The early postoperative period (the first four days) factor analysis included the average white blood cell count, C reactive protein (CRP) values, postoperative body temperature, and drain output.

Some analyzed prognostic risk factors were rated: ASA functional class into low risk (I and II functional class) and high risk (III and IV functional class), patients' age – below the average and above the average, tumor stage (T) – early (T1, T2) and late (T3, T4), resection margins (R) – radical resection (R0) and non-radical resection (R1, R2).

The relationship between the variables was evaluated initially by the univariate analysis, contingency table, chi-square or Fisher's exact test for categorical data and t-test for quantitative data. Predictive risk factors were determined using the ROC curve and binary logistic regression. Data analysis was performed using SPSS software version 16 (SPSS, Chicago, IL, USA).

Results

The average age of the patients was 63.2 years. The youngest patient was 33 years old and the oldest had 83

years. EJAL developed in 11 (6.3%) from 175 patients. Mortality rate among the patients with EJAL was 9%. The results of the univariate analysis of patient-related and operation-related risk factors for anastomotic leakage are summarized in Table 1. There was no significant difference in the age, gender, ASA functional class, tumor status, lymphnodes removed and anastomosis technique between the groups, only the operation time was significantly longer in the EJAL group ($p = 0.011$).

The results of the univariate analysis of early postoperative period related factors are shown in Table 2. The anastomotic leakage rate was significantly associated with four postoperative days' average temperature, white blood cell count and C-reactive protein blood level ($p < 0.05$).

The cut-off prognostic values of four significant factors were calculated using the ROC analysis (Table 3): the average temperature of 4 postoperative days $>37.2^{\circ}\text{C}$ ($p=0.018$), white blood cell count $>16.7 \times 10^9/\text{l}$ ($p=0.031$), postoperative CRP level $>160 \text{ mg/l}$, ($p=0.001$) and operative time $>248 \text{ min}$ ($p=0.009$), although the binary logistic regression analysis revealed that none of these variables can be used as statistically significant predictors for EJAL (Table 3).

Discussion

Anastomotic leakage increases the duration of in-hospital stay, the risk of reoperation and also can lead to a fatal outcome. Sierzega et al. [7] retrospectively analyzed 690 patients who underwent total gastrectomy and found, that esophagojejunal anastomotic leakage increased postoperative mortality rates and significantly impaired the long-term survival of patients after total gastrectomy for cancer. In our retrospective study, one (9.1%) of 11 patients who developed EJAL died within the hospital stay. Surgeons must pay special attention when creating the anastomosis to avoid this dangerous complication.

The rates of EJAL vary, ranging from 1.0 to 11.5% [5–9]. The leakage rate reported from Japanese high-volume centers is 1.0 and 2.1% [5, 8]. Most EJAL are likely to result from intraoperative technical failures. It is also important that the technical failures not detected during surgery lead to postoperative EJAL [9]. Taken together, the rate of EJAL might be decreased nearly to zero by the prevention and proper intraoperative

Table 1. Univariate analysis of patient-related and operation-related variables for anastomotic leakage

Criteria		No EJAL group n=164		EJAL group n=11		p value
Gender	Male	83	(50.6%)	5	(45.5%)	0.766
	Female	81	(49.4%)	6	(54.5%)	
Age	< 60	74	(45.1%)	3	(27.3%)	0.351
	≥ 60	90	(54.9%)	8	(72.7%)	
ASA class	I,II	94	(65.7%)	4	(36.4%)	0.099
	III,IV	49	(34.3%)	7	(63.6%)	
T (Tumor size)	T1,T2	65	(40.1%)	3	(30%)	0.742
	T3,T4	97	(59.9%)	7	(70%)	
R (resection boundaries)	Radical	136	(86.1%)	7	(77.8%)	0.619
	Not radical	22	(13.9%)	2	(22.2%)	
Splenectomy	Yes	27	(16.5%)	1	(9.1%)	0.696
	No	137	(83.5%)	10	(90.9%)	
Died	Yes	2	(1.2%)	1	(9.1%)	0.179
	No	161	(98.8%)	10	(90.9%)	
Anastomosis technique	Manual	32	(22.5%)	2	(18.2%)	0.982
	Stapler	87	(61.3%)	8	(72.7%)	
	Stapler+ manual	23	(16.2%)	1	(9.1%)	
Operation duration (min)		222.2 ± 53.6		284.5 ± 97.6		0.011
Lymph nodes	Removed	21.2 ± 8.7		22.8 ± 7.6		0.4
	Metastatic	6.8 ± 8.7		9.5 ± 8.7		0.2

Table 2. Univariate analysis of early postoperative period variables for anastomotic leakage

Criteria	No EJAL group n=164	EJAL group n=11	p value
Temperature (°C) 4 postop. days' average	36.9 ± 0.4	37.2 ± 0.3	0.02
WBC (× 10⁹/l) 4 postop. days' average	14.0 ± 6.6	17.7 ± 7.1	0.052
CRP (mg/l) 4 postop. days' average	150.7 ± 82.7	230.4 ± 86.4	0.007
Drain secretion (ml/day) 4 postop. days' average	280.3 ± 156.3	508.3 ± 712.0	0.8

Table 3. Multivariate analysis of clinical factors for esophagojejunal anastomotic leakage

Criteria	Value	p value	Sensitivity	1 - Specificity
Temperature (°C) 4 postop. days' average	>37.2	p = 0.018	0.56	0.19
WBC (× 10⁹/l) 4 postop. days' average	>17.7	p = 0.031	0.9	0.548
CRP (mg/l) 4 postop. days' average	>160	p = 0.001	1.0	0.448
Operation duration (min)	>248	p = 0.009	0.55	0.2

management of an incomplete anastomosis, as well as a detailed observation of the anastomosis site. In our study, the EJAL rate was 6.3%, and this result is acceptable when comparing with the literature data. On the other hand, to decrease to 1–2% the rate of EJAL, we need to choose the best.

Our retrospective study didn't identify any patient-related and operation-related independent risk factors for EJAL. This is the weakest point of our study. Yasunori Deguchi et al. [8] in their retrospective study identified pulmonary insufficiency and the duration of the operation as the predictors of EJAL in patients after total gastrectomy. Our study results also demonstrate that operation time in the EJAL group was significantly longer as compared with the no-leakage group. Some other studies [10, 11] have also indicated that the duration of the operation is associated with morbidity after gastrectomy. However, the longer procedure time can be a consequence of many factors. A complicated operative procedure leads to a longer operative time and increases the risk of morbidity. In cases of advanced tumor, the operation is often extended, however, it not always results in EJAL. So, many authors conclude that

a longer operating time is not directly related to this complication.

In the univariate analysis of early postoperative period related factors, our study revealed the anastomotic leakage rate to be significantly associated with the four postoperative days' average temperature, white blood cell count and C-reactive protein blood level. All these factors mainly refer only to the inflammatory response which is a consequence of EJAL. All these markers are not specific of EJAL.

The other limitation of our study is that the sample the of EJAL group was too small (11 patients). From the statistical point of view, it is very complicated to find out the independent risk factors from such a small sample.

Conclusions

The esophagojejunal anastomotic leakage rate of 6.3% was found among patients after radical gastrectomy due to gastric carcinoma. Mortality rate in case of EJAL increased up to 9%. In our study, we didn't find any independent predictors of EJAL.

REFERENCES

1. World Health Organization. Cancer (Fact sheet N°297) February 2009. Retrieved 2009-05-11.
2. Songun I, Putter H, Kranenbarg EM et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; 11: 439–449.
3. Roder JD, Bottcher K, Siewert JR et al. Prognostic factors in gastric carcinoma. *Results Germ Gastric Carcinoma Study Cancer* 1992; 72: 2089–2097.
4. Ichikawa D, Kurioka H, Yamaguchi T et al. Postoperative complications following gastrectomy for gastric cancer during the last decade. *Hepatogastroenterology* 2004; 51: 613–317.
5. Nomura S, Sasako M, Katai H et al. Decreasing complications rate with stapled esophagojejunostomy following a learning curve. *Gastric Cancer* 2000; 3: 97–101.
6. Park DJ, Lee HJ, Kim HH et al. Predictors of operative morbidity and mortality in gastric cancer surgery. *Br J Surg* 2005; 92: 1099–1102.
7. Sierzega M, Kolodziejczyk P, Kulig J et al. Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. *Br J Surg* 2010; 97: 1035–42.
8. Deguchi Y, Fukagawa T, Morita S et al. Identification of Risk Factors for Esophagojejunal Anastomotic Leakage after Gastric Surgery. *World J Surg* 2012; 36: 1617–1622.
9. Kataoka M, Masaoka A, Hayashi S et al. Problems associated with the EEA stapling technique for esophagojejunostomy after total gastrectomy. *Ann Surg* 1989; 209: 99–104.
10. Kodera Y, Sasako M, Yamamoto S et al. Identification of risk factors for the development of complications following extended and super-extended lymphadenectomies for gastric cancer. *Br J Surg* 2005; 92: 1103–1109.
11. Lo CH, Chen JH, Wu CW et al. Risk factors and management of intra-abdominal infection after extended radical gastrectomy. *Am J Surg* 2008; 196: 741–745.