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Analyses of Risk Factors of Diarrhea in Patients with Esophagectomy

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Liu S, Qi S, Kuai W, He M, Zhao J, Xu X and all these authors are equally contributed to this work

1. Abstract

1.1. Background: Esophageal cancer is one of the most common cancers of the world and surgery is an effective treatment for that. However, long-term complications, such as diarrhea, are the focus on the postoperative quality of life. Until now, the etiologies of diarrhea after esophagectomy are still ill-defined.

1.2. Materials and Methods: Retrospective study was performed and a total of 398 patients were enrolled. Categorical variables were analyzed by chi-square test, non-normalized variables were shown by median, upper and lower quartile M (P25, P75), and Mann-Whitney U test was used to analyze the relationship between clinical parameters and diarrhea. Risk factors of diarrhea were determined by the univariate and multivariate logistic regression analyses.

1.3. Results: The morbidity rate of postoperative diarrhea was 17.34% (69/398). The incidence of diarrhea was lower in EGC than in EC (P = 0.008), lower in stage T4 than in T1-3(P = 0.002), lower in N1-3 than in N0 (P < 0.001), and lower in patients accompanied with perineural invasion (PNI) than that with no PNI. Logistic regression analyses show that T1 (vs. T2/T3/T4), no PNI (vs. PNI), N0 (vs. N+) and EC (vs. EGC) are the risk factors of diarrhea (P < 0.005). N0 (OR = 0.449, 95% CI: 0.233 - 0.863, P = 0.016) is the single risk factor of diarrhea. No patient complained of intestinal discomforts when vagal-sparing esophagectomy was performed for T1-2 patients.

1.4. Conclusions: The earlier the stage, the higher the incidence of postoperative diarrhea in patients with esophagectomy, vagal-sparing esophagectomy could prevent it.

2. Introduction

Esophageal Cancer (EC) is one of the top 10 malignant cancers in the world, ranking 7th in incidence and 6th in mortality rate. [1] Radical esophagectomy is often considered an effective treatment option for patients with esophageal cancer, as well as Esophagogastric Cancer (EGC) of seiwert I-II. However, surgical trauma along with long-term complications such as reflux, dysphagia and diarrhea are still the focus for improving postoperative quality of life for the long term.2 It has been reported that 12% - 27% of patients are accompanied by post-esophagectomy diarrhea which is a negative factor impacting the long-term quality of life [2, 3].

The etiologies of diarrhea after esophagectomy are still poorly defined. The most commonly endorsed etiologies are extensive anatomical alterations of upper gastro-intestinal, vagotomy or dysbiosis of gut flora. Nevertheless, the exact pathological process has not been fully elucidated yet. In recent decades, diarrhea that occurs after upper gastrointestinal surgery has always been classified as a subtype of dumping syndrome which could be caused by fast gastric emptying. An investigation showed that the incidence of diarrhea after esophagectomy was higher in the patients who received colonic replacement of esophagus than those with esophagogastric anastomosis. [4] This suggests that the anatomi-

cal alterations of gastric may not play a key role in the process of diarrhea after esophagectomy, thus, other factors should be noticed and investigated.

Recently, some evidence has been identified that vagotomy or injury of vagus nerve may be closely related to diarrhea even in non-gastrointestinal diseases, while vagus nerve-preservation can decrease the occurrence of diarrhea [5-7] Hence, in this study we have identified the risk factors of diarrhea after esophagectomy, which contain cancer-related pathological factors and vagotomy.

3. Materials and Methods

3.1. Patients

Patients who were diagnosed with esophageal or esophagogastric cancer (seiwert I-II) were enrolled and underwent standard radical surgery treatment from March 2016 to October 2018 in the department of the Fourth Hospital of Hebei Medical University. T1-2 patients were treated with surgery and postoperative adjuvant chemotherapy for 4 cycles, T3-4patients were treated with neoadjuvant chemotherapy for 2 cycles followed with radical surgery and postoperative adjuvant chemotherapy for 2 cycles, all regiments of chemotherapy were platinum and taxol. Collected laboratory examination before patients were administered any treatment. Middle and lower thoracic EC or EGC were all performed with Ivor-Lewis, EGCs were performed esophagogastrostomy at the level of the lower pulmonary vein, while ECs were performed esophagogastrostomy in the cupula of pleura, Mckeown was performed for uper thoracic ECs, and esophagogastrostomy was administered in left cervical, lymph nodes were all resected according to the R0 standard. Postoperative follow-up was done every three months and the living situation was recorded with notes of whether it was accompanied by diarrhea. The criterion of diarrhea followed the new BSG guidance 8 for chronic diarrhea: changing of defecate habit or increased frequency, the stool characterized with Bristol type [5-7], the symptoms sustained more than 4 weeks. When all treatment such as enteral nutrition and chemoradiotherapy were completed for more than 6 months, patients whose symptoms conform to above-mentioned standards were clarified as “postoperative diarrhea”. All clinical data of the patients were collected and analyzed for risk factors related to diarrhea. 11 patients of T1-2 were enrolled and administered vagal-sparing esophagectomy, and all the patients were followed up for one year when the information was collected.

3.2. Statistical Analysis

Statistical analysis was conducted with SPSS statistical 21.0. Categorical variables were analyzed by chi-square test, while the non-normalized variables were shown in median, upper and lower quartile M (P25, P75), and Mann-Whitney U test was used to analyze the relationship between clinical parameters and diarrhea. Risk factors of diarrhea were determined by the univariate and multivariate logisticregression analyses.

4. Results

A total of 398 patients were enrolled, including 255 cases of esophageal cancer (64.1%) which contain squamous cell carcinoma 230 cases, adenocarcinoma 22cases and small cell cancer 3 cases, as well as esophagogastric adenocarcinoma 142 cases and 1 small cell cancer (35.9%). Overall, the postoperative diarrhea morbidity was 17.34% (69/398). Sex, age, body mass index (BMI), smoke, alcohol, blood pressure, heart disease and diabetes did not correlate with the morbidity of diarrhea (Table B1). The incidence of diarrhea was lower in EGC patients than in EC patients ($P = 0.008$), lower in patients of T4 stage than in those of T1-3 stage ($P = 0.002$), lower in N1-3 patients than in N0 patients ($P < 0.001$). Additionally, patients accompanied with perineural invasion (PNI) had lower incidence of diarrhea than the patients with no PNI (Table B2). Chemotherapy, neutrophil, lymphocyte, platelet, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), neutrophil/ (white blood cell-neutrophil) ratio (dNLR), SCC, CEA, cholinesterase and alkaline phosphatase did not correlate with the morbidity of diarrhea (Table B3).

Univariate and multivariate logistic regression analyses were used to detect risk factors associated with diarrhea (Table B4). The results show that T1 (vs. T2/T3/T4), no PNI (vs. PNI), N0 (vs. N+) and EC (vs. EGC) are the risk factors of diarrhea by univariable logistic regression. Further analysis using multivariable logistic regression shows that N0 (OR = 0.449, 95% CI: 0.233 - 0.863, $P = 0.016$) is the single risk factor of diarrhea. Otherwise, the general data of patients and laboratory examination show no correlation with postoperative diarrhea. These results suggest that patients with early TNM stage may be at a high risk of diarrhea when they undergo radical surgery of esophageal cancer.

The previous results suggest that patients with early tumor stage are accompanied with high risk of diarrhea when they receive radical surgery of EC or EGC. Therefore, we speculated that diarrhea in patients might correlate with decompensation of digestive system when vagus nerve was cut off suddenly, as patients with late tumor stage may have pre-existing malfunction of the vagus nerve due to tumor invasion and partial compensatory effects via humoral regulation. Hence, we enrolled 11 patients of T1-2 stage and performed vagal-sparing esophagectomy (Figure A 1), which contain 8 male patients and 3 females, 2 patients were younger than 60 years old, 3 smoking and 3 drinking, 2 cases of hypertension and 2 cases of diabetes, all patients were not administered adjuvant chemotherapy. Among those patients, 9 of them were T1b stage, and the rest were T2 stage, which were all confirmed as squamous cell carcinoma of middle esophagus by pathological examination. All patients recovered uneventfully and were followed up for at least one year, and no patient complained of intestinal discomforts, such as abdominal distension, or diarrhea.

Table B1: Relationship between general data of patients and postoperative diarrhea BMI: Body mass index

	Case (n.%)	Diarrhea	No-Diarrhea	c2	P
Gender				0.317	0.657
Male	289 (72.61%)	52 (17.99%)	237 (82.01%)		
Female	109 (27.39%)	17 (15.60%)	92 (84.40%)		
Age (years)				0.002	1
≤60	126 (31.66%)	22 (17.46%)	104 (82.54%)		
>60	272 (68.34%)	47 (17.28%)	225 (82.72%)		
BMI				1.515	0.469
BMI<18.5	18 (4.52%)	4 (22.22%)	14 (77.78%)		
18.5 ≤ BMI<24	199 (50.00%)	30 (15.08%)	169 (84.92%)		
BMI ≥ 24	181 (45.48%)	35 (19.34%)	146 (80.66%)		
Smoking				0.291	0.652
No	293 (73.62%)	49 (16.72%)	244 (83.28%)		
Yes	105 (26.38%)	20 (19.05%)	85 (80.95%)		
Alcohol				0.903	0.365
No	295 (74.12%)	48 (16.27%)	247 (83.73%)		
Yes	103 (25.88%)	21 (20.39%)	82 (79.61%)		
Heart disease				0.023	0.746
No	382 (95.98%)	66 (17.28%)	316 (82.72%)		
Yes	16 (4.02%)	3 (18.75%)	13 (81.25%)		
Hypertension				0.007	1
No	281 (70.60%)	49 (17.44%)	232 (82.56%)		
Yes	117 (29.40%)	20 (17.09%)	97 (82.91%)		
Diabetes				0.328	0.817
No	362 (90.95%)	64 (17.68%)	298 (82.32%)		
Yes	36 (9.05%)	5 (13.89%)	31 (86.11%)		

Table B2: Relationship between pathological factors and postoperative diarrhea EC: Esophageal cancer, EGC: Esophagogastric cancer, PNI:Perineural invasion

	Case(n.%)	Diarrhea	No-Diarrhea	χ2	P
Tumor site				7.302	0.008
EC	255 (64.07%)	54 (21.18%)	201 (78.82%)		
EGC	143 (35.93%)	15 (10.49%)	128 (89.51%)		
T stage				14.706	0.002
T1	83 (20.85%)	20 (24.10%)	63 (75.90%)		
T2	60 (15.08%)	14 (23.33%)	46 (76.67%)		
T3	149 (37.44%)	29 (19.46%)	120 (80.54%)		
T4	106 (26.63%)	6 (5.67%)	100 (94.33%)		
N stage				14.724	＜0.001
N-	203 (51.01%)	49 (24.14%)	154 (75.86%)		
N+	195 (48.99%)	19 (9.74%)	176 (90.26%)		
PNI				8.346	0.004
No	270 (67.84%)	57 (21.11%)	213 (78.89%)		
Yes	128(32.16%)	12(9.38%)	116(90.62%)		
Chemotherapy				3.152	0.082
No	233(58.54%)	47(20.17%)	186(79.83%)		
Yes	165(41.46%)	22(13.33%)	143(86.67%)		

Table B3: Relationship between laboratory examination and postoperative diarrhea WBC: White blood cell, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio,DNLR:neutrophil/(white blood cell-neutrophil) ratio, CEA: Carcinoembryonic antigen, SCC: Squamous cell carcinoma antigen

	Diarrhea	No-Diarrhea	t/Z	p
Platelet	193 (154,262)	213 (176,264)	-1.339	0.181
Neutrophil	6.15 (3.94,8.4)	5.6 (3.88,8.93)	-0.159	0.873
WBC	7.76 (6.32,9.97)	7.81 (5.98,10.47)	-0.087	0.931
Lymphocyte	1.08 (0.79,1.58)	1.18 (0.76,1.62)	-0.39	0.697
NLR	5.50 (3.05,10.12)	4.54 (2.45,11.42)	-0.591	0.554
PLR	180.68 (138.84,262.37)	196.43 (137.5,270)	-0.466	0.641
DNLR	1.64 (1.35,1.96)	1.54 (1.32,1.91)	-0.985	0.324
CEA	2.515 (1.685,3.833)	2.28 (1.72,3.43)	-0.498	0.619
SCC	0.8 (0.6,1.275)	1 (0.7,1.375)	-0.389	0.697
Alkaline phosphatase	73.8 (62.9,84.8)	71.8 (60.3,87)	-0.558	0.577
Cholinesterase	7495.02 ± 1694.03	7338.31 ± 1943.19	0.618	0.537

Table B4: Risk factors of diarrhea analyzed by logistic regression analyses

	Univariate logistics			Multivariate logistics		
	OR	95%CI	P	OR	95%CI	P
Tumor site(EGC vs EC)	0.436	0.236 - 0.806	0.008	1.069	0.467 - 2.448	0.875
T2 vs T1	0.189	0.072 - 0.496	0.001	0.503	0.132 - 1.910	0.313
T3 vs T1	0.197	0.071 - 0.546	0.002	0.426	0.124 - 1.465	0.175
T4 vs T1	0.248	0.099 - 0.622	0.003	0.381	0.114 - 1.275	0.117
N+ vs N0 stage	0.337	0.190 - 0.597	<0.001	0.449	0.233 - 0.863	0.016
PNI vs no PNI	0.387	0.199 - 0.750	0.005	0.493	0.233 - 1.042	0.064

PNI: Perineural invasion

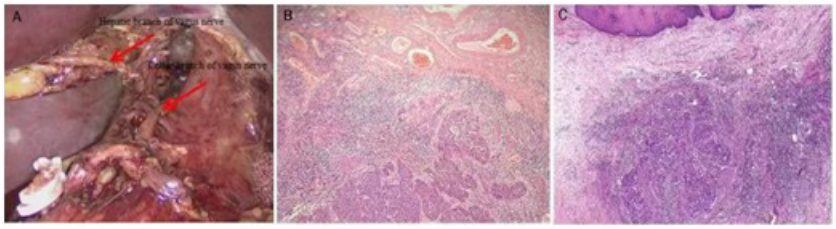

Figure A1: Spared vagus nerve during esophagectomy

5. Discussion

Our results suggest that T stage, N stage and PNI are closely related to the occurrence of postoperative diarrhea of esophageal cancer. The earlier the T stage and N stage, or coexisting without PNI, the higher the incidence of postoperative diarrhea occurs in esophageal cancer patients. Particularly, N0 is an independent risk factor. Thus, we performed minimally invasive esophagectomy with vagus nerve preservation for T1-2 esophageal cancer patients and found that no obvious gastrointestinal symptoms such as abdominal distension and diarrhea occurred after operation. All these results suggest that vagus nerve may play an important role in the occurrence of diarrhea after esophagectomy.

Currently, there is no report to illustrate the relationship between pathological factors and postoperative diarrhea. Nevertheless, some studies have shown that the incidence of postoperative diarrhea of esophageal cancer were ranging from 12% to 27%, which also suggests that different composition of tumor stage in the cohort may not be neglected as the factor for different diarrhea incidence, especially in studies with low incidence and only 1.2% of patients in stage I.2 While our research confirmed the correlation between different tumor stages and postoperative diarrhea of esophageal cancer. A number of studies have confirmed that tumors were always accompanied by nerve infiltration and PNI, which positively correlate with tumor stages and poor prognosis. [9-11] These findings indicate that vagus nerve plays a regulatory role in the occurrence and development of tumors. In contrast, the function of vagus nerve is also affected by local tumor microenvironment. It has been reported that the excitability of vagus nerve is obviously reduced in cancer patients. [12, 13] In addition, studies on patients with lung cancer and gastric cancer also suggest that vagus nerve excitability has decreased along with tumor progression, which can be used as an auxiliary index for diagnosis in patients, despite the mechanisms are still unclear [14, 15].

In our study, the morbidity resulted from diarrhea in esophageal cancer patients with PNI is significantly lower than those without PNI. This indicates that tumor progression and decreased vagus nerve excitability may be accompanied by the activation of another compensatory signaling, as when vagus nerve is severed, the innervation of the nervous system can be fulfilled through compensatory pathway. While the vagus nerve function of patients with early esophageal cancer is less affected by tumor, the compensatory mechanism may not be established yet. When vagus nerve is suddenly cut off, it may result in decompensation, which eventually leads to diarrhea. Thus, we performed vagal-preserving esophagectomy for early stage patients, and found that 11 patients had no postoperative diarrhea, which is consistent with other reported studies. [5, 6, 16] Interestingly, an investigation of endoscopy therapy in T1a esophageal cancer patients shows that there was no diarrhea occurred in these patients compared to those who received esophagectomy. [17] This suggests that vagal disconnection may be an important factor of postoperative diarrhea in patients with esophageal cancer.

It is found that the nervous system plays an important role in inflammatory bowel disease, especially in maintaining the integrity of mucosal barrier. [18, 19] Acetylcholine is the main neurotransmitter of vagus nerve, which can affect the collateral and transcellular permeability of intestinal epithelial cells, and cholinergic blockers or agonists can substantially regulate this process in inflammatory bowel disease. [20, 21] Choline acetyltransferase is the key enzyme for acetylcholine synthesis, and the activity of choline acetyltransferase also regulates the permeability of intestinal epithelial barrier. The application of cholinergic receptor antagonist can also block this process. [22] All these reports suggest that vagus nerve injury is closely related to the occurrence of diarrhea. Bilateral vagus nerve removal during radical surgery of esophageal cancer blocks the main way of vagus nerve inner-

vation, which may cause changes in neurotransmitters, immune status and intestinal epithelial barrier permeability, thus leads to diarrhea. However, its process and mechanism still require further investigation.

In conclusion, our results suggest that the later the stage, the lower the incidence of postoperative diarrhea in patients with esophageal cancer, and the incidence of postoperative diarrhea is lower in patients with PNI than those with no PNI, which suggests that the occurrence of postoperative diarrhea may be related with vagus nerve dysfunction. Moreover, we reduced the incidence of postoperative diarrhea by esophagectomy with vagus nerve preservation, which further confirms the important role of vagotomy in the occurrence of postoperative diarrhea in esophageal cancer. However, because this is a retrospective study, so we do not evaluate the vagus nerve excitability and analysis the relationship between it and clinicopathological factors, as well as the change of neurotransmitters, thus the process and mechanism still need to be elucidated. Lastly, there are few clinical cases of radical esophagectomy with vagus nerve preservation, and it is necessary to further expand the samples to confirm the value of vagus nerve preservation in preventing diarrhea after esophageal cancer surgery.

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