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Original Article

New-onset anastomotic leakage is not associated with changes in preoperative nutritional status induced by concurrent chemoradiotherapy in esophageal cancer patients

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Abstract: This study explored the frequency and nutritional prognostic impact of anastomotic leakage in surgical patients with concurrent chemoradiotherapy (CCR) for esophageal cancer, and the possible association between preoperative nutritional status and occurrence of anastomotic leakage. Data were collected from 178 patients in a prospective randomised study of preoperative CCR for esophageal cancer in our center, 102 patients underwent surgery only and 76 patients received CCR followed by surgery. CCR decreased the blood cell counts, including red (P = 0.000) and white blood cells (P = 0.000), as well as the serum albumin level (P = 0.000). In contrast, serum uric acid (P = 0.029), cholesterol (P = 0.026) and triglyceride (P = 0.023) were higher in patients with preoperative CCR. After surgery, 25 patients (14.0%) had new-onset anastomotic leaks; 15 of 102 (14.7%) of the patients who received surgery only and 10 of 76 (13.2%) among the patients who received CCR followed by surgery. Multivariate analysis suggested that all of the relevant markers that were altered by CCR, including decreased blood cell counts and serum albumin level, and increased serum uric acid, cholesterol and triglyceride, did not predict occurrence of an anastomotic leak. Regarding anastomotic leakage, preoperative CCR does not complicate surgery in esophageal cancer patients. Alterations in nutritional markers induced by preoperative CCR do not appear to predict a new-onset anastomotic complication.

Keywords: Anastomotic leakage, nutrition, concurrent chemoradiotherapy, esophageal cancer, surgery

Introduction

Anastomotic leakage is the most common complication in esophageal cancer patients undergoing tumor resection [1-3], and it is a significant cause of morbidity and mortality after surgery [3]. Despite the identification of risk factors for developing anastomotic leakage, such as ischemia of the gastric conduit and errors in surgical techniques [4, 5], the role of preoperative nutritional status in the development of anastomotic leakage has not yet been fully elucidated.

The efficacy of concurrent chemoradiotherapy (CCR) has been debated for several decades. Recent advances in the management of CCR followed by surgery have resulted in a significant increase in overall survival among patients with esophageal cancer, and the regimen was associated with acceptable adverse-event rates [6].

Between 50 and 80% of esophageal cancer patients present with malnutrition at diagnosis [7-9]. Currently, the potentially considerable effect of CCR on preoperative nutritional state is unclear. Furthermore, some investigators have reported that preoperative CCR in esophageal cancer patients increases the incidence of postoperative complications (including anastomotic leakage) after surgery, whereas others reported a similar incidence rate of complications as that observed in patients that did not receive preoperative CCR [10]. Therefore, in this context the question remains

whether CCR affects preoperative nutritional state, and whether the changes in nutritional markers induced by CCR represent important risk factors for the development of anastomotic leakage in patients after esophagectomy.

Materials and methods

Subjects

The objectives of the present study were to compare the frequency of anastomotic leakage between patients with CCR before surgery and those with surgery only (SO). Further, we sought to clarify whether CCR could initiate changes of preoperative nutritional state, and to then determine whether the changes in nutritional markers induced by CCR, may predict postoperative new-onset anastomotic leakage.

A total of 178 esophageal cancer patients underwent a transthoracic esophagectomy at the Sun Yat-sen University Cancer Center between December 2012 and December 2013. Seventy-six patients, who had been radiographic diagnosed with locally advanced esophageal cancer without any suspected distant metastasisby CT scan and/or MRI, received preoperative CCR followed by surgery. The other 102 patients who did not receive CCR and who had a tumor without any distant metastasis, were also enrolled in the study. The clinical stage of these patients was assigned according to the International Union against Cancer's TMN classification of Malignant Tumors [11]. Patients with previous chemotherapy and/or radiotherapy were excluded. The data used in this study were collected from a prospective random study of preoperative CCR for esophageal cancer in our center, which was approved by the Regional Research Ethics Committee. Each patient provided written informed consent and was clearly informed about the details of the study.

Data collection

The nutritional status was evaluated for both patient groups prior to surgery. Next, red blood cells and hemoglobin, serum total protein and albumin, total serum cholesterol and series lipoprotein-cholesterol levels, serum triglyceride, blood glucose, and serum uric acid were measured. To monitor the inflammatory response, changes in the levels of C-reactive protein (CRP) and white blood cells, especially lymphocytes, were also compared at the same observation points. Concordantly, the percentage body weight loss (PBL) and body mass index (BMI) were also evaluated to inform overall nutritional status. The classification of anastomotic leakage complications was applied to determine postoperative complications until the 7th postoperative day or later.

Preoperative concurrent chemoradiotherapy

In the CCR group, patients were assigned administration of navelbine (25 mg/m^2, at 1, 8, 22, 29 days) and cisplatin (75 mg/m^2, at 1 and 22 days or 25 mg/m^2, at 1-4 and 22-25 days) by intravenous infusion before each radiation therapy for 3 weeks. The concurrent radiation therapy was planned to be administered in daily fractions of 2 Gy for a total dose of 40 Gy (2.0 Gy/day, 5 days/week, continuously for 4 weeks). The period of CCR was 7 weeks.

Surgery

Patients in the CCR group underwent surgery as soon as possible after completion of CCR and recovery of blood cells, liver and kidney function, whereas patients in the surgery alone group were treated as soon as possible after hospital admission. The surgical procedures included a transthoracic esophagectomy through a right thoracotomy and a cervical esophagogastrostomy via the antethoracic, retrosternal or posterior mediastinal route with a two-field lymphadenectomy.

Diagnosis of postoperative anastomotic leakage

Patients were assessed for anastomotic leakage by a meglumine diatrizoate (gastrografin) contrast study, and usually an upper endoscopy, performed depending on the condition of the patient until the 7th postoperative day [3]. In certain critically ill patients with a chest drain still in place, methylene blue injection through the nasogastric tube was used as a diagnostic bedside test. The diagnosis of anastomotic leakage was based on clinical as well as radiologic evidence.

Postoperative intensive nutritional support

All of the patients received intensive nutritional support (INS) for 7 to 9 days immediately following after surgery. A dietician aimed to improve the intake of the patient towards 1.2-

Table 1. Characteristics of patients according to treatment group (n = 178)

	Surgery only (n = 102)	CCR and Surgery (n = 76)	*P* value
Age (yr)	56.1 ± 7.5	55.3 ± 6.4	0.456
Male gender (No)	75	63	0.140
Tumor Type (No)			0.453
Squamous-cell carcinoma	98	75	
Adenocarcinoma	4	1	
Tumor location (No)			0.343
Esophagus			
Proximal Third	7	4	
Middle Third	63	44	
Distol Third	32	27	
Esophagogastric junction	0	1	
Clinical stage (No)			0.368
II B	68	51	
III	34	25	
The hospital stay (Days)	25.78 ± 11.17	24.30 ± 8.98	0.344
Nutritional status before surgery			
Average weight (kg)	59.7 ± 10.1	59.5 ± 8.1	0.909
PBL (%)	3.63 ± 4.50	3.05 ± 5.37	0.434
BMI	21.76 ± 2.59	21.90 ± 2.92	0.748
Anastomotic leak (No)	15	10	0.797

Notes: CCR: Concurrent chemoradiotherapy; PBL: Percentage body loss; BMI: Body mass index.

1.5 g protein per kilogram of body weight per day (7). The energy goal was calculated using the Harris-Benedict equation multiplied by 1.3-1.5 (20% extra for postoperative recovery) [7]. When the patient was not able to meet the nutritional goals by tube feeding, parenteral nutrition was provided.

Statistical analysis

Data are described using mean, standard deviation, frequency, percentage and 95% confidence interval (CI). Group comparisons were performed using a Student t-test or Mann-Whitney U-test, and categorical variables with a chi-square test or the Fisher's exact test. The altered nutritional variables induced by CCR were entered into a multivariable logistic regression model with a forward stepwise selection procedure. The probability for entry of each variable in the model was set at 0.05. A *P*-value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the patient characteristics. There were no differences attributable to age, gender, body weight, location and depth of tumor, reconstruction route, operation time, the amount of intraoperative blood loss, blood transfusion, and the methods of postoperative care including nutrition support between the two groups. In addition, we did not observe any difference between the two groups regarding the pathological tumor stage, the fields of lymphadenectomy, or the length of stay in the intensive care unit or the overall hospital stay.

An overall summary of preoperative laboratory metrics for the patients in the two groups are listed in **Table 2**. The preoperative RBC count (CCR 3.64 ± 0.06 × 10^{12} Vs. SO 4.55 ± 0.05 × 10^{12}, P = 0.000), as well as hemoglobin levels (CCR 113.2 ± 1.8 g/L Vs. SO 137.5 ± 1.8 g/L, P = 0.000) in CCR patients was significantly less than that in the SO group. The average absolute lymphocyte number in patients with CCR was also less than that of the patients in the SO group (CCR 0.24 ± 0.01 × 10^{9} Vs. SO 0.28 ± 0.01 × 10^{9}, P = 0.000). The total protein level did not decrease at the observation points for patients who underwent CCR, but the serum albumin level before surgery showed a statistically significant decrease (CCR 41.2 ± 0.3 g/L Vs. SO 43.2 ± 0.3 g/L, P = 0.000). Interestingly, serum total cholesterol (CCR 5.62 ± 0.13 mmol/L Vs. SO 5.27 ± 0.09 mmol/L, P = 0.026), triglyceride (CCR 1.58 ± 0.10 mmol/L Vs. SO 1.31 ± 0.08 mmol/L, P = 0.023), and serum uric acid levels (CCR 378.6 ± 11.9 μmol/L Vs. SO 347.2 ± 7.9 μmol/L, P = 0.029) in patients with CCR were markedly higher than those with SO. No difference was observed in the other nutritional and inflammatory parameters levels, including percentage body weight loss BMI, and CRP, between the two groups (P > 0.05).

Table 2. Changes of preoperative nutritional markers induced by CCR

	CCR	SO	*P* value
PBL (%)	3.05 ± 5.36	3.63 ± 4.50	0.434
BMI	21.76 ± 2.59	21.90 ± 2.92	0.748
RBC	3.64 ± 0.53	4.55 ± 0.55	0.000
Hemoglobin	113.2 ± 15.9	137.5 ± 13.8	0.000
Lymphocyte	0.238 ± 0.087	0.283 ± 0.081	0.000
Albumin	41.2 ± 2.9	43.2 ± 3.4	0.000
Uric acid	377.6 ± 103.8	347.2 ± 79.3	0.029
Cholesterol	5.62 ± 1.14	5.27 ± 0.94	0.026
Triglyceride	1.59 ± 0.84	1.31 ± 0.77	0.023

Notes: CCR: Concurrent chemoradiotherapy; SO: Surgery only; PBL: Percentage body loss; BMI: Body mass index; RBC: Red blood cell.

Table 3. Multivariable analysis to determine the nutritional predictors for anastomotic complication in all 178 patients with esophagus cancer

	OR	95% CI	*P* value
RBC	1.353	0.730-2.507	0.337
Hemoglobin	0.997	0.975-1.019	0.791
Lymphocyte	14.337	0.105-1950	0.288
Albumin	1.026	0.900-1.168	0.704
Cholesterol	1.067	0.715-1.594	0.750
Triglyceride	1.213	0.754-1.951	0.426
Uric acid	0.999	0.994-1.003	0.572

Notes: RBC: Red blood cell.

The frequency of anastomotic leakage in patients in each of the two groups (CCR group and SO group) is also shown in **Table 1**. Anastomotic leakage was diagnosed based on radiological examinationand clinical features. After surgery, 25 patients (14.0%) had new-onset anastomotic leaks, 15 of 102 (14.7%) in the surgery only group and 10 of 76 (13.2%) in the CCR followed by surgery group. There was no difference in the frequency of anastomotic complication between the two groups ($P > 0.05$).

Table 3 shows the results of the multivariate logistic regression analysis that was performed to determine the significance of the changed nutritional variables, induced by preoperative CCR, to predict the development of anastomotic leakage. Occurrence of anastomotic leakage was not significantly associated with the changes inblood cell counts or neither RBC counts (OR 1.353, 95% CI 0.730-2.507, P = 0.337), including hemoglobin (OR 0.997, 95% CI 0.975-1.019, P = 0.791) and lymphocytes (OR 14.337, 95% CI 0.105-1950, P = 0.288). There was no increased anastomotic leakage among patients with lower serum albumin compared to those with higher serum albumin (OR 1.026, 95% CI 0.900-1.168, P = 0.704). No trend towards fewer incidences of anastomotic leakage was observed in the group with lower cholesterol levels (OR 1.067, 95% CI 0.715-1.594, P = 0.750). There was also no association between anastomotic leakage and any high or low serum triglyceride level (OR 1.213, 95% CI 0.754-1.951, P = 0.426). The association between anastomotic leakage and serum uric acid was small and was not significant (OR 0.999, 95% CI 0.994-1.003, P = 0.572).

Discussion

Although surgical resection is the primary treatment used for esophageal cancer, focus has recently shifted to therapies that combine chemotherapy and radiation with surgery [12]. Recent studies have argued that preoperative chemoradiotherapy should be the standard of care in esophageal cancer treatment [6, 12, 13]. Previous studies reported mortality ranges from 5 to 18% among pretreated patients, while mortality was 8.6% for patients who underwent surgery alone [12]. Anastomotic leakage, which results in increased mortality, usually occurs subsequent to esophagectomy [1-5]. In some studies, the incidence of anastomotic leakage was similar between patients with preoperative CCR and those with surgery only [6], while a dramatic increase in this complication has been observed in other studies [10]. The reason considered responsible for the higher anastomotic complication may be further deterioration of the patient's nutritional status due to preoperative CCR? Therefore, our prospective random study examined the effects of chemoradiotherapy on preoperative nutritional status, and further determined the nutritional risk factor responsible for anastomotic leakage.

In our study, although CCR initiated changes in several nutritional markers before surgery, the incidence of anastomotic leakage did not increase in patients that received chemoradio-

therapy. Further, the alterations in nutritional variables did not predict the incidence of anastomotic complication. Thus, regarding anastomotic leakage, preoperative CCR did not complicate surgery. The specific nutritional marker changes were decreased blood cell counts and serum albumin, and increased serum total cholesterol, serum triglyceride, and serum uric acid. The nutritional status of the patients did not dramatically change at preoperative observation points, although statistically significant differences were observed for these parameters. Moreover, percentage of body weight loss and BMI, which are evaluated to understand the overall nutritional status of the patient, were also not affected by preoperative CCR.

Many factors, local and systemic, influence the process of wound healing and hence influencing the incidence of anastomotic complications [2]. Among systemic factors, malnutrition and neoadjuvant therapies, are considered to contribute to an uneventful anastomotic complication [1, 2]. However, preoperative nutritional condition has received only minor attention in risk analyses for esophagectomy. In our study, the frequency of anastomotic leakage was not significantly higher in patients who received chemoradiotherapy compared to those who underwent surgery alone, without chemoradiotherapy. There was also no association between alterations in nutritional status markers induced by chemoradiotherapy and an anastomotic leak. The reason for this is likely that tumor size decreased following chemoradiotherapy, resulting in a decrease in the regimen of tumor resection. The higher serum uric acid and lipid levels [14-16], including cholesterol and triglyceride, may reflect a decrease of tumor size. Additionally, hypoalbuminemia may indicate protein-energy malnutrition, which results in adverse surgical outcomes [17, 18]. In a previous study, the serum albumin level on the first postoperative day was independently associated with postoperative complications in cancer patients who underwent an esophagectomy [19]. However, our results demonstrated that preoperative chemoradiotherapy initiated the decrease of serum albumin level, while it remained in the normal range. A majority of anastomotic complications are expected to be observed as the result of a technical failure, and refinements in techniques have also contributed to the decrease of anastomotic complications.

In conclusion, preoperative chemoradiotherapy did not increase the development of anastomotic complications. Chemoradiotherapy initiated changes in several preoperative nutritional parameters, but the effects were minor. Subsequently, the minor changes in nutritional markers were not associated with incidence of anastomotic leakage. Therefore, preoperative chemoradiotherapy is safe in regard to nutrition as well as anastomotic leakage.

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Disclosure of conflict of interest

None.

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