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Original Article

Effects of postoperative chemotherapy on cardiopulmonary complications in patients with esophageal cancer

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Abstract: Objective: Postoperative chemotherapy (pCT) for patients with esophageal cancer has been well-established. However, adjuvant therapy may induce severe adverse effects that could increase postoperative morbidity. The aim of this study was to assess the impact of pCT on postoperative cardiopulmonary complications in esophageal cancer patients. Methods: This prospective study was conducted for esophageal cancer patients after surgery. They were treated with pCT (n=62) or without pCT (non-pCT, n=41) for 30 days. Multivariate analyses were carried out to determine the impact of pCT on postoperative complications. Results: Significantly more patients were diagnosed with pneumonia in the pCT treated group than the non-pCT group ($p<0.01$). In the pCT group, early diastolic filling velocity (E-velocity) was decreased, significantly, compared with that in the non-pCT group ($p<0.01$). Conclusion: More cardiopulmonary complications were found in the pCT group, compared with the non-pCT group, for patients with esophageal cancer after surgery. Management for prevention of postoperative cardiopulmonary complications should be considered when starting postoperative chemotherapy.

Keywords: Chemotherapy, postoperative, esophageal cancer, cardiopulmonary complications

Introduction

Esophageal cancer is one of the most aggressive cancers, worldwide, with approximately 70% of cases occurring in China [1, 2]. The current treatment strategy for locoregional esophageal squamous cell cancer (ESCC) in China is surgical resection, along with postoperative chemotherapy and/or radiotherapy [3]. The 5-year overall survival (OS) of postoperative patients is approximately 20-50% [4, 5]. Due to advances in imaging, anesthesia, and surgical techniques in recent years, the rate of surgical resections has increased. Surgical morbidity and mortality rates have both significantly decreased for 30 days [6]. However, the OS for resectable ESCC has not markedly improved [7]. More than half of the patients eventually die from tumor recurrence or metastasis [8, 9]. Limited clinical studies have reported controversial results regarding the value of postoperative adjuvant therapy for patients that have undergone esophagectomy procedures [10-12]. Although adenocarcinoma predominates in Western countries, the most common histological type of esophageal carcinoma in China is squamous cell carcinoma [13]. For this reason, treatment protocols, such as the National Comprehensive Cancer Network (NCCN) guidelines, may not be appropriate for Chinese patients with ESCC [14]. Therefore, it is necessary to evaluate the impact of current postoperative adjuvant therapy on patients with resectable ESCC in China.

Regarding long-term survival, oncological benefits from the addition of chemotherapy may be countered by significant increases in mortality because of serious adverse events and postoperative complications in the chemoradiotherapy arm during the first year after randomization. In addition, postoperative complications have been shown to be more severe after chemoradiotherapy [15]. These data suggest that the addition of chemotherapy may have significant adverse effects on the lungs and heart, which

are in the radiation field. It has been well-established that pneumonia is a serious medical complication and a serious surgical complication after esophagectomy procedures [16]. Pneumonia has a negative impact on overall survival [17]. Additionally, recent studies have demonstrated an acute decrease in left ventricular systolic and diastolic function following chemotherapy. However, results have not been consistent [18, 19]. Moreover, N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), widely used to diagnose and prognose heart failure, has been observed to increase following chemotherapy [21, 22]. Incidence of postoperative cardiac complications after esophagectomies has been reported to be in the range of 15-30% for both chemo-and chemoradiotherapy [23]. However, the impact of postoperative chemotherapy (pCT) on lung and heart function of esophageal cancer patients after esophagectomy procedures has not been fully discussed.

Therefore, the present study aimed to investigate the influence of pCT on postoperative cardiopulmonary complications in esophageal cancer patients.

Materials and methods

Patient characteristics

In the present study, 103 patients were consecutively enrolled from January to October 2018. Patients were divided into 2 groups, according to adjuvant treatment, including 62 patients with pCT and 41 patients without pCT (non-pCT). Inclusion criteria: 1) Patients that underwent a transthoracic esophagectomy with two-field lymphadenectomy by two experienced surgeons; and 2) Patients with resectable and histologically proven esophageal cancer, requiring treatment with pCT. Chemotherapy was recommended for patients with cancer TNM stage > T1BN0 [24, 25]. Exclusion criteria: 1) Pre-existing cardiopulmonary disease or prior radiotherapy to the heart and lungs; and 2) Patients with a history of cardiopulmonary events, assessed by the cardiologist or pulmonologist for perioperative recommendations.

Various data was collected, including demographic characteristics, comorbidity, adjuvant treatment, tumor characteristics, therapeutic information, complications for chemotherapy for 30 days, and survival data. The study protocol was approved by the Ethics Committee of Hetao College. Methods were carried out in accordance with approved guidelines. Informed consent was obtained from all patients.

Surgery

Esophagectomy procedures were performed in all 103 patients. All patients underwent a transthoracic esophagectomy with two-field lymphadenectomy by two experienced surgeons. Tumors around the gastroesophageal junction were approached through a left thoracolaparotomy, while more esophageal tumors were approached through a right-sided procedure.

Adjuvant treatment

Chemotherapy was given for three cycles and a total of 21 days. Cisplatin 100 mg/m^2 was given on day 1 and 5-fluorouracil 750 mg/m^2/24 hrs was given on days 1-5. Cisplatin was switched to carboplatin or oxaliplatin in cases of hearing impairment or renal dysfunction. Dose reduction was allowed for side effects.

Cardiac exams

Complications during hospital admission were divided into pulmonary, cardiac, and other complications. Complications were scored with the same criteria described previously, except for pneumonia. It was supplemented with the use of antibiotic treatment on clinical indications [26]. Comorbidities were classified according to the American Society of Anesthesiologists (ASA) scores, which varied from ASA 1 (very good condition) to ASA 5 (moribund patient) [27]. Cardiac exams were performed on all subjects. Echocardiographic parameters were chosen in accordance with European Association of Echocardiography guidelines [25]. One or more loops of three heartbeats were recorded online for each view. The best cardiac cycle was selected for analysis during post processing. Ejection fraction (EF) was calculated according to Simpson's biplane method. Mitral inflow was measured using pulsed-wave Doppler. Peak velocity in the early rapid filling phase, when the ventricle relaxes (E-velocity) and peak velocity of the late filling due to atrial contraction (A-velocity), were measured by pulsed Doppler across the mitral valve during diastole. For serum N-terminal pro-brain natriuretic peptide (NT-proBNP) testing, venous blood was collected in EDTA tubes. NT-proBNP ELISA Kit

Table 1. Baseline patient characteristics

Characteristics	non-pCT (n=41)	pCT (n=62)	*p* value
Age	61.7 (45-73)	62.3 (44-75)	0.76
Male/Female	25/16	36/26	0.47
Body mass index (kg/m^2)	22.3 (18.4-26.9)	21.7 (17.5-28.1)	0.73
Medical history, n (%)			
Hypertension	9 (22.0)	17 (27.4)	0.41
Diabetes mellitus	5 (12.2)	7 (11.3)	0.55
Respiratory	12 (29.3)	16 (25.8)	0.51
Ischemic heart disease, n (%)	4 (9.8)	6 (9.7)	0.63
Tumor type			
Adenocarcinoma, n (%)	26 (63.4)	37 (59.7)	0.47
Squamous-cell carcinoma, n (%)	14 (34.1)	22 (35.5)	
Tumor localization, n (%)			
Upper	3 (7.3)	5 (8.1)	0.32
Middle	13 (31.7)	18 (29.0)	
Lower	25 (61.0)	39 (62.9)	
Clinical T stage			
T1/T2	19 (46.3)	27 (43.5)	0.39
T3/T4	22 (53.7)	35 (56.5)	
ASA classification, n			
I	5	7	0.48
II	23	36	
III	9	15	
IV	4	4	

pCT: Postoperative chemotherapy; ASA: American Society of Anesthesiologists.

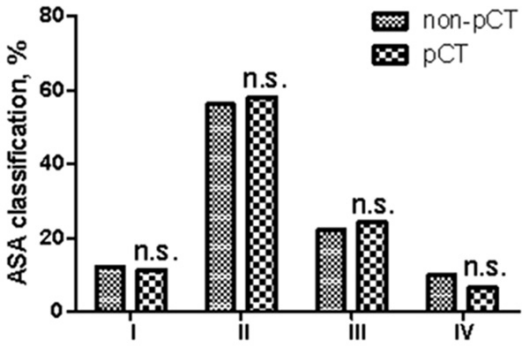

Figure 1. Baseline patient characteristics of American Society of Anesthesiologists (ASA). Note. n.s. mean P>0.05, pCT compared with pCRT (p=0.96; p=0.85; p=0.73; p=0.82).

(Biocompare, CA, USA) was used for analyses after the last cardiac exam. The detection limit of the assay was 0.31 ng/mL.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. They were evaluated by independent Student's t tests. Categoric variables are presented as frequencies and percentages and were analyzed by X^2 tests or Fisher's exact tests, as appropriate. Multivariate analyses were carried out to determine the impact of pCT on postoperative complications. All probabilities were two-tailed and *p*-values less than 0.05 indicate statistical significance. All statistical analyses were performed using SPSS (version 17.0, SPSS Inc., Chicago, IL).

Results

Patient characteristics

A total of 103 patients (pCT, n=62; non-pCT, n=41) participated in the study. Clinicopathological characteristics of all patients are shown in **Table 1**. There were no statistically significant differences between study groups, regarding demographic and disease-specific characteristics. Patients were matched for age, gender, body mass index, medical history, ischemic heart disease, tumor type, tumor localization, clinical T stage, and American Society of Anesthesiologists (ASA) classification (**Table 1** and **Figure 1**).

Mortality and morbidity

As shown in **Table 2**, 30-day mortality rates were not significantly different between non-pCT (5.0%) and pCT (4.9%) groups. In addition, overall morbidity rates in the non-pCT group (76.5%) and pCT group (73.1%) were not significantly different (**Table 2**).

Impact of pCT on pulmonary complications

Pulmonary complications were observed frequently in both non-pCT and pCT groups. Pneumonia was the most commonly reported complication. It was more frequently observed in the pCT group than the non-pCT group (56.2% vs. 25.8%; p<0.01) (**Figure 2**). Other

Table 2. Postoperative data of patients with pCT or pCRT treatment

Variable	non-pCT (n=41)	pCT (n=62)	*p* value
30-day mortality, n (%)	3 (7.3)	4 (6.5)	0.76
Overall morbidity, n (%)	28 (68.3)	44 (71.0)	0.34
Pulmonary complications			
Pneumonia, n (%)	11 (26.8)	33 (53.2)	<0.01
Pleural effusion, n (%)	10 (24.4)	19 (30.6)	0.32
ARDS, n (%)	2 (4.9)	4 (6.5)	0.56
Atelectasis, n (%)	5 (12.2)	9 (14.5)	0.62
Respiratory failure, n (%)	9 (22.0)	17 (27.4)	0.38
Pulmonary embolism, n (%)	3 (7.3)	5 (8.1)	0.62
Reintubation, n (%)	7 (17.1)	12 (19.4)	0.45
Cardiac complication			
EF (%)	59.3 (51.4-67.8)	60.8 (52.6-69.7)	0.76
E-velocity (cm/s)	72.6 (57.1-79.6)	54.3(47.1-65.4)	<0.01
A-velocity (cm/s)	79.8 (63.1-85.9)	85.2 (69.4-97.3)	0.36
E/A	0.93 (0.67-1.37)	0.57 (0.44-0.96)	<0.01
NT-proBNP (ng/ml)	82.1 (62.3-169.5)	186.7 (81.5-245.3)	<0.01
Arrhythmia, n (%)	8 (19.5)	14 (22.6)	0.34
Other complications			
SIRS, n (%)	3 (7.3)	6 (9.7)	0.45
Sepsis, n (%)	2 (4.9)	4 (6.5)	0.61
Anastomotic leakage, n (%)	4 (9.8)	8 (12.9)	0.57
Chylothorax, n (%)	3 (7.3)	5 (8.1)	0.68
Wound infections, n (%)	1 (2.4)	2 (3.2)	0.42
Renal failure, n (%)	2 (4.9)	4 (6.5)	0.72
Liver failure, n (%)	1 (2.4)	2 (3.2)	0.54

pCT: Postoperative chemotherapy; ARDS: acute respiratory distress syndrome; EF: ejection fraction; E-velocity: peak velocity in the early rapid filling phase when the ventricle relaxes; A-velocity: peak velocity of the late filling due to atrial contraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; SIRS: systemic inflammatory response syndrome.

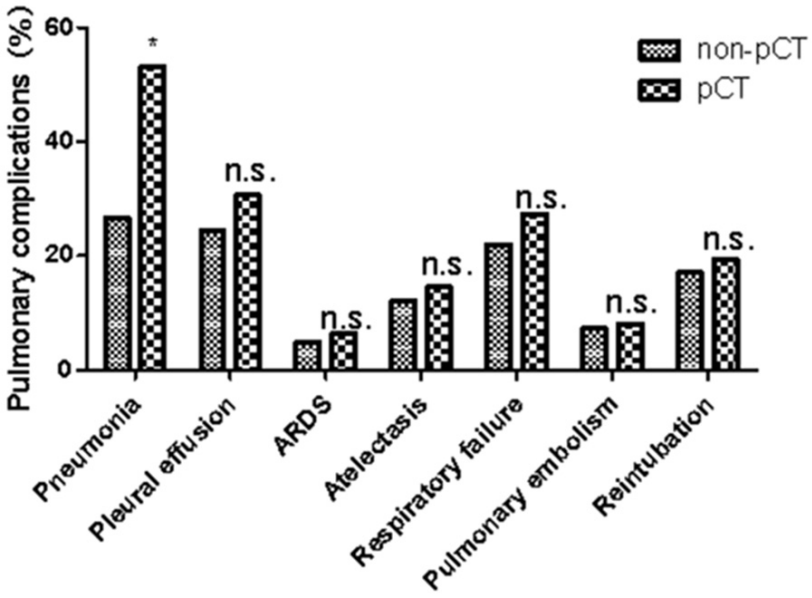

Figure 2. Pulmonary complications data of patients with pCT or pCRT treatment. Note. n.s. P>0.05, *P<0.05. pCT compared with pCRT treatment (*p=0.021; p=0.94; p=0.65; p=0.84; p=0.76; p=0.63; p=0.69).

pulmonary complications, including pleural effusion, acute respiratory distress syndrome (ARDS), atelectasis, respiratory failure, pulmonary embolisms, and reintubation, were not significantly different between groups (**Table 2**).

Impact of pCT on cardiac function parameters

Cardiac complications of patients after esophagectomy procedures are shown in **Table 2** and **Figures 3**-**4**. Postoperative treatment induced no changes in EF in either the non-pCT group or pCT group. E velocity in the pCT group decreased significantly (p<0.01), while coupled with an unchanged A velocity, compared with the non-pCT group. In addition, E/A ratios in the pCT group decreased significantly (p<0.01). This was due to a significant decrease of E velocity. No significant differences were found in arrhythmias and other complications, including systemic inflammatory response syndrome (SIRS), sepsis, anastomotic leakage, chylothorax, wound infections, renal failure, and liver failure.

Multivariate analysis

To determine the influence of pCT on development

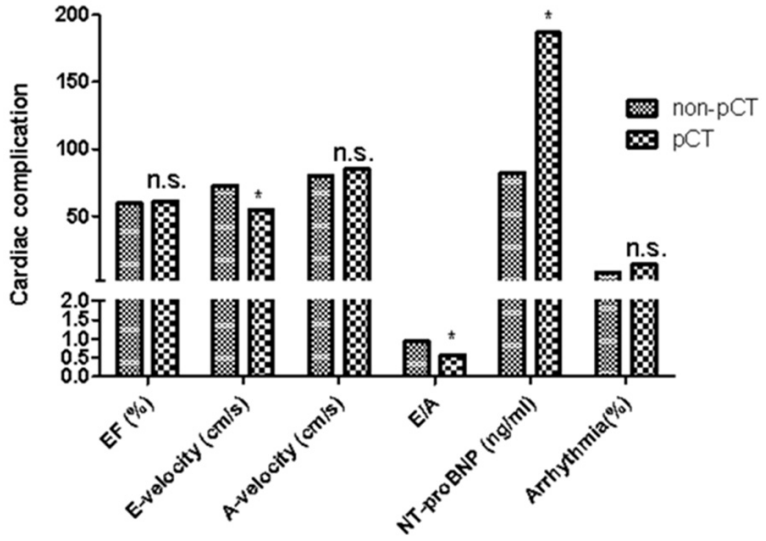

Figure 3. Cardiac complications data of patients with pCT or pCRT treatment. Note. n.s. P>0.05, *P<0.05. pCT compared with pCRT treatment (p=0.75; p=0.62; p=0.68; *p=0.042; *p=0.026; p=0.79).

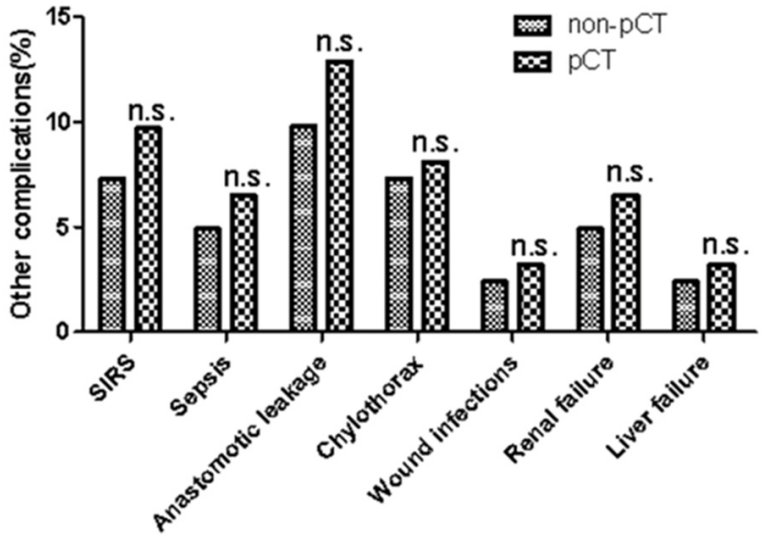

Figure 4. Other complications data of patients with pCT or pCRT treatment. Note. n.s. P>0.05, *P<0.05. pCT compared with pCRT treatment (p=0.56; p=0.64; p=0.71; p=0.61; p=0.75; p=0.64; p=0.82).

Table 3. Outcomes of multivariate analysis

Variable	*β*	*SE*	*Wald*	*P*	*Exp (β)*	*95% CI*
Pneumonia	0.883	0.286	8.183	<0.01	3.65	1.27-6.93
Pleural effusion	0.802	0.214	8.113	0.28	1.36	0.79-2.68
Arrhythmia	0.581	0.297	9.643	0.19	1.47	0.81-2.83

of postoperative complications, multivariate analysis was conducted for pneumonia, pleural effusion, NT-proBNP levels, and arrhythmia. As shown in **Table 3**, pCT was significantly associated with the development of pneumonia (OR 3.74, CI 1.36-6.85,) and NT-proBNP levels (OR 2.65, CI 1.12-5.37,), but not pleural effusion or arrhythmias.

Discussion

After esophagectomy procedures, postoperative complications occur in 30% to 50% of patients [28]. Despite recent improvements in surgical procedures and perioperative management, esophagectomy procedures have been associated with higher rates of morbidity and mortality [29]. Kinugasa et al. [30] suggested a potential negative prognostic impact of postoperative respiratory complications. There have been other reports indicating the negative impact of postoperative complications on long-term outcomes [31]. Present data demonstrates an increased incidence of postoperative pneumonia after the introduction of pCT, compared with the non-pCT group. The current study also provides results indicating that pCT for cancer of the esophagus induces acute impairment of heart function.

Part of this prolonged discussion was the occurrence of toxic cardiopulmonary adverse events and raised postoperative risks for morbidity and mortality [32]. Besides cardiopulmonary complications, inflammation and anastomotic leakage are feared [33]. Recently, Bosch et al. found an increase of cardiopulmonary complications in the adjuvant pCT group [23]. In accord with previous studies, the current study found that significantly more patients were diagnosed with pneumonia in the pCT group than the non-pCT group. Moreover, pCT was significantly associ-

ated with an increased risk of pneumonia. Improvements in advanced radiation technologies using intensity-modulated radiotherapy are promising. However, further research is warranted.

It has been reported that pCT decreases blood flow velocities over the mitral valve during the fast, passive filling phase of the left ventricle (E), coupled with an unchanged blood flow during atrial contraction (A), thus decreasing E/A [36]. These data suggest impaired diastolic function due to impaired relaxation of the left ventricle. Hatakenaka and coworkers also reported an impairment of left ventricular relaxation after radiotherapy [36]. Adjuvant chemoradiotherapy also increases NT-proBNP. This has been studied as a predictor for the risk of perioperative cardiac complications, with cut-off values between 201-791 ng/mL having been suggested [37-39]. The current study observed that diastolic changes were larger, with mean E/A levels after adjuvant therapy reaching grade I diastolic dysfunction, which could have clinical implications. NT-proBNP levels increased following chemotherapy, possibly indicating an increased risk for postoperative cardiac events and atrial fibrillation [40]. Impaired left ventricular systolic and diastolic function following adjuvant pCT could well have a bearing on incidence and grades of the innately high postoperative cardiovascular after esophagectomy procedures [41]. Taken together, current data emphasizes the relevance of dedicated studies aimed at further clarifying the details and consequences of the cardiotoxicity of current chemotherapy regimens.

One of the limitations of the current study was that it only included patients with resectable tumors. Present findings may only apply to patients undergoing resections. To confirm the results of this study, further investigations, including more patients and more races, are needed.

In conclusion, the current study shows increased incidence of pneumonia after pCT in the treatment of esophageal cancer patients. According to multivariate analysis, pCT was significantly associated with risk of pneumonia. Moreover, pCT after surgery for cancer of the esophagus seems to induce acute negative effects on hearing ability. Present results underline the need for cautious use of pCT in this group of patients, given the increased risk of cardiopulmonary complications. Future studies concerning adjuvant treatment for esophageal cancer are necessary, adding measurements of cardiopulmonary function and limiting pCT-induced lung and heart toxicity.

Disclosure of conflict of interest

None.

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