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Original Article

Early altered left heart function in non-operative advanced distal esophageal cancer patients treated with concurrent chemoradiotherapy: a single institutional retrospective analysis

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Abstract: In this study, we retrospectively evaluate early impairment of left heart function assessed by tissue Doppler imaging (TDI) in patients with non-operative advanced distal esophageal cancer after concurrent chemoradiotherapy (CCRT). The left heart functions of 40 patients with inoperative advanced distal esophageal cancer who received CCRT were evaluated before and after CCRT. And the parameters related to left ventricular ejection fraction (LVEF), the peak early (E) and late (A) mitral inflow velocities and E/A ratio, the parameters related to the peak systolic wave Sm, early (Em) and late (Am) mitral annular velocities, E/Em and Em/Am ratios detected by TDI and left atrial volume index (LAVI) were also compared. After CCRT, there were no patients with pericardial effusion and valvular disease. There were marginally significant decrease in LVEF and peak E mitral inflow velocity and a significant increase in peak A mitral inflow velocity after CCRT, but the E/A ratio was not changed after CCRT. By using TDI examination, there were significant decreases in Sm, Em and Em/Am ratio and significant increases in Am and E/Em ratio after CCRT. The LAVI was significantly increased when compared with the one before CCRT. And there was a positive correlation between LAVI and E/Em ratio. Therefore, early heart toxicity as indicated by altered LAVI and LV diastolic function is detected after CCRT in patients with esophageal cancer. And the implementation of TDI technology can provide important information of LV impairment earlier than the standard echocardiography.

Keywords: Diastolic function, echocardiography, left ventricular function, radiation, tissue Doppler echocardiography, esophageal cancer, chemoradiotherapy

Introduction

Mediastinal radiotherapy has been considered as an important curative treatment option for various thoracic cancers. Since more and more cancer patients benefit from radiotherapy and survive worldwide, it is needed to be more aware that many patients are at risk of radiotherapy related normal tissue toxicity.

Radiotherapy related heart toxicity is one such tissue toxicity which has been extensively studied in breast cancer or Hodgkin lymphoma with left breast or mediastina radiotherapy respectively. The follow up data on radiotherapy related heart toxicity mainly come from these two long-term cancer survivors [1-4]. However, limited data could be provided from esophageal cancer even though a markedly higher dose is delivered to the heart because the location of heart is usually close to the high dose region near the tumor target [5]. Recently, Beukema *et al*. had reviewed the radiotherapy related heart toxicity in esophageal cancer with radiotherapy [6]. Since there are no specific prevention and treatments for radiotherapy related heart toxicity which might offset the improvement in cancer specific mortality [7], careful monitoring and early intervention seem to be essential to manage morbidity and therefore minimize mortality.

Echocardiography is currently considered to be the most frequently used noninvasive diagnostic tool for monitoring cardiac function [8]. As a new echocardiography tool, tissue Doppler

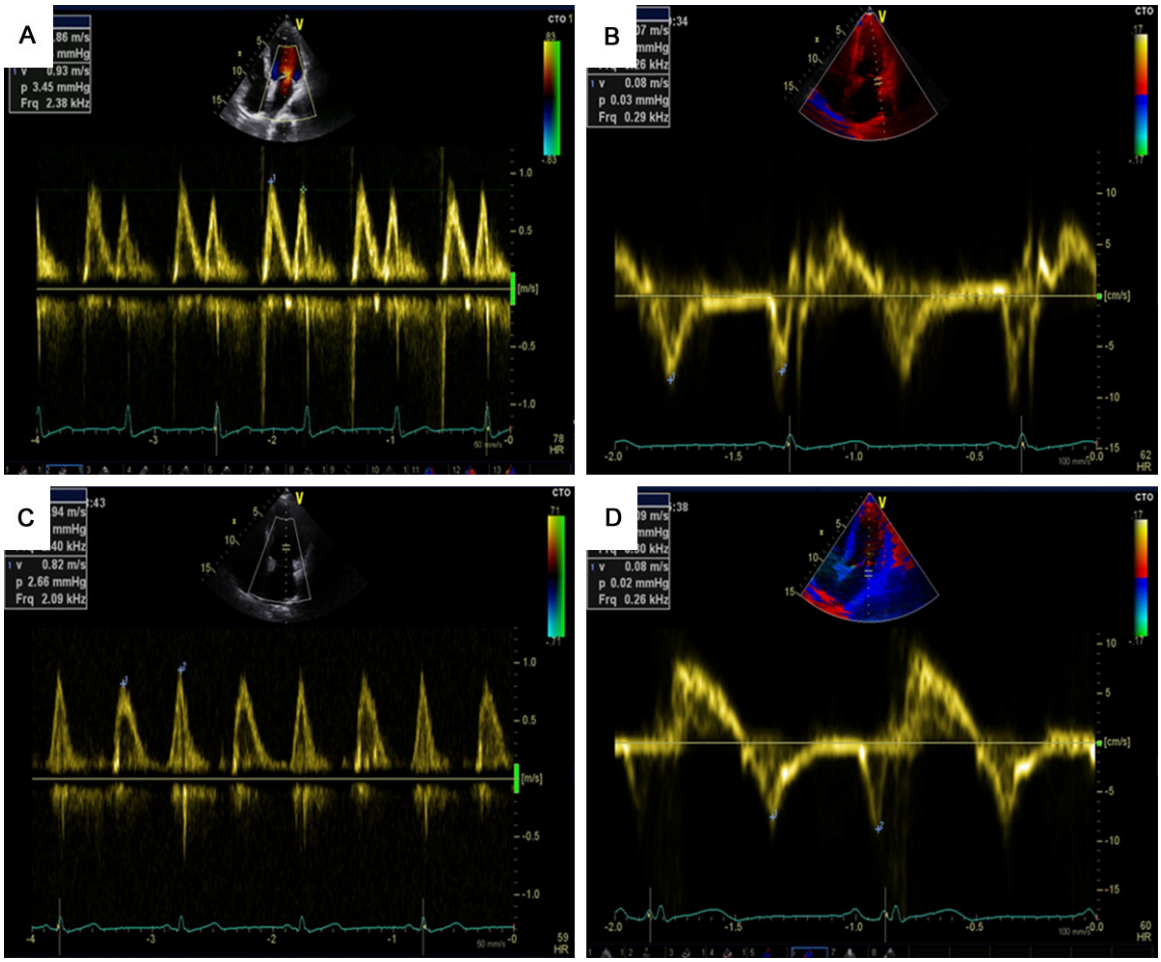

Figure 1. Represent images of mitral inflow velocities (A and C) and tissue Doppler imaging (B and D) respectively in the same patient before (A and B) and after (C and D) concurrent chemoradiotherapy.

imaging (TDI) seems to be have important advantages in the analysis of diastolic function because it could identify additional patients with abnormal diastolic function which was initially classified as normal [9, 10]. Moreover, TDI is also expected to improve the identification of early cardiac impairment [11].

The present study was aimed to retrospectively evaluate early altered left heart function impairment in distal esophageal cancer treated with concurrent chemoradiotherapy (CCRT) by using standard echocardiography and TDI technology.

Material and methods

Ethical approval of the study protocol

The present study was approved by the Ethics Committee of Northern People's Hospital (Jiangsu, China).

Patients and treatment

In this study, a total of 40 patients (32 males and 8 females; 53-72 years of age) with newly diagnosed and pathologically confirmed middle or lower thoracic local advanced esophageal squamous cell carcinoma were retrospectively analyzed from June 2014 to September 2016. Patients who had a history of hypertension, coronary heart disease, left ventricular (LV) systolic dysfunction and obesity were excluded. And patients with abnormal electrocardiogram and myocardial enzymes before treatment were also excluded. All the patients had stage II-III carcinoma, Eastern Cooperative Oncology Group performance status of 0-1 scores, and received intensity-modulated radiotherapy using CT-based planning. Radiotherapy was performed at a daily dose of 2.0 Gy, 5 times per week using a Varian 23EX linear accelerator (Varian Medical Systems, Palo Alto, CA). The

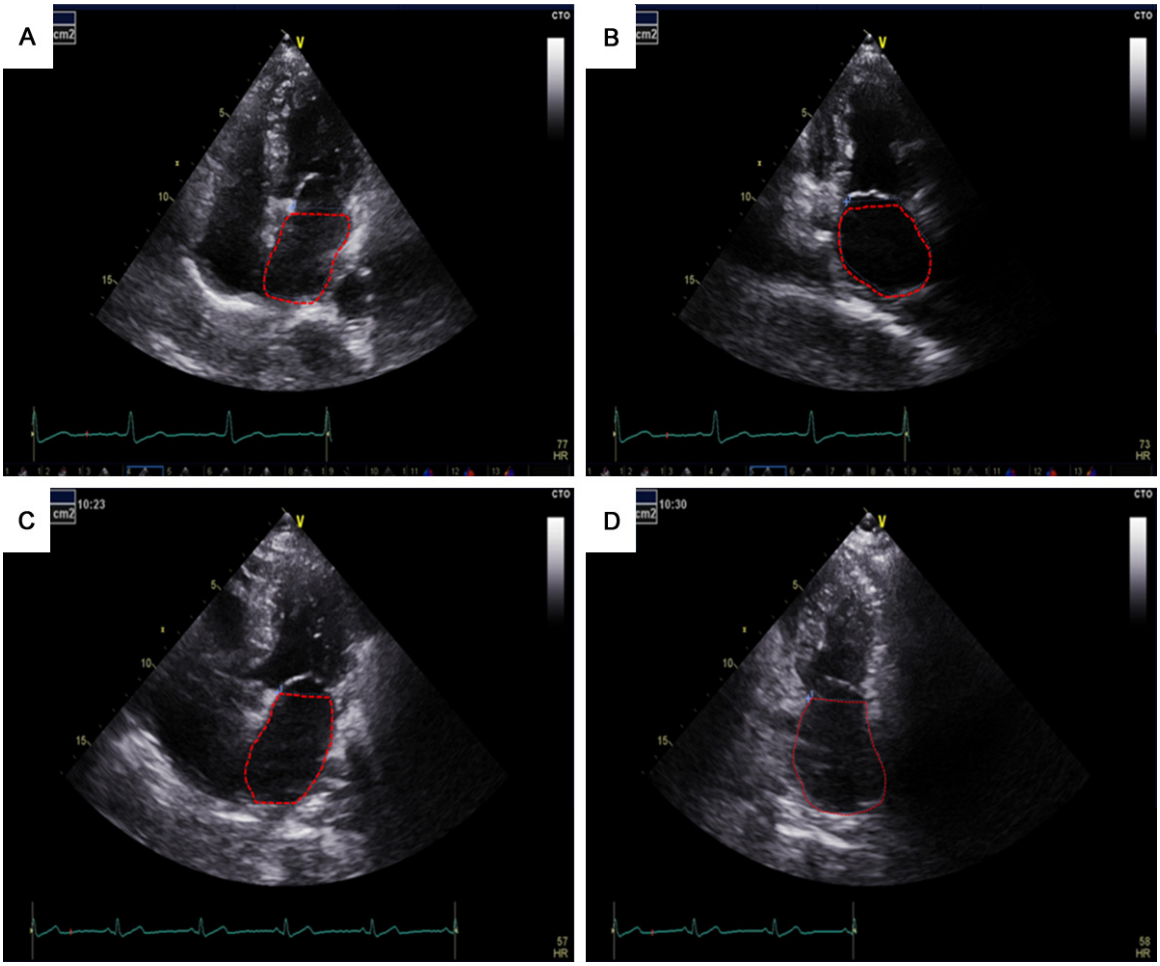

Figure 2. Measurement of maximal planimetered LA area using apical 4-chamber (A, C) and apical 2-chamber (B, D) views respectively in the same patient before (A and B) and after (C and D) concurrent chemoradiotherapy.

gross tumor volume (GTV), clinical target volumes (CTVs) and planning target volumes (PTVs) were delineated by the original oncologist according to the treatment guideline of radiotherapy for Chinese esophageal carcinoma (draft) [12]. And the prescribed doses were 60 Gy in 30 fractions for GTV and 50 Gy in 25 fractions for CTVs. Concurrent chemotherapy with cisplatin 25 mg/m^2 day 1~3 and paclitaxel 175 mg/m^2 was delivered every 4 week throughout the treatment course.

Echocardiographic and TDI evaluation

All the patients were received echocardiographic examinations before and after concurrent chemoradiotherapy (CCRT). Standard echocardiography was performed using VividE 9 System (GE, Horten, Norway). The following parameters were measured: LV ejection fraction (LVEF) and the peak early (E; m/sec) and late (A; m/sec) mitral inflow velocities (**Figure 1**). TDI examinations were performed by the same device using 1.7-3.3 MHz transducers by switching to pulsed wave TDI mode. Under this mode, three waves were obtained in each cardiac cycle: a systolic wave (Sm), an early diastolic wave (Em), and a late diastolic wave (Am). Peak Sm (cm/sec), Em (cm/sec) and Am (cm/sec) velocities and E/Em ratio were measured (**Figure 1**). Furthermore, left atrial volume index (LAVI) was calculated by dividing LA volume by body surface area. Left atrial (LA) volume was measured through biplane area-length formula using standard apical 2-chamber (A2C) and apical 4-chamber (A4C) views at ventricular end systole (maximal LA size, **Figure 2**) as previously described [13]. In brief, LA volume=8/3π*(A1*A2/L), where A1 and A2 represent the maximal planimetered LA area acquired from the A2C and A4C views,

Table 1. Comparison of LV and LA Doppler parameters before and after CCRT

	Before CCRT	After CCRT	*P* value
LVEF	66.31±4.01	65.88±3.72	0.079
E	77.62±13.0	76.97±13.54	0.09
A	66.82±11.47	68.12±12.01	0.02
E/A	1.16±0.26	1.12±0.22	0.152
Sm	8.22±1.54	7.67±1.62	<0.001
Em	9.28±1.64	8.55±1.54	0.003
Am	8.22±1.70	8.71±1.86	0.003
Em/Am	1.15±0.05	0.99±0.04	0.001
E/Em	8.32±1.01	9.64±1.39	<0.001
LAVI	22.27±3.40	32.74±4.78	<0.001

LV: left ventricular; LA: left atrium; CCRT: concurrent chemoradiotherapy.

respectively, and L is measured from back wall to line across hinge points of mitral valve in both the A2C and A4C views and the shortest one of these 2 length measurements is used in the formula. And the formula for calculating body surface area is used: 0.0061×height (cm) +0.0128×weight (kg)-0.1529. All measurements were obtained from 3 consecutive cardiac cycles, and then, the data were averaged.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL). All data were expressed as the mean ± SE and a p value <0.05 was considered statistically significant. T test was used to compare the differences among groups. The spearman correlation analysis was carried out to analyze the association between LAVI and E/Em ratios.

Results

After CCRT, standard echocardiographic examinations showed that there were no patients with pericardial effusion and valvular disease. The LVEF and peak E mitral inflow velocity decreased with marginally significant p values (P=0.079 and P=0.09 respectively) when compared with the ones before CCRT, while the peak A mitral inflow velocity significantly increased after CCRT (P=0.02, **Figure 1** and **Table 1**). Since the E/A ratio is a widely used marker to assess LV diastolic function of heart, we further detected the E/A ratio to analyze early change of LV diastolic function. Our results showed that there was a very slightly decrease of E/A ratio after CCRT, and p value was 0.152 (**Table 1**).

As mentioned above, TDI might identify additional patients with abnormal diastolic function, we next used TDI to assess the impairment of LV diastolic function again. Our results showed that TDI seemed to have the ability to find early impairment of LV diastolic function that the standard echocardiography couldn't have when compared with the standard echocardiography. We found that there were significant decreases in Sm, Em and Em/Am ratio and significant increases in Am and E/Em ratio (P<0.05, **Figure 1** and **Table 1**). These results suggested that it was more suitable for TDI to assess and identify early treatment-related heart impairment.

We further analyzed the relationship between LAVI and the LV diastolic function maker E/Em ratio. Our results indicated that the LAVI after CCRT was significantly higher than the one before CCRT (32.74±4.78 versus 22.27±3.40, P<0.001, **Table 1**). Furthermore, there was a positive correlation between LAVI and E/Em ratio, and the correlation coefficience was 0.87 (P<0.001).

Discussion

The present results of our study had shown an early impaired left heart function in esophageal cancer patients who received CCRT. Meanwhile, our result indicated an important advantage of TDI in the assessment of LV diastolic function as compared with standard echocardiography examination. And we also found a close correlation between LAVI and LV diastolic function maker E/Em ratio.

Similar with previous experiences of breast cancer and mediastinal Hodgkin lymphoma, the heart injury induced by CCRT for esophageal cancer has been traditionally considered as a late radiotherapy-related toxicity [14-16]. However, recent study had reported that the heart toxicity after high-dose thoracic radiotherapy might happen earlier than historically understood in stage III NSCLC [17]. As for esophageal cancer, similar toxicity may be present in patients who receive thoracic radiotherapy, but it was still unclear that how radiotherapy could increase the risk of early heart toxicity. One reason might be that radiotherapy could

cause early radiation-induced microvascular changes as evidenced by animal models and clinic studies [17-19]. Recently, there were two reports concerning early impairment of heart in esophageal cancer patients with CCRT by using different detection methods. By using multiple-gated acquisition (MUGA) scan, Miriyala *et al.* [5] found a significant decline in heart contractility function, with a mean decline of right ventricular ejection fraction by 6.5% and LVEF by 5.6% after treatment. Moreover, Hatakenaka *et al.* [20] found a significant decrease in LV function (LVEF, LV-EDVI and LV-STVI) by using magnetic resonance (MR) evaluation. In the present study, we detected an early impairment of LV diastolic function in esophageal cancer patients treated with CCRT. Furthermore, there was a marginally significant decrease LVEF, which was a slightly different from previously reports [5, 20]. The reasons might be as follows: Firstly, we utilized the standard echocardiography which might be less sensitive than MUGA or MR. Secondly, the sample population was a relatively too small to get enough information. If more patients were enrolled, the results might be more convinced. Corresponding to the changes of LV diastolic function, our results also found a significant increase of LAVI after CCRT. Taken together, the present study supported an impairment of LV diastolic function from an early treatment stage in esophageal patients treated with CCRT, which needed careful monitoring of treated patients in long term observation in clinic.

In this study, we found that TDI seemed to have important advantages in the analysis of early LV diastolic function when compared with the standard echocardiography. Doppler echocardiography technology is a noninvasive and readily repeatable technique without utilizing ionizing radiation, which has ability to assess blood flow velocity directly and renders it more suitable to evaluate diastolic filling than other invasive techniques such as radionuclide angiography, left ventriculography [21]. Therefore, it became a unique technique for evaluating diastolic function in early time [22]. And the E/A ratio, determined on echocardiography, are a marker of the LV diastolic function of the heart in the period between contractions [23]. In our study, we found a significantly increased peak A mitral inflow velocity and a decreased peak E mitral inflow velocity with marginally statistical significance, which suggest an early changed function of left ventricle. However, the E/A ratio was unchanged. So it seemed to have a limitation to solely use E/A ratio for diagnosis of early impairment of LV diastolic dysfunction induced by CCRT. To further analyze the early impairment of LV diastolic function, we used TDI to measure parameters of LV diastolic function. TDI is a relatively new echocardiographic technique with the capability of measuring the movement of cardiac structures, which is considered to have great advantages in diagnosing LV diastolic dysfunction and provide important information earlier than standard echocardiography by overcoming the limitation of loading-dependence for the standard echocardiography [9-11, 24]. In this study, we detected a systolic wave (Sm), two diastolic waves (Em and Am), and calculated Em/Am and E/Em ratios. Our results showed decreased Sm, Em and Em/Am ratio and increased Am in esophageal patients after CCRT, suggesting an early impaired function of LV relaxation and enhanced compensatory contraction of right atrium. Since the LV filling index E/Em was considered as the best index to assess diastolic dysfunction and was recommended to use as a noninvasive diagnosis tool of diastolic function in heart disease [25], we also found that the LV filling index E/Em was increased after treatment, which also indicated an early impairment of LV diastolic function. Altogether, our results considered TDI as an essential tool to detect the early impairment of LV diastolic function because it seemed to be more sensitive than standard echocardiography.

When LV diastolic dysfunction happens, elevated LA pressure subsequently results in LA enlargement in order to provide adequate LV filling [26, 27]. And now, LAVI, the value of LA volume divided by body surface area, has been recommended by both the European Association of Echocardiography and the American Society of Echocardiography to measure LA size [13, 28]. And LAVI also correlated closely with E/Em and severity of LV diastolic dysfunction, indicating that the greater the LA volume, the higher filling pressures of left ventricle as indicated by E/Em, and the more serious the diastolic dysfunction of left ventricle [27, 29-31]. Similar to previous studies, our results showed an increased LAVI after CCRT and a positive correlation between LAVI and LV filling index E/Em.

In conclusion, CCRT for esophageal cancer could cause an early left heart toxicity as indicated by altered LAVI and diastolic function. Our results support the implementation of TDI technology for measuring the left function as compared with standard echocardiography. Further study may be needed to determine the long-term clinical significance of this early cardiac impairment and its relationship with late heart toxicity.

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Disclosure of conflict of interest

None.

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