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Dynamic changes in cardiac biomarkers in radiotherapy for oesophageal cancer and their correlations with cardiac radiation dosimetry

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ABSTRACT

Background and purpose: To investigate the dynamic changes in cardiac enzymes, high-sensitivity troponin T (hs-TnT), pro-brain natriuretic peptide (pro-BNP) and left ventricular ejection fraction (LVEF) during radiotherapy (RT) and 6 months after RT for oesophageal squamous cell carcinoma (ESCC) in the middle and lower locations and to analyse the correlations between these indicators and cardiac radiation dosimetry parameters.

Methods: For 35 patients with ESCC in the middle and lower locations receiving radical concurrent chemoradiotherapy (cCRT), intensity-modulated RT was performed at 1.8 Gy or 2.0 Gy per day, and the totle dose was 50.4 Gy or 60 Gy. Serum creatine kinase (CK), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), alpha-hydroxybutyrate dehydrogenase (α-HBDH), hs-TnT, pro-BNP and LVEF were measured before, during, and at the end of RT and 1, 3 and 6 months after RT, and correlations of these indicators with mean heart dose (MHD) and heart V_5-V_{50} were analysed.

Results: hs-TnT during, at the end and 6 months after RT for oesophageal cancer showed increasing trends, however, LVEF showed a downward trend. pro-BNP showed an increasing trend during RT and gradually returned to normal after RT. CK and CK-MB showed decreasing trends during RT and continued until one month after RT and then gradually returned to normal. Compared with the low-dose group (MHD $<$ 2000 cGy), the high-dose group (MHD $\geq$ 2000 cGy) had larger increases in hs-TnT and pro-BNP, a more significant decrease in LVEF, and a longer recovery time for these indicators. MHD and V_{35} were positively correlated with dynamic changes in hs-TnT.

Conclusions: Cardiac injury caused by cCRT for ESCC in the middle and lower locations led to increased hs-TnT and pro-BNP levels and a decrease in LVEF in the early stage of treatment, effects that were more pronounced in the high-dose group. MHD and V_{35} may be potential indicators to predict the degree of cardiac damage. hs-TnT and pro-BNP are sensitive indicators reflecting cardiac injury in RT for oesophageal cancer. Continuous dynamic monitoring of these markers can provide a reference for cardiac protection in clinical RT.

Introduction

Worldwide, oesophageal cancer is a high-incidence malignant tumour. In 2020, there were an estimated 641,100 new cases and 544,100 deaths worldwide, ranking seventh and sixth in morbidity and mortality, respectively [1,2]. Among regions, the incidence of oesophageal cancer in East Asia is highest, with more than half of cases occurring in China [1], and more than 90 % of confirmed cases are

Abbreviations: hs-TnT, high-sensitivity troponin T; pro-BNP, pro-brain natriuretic peptideand; LVEF, left ventricular ejection fraction; RT, radiotherapy; ESCC, oesophageal squamous cell carcinoma; cCRT, concurrent chemoradiotherapy; CK, creatine kinase; CK-MB, creatine kinase isoenzyme; LDH, lactate dehydrogenase; α-HBDH, alpha-hydroxybutyrate dehydrogenase; MHD, mean heart dose; RIHD, Radiation-induced heart disease; DVH, dose-volume histograms; 3DCT, three-dimensional computed tomography; 4DCT, four-dimensional computed tomography; GTV, gross tumour volume; CTV, clinical target volume; PTV, planning target volume (PTV); SD, standard deviation.

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squamous cell carcinoma [3]. The 5-year survival rate for patients with operable oesophageal cancer is only 15–25 % [4], but most patients already have locally advanced disease at the time of diagnosis. Concurrent chemoradiotherapy (cCRT) is the standard treatment for non-surgical locally advanced oesophageal squamous cell carcinoma (ESCC).

Radiation-induced heart disease (RIHD) is a complication of radiotherapy (RT) for oesophageal cancer. Cardiotoxicity caused by RT has been reported in Hodgkin lymphoma and breast cancer, mainly manifesting as pericarditis, cardiomyopathy, coronary artery disease, valve disease and conduction system disease, and cardiotoxicity is related to heart dose and irradiated heart volume [5–7]. Large-scale population-based cohort studies have found that RIHD is the leading cause of nontumor death and that the 5-year cardiovascular mortality of patients with a history of heart disease exceeds the 5-year tumour mortality [8,9]. The oesophagus runs through the mediastinum. The middle and lower segments of the oesophagus are close to the posterior border of the heart and are closely related to the anatomy of the heart. Most of the upper and lower boundaries of the clinical target volume (CTV) of oesophageal cancer contain 3–5 cm of normal oesophagus. Therefore, the heart dose and irradiated heart volume during RT for oesophageal cancer in the middle and lower locations are higher than those for breast cancer and Hodgkin's lymphoma, and recent studies have shown that the incidence of symptomatic cardiotoxicity after RT for oesophageal cancer is approximately 10 % and occurs mostly within 2 years after RT [10,11]. Some experts have noted that RIHD caused by thoracic RT is as important as traditional radiation-induced pulmonary fibrosis and that clinicians should be fully aware of and address this complication of RT. There is no effective treatment for RIHD; therefore, it is particularly important to detect cardiac damage in a timely manner and intervene as soon as possible.

Cardiac enzymes and cardiac troponin are the most used clinical indicators to detect acute myocardial injury. The European Society of Cardiology (ESC) guidelines indicate that serum troponin T can reflect minor cardiac damage with high sensitivity and specificity and that elevated troponin is the "minimum marker of myocardial damage" [12]. Brain natriuretic peptide (BNP) is an indicator of atrial strain and cardiac pump function and is significantly elevated in patients with heart failure. Several studies have confirmed that troponin and BNP are of great value in evaluating the effects of anthracyclines and trastuzumab on cardiotoxicity [13]. In this study, which included patients who received RT for oesophageal cancer, the dynamic changes in myocardial injury markers during RT and 1, 3, and 6 months after RT and their correlations with heart dose-volume parameters were investigated; the results provide a basis for early intervention for cardiac injury during RT for oesophageal cancer.

Methods and materials

Patient data

Thirty-five patients with ESCC who received radical cCRT in our hospital from February 2019 to May 2022 and had no history of immunotherapy were included in this study. All patients completed the simulation three-dimensional computed tomography (3DCT) and four-dimensional computed tomography (4DCT) scan. The mean age was 67.2 years, and there were 24 males and 11 females. There were 23 cases of ESCC in the middle location and 12 cases of ESCC in the lower location. This study has been approved by the Ethics committee of Shandong Cancer Hospital and Institute. All patients enrolled voluntarily and signed an informed consent form. The basic information of the patients is shown in Table 1.

Table 1
Basic information of the patients.

Characteristic		Number
Age, y, mean (SD)		67.2 (10.3)
Sex, n (%)		
	M	24 (68.6)
	F	11 (31.4)
Location, n, (%)		
	Middle	23 (65.7)
	Lower	12 (34.3)
Total dose (cGy, n, %)		
	5040	22 (62.9)
	6000	13 (37.1)
Heart dose volume parameters, mean (SD)		
	MHD (cGy)	1960.6 (515.1)
	V5	82.3 % (20.2 %)
	V10	69.0 % (21.2 %)
	V15	54.3 % (18.2 %)
	V20	41.3 % (14.2 %)
	V30	21.2 % (8.4 %)
	V35	15.0 % (6.4 %)
	V40	10.4 % (4.6 %)
	V45	7.4 % (3.7 %)
	V50	4.7 % (2.8 %)
Cardiac biomarkers, mean (SD) or median [quartile]		
	hs-TnT (pg/ml)	7.2 (3.2)
	pro-BNP (pg/ml)	75.3[48.3,126.7]
	CK (U/L)	71.1 (43.3)
	CK-MB (ng/ml)	2.3 (0.8)
	LDH (U/L)	186.2 (35.8)
	α-HBDH (U/L)	143.9 (29.0)
LVEF, mean (SD)		63.7 % (2.3 %)
Chronic disease, n (%)		
	CHD	3 (8.6)
	Hypertension	6 (17.1)
	Diabetes	4 (11.4)

Abbreviations: SD standard deviation, CHD, coronary heart disease.

Collection of serum biomarkers and determination of cardiac function

Fasting venous blood was drawn from all patients before RT, during RT, and at the end of RT and 1, 3, and 6 months after RT to measure cardiac enzymes (creatine kinase (CK), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), alpha-hydroxybutyrate dehydrogenase (α-HBDH)), high-sensitivity troponin T (hs-TnT), and pro-brain natriuretic peptide (pro-BNP), and echocardiography was performed at the same time points to assess cardiac function. Fasting blood was collected from all patients within 1 week before the initial radiotherapy. Fasting blood was collected again after 15–17 fractions. The third blood collection time was on the second day after the last radiotherapy. The follow-up blood collection time after radiotherapy was 1 month, 3 months and 6 months after radiotherapy. Routine ultrasound parameters were collected using GE Vivid E95 ultrasound diagnostic instrument in all patients. Patients without segmental motion abnormality of left ventricular wall, the LVEF was measured by M-mode echocardiography from the parasternal left ventricular long axis section; Patients with segmental motion abnormality of left ventricular wall, the LVEF was measured by left ventricular Simpson's biplane method. Synchronous connection echocardiography, the four-chamber and two-chamber apical incisal images were recorded by two-dimensional ultrasound technology, the end-diastolic and end-systolic endocardial contours of the left ventricle were recorded manually, and LVEF was calculated automatically by the machine built-in software.

Target volume delineation

The gross tumour volume (GTV) of oesophageal lesions was determined using imaging or endoscopy/endoscopic ultrasound (EUS). GTV_{nd} represents the gross tumour volume of metastatic lymph nodes. Using GTV, CTV_p was obtained by expanding 3 cm in the vertical directions (up and down) and 0.5 cm in the horizontal directions (left and right, anterior and posterior), and necessary revisions were performed based on the anatomical boundary. CTV_{nd} represents the lymphatic

drainage area where metastatic lymph nodes were located. Using CTV_p and CTV_{nd}, planning target volume (PTV) was determined by expanding 0.5 cm in all directions. According to the standard delineation of the heart by Feng et al. [14], the upper edge of the mediastinal window starts at the lower edge of the left pulmonary artery, the lower edge ends at the intersection of the heart and diaphragm, the periphery follows the outer edge of the pericardium, and the superior vena cava and inferior vena cava are excluded.

Treatment plan

All patients were treated with cCRT, and the target volume of RT was involved-field RT. Patients were treated with Intensity-Modulated RT to a total dose of 50.4 Gy in 28 daily fraction or 60 Gy in 30 daily fraction. Mean heart dose (MHD) and V_5-V_{50} were obtained from dose-volume histograms (DVHs). The chemotherapy (CT) regimen was fluorouracil combined with platinum or paclitaxel combined with platinum. Twenty-four patients received paclitaxel combined with platinum chemotherapy, eleven patients received fluorouracil combined with platinum chemotherapy. Twenty-three patients completed two cycles of synchronous chemotherapy, and twelve patients completed one cycle of synchronous chemotherapy.

Statistical analysis

SPSS 23.0 software was used for statistical analyses, and the paired *t*-test was used to assess the dynamic changes in cardiac enzymes, hs-TnT, pro-BNP and left ventricular ejection fraction (LVEF) during treatment. Pearson's correlation test was used to assess correlations between heart dose volume parameters and dynamic changes in cardiac biomarkers. $P < 0.05$ was considered statistically significant.

Results

Changes in hs-TnT, pro-BNP, cardiac enzymes and LVEF during treatment and 6 months after RT

Compared with that before RT, hs-TnT increased during RT, after RT and within 6 months after RT. hs-TnT levels before, during, and at the end of RT and 1, 3 and 6 months after RT were 7.2 pg/ml, 9.1 pg/ml, 9.1 pg/ml, 9.0 pg/ml, 9.4 pg/ml, and 8.1 pg/ml, respectively ($P < 0.05$, Table 2), but the increases were limited. The level of hs-TnT in most patients fluctuated within the normal range, and the level of hs-TnT in 14.3 % (5/35) of patients was above the upper limit of normal during treatment. LVEF showed a decreasing trend, with an average decrease of 2.4 %, and LVEF in all patients fluctuated within the normal range. pro-BNP showed an increasing trend during RT, was higher than the upper limit of normal in 13/35 (37.1 %) patients, and gradually returned to normal after RT. The change trends of hs-TnT, pro-BNP and LVEF are shown in Fig. 1. CK and CK-MB showed a decreasing trend during RT and 1 month after RT and then gradually returned to normal. There were no significant changes in LDH and α-HBDH at these time points.

hs-TnT, pro-BNP and LVEF trends based different heart doses

Compared with those in the low-dose group (MHD < 2000 cGy), the hs-TnT and pro-BNP levels increased more significantly and LVEF decreased more significantly in the high-dose group (MHD ≥ 2000 cGy), and the recovery time of these indicators was longer, The data were listed in Table 3. Fig. 2 showed the trend of the above indicators.

Correlation between dynamic changes in cardiac biomarkers and heart dose-volume parameters

MHD and V_{35} were positively correlated with dynamic changes in hs-TnT (Table 4), there is no obvious regularity between other cardiac parameters and the dynamic changes of hs-TnT. MHD and V_5-V_{50} were not correlated with the dynamic changes in cardiac enzymes, pro-BNP and LVEF ($P < 0.05$).

Table 2
Dynamic changes in serum biomarkers and LVEF, mean (SD) or median [quartile].

Parameters	Baseline	During	End	1st month	3rd month	6th month
hs-TnT	7.2 (3.2)	9.1 (3.0) *	9.1 (3.4) **	9.0 (3.1) †	9.4 (4.0) ‡	8.7 (3.6) §
pro-BNP	75.3 [48.3, 126.7]	90.3 [56.8, 147.5] *	79.7 [55, 150] **	76.5 [52.3, 133.3]	73.3 [50.0, 124.8]	76.6 [43.1, 127.0]
LVEF	63.7 (2.3)	62.4 (2.0) *	62.0 (2.3) **	62.5 (2.1) †	62.2 (3.3) ‡	61.9 (3.3) §
CK	71.1 (43.3)	42 (18.1) *	39.2 (17.2) **	39.2 (17.2) †	59.9 (41.9)	65.6 (32.1)
CK-MB	2.3 (0.8)	2.0 (0.7) *	2.0 (0.8) **	1.9 (0.8) †	2.3 (1.0)	2.3 (0.8)
LDH	186.2 (35.8)	183.4 (43.0)	183.2 (37.8)	200.6 (45.4)	190.3 (36.5)	189.3 (32.3)
α-HBDH	143.9 (29.0)	141.8 (31.2)	143.5 (24.6)	152.5 (28.4)	150.6 (33.2)	153.5 (34.9)

Baseline: before radiation; During: among 10th to 20th fraction; End: at the end of radiation; 1st month: 1 month after radiation; 3rd month: 3 months after radiation; 6th month: 6 months after radiation; hs-TnT, pro-BNP: ng/ml; LVEF: %; CK-MB: ng/ml; CK, LDH, α-HBDH: U/L.
*Differences in biomarkers between baseline and during ($P < 0.05$).
**Differences in biomarkers between baseline and end ($P < 0.05$).
†Differences in biomarkers between baseline and 1st month ($P < 0.05$).
‡Differences in biomarkers between baseline and 3rd month ($P < 0.05$).
§Differences in biomarkers between baseline and 6th month ($P < 0.05$).

Discussion

RIHD has attracted the attention of clinicians. RIHD is usually in a subclinical state in the early stage, with no obvious symptoms, and gradually progresses to irreversible damage. Identifying the critical point of early injury, adjusting the RT plan in a timely manner and intervening in advance are crucial for the risk assessment and management of RIHD. In this study, patients with ESCC in the middle and lower locations with obvious heart dose and irradiated heart volume were selected as the research objects, the most widely used clinical cardiac enzymes, hs-TnT and pro-BNP were selected as myocardial injury indicators, and LVEF was used to assess cardiac function, so as to explore the dynamic changes in these indicators during the course of treatment and within 6 months after RT and their correlations with heart dose volume parameters to provide a reference for cardiac protection in clinical RT.

The results of this study showed that hs-TnT increased and LVEF decreased during RT after RT, and 6 months after RT, indicating that RIHD occurred in the early stage of RT. Nellessen et al. [15] performed weekly monitoring of troponin I and BNP in patients with lung cancer and breast cancer treated with RT, and the results showed that troponin I and BNP tended to increase during the course of treatment but that increases in both absolute and mean values were minimal. Due to the anatomical positions of middle and lower oesophageal cancer, when patients are treated with radical RT, the heart dose and irradiated heart volume are no less than those for breast cancer and lymphoma [10,11]. Darby et al. [16] collected 2,168 patients treated with radiation therapy for breast cancer to assess the risk of ischemic heart disease, the overall average of the mean doses to the whole heart was 4.9 Gy. Macomber et al. [17] analyzed the effects of cardiac doses of neoadjuvant chemoradiation (50.4 Gy) on survival for esophageal cancer. Three-dimensional conformal radiotherapy (3D-CRT), intensity modulate-dradiotherapy (IMRT), and proton beam radiation therapy (PBT) were

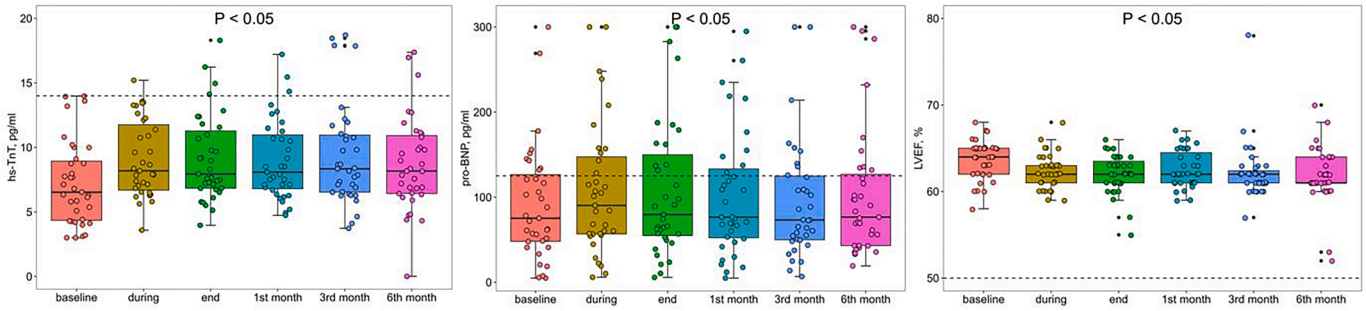

Fig. 1. hs-TnT and pro-BNP showed an upward trend while LVEF showed a downward trend during treatment course.

Table 3
Dynamic changes in serum biomarkers and LVEF between high-dose group and low-dose group, mean (SD) or median [quartile].

Parameters	MHD ≥ 2000 cGy (n = 17)						MHD < 2000 cGy (n = 18)					
	Baseline	During	end	1 st month	3 rd month	6 th month	Baseline	during	end	1 st month	3rd month	6th month
hs-TnT	6.3 (2.8)	9.1 (3.2) *	9.3 (4.1) **	9.3 (3.8) †	10.7 (4.8) ‡	9.6 (3.9) §	8.1 (3.4)	9.1 (2.8)*	9.0 (2.6)	8.7 (2.3)	8.1 (2.6)	7.9 (3.3)
pro-BNP	72 [40.9, 106.0]	90.3 [56.5, 117.7] *	89.2 [38.9, 136.9]	68.9 [29.8, 119.0]	85.9 [49.6, 109.0]	83.3 [43.3, 101.0]	89.2 [57.4, 149.3]	92.8 [57.2, 155.8]	76.9 [57.0, 157]	76.7 [62.6, 143.0]	73 [58.8, 133.4]	72.8 [46.2, 148.8]
LVEF	63.6 (2.1)	62.6 (2.1) *	61.7 (2.8) **	62.5 (2.4) †	61.9 (2.4) ‡	61.8 (4.2)	63.7 (2.5)	62.2 (1.9) *	62.3 (1.6)**	62.6 (1.9)	62.4 (4.0)	61.9 (2.4)
CK	75.4 (50.6)	46.4 (17.6)*	38.1 (17.8)**	47.6 (22.6) †	63.8 (52.5)	67.4 (30.3)	67.2 (36.2)	37.8 (18.1)*	40.2 (17.0) **	45.2 (18.8) †	56.1 (29.7)	63.9 (34.5)
CK-MB	2.2 (0.9)	2.0 (0.9)	1.9 (0.9)	2.0 (1.0)	2.3 (1.3)	2.2 (1.1)	2.4 (0.7)	1.9 (0.6)*	2.0 (0.6)**	1.9 (0.6) †	2.3 (0.6)	2.3 (0.5)
LDH	185.4 (44.4)	194.7 (55.1)	188.0 (42.8)	216.1 (57.7)	185.1 (31.9)	185.4 (29.0)	187.0 (26.4)	172.8 (24.3)*	178.7 (33.0)	186.0 (22.9)	195.2 (40.7)	193.1 (35.6)
α-HBDH	141.9 (33.4)	147.2 (40.2)	142.4 (25.1)	157.5 (35.6)	143.4 (27.0)	146.9 (26.8)	145.7 (24.9)	136.7 (19.3)	144.6 (24.8)	147.7 (19.1)	157.4 (37.7)	159.6 (40.9)

Baseline: before radiation; During: among 10th to 20th fraction; End: at the end of radiation; 1st month: 1 month after radiation; 3rd month: 3 months after radiation; 6th month: 6 months after radiation; hs-TnT, pro-BNP: ng/ml; LVEF: %; CK-MB: ng/ml; CK, LDH, α-HBDH: U/L.
*Differences in biomarkers between baseline and during ($P < 0.05$).
**Differences in biomarkers between baseline and end ($P < 0.05$).
†Differences in biomarkers between baseline and 1st month ($P < 0.05$).
‡Differences in biomarkers between baseline and 3rd month ($P < 0.05$).
§Differences in biomarkers between baseline and 6th month ($P < 0.05$).

used. The MHD of the three treatment modalities was 34.8 Gy, 25.8 Gy, 9.7 Gy, respectively. It can be seen from the above literature that the cardiac dose of radical radiotherapy for esophageal cancer is usually higher than that for breast cancer. Therefore, the degree of cardiac damage in RT for oesophageal cancer may be more serious than that for breast cancer and lymphoma. Early cardiac injury during RT for oesophageal cancer has also been confirmed by imaging. Zhang et al. [18] conducted a SPECT-gated myocardial perfusion imaging study on cardiac injury in patients with oesophageal cancer treated with radical CRT and found that when patients with oesophageal cancer received approximately 40 Gy of RT, 8/18 (44.4 %) of the patients had new myocardial perfusion defects compared with baseline. In addition, some patients also developed abnormal wall motion, end-systolic perfusion, and end-diastolic perfusion. This study and these literature reports confirm that RIHD can occur in the early stage of RT for oesophageal cancer. There are few literature reports on how heart damage evolves after RT. This study tracked and monitored cardiac enzymes, hs-TnT, pro-BNP and LVEF from the end of RT to 6 months after RT. hs-TnT showed an increasing trend and LVEF showed a decreasing trend from the end of RT to 6 months after RT, and pro-BNP gradually returned to normal after RT, suggesting that heart damage may persist for a period of time after RT. Burke et al. [19] used cardiac magnetic resonance (CMR) to study the cardiac structure and function of patients with oesophageal cancer who received neoadjuvant CRT (nCRT) and found that reversible myocardial ischaemia and/or fibrosis occurred 3 months after nCRT for oesophageal cancer, in turn affecting the compliance of cardiomyocytes and leading to systolic and diastolic dysfunction. Further studies have found that patients with myocardial ischaemia or fibrosis have significantly decreased LVEF. However, in the above study, Burke et al. found there were no significant changes in cardiac biomarkers when comparing pre-treatment and post treatment values amongst all patients. Only 11 patients were enrolled in the above study, and negative results due to the small number of cases cannot be ruled out. In our study, different from hs-TnT and pro-BNP, we found that myocardial enzymes did not change significantly during the course of treatment. This may be related to the different sensitivity of different parameters to heart damage. It is also incomplete to determine the severity of heart injury from biomarkers alone. The involvement of more imaging methods, such as cardiac MR and SPECT myocardial perfusion imaging, has greater significance in evaluating the heart injury caused by radiotherapy. Can elevated hs-TnT cause cardiac adverse events and even affect survival? Xu et al. [20] analyzed the dynamic changes of hs-TnT in non-small cell lung cancer during cCRT, found that elevation of hs-TnT during cCRT was radiation heart dose–dependent, and high hs-TnT levels during the course of cCRT were associated with cardiac adverse events (CAEs) and mortality. Therefore, continuous dynamic monitoring of myocardial injury markers and cardiac pump function after RT for oesophageal cancer is necessary and is of great significance for the early detection and management of subclinical cardiac injury and the identification of subgroups of patients in whom clinically significant

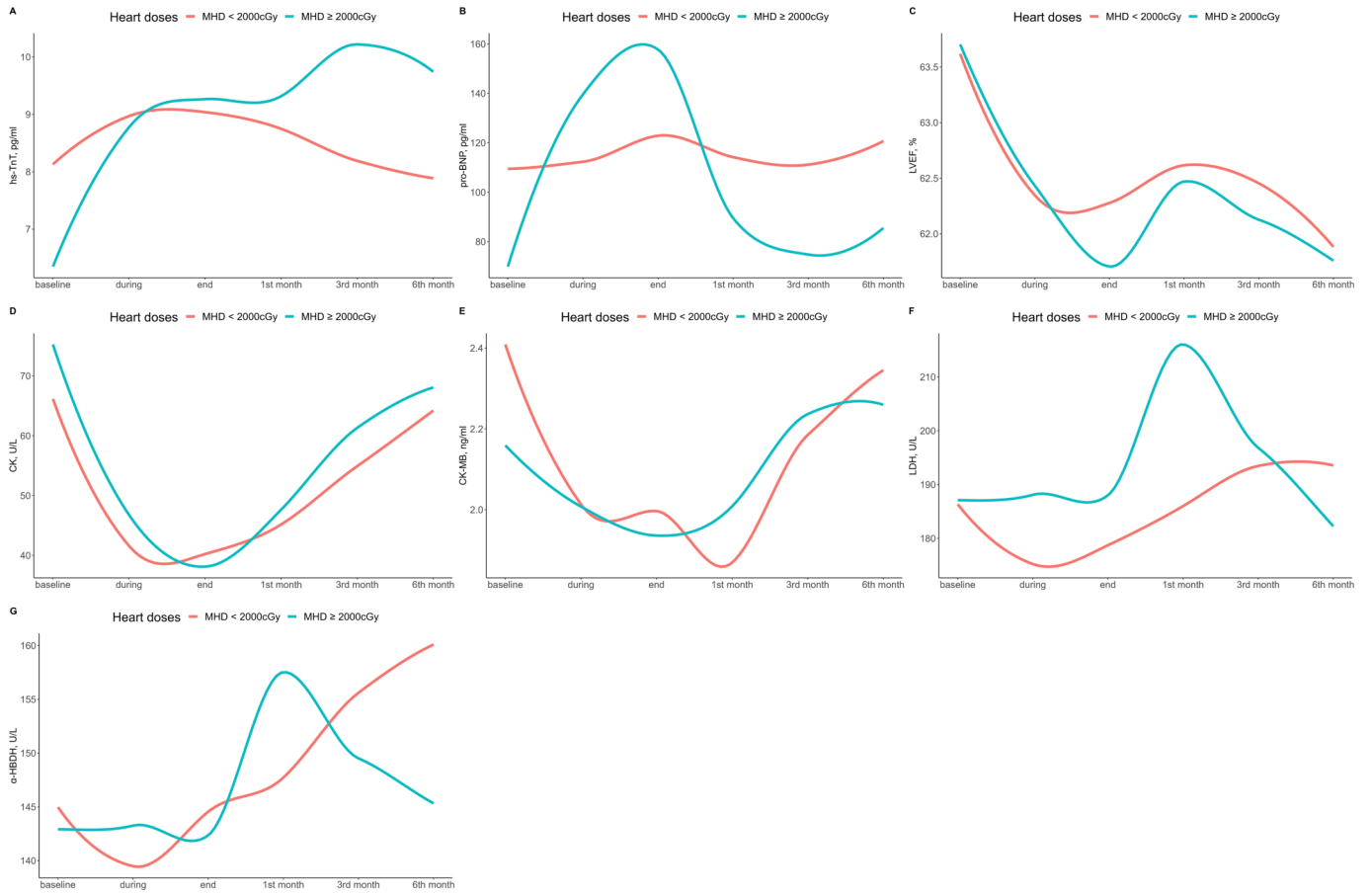

Fig. 2. Dynamic changes of cardiac biomarkers and LVEF.

Table 4
Correlations between heart dose volume parameters and dynamic changes in hs-TnT.

Parameters	During-Baseline		End -Baseline		1st month-Baseline		3rd month-Baseline		6th month-Baseline	
	r	P	r	P	r	P	r	P	r	P
MHD	0.336	0.049	0.342	0.042	0.352	0.038	0.404	0.016	0.519	0.001
V_5	0.160	0.358	0.236	0.172	0.226	0.191	0.346	0.042	0.472	0.004
V_{10}	0.208	0.229	0.215	0.215	0.281	0.102	0.425	0.011	0.491	0.003
V_{15}	0.310	0.070	0.247	0.152	0.343	0.044	0.465	0.005	0.498	0.002
V_{20}	0.269	0.029	0.249	0.149	0.385	0.022	0.485	0.006	0.512	0.002
V_{25}	0.407	0.015	0.271	0.115	0.391	0.020	0.407	0.015	0.518	0.001
V_{30}	0.360	0.034	0.248	0.151	0.347	0.041	0.331	0.052	0.466	0.005
V_{35}	0.350	0.039	0.339	0.046	0.349	0.040	0.482	0.003	0.451	0.001
V_{40}	0.424	0.011	0.259	0.134	0.305	0.075	0.326	0.056	0.450	0.007
V_{45}	0.400	0.017	0.204	0.240	0.292	0.089	0.310	0.070	0.446	0.007
V_{50}	0.383	0.023	0.209	0.227	0.263	0.126	0.225	0.140	0.435	0.009

Baseline: before radiation, During: among 10th to 20th fraction, End: at the end of radiation, 1st month: 1 month after radiation, 3rd month: 3 months after radiation, 6th month: 6 months after radiation, r: correlation coefficient,
Values of $P < 0.05$ were considered significant.

cardiotoxicity may occur in the future.

At present, it is generally believed that RIHD is related to heart dose and irradiated heart volume [21]. In this study, compared with those in patients with a low mean heart dose (MHD < 2000 cGy), increases in hs-TnT and pro-BNP were greater and the decrease in LVEF was more significant in the high-dose group (MHD ≥ 2000 cGy), and the recovery time of these indicators was longer, indicating that the higher the heart dose, the greater is the cardiac damage. Given that DVH parameters can effectively predict radiation pneumonitis, what is their ability to predict RIHD? This study further analysed the correlations between MHD,V_5-V_{50} and the dynamic changes in cardiac enzymes, hs-TnT, pro-BNP, and LVEF. The results showed that MHD and V_{35} were positively correlated with dynamic changes in hs-TnT and that there was no significant correlation between dynamic changes in other cardiac biomarkers and heart dose parameters, indicating that MHD and V_{35} may be potential indicators that predict the degree of cardiac injury. Similar to our study, the results from Xu et al. [20]. showed that the change (delta) in hs-TnT levels during cCRT correlated with MHD. MHD is an important indicator for evaluating RT plans. Several recent studies have confirmed that MHD is associated with independent cardiac events. With the increase in MHD, the incidence of cardiac events increases significantly [22,23], and for every 1 Gy increase in MHD, cardiac events increase by 16.5 % [24]. In addition, most heart dose volume parameters in this study were not correlated with the dynamic changes in cardiac biomarkers,

indicating that whole-heart dose parameters may not be good predictors of cardiac injury. The structure of the heart is complex, and the tolerated dose may not be similar for each part. For example, Burke et al. [19] found that the area of early cardiac injury was not the area with the highest radiation dose, and they also found that the basalor mid inferior and inferoseptal segments are potentially important substructures of the heart and are sensitive to radiation damage. In recent years, an increasing number of studies have shown that the whole-heart dose index is not a good predictor of cardiac injury [25], and therefore, the dosimetry parameters of specific cardiac substructures have gradually received more attention with regard to predicting future cardiac events and survival [26]. However, the specific limiting dose for cardiac substructures was not determined. Therefore, finding which part of the heart receives doses and specific limiting doses are focuses of research. Currently, there is a lack of data on the relationship between RIHD and heart dose volume.

This study has the following limitations. First, only echocardiography was used to evaluate changes in cardiac function, and other means, such as CMR and nuclear medicine, were not used to evaluate the location and degree of cardiac injury. Second, in this study, the collection time interval of myocardial injury markers was long; the optimal collection time interval and threshold of biomarkers need to be further explored. Third, patients enrolled in this study were treated with cCRT, and some chemotherapy regimens can damage the heart; therefore, the factors that cause cardiac damage cannot easily be distinguished, a challenge also experienced in clinical practice. Forth, the follow-up in this study was only 6 months after RT, and thus, the evolution of heart damage in later periods was not explored; therefore, longer dynamic monitoring is necessary.

Conclusions

In conclusion, continuous dynamic monitoring of cardiac injury (serum cardiac biomarkers and echocardiography) was performed in patients with oesophageal cancer who received cCRT. The results indicated that increased serum hs-TnT and pro-BNP levels and a decrease in LVEF occurred in the early stage of RT and were more pronounced in the high-dose group. MHD and V_{35} may be potential indicators for predicting the degree of cardiac damage. The relationship between RIHD and cardiac substructure dose volume requires further investigation. Serum hs-TnT and pro-BNP may be sensitive indicators of cardiac injury in response to RT for oesophageal cancer.

Ethics approval and consent to participate

This study has been approved by the Ethics committee of Shandong Cancer Hospital and Institute. All patients enrolled voluntarily and signed an informed consent form.

Consent for publication

All authors of this study were aware of the data and consented to publication.

CRediT authorship contribution statement

Jin-zhi Wang: Conceptualization, Writing – original draft. **Yue Wang:** Data curation, Formal analysis. **Qian Shao:** Methodology, Validation. **Jian-bin Li:** Conceptualization, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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