The effect of radiotherapy on cardiac function

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Background **Radiation-induced heart disease is a complication that may be encountered after radiotherapy (RT) of tumors in the vicinity of the heart. In this study, we aimed to evaluate the effect of RT on the heart, by comparing conventional and tissue Doppler echocardiography parameters obtained before and after RT.**

Methods **Forty patients who had undergone RT for either lung or left breast cancer were included in the study. ECG, conventional, and tissue Doppler echocardiography were performed before and 4–6 weeks after RT.**

Results **The mean value of the radiation dose applied to all regions of the heart was calculated as 13.1 ± 2.2 Gy (maximum 41.7 Gy). The value for the left ventricle was 10.2 ± 2.0 Gy (maximum 43.6 Gy). A decrease in early transmitral diastolic velocity (*E*), *E/A* ratio, EF, E_m, and E_m/A_m, and an increase in E-wave deceleration time, isovolumic relaxation time, isovolumic contraction time, ejection time, and QT_c were found after RT.**

Conclusion **We found detrimental effects of RT on systolic and diastolic cardiac functions and the electrical conduction system of the heart. Maximal prevention should be provided for the patients during RT.** ***Coron Artery Dis*** **23:146–154 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Radiotherapy (RT) involves the use of ionizing radiation such as X-rays, γ-rays, and electrons for the treatment of cancer [1,2]. In the early 1900s, RT was thought to be a useful modality to cure many cancers but serious damage of normal uninvolved neighborhood tissues was one of the major problems [3,4]. To spare normal tissues (such as skin or organs which radiation must pass through in order to treat the tumor), radiation beams are aimed from several angles of exposure to intersect at the tumor, providing a much larger absorbed dose there than in the surrounding, healthy tissue.

Heart and great vessels were reported to be resistant to radiation in the early years of RT; however, in later experimental works, cardiac damage was shown with high-dose radiation [5]. Cardiac complications may develop incidentally within days, months, and years after the treatment of thoracic neoplasms. Cardiac lesions during RT have been shown both clinically and pathologically and the term 'radiation-induced heart disease' was first used by the late 1960s [6]. This condition is usually observed during the RT of thoracic tumors adjacent to the heart such as lymphoma, thymoma, esophageal, lung, and breast cancers [7].

Tissue Doppler echocardiography [tissue Doppler imaging (TDI)] has been shown to be more advantageous than conventional Doppler in the noninvasive assessment of cardiac function [8]. Although there are many studies on the effects of chemotherapeutic agents on the heart using TDI, we could not find any study evaluating the effects of RT on the heart by this modality. The aim of our study is to evaluate the effects of RT on the heart by means of TDI.

Materials and methods

A total of 40 consecutive patients (30 men, mean age ± SD: 57 ± 1.4 years) who had been admitted to the Department of Radiation Oncology, Faculty of Medicine, University of Zonguldak Karaelmas, for RT of lung cancer or breast cancer between May 2008 and September 2009 were prospectively included in the study. Patients with congenital and/or acquired valvular diseases, hypertrophic cardiomyopathy, cardiac conduction defects, and arrhythmias, ECG QRS duration greater than 120 ms, were excluded from the study. Patients who had undergone cardiotoxic chemotherapy at any time were also excluded from the study. Adjuvant chemotherapy is given before RT to all patients.

Data of age, sex, and cardiac disease associated with significant risk factors for coronary artery disease were recorded. All patients underwent standard 12-lead ECG, echocardiography, Doppler echocardiography, and TDI before RT and the tests were repeated 4–6 weeks after RT.

The study protocol was approved by the university ethics committee of our institution and written consent was obtained from all participants.

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Radiotherapy

All patients underwent a thoracic computed tomography scan for three-dimensional (3-D) conformal RT planning (Somatom Spirit; Siemens Medical Solutions, Erlangen, Germany). Breast/chest wall RT was performed with tangential photon beams. If indicated, supraclavicular and level 3 axillary lymph nodes were also irradiated with an anterior photon beam. None of the patients had internal mammary irradiation. Lung RT was performed according to the tumor localization, either with the anterior–posterior or the posterior–anterior field alone, or with a combination of oblique photon beams. 3-D dose calculation was performed using an isodose planning system (V2.0; Dosisoft, Cachan, France). RT was applied using a 6 MV linear accelerator (Clinac; Varian, USA) at a dose of 50–66 Gy in patients with breast cancer and 60–64 Gy in patients with lung cancer. The 100% isodose line was defined at the isocenter of the treatment plan, and the total dose was prescribed at this point. Treatment planning required the 95% isodose line to encompass the whole planning target volume. The heart was delineated as left ventricles (LVs) and the whole heart. The mean and maximal doses to these volumes were all calculated.

ECG

All standard 12-lead ECGs were obtained simultaneously using an ECG recorder (Hewlett Packard; Pagewriter, Palo Alto, California, USA) set at a 50 mm/s paper speed and 2 mV/cm standardization. All recordings were performed in the same quiet room during spontaneous breathing after 10 min of adjustment in the supine position. The ECGs were numbered and presented to the analyzing investigators without name and date information. All measurements (heart rates, R–R intervals, QT intervals QRS widths) of ECGs were made blindly by two medically qualified observers (S.M.D. and H.M.B.). The QT_d was defined as the difference between the maximum and the minimum QT values, and the mean value of two consecutive cycles was calculated. Bazett's formula was used to obtain HR-corrected (c) values of the QT intervals and dispersions, as follows [9]: ($QT_c = QT/\sqrt{R–R}$); to estimate the intraobserver variability, two photocopies of a random sample of 10 ECGs were taken and the QT interval was measured again. The relative difference (mean absolute difference in the percentage of the mean measured value) was 1.4% for the QT interval and 4.0% for the QT_d.

Echocardiography

The patients were subjected to a transthoracic echocardiographic evaluation. In this study, a Vingmed Vivid FiVe Doppler echocardiographic (GE Vingmed Ultrasound, Horten, Norway) unit with a 2.5 MHz flat plane arrow probe with a second harmonic function was used. Examination was performed by one experienced investigator with the participant lying on the left side with the head of the bed elevated by 30°. The entire examination was recorded on a videotape, including three cardiac cycles of LV 2-D and M-mode, at least. Two 2-D and M-mode sequences of three cardiac cycles were at first retrieved from the videotape on the screen, and then frozen and measured by two readers using electronic calipers, in accordance with the recommendations of the American Society of Echocardiography [10]. Left atrial diameter, LV end-systolic, and end-diastolic diameters were measured by M-mode echocardiography. Isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), ejection time (ET), and mitral valve diastolic waves [E waves, A waves, *E*/*A* ratio, E-wave deceleration time (EDT)] were also calculated by Doppler studies. Myocardial performance index (MPI) was calculated using the formula (IVCT + IVRT)/ET. Color flow Doppler (GE Vingmed Ultrasound) was used to detect the presence of valvular regurgitation. LV ejection fraction (EF) was calculated using modified Simpson's method.

TDI was performed using apical views for the long-axis motion of the ventricles. 2-D echocardiography with TDI color imaging was performed with a 2.5 MHz phase-array transducer. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation, and sector size and depth were optimized for the highest possible frame rate. At least three consecutive beats were stored, and the images were digitized and computer analyzed offline (EchoPac 6.3; GE Vingmed Ultrasound). Myocardial pulse-Doppler velocity profile signals were reconstituted offline from the TDI color images that provided regional myocardial velocity curves. The peak myocardial sustained systolic velocity (S_m), early diastolic (E_m), and late diastolic (A_m) were measured. Mitral valve early diastolic waves (E) and E/E_m were calculated for each region and segment.

Statistical analysis

Results were expressed as mean ± SD. Preradiation and postradiation values were obtained. The relationships between radiation doses were analyzed using Pearson's correlation analysis. Differences were considered significant when $P < 0.05$. All statistical procedures were performed by means of a personal computer using software (SPSS, Release 16.0; SPSS Inc., Chicago, Illinois, USA).

Reproducibility

Relatively low intraobserver and interobserver variability values (8–10%) for TDI measurements have been reported previously from our laboratory [11].

Results

The clinical features of the 40 patients enrolled in the study are listed in Table 1.

Table 1 Clinical characteristics

	n (%)
Hypertension	11 (27.5)
Diabetes mellitus	9 (22.5)
Hyperlipidemia	9 (22.5)

The average radiation exposure of both the LV and the whole heart was calculated for each patient. The mean value of the radiation dose applied to all the regions of the heart was calculated to be 13.1 ± 2.2 Gy (maximum 41.7 Gy). The corresponding value for LV was 10.2 ± 2.0 Gy (maximum 43.6 Gy).

Comparisons of echocardiographic measurements before and 4–6 weeks after RT are shown in Table 2. Although early diastolic transmitral velocity (*E*) was found to be reduced ($P = 0.008$), late transmitral velocity (*A*) remained unchanged after RT. The *E*/*A* ratio was found to be decreased, whereas EDT, IVRT, IVCT, and ET significantly increased after RT ($P < 0.05$). EF also decreased after RT ($P < 0.05$). The MPI values were found to be similar ($P > 0.05$) (Fig. 1).

Correlations between the LV radiation exposure dose and EF reduction ($P = 0.001$, $r = -0.524$), prolonged ET ($P = 0.001$, $r = 0.525$), and increased MPI ($P = 0.021$, $r = 0.394$) are listed in Figs 2–4.

The tissue Doppler parameters before and after RT are presented in Table 3. According to the TDI measurements obtained from the basal septum, basal anulus, lateral septum, and lateral anulus, E_m and E_m/A_m were found to be significantly reduced but A_m, S_m, and E/E_m were found to be similar after RT (Fig. 5).

Electrocardiographic parameters before and after RT such as QRS width and QT_c are presented in Table 4. After RT, QT_c increased ($P = 0.002$). QRS values also increased, although not statistically significant ($P = 0.063$).

Discussion

We found that RT not only worsens systolic and diastolic cardiac function but also prolongs the QT_c interval in patients who undergo mediastinal irradiation.

Radiation leads to structural and functional cardiac disorders. The main structural defects of the heart induced by radiation are pericarditis (pericardial effusion, constrictive pericarditis, pericardial fibrosis), endocardial fibrosis, myocardial fibrosis, coronary artery disease, damage to the large vessels, and the conduction system [12–14].

Heidenreich *et al.* investigated the effects of radiation in patients with Hodgkin's disease. After mediastinal irradiation of at least 35 Gy, a high prevalence of diastolic dysfunction was found [15]. Although they investigated the effects of mediastinal irradiation, they did not calculate the dose of radiation exposed directly to the heart. Our findings are compatible with the aforementioned study, but our work also includes the exact radiation dose to the heart. In addition, we found systolic dysfunction besides the diastolic dysfunction after RT.

Table 2 Comparison of the echocardiographic parameters before and after radiotherapy

	Before RT	After RT	*P*
E (m/s)	0.69 ± 0.02	0.64 ± 0.02	0.008
A (m/s)	0.86 ± 0.03	0.89 ± 0.02	0.120
E/*A*	0.82 ± 0.03	0.73 ± 0.02	0.001
EDT (ms)	247.6 ± 6.2	278.6 ± 9.2	0.001
IVRT (ms)	99.8 ± 2.4	112.1 ± 3.0	0,001
IVCT (ms)	64.5 ± 1.8	71.0 ± 1.9	0.001
ET (ms)	244.2 ± 4.6	265.2 ± 4.9	0.001
MPI	0.68 ± 0.02	0.70 ± 0.02	0.266
EF (%)	59.85 ± 6.1	57.88 ± 6.66	0.001

A, transmitral late diastolic velocity; *E*, transmitral early diastolic velocity; EDT, E-wave deceleration time; EF, ejection fraction; ET, ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; MPI, myocardial performance index; RT, radiotherapy.

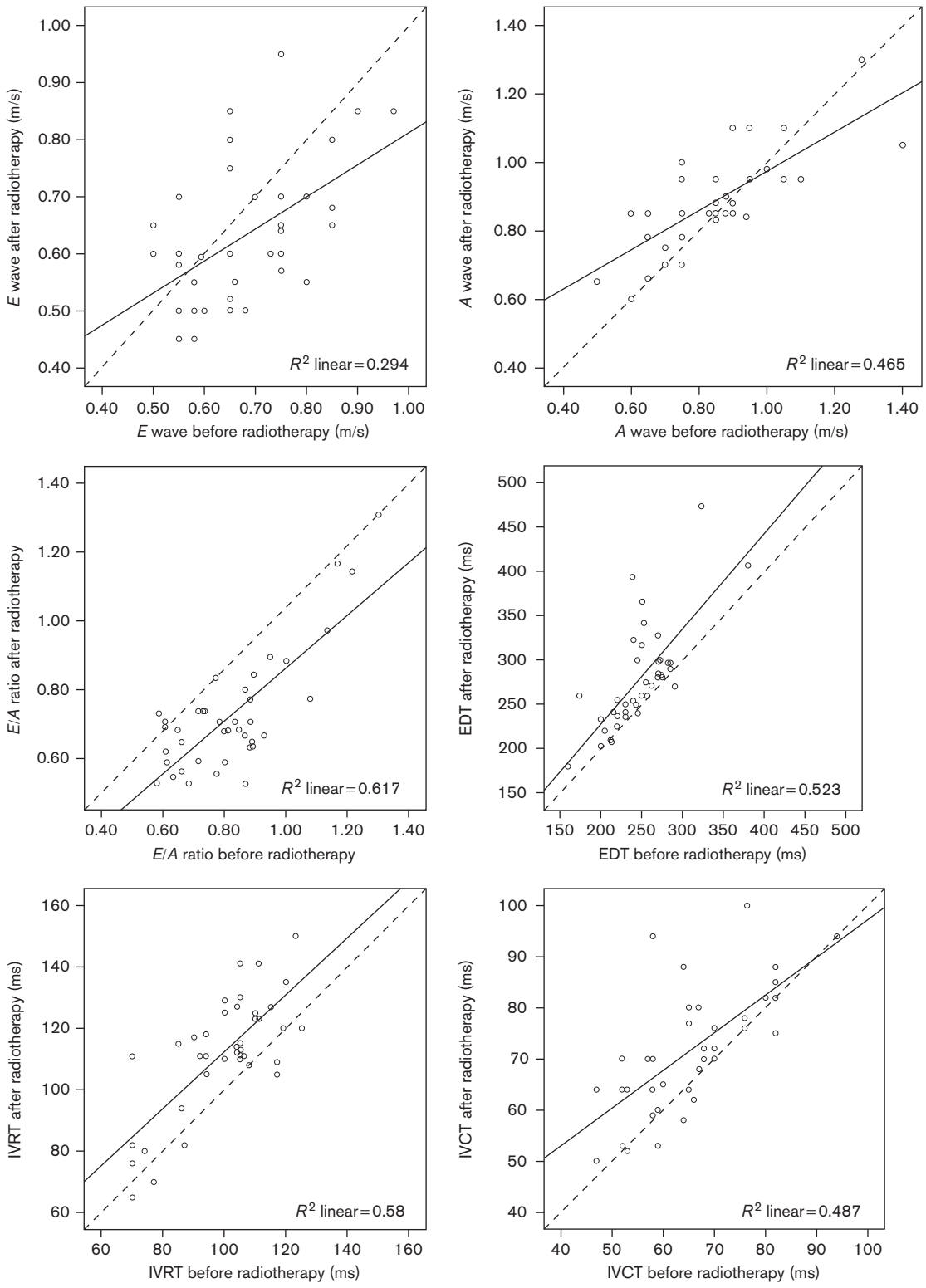
Radelescu found a decrease in E_{max} and an increase in A_{max} after RT in a population with cancer of the left breast, using conventional echocardiography. In his study, radiation was given after surgery and adjuvant chemotherapy [16]. In our paper, we used TDI in addition to conventional echocardiography. Also, the dose of radiation to the heart is not clear in the aforementioned study. We similarly found that E_{max} decreased. In addition, the *E*/*A* ratio was found to be decreased. Alterations in left ventricular diastolic function may reduce the height of the E-wave and increase the height of the A-wave. This type of abnormality is usually accompanied by prolongation of the IVRT and prolongation of the EDT. Finally, the *E* to *A* ratio across the mitral valve reverses, indicating impaired relaxation [17–19]. Our study found prolongation of the IVRT, prolongation of the EDT, reduction of the E-wave, and finally alteration in the *E* to *A* ratio, in agreement with other studies [15–18]. We found no correlation between the dose of radiation exposure and the degree of diastolic dysfunction. This may be attributed to either the limited number of the cases or the limited follow-up period.

In a recently published study, Erven *et al.* [19] found a dose-related regional decrease in myocardial function after RT in patients with breast cancer by means of strain rate echocardiography. Our findings are consistent with their article. Unlike their article, we found that EF calculated using modified Simpson's method had decreased. We also evaluated electrocardiographic changes such as QT_c after RT.

Left ventricular performance after RT by means of radionuclide methods in patients with Hodgkin's disease has been investigated in another study. Left ventricular EF was found to be decreased in that population [20]. We did not evaluate EF either by an invasive method or by a nuclear method. Our findings with echocardiography as a

noninvasive method are consistent with these. Echocardiography is widely used for the evaluation of EF as it is readily available and relatively less expensive than other techniques. For this reason, echocardiography can be used as 'the method of choice' to evaluate EF after RT during the follow-up period.

Fig. 1



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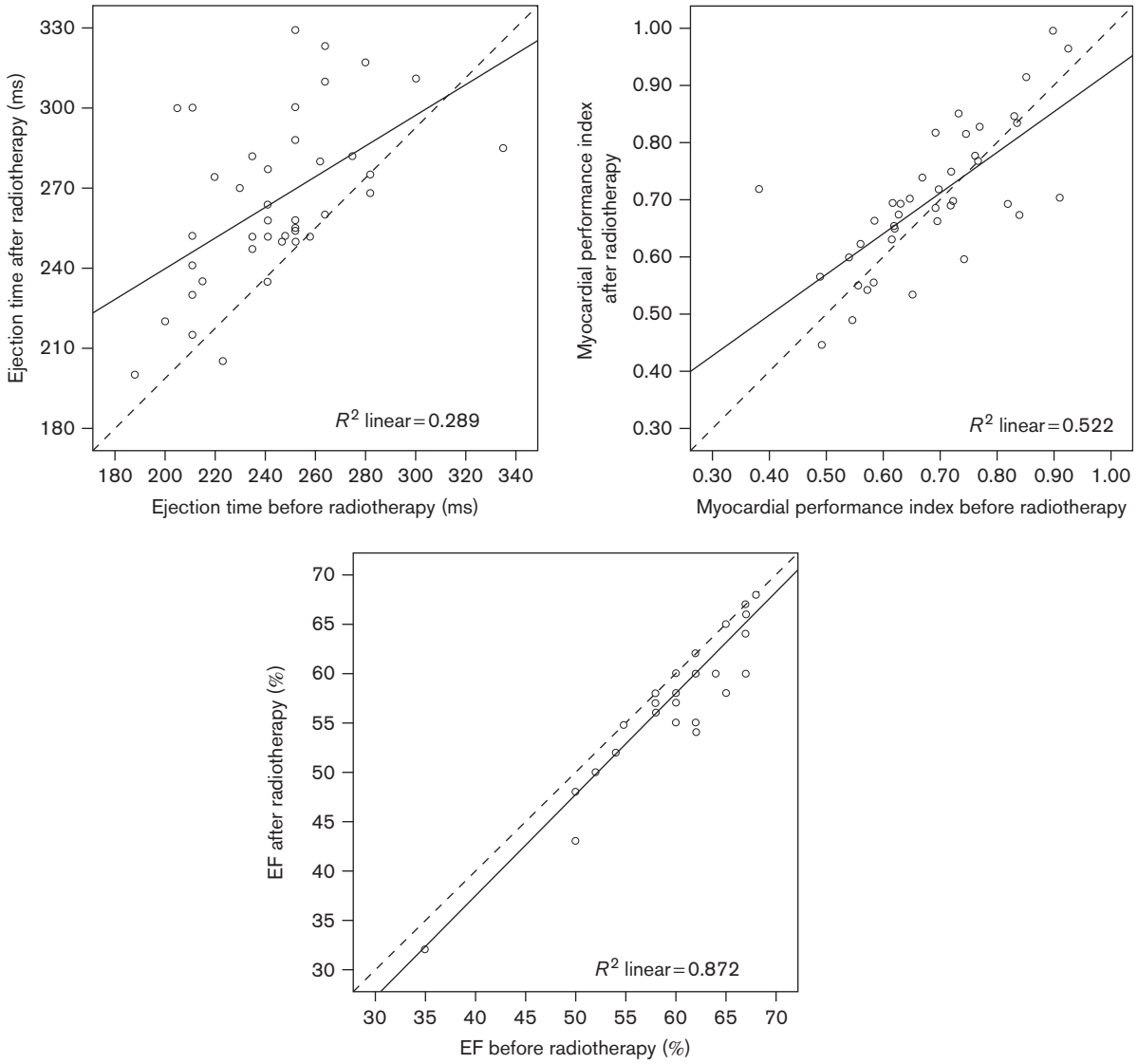


Relationship between the echocardiographic parameters before and after radiotherapy. A, transmitral late diastolic velocity; E, transmitral early diastolic velocity; EDT, E-wave deceleration time; EF, ejection fraction; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time.

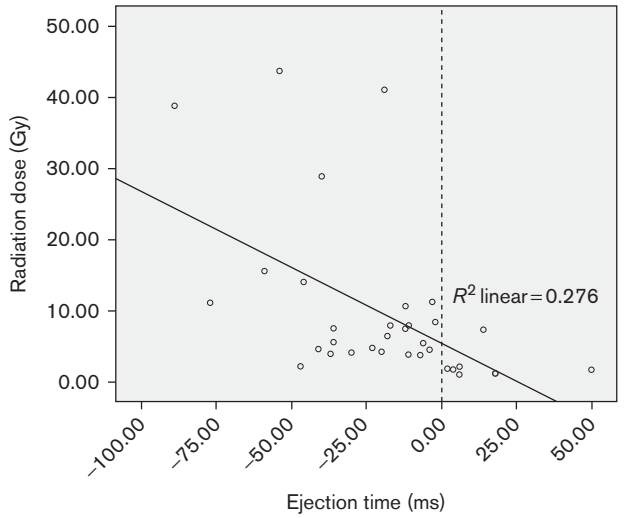
Gomez *et al.* found lower EF values after RT compared with normal individuals. Subclinical signs of cardiomyopathy were shown in more than one-half of these RT patients. They concluded that cardiac damage may be higher than expected [21]. Unlike our study, they did not compare the EF before and after irradiation of the mediastinum. In our study, left ventricular EF was found to be decreased after RT. In addition, we found a positive correlation between radiation dose and cardiac damage. IVCT, another indicator of systolic dysfunction, was found to be elongated.

Lagrange *et al.* [22] found reversible alterations in EF after 2 months in patients who received mediastinal radiation. We measured all echocardiographic parameters before and 4–6 weeks after mediastinal irradiation. Alterations in cardiac functions may be acute or temporary. Acute cardiac damage may also progress to late sequelae such as hypertrophic, restrictive, or dilated cardiomyopathy. Therefore, long-term follow-up is mandatory.

Another finding of our study is the increased ET after RT. A positive correlation was found between ET and radiation exposure of the heart. A negative correlation between ET and global ventricular function is well known [23,24], which may be because of direct myocyte damage or ischemia due to coronary artery fibrosis.

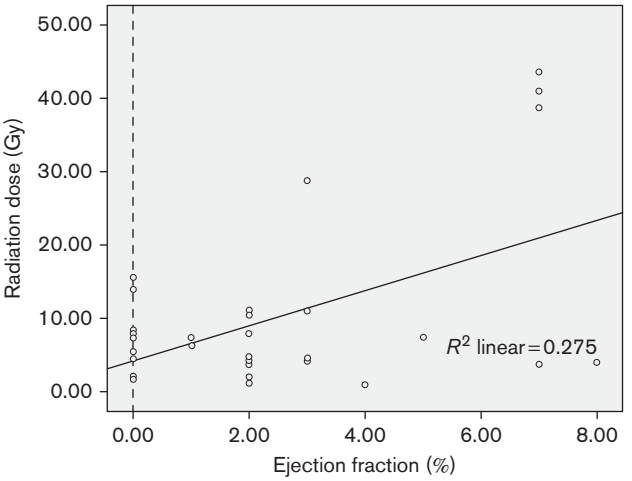
The MPI, or the Tei index, a useful index in the assessment of global myocardial performance [23,24], was

Fig. 2



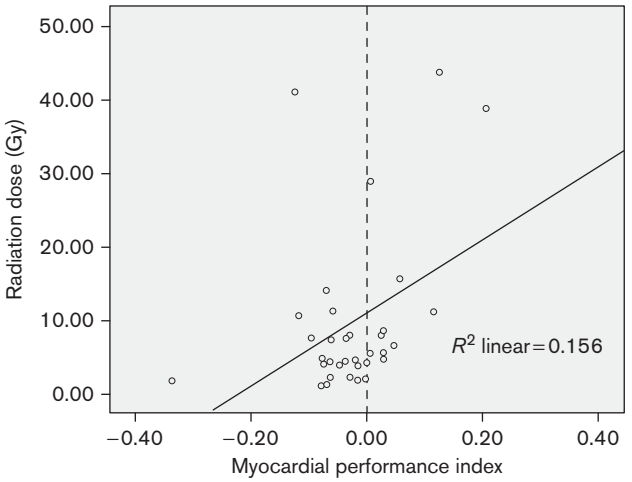
Relationship between ejection time and radiation dose of the left ventricle.

Fig. 3



Relationship between ejection fraction and radiation dose of the whole heart.

Fig. 4



Relationship between the myocardial performance index and radiation dose of the left ventricle.

Table 3 Comparison of the tissue Doppler echocardiographic parameters before and after radiotherapy

Parameters	Before RT	After RT	*P*
Basal septum			
E_m (cm/s)	5.71 ± 0.2	5.08 ± 0.2	0.001
A_m (cm/s)	7.91 ± 0.3	8.15 ± 0.3	0.155
S (cm/s)	5.95 ± 0.2	5.98 ± 0.2	0.857
E_m/A_m	0.77 ± 0.3	0.66 ± 0.3	0.001
Septal annulus			
E_m (cm/s)	6.58 ± 0.2	5.83 ± 0.2	0.001
A_m (cm/s)	8.61 ± 0.3	8.85 ± 0.3	0.177
S (cm/s)	6.58 ± 0.2	6.49 ± 0.2	0.606
E_m/A_m	0.79 ± 0.03	0.69 ± 0.03	0.001
Lateral basal			
E_m (cm/s)	6.04 ± 0.3	5.50 ± 0.3	0.001
A_m (cm/s)	7.65 ± 0.3	8.22 ± 0.41	0.074
S (cm/s)	5.83 ± 0.3	5.89 ± 0.37	0.639
E_m/A_m	0.86 ± 0.06	0.74 ± 0.06	0.004
Lateral annulus			
E_m (cm/s)	6.67 ± 0.3	6.19 ± 0.3	0.008
A_m (cm/s)	8.55 ± 0.3	9.02 ± 0.4	0.039
S (cm/s)	7.03 ± 0.3	7.01 ± 0.3	0.912
E_m/A_m	0.81 ± 0.04	0.72 ± 0.05	0.009

A_m, myocardial *A* velocity; E_m, myocardial *E* velocity; RT, radiotherapy; S, mitral peak systolic velocity.

found to be increased slightly but not significantly in the present study. A direct proportion between MPI and radiation dose was also found.

We also found electrocardiographic changes after mediastinal irradiation. Although there were no significant changes on ST segments and T waves, QT_c values were found to be increased. We assessed the ECGs before and 4–6 weeks after RT. Similar ST and T-wave changes could be seen after long-term follow-up. Strender *et al.* found T-wave abnormalities after 6 months. Ten years later, not only were T-waves seen to be normalized but ST segment depression and ectopic beats had disappeared as well [25].

Larsen *et al.* studied patients who underwent mediastinal RT 5 years later. In three of 24 patients who underwent RT, QT_c values were higher than 0.44 s. Supraventricular premature complexes, supraventricular tachycardia, and ventricular tachycardia were seen frequently in the study group [26]. In our study, long-term rhythm disturbances were not assessed. To evaluate cardiac arrhythmias in the future, Holter rhythm monitoring can also be performed.

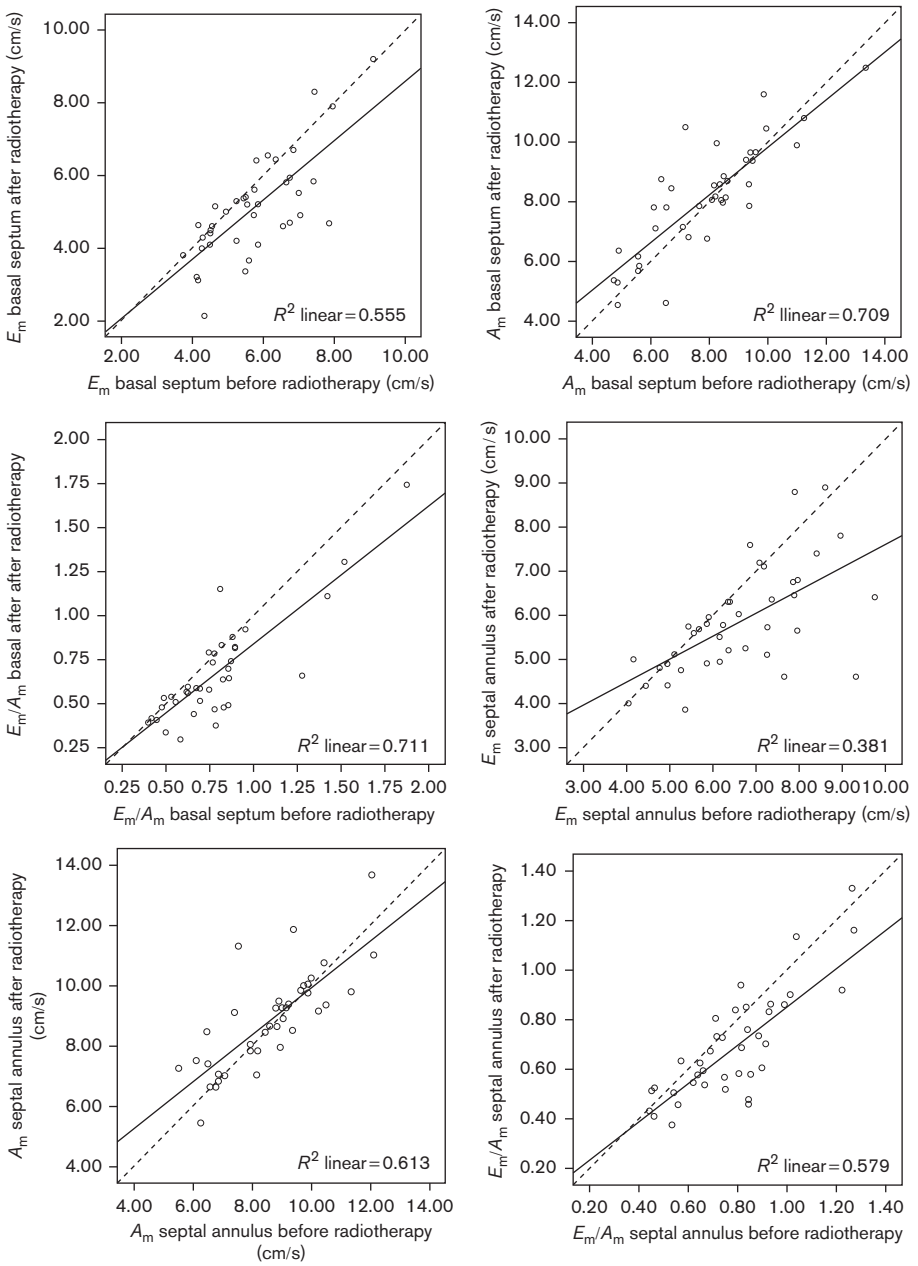
Radiation-induced valvular lesions have been reported earlier. Although fibrotic leaflets with or without calcifi-

cation are rare but possible complications [7], we did not observe any of these. This may be attributed to either the short-term follow-up or the small number of patients.

Therapeutic exposure of radiation can lead to serious morbidity and mortality. Radiation-induced heart diseases have a wide range of severities. First, there is microvascular tissue damage. Patients may remain asymptomatic for years. Subclinical diastolic dysfunction can progress insidiously. As the long-term effects of radiation on the heart are not clear, it is mandatory to protect the heart from radiation [27].

According to our data, mediastinal irradiation may lead to deterioration of both systolic and diastolic functions of the heart. These effects are shown with both conventional and TDI echocardiography. Short-term ECG changes may lead to long-term rhythm disturbances. These side effects can be progressive. For a close follow-up,

Fig. 5



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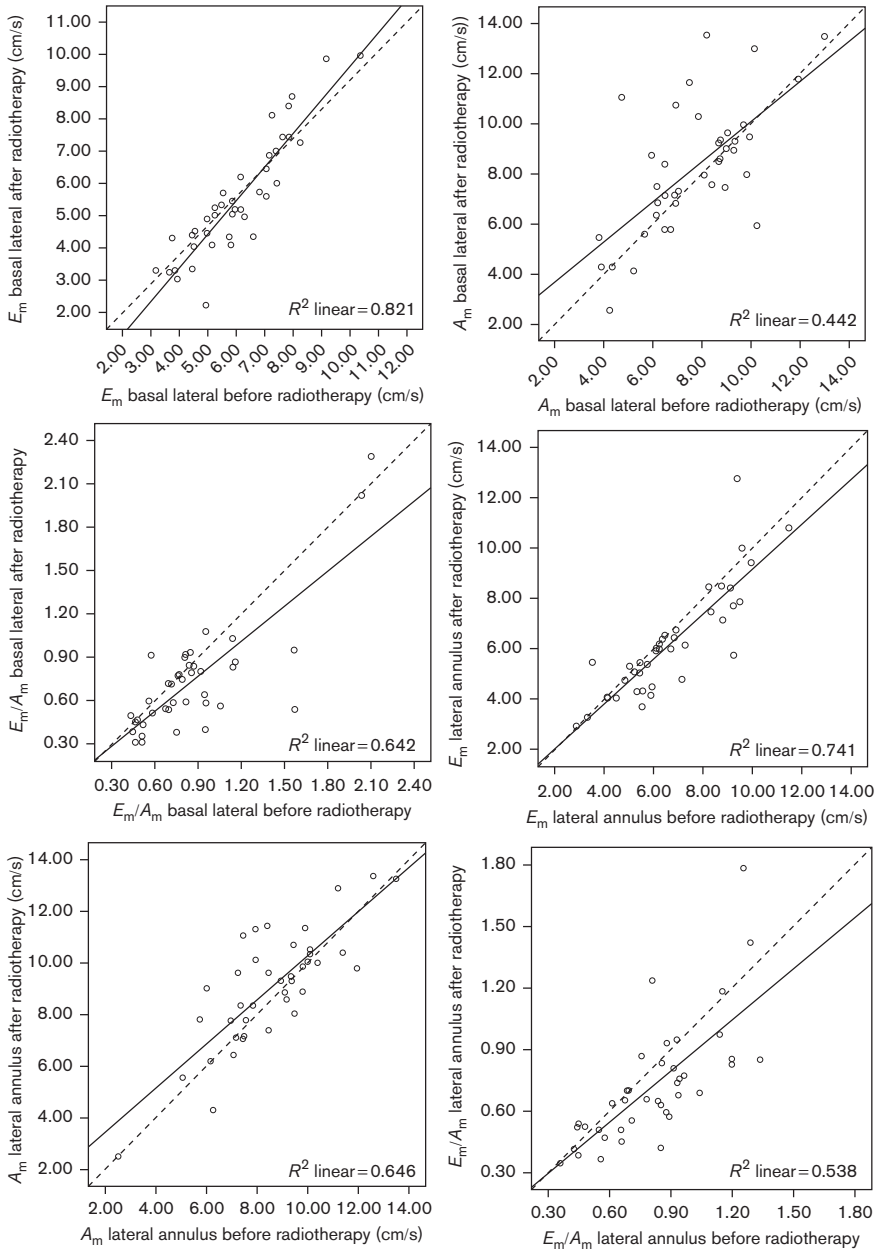

Relationship between the tissue Doppler echocardiographic parameters before and after radiotherapy. A_m, myocardial A velocity; E_m, myocardial E velocity

ECG and echocardiograpy may be used to monitor the effects of RT to the mediastium. Echocardiography is a noninvasive, relatively cheap, reliable, well-tolerable method. Ventricular functions, valve lesions, pericarditis, myocarditis, and regional wall motion abnormalities can be easily evaluated by means of echocardiography. For this reason, echocardiography can be considered the 'method of choice' for the evaluation of cardiac complications after RT.

Some limitations exist in our study. First, the number of study participants is not large. Second, the exact cause of cardiac dysfunction after irradiation is not clear. Our study describes changes in myocardial function only. Histology-based studies are needed to explain a pathophysiological mechanism. Previous studies demonstrated that radiation causes an initial injury to the endothelial

Table 4 Comparison of the QRS versus QT_c values before and after radiotherapy

	Before RT	After RT	*P*
QTc (ms)	412.0 ± 3.9	419.1 ± 4.0	0.002
QRS (ms)	88.0 ± 2.4	89.7 ± 2.4	0.063

RT, radiotherapy.

cells of myocardial capillaries, resulting in microvascular thrombosis, ischemia, and ultimately fibrosis in an animal model [6]. The possible explanation might be damage to the endothelial cells of myocardial capillaries, leading to inflammation, edema, and finally loss of endothelial cells for RT-induced cardiac injury. This mechanism could impair the function of the myocardial fibers after RT, possibly explaining the changes observed in TDI parameters. Third, as the ECG and echocardiography were performed 4–6 weeks after RT, the long-term effects of radiation on the heart were not investigated in our study. Large-scale studies and long-term follow-up are needed to clarify the exact effects of RT on the heart. Any cardiac problem can be seen earlier by serial ECG and echocardiography. Although the long-term cardiac side effects of radiation are unclear, it may be responsible for future cardiac problems. For this reason, maximal heart protection is strictly recommended.

Acknowledgements

Conflicts of interest

There are no conflict of interest.

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