

CAN TP-E INTERVAL BE AN EARLY INDICATOR OF RADIOTHERAPY-INDUCED CARDIAC DAMAGE?

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ABSTRACT

Introduction: This study aimed to evaluate the effects of radiotherapy (RT) on electrocardiographic parameters, including QT, corrected QT (QTc), Tp-e interval, and Tp-e/QT and Tp-e/QTc ratios, in patients with breast and lung cancer.

Methods: A total of 27 patients (15 with lung cancer and 12 with breast cancer) were included. The decision for RT was made by a multidisciplinary oncology board. Standard 12-lead electrocardiography (ECG) and transthoracic echocardiography were performed before and after RT. Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were calculated. The mean myocardial radiation dose ranged between 5.0 and 6.5 Gy. Cardiac radiation exposure was similar between groups.

Results: There were no significant changes in blood pressure, heart rate, or left ventricular ejection fraction after RT. However, Tp-e interval and Tp-e/QT ratio were significantly prolonged following RT in both groups. In patients with lung cancer, the Tp-e interval increased from 72.94±7.32 ms to 80.20±5.87 ms. In patients with breast cancer, it increased from 65.41±4.02 ms to 73.00±2.64 ms.

Conclusion: Radiotherapy may lead to early alterations in ventricular repolarization parameters. Tp-e interval and related indices may serve as early markers of radiotherapy-induced cardiac damage. Routine ECG monitoring may be beneficial in these patients.

Keywords: Radiotherapy, Tp-e interval, Arrhythmia

INTRODUCTION

Radiation-induced fibrosis is a well-recognized pathological process that can lead to a wide spectrum of cardiovascular complications (1,2). Depending on the structures involved, patients may develop pericarditis, myocardial dysfunction, heart failure, valvular abnormalities, coronary artery disease, and various rhythm disturbances (1–3). These radiation-associated cardiovascular conditions may significantly impair quality of life and are associated with increased morbidity, mortality, and risk of sudden cardiac death (2,4).

In recent years, increasing attention has been directed toward the early detection of subclinical cardiac damage before the onset of overt clinical manifestations (5). However, conventional imaging modalities and routine clinical assessments may not be sufficiently sensitive to detect early electrophysiological alterations induced by radiotherapy (6). Therefore, there is a growing need for simple, non-invasive, and reproducible markers that can identify patients at risk in the early stages (5,6).

Ventricular arrhythmias represent one of the most serious consequences of radiation-induced cardiac injury (4,7). The T wave peak-to-end (Tp-e) interval has emerged as a novel electrocardiographic parameter reflecting transmural dispersion of ventricular repolarization, which is closely associated with

ventricular arrhythmogenesis (8,9). Prolongation of the Tp-e interval has been linked to an increased risk of malignant ventricular arrhythmias and sudden cardiac death (9,10). In addition, Tp-e/QT and Tp-e corrected QT (Tp-e/QTc) ratios have been proposed as more stable and reliable indices of ventricular repolarization heterogeneity (8,11).

In this study, we aimed to evaluate ventricular repolarization by assessing Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios in individuals undergoing radiotherapy, and to investigate whether these parameters may serve as early indicators of radiation-induced cardiac damage.

METHODS

This study was designed as a single-center prospective observational cohort study with retrospective analysis. A total of 27 patients diagnosed with breast cancer (n=12) and lung cancer (n=15) who were scheduled to receive radiotherapy (RT) were included. The decision for RT was made by a multidisciplinary oncology board.

Standard 12-lead electrocardiography (ECG) was performed in all patients before and after receiving 6 weeks RT. All ECG recordings were obtained at rest in the supine position using a recorder (Schiller AT-2 Plus) with a paper speed of 50 mm/s and a

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calibration of 1 mV/cm. All patients were in sinus rhythm during ECG acquisition. The ECG recordings were independently evaluated by two experienced cardiologists.

The QT interval was defined as the time from the onset of the QRS complex to the end of the T wave, as described by Wolff. The corrected QT interval (QTc) was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$). QT dispersion (QTd) was determined as the difference between the maximum and minimum QT intervals. The Tp-e interval was measured from the peak to the end of the T wave. The end of the T wave was defined as the intersection point between the tangent drawn to the descending limb of the T wave and the isoelectric line. The Tp-e/QT and Tp-e/QTc ratios were subsequently calculated.

Transthoracic echocardiography was performed before and after RT to assess left ventricular systolic function. The timing for echocardiography was approximately 6 weeks after the beginning of RT.

Radiotherapy doses were determined according to cancer type and treatment protocol. Patients with breast cancer received a total radiation dose of 50–60 Gy following mastectomy or up to 60 Gy after breast-conserving surgery. Patients with lung cancer received a total dose ranging from 45 to 60 Gy. All breast cancer patients had left-sided disease. Among lung cancer patients, 7 patients had right-sided tumors and 8 patients had left-sided tumors. Some patients had received chemotherapy; however, none of the administered agents were known to have significant cardiotoxic effects or established effects on ventricular repolarization parameters.

Exclusion criteria included electrolyte imbalance, active infection, atrial fibrillation or flutter, chronic obstructive pulmonary disease, known cardiovascular disease, hypertension, diabetes mellitus, significant systemic comorbidities, and treatment with known cardiotoxic chemotherapeutic agents. These criteria were applied to minimize potential confounding effects on ventricular repolarization parameters.

Statistics were conducted utilizing the Statistical Package for Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze the data. Continuous data with a normal distribution are expressed as the mean $\pm$ standard deviation, and categorical variables are expressed as number and percentage (%). Differences between categorical variables were determined by the chi-square test. Student's T-test or the Mann-Whitney U test was utilized to compare continuous variables. Significance was assumed as $p < 0.05$ value.

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of our university (Approval No: E-40839601-50.04-22).

RESULT

A total of 27 patients diagnosed with breast cancer ($n=12$) and lung cancer ($n=15$) included in our study. Mean age of patients with lung cancer were 60 years old and 47.9 years old with breast cancer. All patients with lung cancer were male. Patients who underwent a left mastectomy constituted approximately half of those with breast cancer. The mean cardiac dose was 5–6.5 Gy, while the overall RT dose ranged between 40–60 Gy (Table 1).

The patients' systolic and diastolic blood pressure values did not significantly change before or after RT in either group. Heart rate significantly increased in the lung cancer group ($p=0.037$), whereas no significant change was observed in the breast cancer group.

Before and after RT, all patients had normal left ventricular ejection fractions in the echocardiographic assessment. QT interval, QTc interval, QRS interval, QT/QRS and QTc/QRS revealed no significant change in both cancer types after RT. The electrocardiogram measurements, echocardiographic findings, systolic and diastolic blood pressure values are shown in Tables 2 and Table 3.

In patients with lung cancer Tp-e interval (72.94 ± 7.32 vs 80.20 ± 5.87), Tp-e/QT ratio (0.19 ± 0.025 vs 0.22 ± 0.018), Tp-e/QTc ratio (0.16 ± 0.017 vs 0.18 ± 0.009) were significantly different after RT, p values were 0.001, 0.001 and 0.008 respectively.

Also in patients with breast cancer Tp-e interval (65.41 ± 4.02 vs 73.00 ± 2.64), Tp-e/QT ratio (0.18 ± 0.017 vs 0.20 ± 0.022), Tp-e/QTc ratio (0.14 ± 0.011 vs 0.15 ± 0.014) were significantly different after RT, p values were 0.001, 0.012 and 0.025 respectively.

Figure 1 showed dose distribution and dose volume histograms of radiotherapy for patients with left breast cancer (A) and lung cancer (B).

DISCUSSION

This study aimed to investigate the effect of RT on ECG and, by extension, on conduction abnormalities and to reveal the markers that will promote early detection of the effects of RT on cardiac arrhythmia.

Radiotherapy is important in the treatment of carcinomas, including lymphoma, breast cancer and esophageal cancer, and contributes significantly to patient survival and quality of life (12,13). However, long-term complications of radiotherapy have been the focus of attention (14). Radiation exposure of the heart has been associated with some complications in patients undergoing thoracic radiotherapy, and one study showed an excessive relative risk of 7.4% per Gy for major coronary events over fifty years of age (1). These complications include pericardial effusion, pericarditis, coronary artery disease, myocardial defect, valve disease and conduction abnormalities (1,15).

Table 1. Comparison of Radiotherapy Doses Between Breast and Lung Cancer Patients

	Breast cancer (n=12)	Lung cancer (n=15)
Total dose (Gy)	54.54 $\pm$ 5.22	56.86 $\pm$ 6.26
Cardiac dose (Gy)	5.12 $\pm$ 1.94	6.50 $\pm$ 4.62

Values are presented as mean $\pm$ standard deviation (SD).

Gy: Gray

Table 2. Cardiovascular and Electrocardiographic Parameters of Patients with Lung Cancer Before and After Radiotherapy (n=15)

	Before RT	After RT	p
LV EF (%)	63.75±2.26	63.75±2.26	>0.05
Systolic blood pressure (mmHg)	118.33±17.49	112.50±22.61	>0.05
Diastolic blood pressure (mmHg)	77.50±8.66	75.83±6.68	>0.05
Heart rate (bpm)	80.83±12.71	87.58±13.09	0.037
QT interval (ms)	368.00±29.43	357.00±30.01	>0.05
QTc interval (ms)	426.50±20.19	430.91±23.49	>0.05
QRS interval (ms)	93.66±9.37	95.33±14.22	>0.05
Tp-e interval (ms)	72.94±7.32	80.20±5.87	0.001
Tp-e/QT ratio	0.19±0.025	0.22±0.018	0.001
Tp-e/QTc ratio	0.16±0.017	0.18±0.009	0.008
QT/QRS	3.96±0.50	3.79±0.54	>0.05
QTc/QRS	4.58±0.44	4.57±0.49	>0.05

Values are presented as mean ± standard deviation (SD). RT: radiotherapy. mmHg: millimeters of mercury; bpm: beats per minute; ms: milliseconds.

Normally, action potentials are shorter in epicardial than in endocardial cells, while M cells have the longest action potentials. These differences cause changes in the morphology and duration of the electrocardiographic T wave. Subsequently, several non-invasive electrocardiographic (ECG) parameters were proposed for the quantification of the dispersion of repolarization such as QT interval duration, QT dispersion (QTd), T wave micro alternans, and more recently, T peak – T end interval (Tp-e), T peak – T end/QT ratio (Tp-e/QT) and T peak – T end interval dispersion (dTp-e). Experimental studies have shown that the peak of the T wave coincides with the full repolarization of the epicardial cells and the end of the T wave with the full repolarization of the M cells, so the Tp-e interval is an indicator of the distribution of ventricular repolarization and is useful for assessing arrhythmic risk (16,17,18).

Recently, the Tp-e interval and Tp-e/QT ratio have emerged as electrocardiographic signs of increased ventricular repolarization (18). These markers may be used as an electrocardiographic index of ventricular arrhythmogenesis and sudden cardiac death. In previous studies, it has been found that prolongation of the Tp-e interval is associated with increased mortality in cases of Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy and myocardial infarction (19).

One hypothesis for increased cardiac events after lung radiotherapy is that the conduction system is directly damaged by radiation or indirectly affected by inflammation, fibrosis, ischemia RT doses delivered to both the superior vena cava and left atrium have been associated with electrocardiogram changes (20). Current guidelines recommend limiting the dose to the whole heart or the pericardium (21) however, it is still not clear whether we should limit the radiation dose to the whole heart or to the sub-structures. Various heart shaping atlases (13,22) have been developed for consistent dose reporting in clinical practice and study named “RTOG 0617” was the first study that highlighted the issue of cardiac dose in lung cancer radiotherapy, revealing that the volume of heart receiving greater than or equal to 5 Gy (V5) or greater than or equal to 30 Gy (V30) was associated with worse overall survival (23). A secondary analysis of RTOG 0617 published 2 years later reported that the dose parameter most strongly associated with survival was the heart volume receiving greater than or equal to 40 Gy (24).

In our study, the dose of RT given to the patients may not change. In our study, while the mean total dose was between 40-60 Gy, the mean cardiac dose was 5-6.5 Gy. However, the dose that the heart receives may vary and can be planned according to the RT technique applied.

Table 3. Cardiovascular and Electrocardiographic Parameters of Patients with Breast Cancer Before and After Radiotherapy (n=12)

	Before RT	After RT	p
LV EF (%)	65.62±1.76	65.62±1.76	>0.05
Systolic blood pressure (mmHg)	112.50±14.88	111.25±16.42	>0.05
Diastolic blood pressure (mmHg)	77.50±7.07	78.75±8.34	>0.05
Heart rate (bpm)	91.12±8.16	92.50±11.42	>0.05
QT interval (ms)	348.57±17.03	349.14±27.24	>0.05
QTc interval (ms)	435.00±9.64	439.57±18.85	>0.05
QRS interval (ms)	78.00±7.11	78.85±5.98	>0.05
Tp-e interval (ms)	65.41±4.02	73.00±2.64	0.001
Tp-e/QT ratio	0.18±0.017	0.20±0.022	0.012
Tp-e/QTc ratio	0.14±0.011	0.15±0.014	0.025
QT/QRS	4.49±0.45	4.43±0.36	>0.05
QTc/QRS	5.61±0.50	5.55±0.47	>0.05

Values are presented as mean ± standard deviation (SD). RT: radiotherapy. mmHg: millimeters of mercury; bpm: beats per minute; ms: milliseconds.

In another study Gurdal et al (25) showed significant increases in Tp-e interval, QT interval, Tp-e/QT ratio and Tp-e/QTc ratio in 51 breast cancer patients after RT. We found similar results in our population except QT interval. Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio was significantly increased after RT also in breast cancer and lung cancer patients.

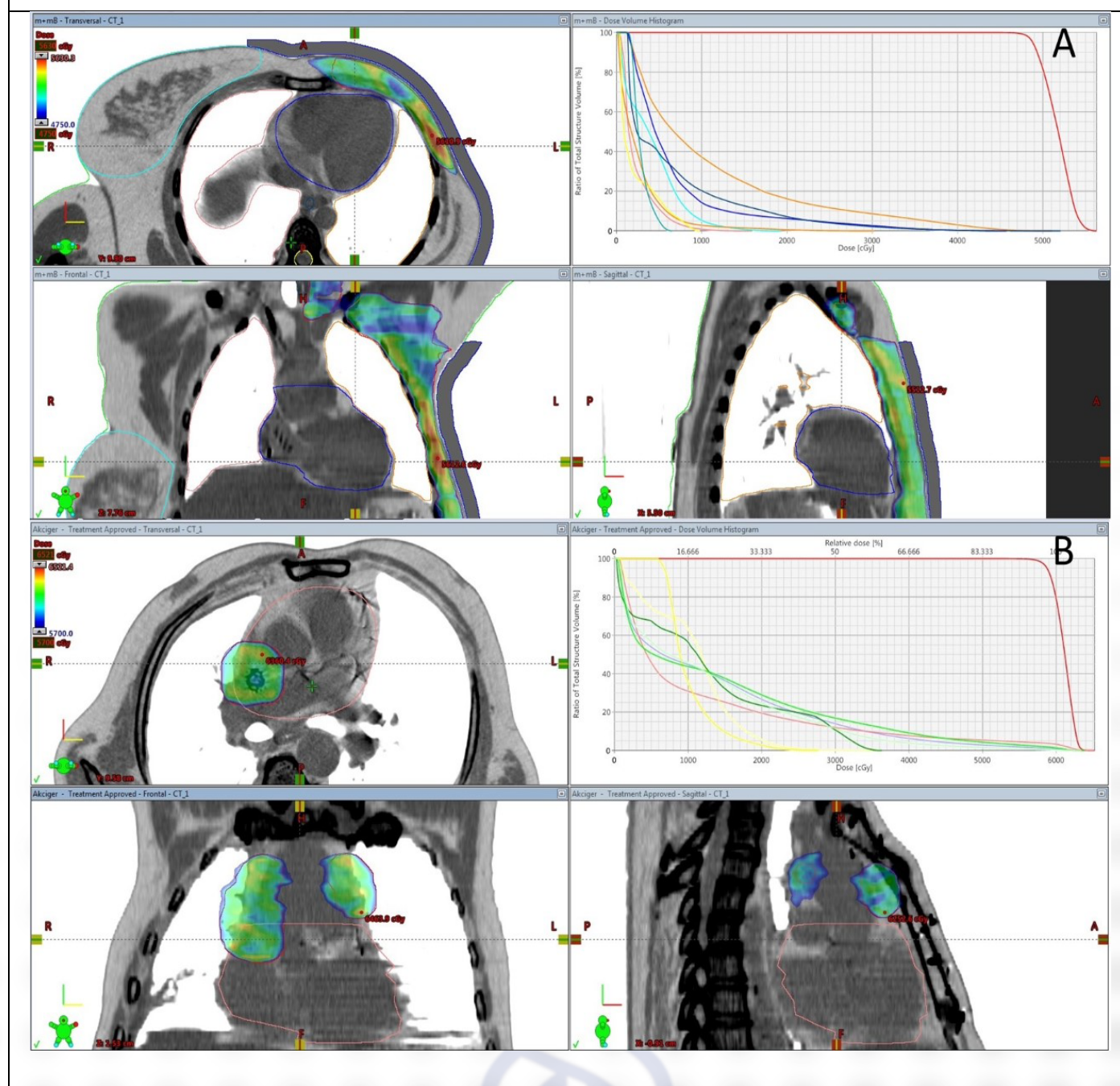
Wu et al (26) investigated short term effects of thoracic radiotherapy on cardiovascular parasympathetic and sympathetic nervous system. In that study, they collected 58 thoracic cancer patients and evaluated acceleration capacity, deceleration capacity, heart rate variability and heart rate. They found increased heart rate after RT. We didn't evaluate other autonomic features but we also found significant heart rate increase in lung patients (80.83±12.71 vs 87.58±13.09) but not in breast cancer patients.

In another study Heckmann et al (27) analysed the arrhythmic burden in patients with implantable electrical devices undergoing thoracic irradiation. They found no difference in atrial and ventricular arrhythmias in this patient population. Also coronary artery disease was associated with increased ventricular

arrhythmias. In our study we had no information about clinical arrhythmias but we just found the prolongation of Tp-e and QT, QTc ratios.

In this study we have done an easy, inexpensive and accessible ECG to show cardiac changes. We think that the increase in the Tp-e interval and the increase in the Tp-e/QT ratio in particular may be early indicators of RT-induced cardiac repolarization. Our study observed that EF did not decrease in any of the patients after RT and wall motion defect did not develop in the echocardiography.

This study has several limitations. First, the sample size was relatively small and the study was conducted at a single center, which may limit the generalizability of the findings. The relatively small sample size was partly related to the strict exclusion criteria applied to minimize confounding factors affecting ventricular repolarization. Second, the study population consisted of both breast and lung cancer patients, resulting in a heterogeneous cohort. Third, interobserver variability for Tp-e measurements was not formally assessed. Finally, clinical arrhythmia outcomes and long-term rhythm monitoring data were unavailable;

Figure 1. Dose distributions and dose-volume histograms of 2 planning techniques: (A) Left Breast Cancer (B) Lung Cancer

therefore, the present findings are limited to surrogate electrocardiographic markers of ventricular repolarization rather than documented arrhythmic events.

CONCLUSION

Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were increased after RT. These findings suggest that Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio may reflect early changes in ventricular repolarization after thoracic radiotherapy. Larger prospective studies with long-term rhythm monitoring and clinical arrhythmia outcomes are needed to confirm their prognostic value.

Ethics Committee Approval: Approval was obtained from the local ethics committee (Mudanya University Ethics Committee, reference number 2024*4), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

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Conflict of Interest: The authors have no declarations of conflicts of interest.

Informed Consent: Consent forms were not obtained due to the retrospective design.

Authorship Contributions: Concept: MCB; Design: MCB, AD; Supervision: KE; Resource: KE, MCB, AD; Data Collection or Processing: AD, MCB; Analysis or Interpretation: KCY; Literature Review: KCY; Writing: KCY; Critical Review: KCY.

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