Serum troponin I as an early marker in determining radiotherapy-induced cardiac damage

*Sema Rakıcı¹, Ş. Bilge Gürsel², Fırat Ural³, Abdülkerim Bedir⁴, Çetin Çelenk⁵, A.Deniz Meydan², Nilgün Özbek Okumuş⁴

¹Trabzon Kanuni Training and Research Hospital, Departments of Radiation Oncology Trabzon, Turkey
²Ondokuz Mayıs University Faculty of Medicine, Departments of Radiation Oncology Samsun, Turkey
³Siirt State Hospital Cardiology Department Siirt, Turkey
⁴Ondokuz Mayıs University Faculty of Medicine, Biochemistry Department Samsun, Turkey
⁵Ondokuz Mayıs University Radiology Department, Samsun, Turkey

*Corresponding author email: sema.nesilhan@gmail.com, Tel: + 90 505 4028302

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Objective: To determine the availability of troponin I in the early determination of cardiac complications that would be developed due to radiotherapy. Methods: Twenty four patients with cancer were included in the prospective study. Dose-volume histograms (DVH) were drawn, and the patients whose heart areas have been included within radiotherapy (RT) field were selected for the study. Serum troponin I level, electrocardiographic (ECG) and echocardiographic (ECHO) measurements were done serially to determine the cardiac damage. Results: During RT, increase in tn I levels nearly up to the significance level (p=0.057) at the 5th week, significant positive correlation between D50 and tn I (p=0.003, r=0.574), positive correlation between the increase in tn I and the increase in left ventricular end-systolic diameters (LVESd) at the 1st month (p=0.019, r=0.476), and the presence of statistically significant negative correlation (p=0.044, r = -0.414) between the increase in Tn I and left ventricle ejection fraction (%EF) at the 1st month after RT and disappearance of this significance at the 6th month (p = 0.07, r = -0.376 ) were recorded as significant parameters that have been compared with Tn I. Conclusion: In the present study, we observed that subclinical cardiac disorders have been increased with the increased dose and volume and there was a correlation with the increase in troponin I, despite the absence of clinical impairment in electrocardiographic and echocardiographic parameters.

Keywords: Troponin I, cardiac toxicity, radiotherapy

INTRODUCTION

It is known that the mediastinal RT and chemotherapeutic agents, such as anthracyclines, mitoxantrone, cyclophosphamide, ifosphamide, paclitaxel, docetaxel, trastuzumab and 5-FU, lead to cardiac side effects (Bovelli et al., ESMO Clinical Practice Guidelines, Pai and Nahata, 2000). The pathological effects of RT on three layers of the heart, as well as on coronary arteries, have been characterized (Adams et al., 2004; Taylor et al., 2006; Stewart et al., 1995; Brosius et al., 1981; Schultz-Hector, 1992; Stewart and Fajardo, 1984; Adams et al., 2003), but was not found no serum marker that reveals the side effects .By means of the present study, we tried to seek an answer to the question “Is there marker that forewarns the radiotherapy-induced cardiac damage?”

MATERIAL AND METHODS

Patients selection

The approval of the Ethical Committee of the Ondokuz Mayıs University was obtained for the present study on 06.12.2005 with the number 333. Thus, this study meets the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989, and 1996. The participants were informed prior to the study and their written consents were obtained. Twenty four patients, who applied to the Radiation Oncology Clinic between August 2006 and January 2008 and diagnosed with cancer and whose heart areas were included within RT
Exclusion criteria

Patients who had ischemic or valvular heart disease, abnormal hepatic and renal tests (Bilirubin >2mg/dL, AST >2 times of the normal values, Creatinine >1.5mg/dL), left ventricle ejection fraction < 50%, who were using ACE inhibitor or β-blocker because of hypertension (HT), and patients with uncontrolled HT and cardiac tumor were not included in the study.

Troponin Measurement

Tn I levels were measured once in a week before and during the therapy as well as at the 1st and 6th months after the therapy. The blood samples were centrifuged in biochemistry laboratory of the emergency department of medical faculty. Thereafter, Tn I levels were measured by means of immunoassay method via a device named Immulite One, using monoclonal antibody kit specific for plasma cardiac Tn I [reference value of the kit; 0–1 ng/ml (upper limit for major myocardial injury is 1 ng/ml)]. The cut-off value for serum Tn I was considered 0.2 ng/ml. This value was obtained by adding 2 standard deviations (SD) to the mean value of serum Tn I level obtained from the control group. The values over the cut-off value were considered “high Tn I level”.

ECG

ECG was taken at the cardiology clinic of our faculty before the therapy and at the 1st and 6th months after the therapy. It was taken by use of 12-lead ECG device (Nihon Kohden and Schiller) at rest, at standard derivations, at a speed of 25mm/sec and with the amplitude 10mm/mV. For QT interval; the distance from the beginning of QRS wave until the point that T wave returned to TP isolectric line was manually measured. In order the QT value not to be affected by the heart rate, corrected QT interval (QTc) was calculated by means of Bazzett’s formula (QTc =QT /√RR) in milliseconds (msec).

ECHO

ECHO was performed via ECHO device (Vivid 3), once before the therapy and at the 1st and 6th months after the therapy in the cardiology clinic of our faculty. All of the measurements and recordings were done by means of Doppler echocardiographic imaging system during spontaneous respiration and at the end of the expiration. It was performed by obtaining M-mode and 2-dimension echocardiographic parameters from the parasternal long axis and apical images while the patients were in the left lateral recumbent position. Endocardial edges were fixed through from the apical 2 and 4 chambers, left ventricle diastolic and end-diastolic volumes were measured, and left ventricle ejection fraction (EF%), left ventricular end diastolic diameter LVEDd and LVESd values were measured in millimeters (mm).

Patients characteristics

The number of the female patients was 18 (75%), whereas the number of male patients was 6 (25%). The mean age of the patients was 50.4 ±2.5 years (mean±SD), and maximum and minimum values were 18–69 years. Total RT dose was 4782.5±158.3 cGy in average.

12 Patients (12 female) had left-sided breast cancer, 5 Patients (3 male and 2 female) had gastric and gastroesophageal junction tumor, 4 Patients (3 male and 1 female) had lung tumor, 1 Patient (female) had thymus tumor, 1 Patient (female) had Non-Hodgkin lymphoma (NHL), and 1 Patient (female) had Hodgkin’s disease (HD). Breast cancer was bilateral in two patients (2 female).

Therapy characteristics

RT Planning

After the conventional primary simulation which has been done in our clinic, the patients, who have been evaluated and decided to have indication for RT, underwent CT imaging (Toshiba) in Radiology clinic of our faculty. CT images were digitally transferred to the computerized planning system (Eclipse or Multidata DSS). According to the characteristics of the tumor and localization site, gross tumor volume (GTV), clinical target volume (CTV), planned target volume (PTV) and the volumes of organs at risk (OAR) were drawn; 3-D reconstruction was created, and 3-D conformal RT was planned. Planning was done according to the fraction dose which has been determined according to the stage and localization of the tumor as well as the total dose. DVHs were drawn and the doses that the heart took were calculated. The isodose curve in the therapy plan is seen in color in Figure 1.

Whereas 3 of the patients were treated via cobalt 60 radioactive based teletherapy device (Theratronics 780-C), 21 were treated via linear accelerator (linac) device (Varian Clinac DHX). According to the characteristics of the patient and the tumor, 6MV or 18MV energies were used in the patients treated with linac.

The heart was contoured drawing the contours from the point that the great vessels have arisen until the
diaphragm. This procedure was performed by the same physician for all patients in order to eliminate the individual variations. The doses of 10% (D10), 30% (D30) and 50% (D50) that the heart have taken, were calculated drawing DVH. DVH sample, which is the graphical transfer of proportional values of the doses that the tissues with and without tumor have taken, is seen in Figure 2.

CT

All of the patients, except for a patient with thymus tumor, took CT prior to RT, whereas 4 patients with gastric and gastroesophageal junction tumor took CT during RT with concurrent FUFA (5 Fluorouracil=5-FU+ Folinic acid=FA), and one patient could not take CT during RT because of poor general status. These patients took 3 more cures of FUFA after RT.

Table I. Doses that the heart takes (cGy)

<table>
<thead>
<tr>
<th></th>
<th>D10</th>
<th>D30</th>
<th>D50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>3259.8±386.5</td>
<td>1175.2±375.8</td>
<td>512.4±267.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>433</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum</td>
<td>6400</td>
<td>6400</td>
<td>4840</td>
</tr>
</tbody>
</table>

Statistical analyses

Statistical evaluation of the data was done by means of SPSS 15.0 package program. The normality of the distribution of the data has been assessed by Shapiro-Wilk test, the significance of the difference between the initial follow-up and later follow-ups was evaluated using paired sample T test, and the correlation between tn level and other cardiac measurements was evaluated using Spearman correlation test. A p value ≤0.05 was assumed to be the significance level.

RESULTS

Evaluation of cardiac symptoms

Patients were questioned concerning cardiac symptoms such as chest pain, getting tired quickly, palpitation and
#### Table 2. Mean, minimum and maximum Tn I values (ng/ml)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RT</td>
<td>0.20</td>
<td>0.00</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; week</td>
<td>0.225</td>
<td>0.173</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; week</td>
<td>0.225</td>
<td>0.173</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; week</td>
<td>0.231</td>
<td>0.179</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; week</td>
<td>0.230</td>
<td>0.176</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt; week</td>
<td>0.239</td>
<td>0.195</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td>After RT 1&lt;sup&gt;st&lt;/sup&gt; month</td>
<td>0.20</td>
<td>0.00</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>After RT 6&lt;sup&gt;th&lt;/sup&gt; month</td>
<td>0.20</td>
<td>0.00</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>After RT 12&lt;sup&gt;th&lt;/sup&gt; month</td>
<td>0.20</td>
<td>0.00</td>
<td>0.20</td>
<td>0.20</td>
</tr>
</tbody>
</table>

#### Table 3. Mean QTc values (msn)

<table>
<thead>
<tr>
<th></th>
<th>Before RT</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; month</th>
<th>6&lt;sup&gt;th&lt;/sup&gt; month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>413.9±6.3</td>
<td>433.4±5.5</td>
<td>441.7±6.5</td>
</tr>
<tr>
<td>P</td>
<td>0.005</td>
<td>0.001</td>
<td></td>
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</table>

#### Table 4. Mean EF values (%)

<table>
<thead>
<tr>
<th></th>
<th>Before RT</th>
<th>After RT 1&lt;sup&gt;st&lt;/sup&gt; month</th>
<th>After RT 6&lt;sup&gt;th&lt;/sup&gt; month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean EF ± SD</td>
<td>66.2±1.1</td>
<td>64.8±1.3</td>
<td>59.5±1.8</td>
</tr>
<tr>
<td>P</td>
<td>0.334</td>
<td>0.003</td>
<td></td>
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</tbody>
</table>

**Calculation of the dose that the heart has taken**

The mean doses of D10, D30 and D50 that the heart took, which have been calculated using DVH of a patient and shown on figure 1, were found in turn 3259.8±386.5 cGy, 1175.2±375.8 cGy and 512.38±267.1 cGy. The minimum and maximum doses were in turn: 433–6400 cGy for D10, 0-6400 cGy for D30, and 0-4840 cGy for D50. The mean, minimum and maximum values of D10, D30 and D50 are shown on Table I as cGy.

**Tn I**

The Tn I value of all patients was 0.2 ng/ml prior to RT, and an increase was determined in 4 patients (2 male, 2 female) during the course of the RT. The maximum increase in Tn I occurred at the 5<sup>th</sup> week. Statistical mean, maximum and minimum weekly Tn I values are shown on Table 2. The highest mean Tn I value was 0.239±0.195, and occurred at the 5<sup>th</sup> week. Increase in Tn I at the 5<sup>th</sup> week was close to the statistical significance level (p=0.057). Statistical p values of Tn I increase at the 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> week during RT were 0.98, 0.97 and 0.057 respectively.

**QTc**

During the follow-up, the mean QTc values both prior to and after RT was found increased (Table 3). The increase in QTc at the 1<sup>st</sup> and 6<sup>th</sup> months was statistically significant when compared with the value before RT (p = 0.005 and p = 0.001 respectively).

**ECHO Findings**

**EF**

Whereas the mean EF was 66.2±1.1 before RT, it was decreased down to 64.8±1.3 at the 1<sup>st</sup> month and to 59.5±1.8 at the 6<sup>th</sup> month after RT. The decrease at the 6<sup>th</sup> month was statistically significant (p = 0.003), whereas the decrease at the 1<sup>st</sup> month was not (p=0.334) (Table 4). The maximum impairment in EF was observed in two patients (2 male) with gastric tumor.

Dyspnea. In addition, nonspecific complaints such as cough, weakness, and fatigue, which could also be cardiac, were questioned as well. Although none of the patients had significant cardiac symptom prior to RT, 4 patients (2 male and 2 female) had the complaints of weakness, fatigue and getting tired quickly at the 6<sup>th</sup> month after RT; 2 patients (1 male and 1 female) had effort dyspnea; one patient (1 male) had dyspnea and chest pain; and one patient (1 male) had chest pain.
Whereas the mean LVEDd (mm) was 47.1±0.9 before RT, it was found 45.8±0.8 at the 1st month and 47.7±1.1 at the 6th month after RT. Changes in the mean LVEDd value at the 1st and 6th months after RT were not statistically significant (p=0.173 and p=0.585 respectively).

Whereas the mean LVESd (mm) was 30.5±0.8 before RT, it was found 29.6±0.7 at the 1st month and 33.1±1.1 at the 6th month after RT. Increase in LVESd at the 6th month was statistically significant (p=0.036), whereas the change in LVESd at the 1st month was not (p=0.241).

Pericardial fluid

While only one patient (female) had pericardial fluid before RT, minimal asymptomatic pericardial fluid was observed by 54.2% at the 6th month after RT.

Correlation between D50 and Cardiac Parameters

D50 and QTc

No statistically significant correlation was determined between D50 and QTc interval during the 1st and 6th month follow-ups (p=0.736, r=0.073 and p=0.245, r=0.247 respectively).

D50 and EF

Statistically significant negative correlation was determined between D50 and EF at the 1st month after RT (p=0.011 r=-0.507). However, although there was a negative correlation at the 6th month, it was not statistically significant (p=0.356, r=-0.197).

D50 and LVEDd

No statistically significant correlation was determined between D50 and increase in LVEDd during the 1st and 6th month follow-ups (p=0.265, r=0.237 and p=0.578, r=0.120 respectively).

D50 and LVESd

There was statistically significant correlation between D50 and increase in LVESd at the 1st month (p=0.008, r=0.528). But, the increase at the 6th month was not statistically significant (p=0.716, r=0.078).

Tn I and Other Parameters

The relation between the increases in tn I level and other parameters were compared by use of nonparametric tests.

Tn I and Volumes

When the relation between tn I increase at the 5th week and D50, D30 and D10 was evaluated, statistically significant positive correlation was determined between tn I and D50, which is the maximum volume of the heart included within the RT field (p=0.003, r=0.574). A positive correlation at statistical significance threshold was determined between D30 and the increase in tn I level (p=0.064, r = 0.384). There was no correlation between D10 and the increase in tn I (p=0.558, r=0.126).

Tn I and QTc

No correlation was determined during the 1st and 6th month follow-ups between the increase in tn I level and the prolongation of QTc interval (p=0.188, r=0.278 and p=0.128, r=0.320 respectively).

Tn I and EF

When the relation between the increase in tn I level and EF value at the 1st month after RT was examined, a statistically significant negative correlation was found (p= 0.044, r = - 0.414). That is to say, the rate of the decrease in EF values in patients with increased tn I value was statistically significant. However, although there was a negative correlation at the 6th month as well, it was not statistically significant (p = 0.07, r = - 0.376) (Table 6).

Tn I and LVEDd

No correlation was determined during the 1st and 6th month follow-ups between the tn I values and the increase in LVEDd (p = 0.542, r = 0.131 and p = 0.649, r = 0.098 respectively).

Tn I and LVESd

Statistically significant correlation was determined
DISCUSSION

Clinical and pathological changes of pericardium are the most common abnormalities defined after cardiac RT (Veinot and Edwards, 1996; Schultz-Hector, 1992). In the study by Brosius et al. (1989), it was reported that the risk for mild pericarditis is below 5% and severe pericarditis is rare if more than 60% of the heart is treated with a dose below 40Gy. The mean dose that D50 which the patients participated in the present study have taken was as low as 512.4±267.1 cGy. Therefore, the patients in the present study had no sign of acute pericarditis. The rate of minimal pericardial effusion was 54.2% at the 6th month visit.

Both the secondary events resulted from the radiation and the cardiac oxidative damage that occurs 1 month after the exposure to radiation lead to the lipid peroxidation in plasma and heart as well as the increase in plasma creatinine kinase (Shappell et al., 1990). Free radicals may occur by means of either the direct effect of the radiation on cells or as the result of the acceleration in oxidative process caused by the inflammatory cells (neutrophils, macrophages) migrated to myocardium early after cardiac radiation (Krüse et al., 1999; Yeung and Hopewell, 1985). Pericardial fluid was present prior to RT in a patient whose tn I level has increased early during RT; increase in tn I in this patient may be related to the oxidative process. Moreover, it has been demonstrated that the inflammatory events in pericardium lead to myocardial damage by being spread over the epicardium. The likely reason for the increase in tn values in acute pericarditis is the limited damage caused by spreading of the inflammation into the subepicardial cells. However, the true incidence, as well as the prognostic value, of the increase in cardiac tn I is not known clearly (Karajalainen and Heikkila, 1986; Brandt et al., 2001; Bonnefoy et al., 2000).

In the study by Auner et al. (2002), significant prolongation in QTc interval, which has been defined as the sign of ventricular repolarization, was observed in 2 patients in the absence of other cardiotoxicity signs. In the present study, QTc interval has progressively prolonged during the follow-up after RT as compared to that before RT. While it was 413.9 before RT, it was 433.6 at the 1st month and 441.7 at the 6th month after RT; both values were statistically significant (p= 0.005 and p= 0.001 respectively).

In a study in which ECHO and serial tn T measurements have been done, tn T elevation was determined in 15% of the patients (Auner et al., 2003). During the follow-ups of the patients, it was determined that the rate of the decrease in left ventricle ejection fraction is higher in those with elevated tn T values compared to those without elevation (10% vs. %2, p =0.017). In the present study as well, a negative correlation was determined between tn I and EF. Statistically significant correlation was determined between the increase in tn I at the 1st month after RT and the decrease in EF (p=0.044 r= -0.414), whereas it was not statistically significant at the 6th month (p= 0.070 r=-0.376). In the study by Lagrange et al. (1992), acute cardiac effects were investigated after the radiation of the mediastinum, and temporary decrease in EF was found 15 days after RT. During the follow-up of these patients, improvement in EF has been determined 2 months after RT. The early decrease of EF after RT exposure may be tried to be returned to normal values by means of work of cardiac compensation mechanisms.

### Table 5. Mean SVESd (mm)

<table>
<thead>
<tr>
<th></th>
<th>Before RT</th>
<th>1st month</th>
<th>6th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LVESd SVESd ± SD</td>
<td>30.5±0.8</td>
<td>29.6±0.7</td>
<td>33.1±1.1</td>
</tr>
<tr>
<td>P</td>
<td>0.241</td>
<td>0.036</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6. Correlation between Tn I and EF

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st month</td>
<td>0.044</td>
<td>-0.414</td>
</tr>
<tr>
<td>6th month</td>
<td>0.07</td>
<td>-0.376</td>
</tr>
</tbody>
</table>

### Table 7. Correlation between Tn I and SVESd

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>r</th>
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</thead>
<tbody>
<tr>
<td>1st month</td>
<td>0.019</td>
<td>0.476</td>
</tr>
<tr>
<td>6th month</td>
<td>0.289</td>
<td>0.226</td>
</tr>
</tbody>
</table>

between tn I value and the increase in LVESd at the 1st month after RT (p = 0.019, r = 0.476). But, there was no statistically significant correlation at the 6th month (p=0.289, r = 0.226) (Table 7).
During the follow-ups of all patients that took RT the rate of the decrease in EF from 66.2% before RT down to 59.4% at the 6th month after RT, independent from the increase in tn I, was statistically significant (p=0.003). However, none of the patients had the sign of heart failure. In previous studies, it has been reported that symptomatic myocardial dysfunction is rare after RT performed with a dose not exceeded 60 Gy Stewart and Fajardo, (1984). In the present study, although the impairment in EF has continued at the 6th month after RT, its correlation with the increase in tn I disappeared during the follow-ups after RT. This raised the thought that impairment at the 6th month may be associated with CT that continued after RT.

In their study including 51 patients who were taking mediastinal RT and simultaneously CT, Sokol et al. (2001), determined an increase in tn I in 3 patients. However, this increase has not been attributed to RT since the increase in tn I was not progressive and the patient was taking simultaneously CT. In the present study, tn I showed a tendency to increase in 4 patients on weekly measurements during the RT. None of the patients with increased tn I has taken simultaneously CT. Increase in tn I may be attributed to the RT because of significant correlation between tn I increase and D50 (p=0.003 r=0.574), nearly significant correlation between tn I increase and D30 (p=0.064, r=0.384), and statistically significant increase in tn I in patients 50% (D50) of which the heart have been included in RT field and at the 5th week of the RT, and because these patients were not taking simultaneously CT.

Hughes et al. (1995) conducted a study consisted of 50 patients with early stage breast cancer without simultaneously CT; tn T levels has been measured both at the beginning and end of the study. Any tendency toward progressive increase in cardiac indicator levels has not been found. As is known, tn T may increase due to the skeletal-muscle system and because of skin reactions as well. Additionally, it is known that the level of RT dose that the heart takes, particularly in patients with right breast tumor, is not that much to cause cardiotoxicity.

In their study, Sedky et al. (2000) followed 26 patients with breast cancer taking anthracycline based CT and RT, and cardiotoxicity was investigated by means of tn I and ECHO parameters. Tn I was measured after CT cures and RT. Although there was no change in tn I levels after the first cure, left ventricle fractional shorting (FS%) was decreased after the 2nd, 4th and 6th cures. A correlation was found between FS% and the increase in tn I associated with the RT dose that the heart took after 2 cures. Furthermore, a significant relation was determined with tn I levels after the 5th cure because of cumulative effect of anthracycline. When the ECHO parameters were compared in terms of the effects of RT in patients with right or left breast cancer, no significant difference was determined.

In the present study, when the 1st and 6th month LVESd data were compared with those prior to RT, increase in LVESd at the 6th month was statistically significant. In addition, there was positive correlation between tn I and LVESd at the 1st month after RT. This may propound the hypothesis that the systolic functions of myocardium are primarily impaired by means of the effects of RT. This effect was met in the literature as a never reported issue because, approximately 70 days after a single dose of 20 Gy RT is applied, myocardium degeneration occurs, stroke volume and left ventricle ejection fraction decrease, and end diastolic volume increases (Kıraç, 2001).

In the study by Cardinale et al. (2002), increase in tn I levels was determined in 70 of 211 patients after a high-dose CT, and the rate of the decrease in EF in these patients was found statistically significant. Authors have emphasized that increase in tn I levels in the patients in this population would be a reliable marker that predicts the decrease in EF.

In their study, Specchia et al. (2005), investigated the anthracycline induced cardiotoxicity in hematological tumors by measuring tn I levels after CT in 79 patients. In the above mentioned study, there was an increase in tn I on the 14th day of CT in 4 of young patients, whereas increase in tn I was determined on the 7th day of CT in 3 of older patients. These increases were within the reference range in both groups. According to the echocardiographic findings, decrease in EF occurred in patients whose tn I levels has increased (over 0.15) on the 14th day. The authors of the above mentioned study emphasized that tn I could determine the patients whose cardiotoxicity risk is high after CT. In the present study as well, although there was an increase (over 0.2 ng/ml) in tn I levels as compared to basic values, this increase was within the reference range. The major problem for cardiac troponins to be used in clinical practice is to determine their upper limit values. Although minimal increase in troponin levels may indicate myocardial damage, progressive increase in its level is needed to be demonstrated to verify that the reason is cardiac (Braunwald et al., 2002). In the present study, tn I level, which has increased during the RT, decreased down to its basic value of 0.2 ng/ml after RT.

In the study by Forni et al. (1992), 360 patients were given 5-FU via continuous infusion for either 90 or 120-hours. Increase in cardiac enzymes was determined only in 2 of 28 patients with dramatic cardiac symptoms including a wide range of symptoms from angina to sudden death, and mortality was determined in 8 patients. In fact, although 5-FU induced cardiac toxicity has been reported in many studies in the literature, it was also reported to be rare (Gopal et al., 2003; Anand, 1994; Ensley et al., 1989).

The decrease in left ventricle ejection fraction resulted from the administration of doxorubicin, of which the cardiotoxicity is well known because it was investigated
more, wi simultaneously mediastinal radiation was reported to be more increased. It was determined that clinically insignificant myocardial dysfunction might develop by use of low-dose doxorubicin (up to 300mg/m²) and 20–40 Gy mediastinal RT (Carlson et al., 1991; Glanzmann et al., 1994; LaMonte et al., 1986; Santoro et al., 1987).

In the present study, 12 patients with breast cancer have taken adriamycin (doxorubicin) CT prior to RT. However, none of the patients has taken simultaneously CT. No tn I elevation, except for one patient with breast cancer, was determined. We did not determine any exaggerated impairment in cardiac functions in our patients taken adriamycin. Is to be considered that the patients in the present study were young, their cardiac functions were normal prior to the therapy, and they did not take concurrent CRT. Because adriamycin increases the risk for the development of cardiac complication in those who take mediastinal RT, in those with left ventricle dysfunction, and in those at advanced age (Chlebowsk, 1979), in such patients taking combined therapy, long-term follow-up is needed to accurately evaluate the potential risks for cardiac toxicity (Steinherz et al., 1991). In addition, long-term follow-up is suggested also to prove the latent subclinical myocardial damage and cardiac myofibrillar system damage (Auner et al., 2003).

In the studies by Dalloz et al. (1999) and Ferrari et al. (1991), it was suggested that the use of antioxidant agents during the tumor treatment with radiation and anthracyclines would reduce the development of cardiac damage. The use of antioxidant agents during RT, particularly in patients with pleural or pericardial fluid, may reduce side effects.

Limited number of data in the literature, concerning the investigations on tn I level, showed that high risk patients for the development of CT induced cardiotoxicity could be determined Saparano et al. (2002). According to the results of the present study, we can conclude that tn I can be used to predetermine the cardiac damage that develops secondary to RT.

In modern ages, cancer therapy is performed by means of CT, RT and biological agents, and powerful methods, which would predict the adverse effects that these treatment modalities would cause, are needed. Therapy resistant malignities are treated more aggressively; therefore the normal tissues are on a knife-edge because of increased toxicity. After the treatment of the disease, detection of normal tissue damage and its rehabilitation requires a different management, because late side effects appear months or years after the completion of the therapy. New therapy strategies are needed to be developed concerning the management and rehabilitation of late side effects.

Although the evidence level of the present study is low because of the limited and nonhomogenous number of the patients, we can say that it includes adequate evidence for the planning of more homogenous studies that would improve our results and make them stronger. In the light of these findings, we think that tn I should be kept in mind as a beneficial marker for cardiac damage to be determined early in patients taking RT.

REFERENCES


