The Prevalence of Myocardial Ischemia After Concurrent Chemoradiation Therapy as Detected by Gated Myocardial Perfusion Imaging in Patients with Esophageal Cancer

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The detection of myocardial perfusion abnormalities after radiation therapy (RT) has been investigated previously in patients with lymphoma and breast cancer. However, the prevalence and association of such abnormalities with RT in esophageal cancer patients have not been investigated previously. **Methods:** The prevalence of myocardial perfusion abnormalities detected using gated myocardial perfusion imaging (GMPI) in patients with esophageal cancer after RT (RT group) was compared with that in patients with esophageal cancer who did not undergo RT (NRT group). The patients' data were extracted from a prospectively collected database. The results of GMPI that were read by multiple readers were tested further by an expert reader who was unaware of the patients' clinical information. This reader's findings were correlated with the different RT isodose lines as seen in the CT for RT planning. Isodose lines containing the affected segments in GMPI as well as the rest of the left ventricle were recorded. Additionally, information with regard to the mean radiation dose to the heart for each patient was collected. An overall, mean radiation dose to the heart in patients with abnormal GMPI studies was compared with that in patients with normal GMPI studies. **Results:** Fifty-one patients were included, 26 in the RT group and 25 in the NRT group. The mean and median interval between RT and GMPI was 7.5 and 3.0 mo, respectively. We identified myocardial perfusion defects in 14 patients (54%) in the RT group and in 4 patients (16%) in the NRT group. Eleven patients (42%) in the RT group had mild inferior wall ischemia versus only 1 patient (4%) in the NRT group ($P = 0.001$). All of the patients with inferior wall ischemia had distal esophageal cancer. The remaining 12 patients in the RT group and 21 patients in the NRT group had normal GMPI results. The mean left ventricular ejection fraction was 59.0% ± 10.7% in the RT group and 59.3% ± 9.8% in the NRT group (P = not significant). Good agreement was found between the GMPI results interpreted by multiple readers and those of the single expert reader ($\kappa = 0.84$). In 7 of 10 patients (70%) who had abnormal GMPI results in the RT group, the myocardial perfusion defect was encompassed in RT isodose lines ≥ 45 Gy, whereas in only 5 of 20 patients (25%) the normal left ventricle was included in the RT isodose line ≥ 45 Gy. **Conclusion:** RT is associated with a high prevalence of inferior left ventricular ischemia, as detected using GMPI in patients with distal esophageal cancer. Most perfusion defects are encompassed within an isodose line ≥ 45 Gy in the RT plan.

Key Words: esophageal cancer; radiation therapy; gated myocardial perfusion imaging; myocardial ischemia

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The incidence of adenocarcinoma in the distal esophagus in western countries has recently increased 5%–10% (*1*). The American Cancer Society (ACS) estimated that, during 2006, approximately 14,550 new esophageal cancer cases will be diagnosed in the United States. Cancer of the esophagus is much more common in some other countries. For example, esophageal cancer rates in Iran, northern China, India, and southern Africa are 10–100 times higher than those in the United States (ACS, 2005). During the early 1960s, only 5% survived at least 5 y after diagnosis. Presently, 25% of American patients survive at least 5 y after diagnosis (ACS, 2005). Concurrent chemoradiation before surgical management of these tumors is becoming the most acceptable management plan for these patients. The location of most esophageal cancers in the distal esophagus and their close proximity to the heart make it difficult to avoid including a portion of the heart in the radiation therapy (RT) field.

The effects of RT on the heart have been well documented in patients with breast cancer and lymphoma (*2–7*). The longer survival duration with these tumors allows the

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cardiac complications of RT to manifest clinically. These cardiac complications include acute and chronic pericarditis, coronary artery disease (CAD), conduction abnormalities, valvular insufficiency, and cardiomyopathy (*8*). Most of these complications were documented with the older techniques of RT planning. Currently, 3-dimensional conformal RT (3DCRT) and intensity-modulated RT (IMRT) have become standard practice in the RT community. The delivery of 3DCRT is typically accomplished with a set of fixed radiation beams, which are shaped using the projection of the target volume in the beam's eye view. The radiation beams normally have a uniform intensity across the field or, where appropriate, have this intensity modified by simple beam fluence–modifying devices such as wedges or compensating filters. On the other hand, IMRT—a novel approach to the planning and delivery of RT—usually involves inverse planning, whereby dose volume constraints for targets and normal tissues are defined a priori and then are optimized with a computer algorithm. Targets and normal tissues are first delineated on a CT scan. The algorithm then identifies beam orientations and patterns of intensity that optimize conformality of the prescription dose to the shape of the target in 3 dimensions while sparing surrounding normal tissues. Preliminary reports involving treated patients have been promising, with low rates of toxicity (*9,10*). Other improvements in RT techniques include respiratory gating and proton therapy, which also aim at reducing surrounding tissue and organ toxicity (*11,12*). However, the incidence and prevalence of radiation-induced cardiac complications with each of these RT techniques have not been investigated adequately.

In this study, we evaluated the prevalence, pattern, and location of myocardial perfusion abnormalities using gated myocardial perfusion imaging (GMPI) in patients with esophageal cancer who received concurrent chemoradiation using primarily 3DCRT compared with those who did not receive RT before GMPI. Although the 5-y survival of esophageal cancer patients may not allow the clinical manifestation of radiation-induced coronary artery disease (RICAD), the results of this study would be beneficial in other cancers in the chest with a higher 5-y survival, as in lung and mediastinal tumors, in which RT is frequently part of the treatment (*13,14*).

MATERIALS AND METHODS

Upon institutional review board approval of our study, the results of GMPI in patients with esophageal cancer who received 3DCRT or IMRT as part of concurrent chemoradiation (RT group) before surgery were compared with the results in esophageal cancer patients who did not receive RT before surgery (NRT group). The patients' data were extracted from a prospectively collected database. All patients with esophageal cancer who had GMPI from March 2005 to January 2006 were included. Prospectively accumulated data on 7 additional consecutive patients who underwent RT before GMPI before March 2005 obtained from a database in the Department of Radiation Oncology at The University of Texas M.D. Anderson Cancer Center were also included. One patient with left bundle branch block was excluded from the study. The patients' demographic data, tumor sites, intervals between RT and GMPI, total RT doses and fractions delivered to the tumors, mean radiation doses delivered to the heart, and concurrent chemotherapy drugs were accumulated for the 2 groups. Risk factors for CAD in the 2 groups were also compared.

GMPI were performed as part of routine standard-of-care studies for risk stratification before esophagectomy. They were performed using a dual-isotope protocol with 111 MBq (3 mCi) of ^{201}Tl for rest SPECT and 925–1,110 MBq (25–30 mCi) of ^{99m}Tc-tetrofosmin injected at peak stress. Stress gated SPECT acquisition was obtained 30 min later. The images were interpreted by 6 different readers who routinely interpret these studies at our institution. Perfusion abnormalities were reported using a 12-segment model of the left ventricle (LV). Perfusion abnormalities were qualitatively graded as mild, moderate, or marked ischemia, scar or mixed scar and ischemia with similar grading of the ischemic component of the mixed abnormalities. Functional information regarding the LV ejection fraction (LVEF), end-diastolic volume (EDV), and end-systolic volume (ESV) was also collected. Wall motion abnormalities were qualitatively evaluated as mild, moderate, or marked hypokinesis, akinesis, and dyskinesis. Also, global hypokinesis was reported to be mild, moderate, or marked. The wall motion abnormalities were graded on the basis of visual inspection of the gated cine slices of the myocardial perfusion imaging studies. The readers used a standard template for reporting of GMPI results to ensure consistency in reporting. An expert reader who was unaware of whether each patient had RT interpreted all GMPI studies according to the same parameters for both perfusion and functional abnormalities used by the 6 readers described. The results of the blinded reader and those of the 6 readers were compared for agreement.

The blinded reader's findings from the GMPI in the RT group patients were visually correlated with the different RT isodose lines as seen on the CT–RT plan used for treating these patients (simulation CT). The isodose lines are contours identifying the boundary of regions within which the dose will be higher than the designated dose level. For example, a 50-Gy isodose contour shows the boundary of regions within which the dose will be $>$50 Gy. Isodose lines are convenient and effective ways to show the distributions of the dose in 3 dimensions.

Isodose lines containing the affected segments in GMPI as well as the rest of the LV were recorded. Isodose lines encompassing the whole LV were recorded in patients with normal myocardial perfusion. This was performed to help identify the threshold RT isodose line above which ischemic changes are seen.

Data were analyzed using the SPSS statistical software program, version 11.5. The analysis consisted of descriptive statistics and testing hypotheses about the difference in the endpoints in the RT and NRT groups. The difference in the discrete endpoints ischemia and wall motion between the 2 groups was analyzed using the Mann–Whitney test. A P value < 0.05 was considered to be significant. The 2-sample t test was used to test for differences in the mean values of the continuous variables LVEF, EDV, and ESV. The level of agreement between the multireaders and the blinded reader was determined using the κ-test.

RESULTS

The total number of patients included in this study was 51, 26 patients in the RT group and 25 patients in the NRT

group. All of the patients in the RT group received concurrent chemoradiation before GMPI. Twenty-three patients were treated using 3DCRT and 3 patients were treated using IMRT. In the NRT group, 2 patients received chemotherapy 15 y and 5 y before GMPI for treatment of other cancers and 2 patients received chemotherapy within the 2 mo before GMPI but none of the patients received RT before GMPI. The mean and median interval between concurrent chemoradiation and GMPI was 7.5 and 3 mo, respectively (range, 1.0–38.0 mo). All of the patients in the RT group received a total dose of 50.4 Gy over 28 fractions, except a patient with proximal esophageal cancer who received 60 Gy and 2 other patients who received 40.0 and 45.0 Gy. The patients' demographic characteristics, tumor sites, and CAD risk factors of the 2 groups are summarized in Table 1. The demographics and CAD risk factors were comparable in the RT and NRT groups, except for a history of smoking, which was significantly more prevalent in the NRT group ($P = 0.000$).

We identified myocardial perfusion defects in 14 patients (54%) in the RT group versus 4 patients (16%) in the NRT group. Eleven patients (42%) in the RT group had mild inferior wall ischemia versus only 1 patient (4%) in the NRT group ($P = 0.001$). All of the patients with inferior wall ischemia had distal esophageal cancer and were treated using 3DCRT. One patient with midesophageal cancer had anterior and anteroseptal ischemia and was also treated with 3DCRT. The remaining 12 patients (2 middle and 10 distal esophageal cancer) and 21 patients (1 proximal and 20 distal esophageal cancer) in the RT and NRT groups, respectively, had normal GMPI results. Two of the patients treated using IMRT had normal GMPI and the third one had proximal esophageal cancer and an inferior scar of the LV. The scar in the inferior LV was out of the IMRT field and was probably due to atherosclerotic CAD unrelated to RT. The pattern and location of the perfusion defects in patients with distal esophageal cancer in the RT and NRT groups are summarized in Figure 1. Fewer patients had wall motion abnormalities in association with perfusion abnormalities because most of the patients with ischemia had a mild degree of ischemia. Among the patients in the RT group with perfusion defects, 4 had mild, 1 had moderate, and 2 had marked hypokinesis, whereas in the NRT group, 2 had mild hypokinesis and 1 had marked hypokinesis. The mean LVEF, EDV, and ESV in the RT and NRT groups were 59.0% ± 10.7%, 84.3 ± 8.6 mL, and 37.5 ± 34.6 mL and 59.3% ± 9.8%, 96.5 ± 31.7 mL, and 41.5 ± 27.9 mL, respectively (P = not significant).

There was good agreement between the interpretation of the GMPI results by the multiple readers and the interpretation by the blinded reader with regard to the detected myocardial perfusion abnormalities, with a κ value of 0.84, and no significant differences in the readings. The

TABLE 1
Patient Characteristics in RT and NRT Groups

Characteristic	RT group	NRT group
Age (y)	65.4 ± 9.0	69.5 ± 10.7
Sex		
Women	2	1
Men	24	24
Tumor location		
Proximal	1	1
Middle	3	0
Distal/GEJ*	22	24
Risk factors of CAD		
Hypertension	16	17
Diabetes mellitus	6	10
Smoking	11	21
Family history of CAD	6	6
Dyslipidemia	7	10
Obesity	2	2
Myocardial infarction	3	2

*GEJ = gastroesophageal junction.

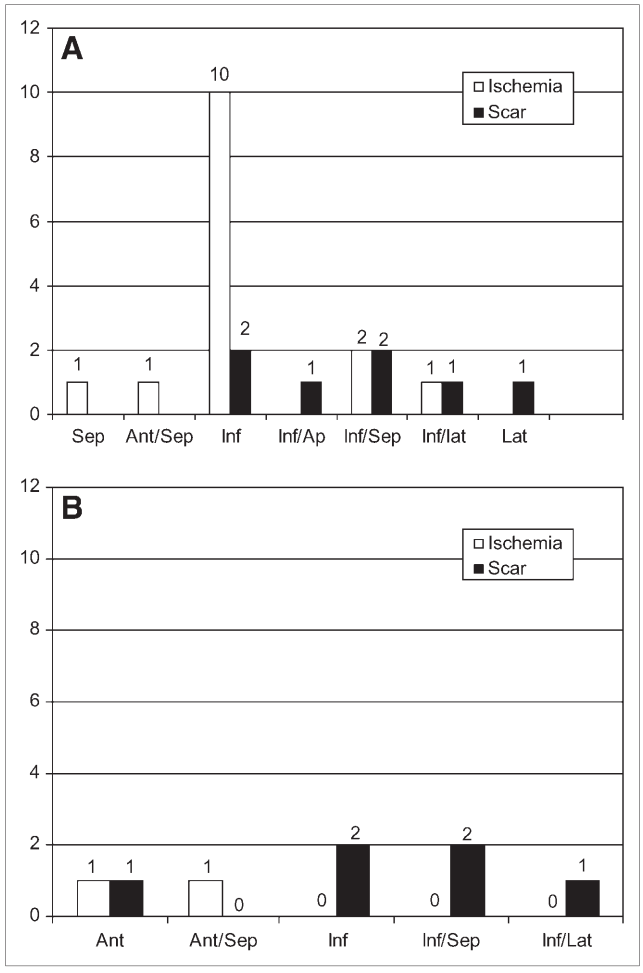

FIGURE 1. Number and location of myocardial perfusion defects in RT group (A) and NRT group (B) in patients with distal esophageal cancer. Sep = septal; Ant/Sep = anteroseptal; Inf = inferior; Inf/Ap = inferoapical; Inf/Sep = inferoseptal; Inf/lat = inferolateral; Lat = lateral; Ant = anterior.

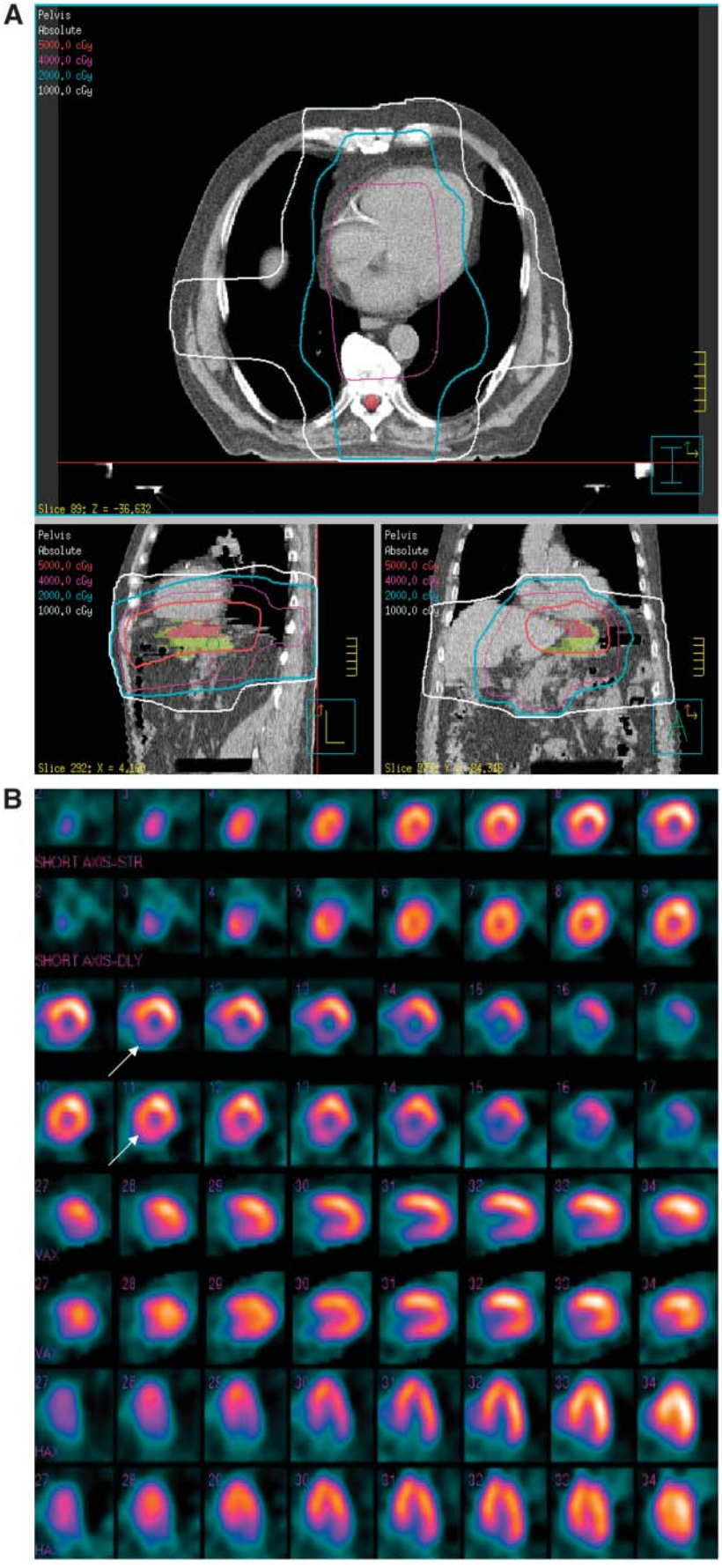

FIGURE 2. Simulation CT slices with RT plan for treating patient with distal esophageal cancer (A) and GMPI images (B) obtained 11 mo after completion of RT. Area of ischemia in inferior wall of heart (arrow) was included in 4,000- to 5,000-cGy isocontours.

agreement for wall motion abnormalities was fair, with a κ value of 0.57, and overall no significant differences in the readings.

Information with regard to the mean radiation dose to the heart was available for 20 of the 26 patients in the RT group. Two of the remaining 6 patients were treated at another facility, and there were technical difficulties in retrieving the RT plans of the other 4 patients. The overall mean radiation dose to the heart in the 20 patients with RT plans was 3,243.1 ± 941.1 cGy. The mean radiation dose was higher in patients with abnormal GMPI results than that in those with normal results but the difference was not statistically significant (3,481.7 vs. 3,036.2 cGy; $P = 0.33$).

We also found that myocardial perfusion defects were encompassed by higher RT isodose lines than the remaining normal LV and totally normal LVs (Fig. 2). In 7 of 10 patients (70%) who had abnormal GMPI results (Fig. 1) and RT plans, the myocardial perfusion defect was encompassed in isodose lines above 45 Gy, whereas in only 5 of 20 patients (25%) the remaining normal LV or a totally normal LV was included in an isodose line above 45 Gy. These results pointed toward the increasing number of myocardial perfusion defects with the 45-Gy or higher RT isodose lines (Fig. 3).

DISCUSSION

Our study demonstrated a high prevalence of myocardial ischemia in the inferior segments of the LV in patients with esophageal cancer who received prior concurrent chemoradiation (54%) compared with 14% in the NRT group. This was a statistically significant difference between the 2 groups. There was also a high level of agreement in the interpretation of the GMPI findings by the multiple readers and the blinded expert reader, which strengthens the role of GMPI in detecting RICAD. Furthermore, our results indicate that the incidence of RICAD with RT for esophageal cancer is high in areas of the heart included in RT isodose lines ≥ 45 Gy. This is primarily due to the unavoidable close proximity of most esophageal tumors to the heart. The close proximity of several other tumors to the heart, including many lung cancers, adds a challenge and a need for even further-targeted RT fields. Our results support the opinion of Prosnitz et al., who suggest that vigilance is still required with the new modalities of RT (*15*). Cardiac toxicity is related to the radiation dose and the volume of myocardium involved (*16*) in the RT field, regardless of the RT technique. However, further improvement in the radiation dose to the target versus the normal tissue is expected with the newer RT techniques as with IMRT, proton therapy, and respiratory gated RT (*17,18*). Our results may help in future comparisons of cardiotoxicity associated with the different RT techniques (*19*).

Few studies demonstrated the capability of GMPI in detecting myocardial perfusion abnormalities in relation to RT in a subclinical setting (*20*). Our study indicates that GMPI is a valuable screening test for silent vascular injury related to RT. Our findings agree with those of several authors (*21–24*) with regard to the correlation between the location of the perfusion defect and the RT field. On the other hand, our findings of a more reversible ischemic pattern with RT are different from the data of Gyenes et al. (*21,22*), indicating 50% new fixed perfusion defects after RT in patients with breast cancer. This difference may be related to the difference in the mean RT dose to the heart, which seems to be of higher range in their population (2,990.0–4,750.0 cGy) than that in this group of patients (3,243.1 ± 941.1 cGy). Thus, we might be detecting a less severe form of RT toxicity in our patient population. Our finding of the ischemia pattern in relation to the RT using 3DCRT is significant as this is a reversible and treatable stage of RICAD, and halting its progression may decrease the incidence of future cardiovascular events. Treatment of RICAD would follow the same lines of management of atherosclerotic CAD either with medical therapy or revascularization, considering the patient's symptoms, cancer stage, expected survival, and comorbidities.

Lack of a significant difference in LV quantitative functional results is most likely due to the mild subclinical nature of most of the myocardial perfusion defects seen in this patient population. This could also be related to the delay time between stressing the patient during myocardial perfusion imaging and the actual acquisition of the gated stress SPECT images. In addition, there was only fair agreement between the multiple readers and the single expert reader for wall motion abnormalities, with a κ value of 0.57. These

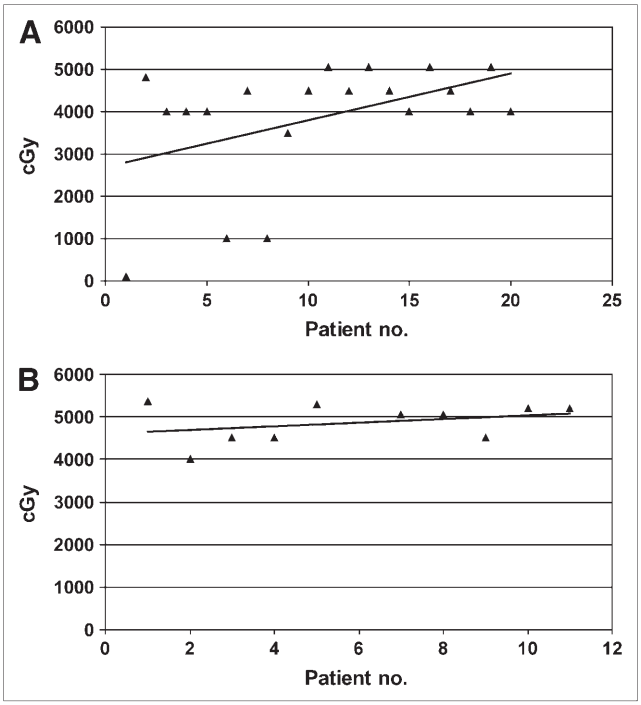

FIGURE 3. Correlation of normally perfused myocardium per patient (A) and abnormally perfused myocardium (B) with radiation dose of encompassing RT isodose line in each patient.

findings do not support the use of radionuclide ventriculography as an imaging modality to screen for radiation-induced myocardial damage. The inability to detect early radiation-induced myocardial toxicity using functional LV information has been described previously (*25,26*). Our results confirm that LV functional information would be an insensitive means to detect RICAD.

The mean and median interval of follow-up with GMPI were 7.5 and 3 mo after RT (range, 1–38 mo). Fifteen patients were imaged at the median interval of 3 mo or earlier from the date of completion of RT. Of these patients' studies, 6 were abnormal and 9 were normal. Four of the abnormal studies had ischemia in the inferior segments of the heart, 1 had an inferior scar and distal esophageal cancer, and the remaining patient had anterior and anteroseptal ischemia with an inferoseptal scar and midesophageal cancer. Three of the patients in the RT group had GMPI before RT and at 6 mo after RT. One of these 3 patients demonstrated new mild inferior ischemia after RT for distal esophageal cancer. Although the numbers may be too small to make a definitive conclusion, we suggest that GMPI should be performed 6 mo after RT for early detection of RICAD (*21,22,24*). This recommendation is supported by the prospective study of Marks et al., demonstrating 27%, 29%, 38%, and 42% incidence of myocardial perfusion abnormalities in asymptomatic patients with breast cancer at 6, 12, 18, and 24 mo after RT, respectively (*24*).

One limitation of our study was our inability to identify the role of chemotherapy and its effects on the coronary arteries separately from RT because all of the patients received concurrent chemoradiation before surgery. However, many of our patients, in a large cancer center, are receiving various chemotherapy combinations, yet the overall abnormal GMPI study rate in our institution is approximately 20%. We also would have preferred that the patients in the 2 study groups be comparable in all risk factors for CAD. The finding that the number of patients with a history of smoking was significantly higher in the NRT group than that in the RT group was unexpected but did not seem to affect our results as the higher prevalence of abnormal GMPI results was noted in the RT group.

Our study is important in that it demonstrates the early subclinical cardiac effects of concurrent chemoradiation using primarily 3DCRT techniques. Our data also suggest that radiation isodose lines of 45 Gy or above are associated with higher ischemic myocardial perfusion defects. This information can be applied to RT for other tumors with longer survival durations if the heart is included in the RT field. Although the exact mechanism behind radiation-induced CAD is not clearly defined, it is thought that endothelial damage leads to significant fibrosis. The risk of fatal CAD may occur at any age, and children as young as 15 y old have shown radiation-induced heart damage within 3 y of exposure to radiotherapy (*27*). RICAD was found to involve primarily the proximal vessels or the coronary ostia (*28*). Our findings also suggest that the effect of RT is mainly on the main coronary arteries because GMPI abnormalities are usually related to major pericardial vessel disease, and most of the perfusion defects noted were ischemic in nature. Future efforts to spare or shield the main coronary arteries using image-guided RT planning techniques may be attempted (*29*). Sparing of the LV or the main coronary arteries using SPECT/CT, contrast CT, or CT angiography for RT planning may be considered. Proton therapy, if available, is also expected to increase the target-to-nontarget effects of RT with possibly less cardiotoxic effects in tumors close to the heart. In the meanwhile, we recommend early screening for RICAD and early management of this side effect of RT to decrease mortality from cardiovascular events in this era of prolonged cancer survival. Additionally, preoperative risk stratification in cancer patients who had prior radiation involving the heart is essential.

CONCLUSION

Inferior LV ischemia is a common finding in distal esophageal cancer patients after concurrent chemoradiation using the 3DCRT technique. The ischemic segments were usually encompassed by RT isodose lines $\geq$ 45 Gy.

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