Patterns of Cardiac Perfusion Abnormalities After Chemoradiotherapy in Patients with Lung Cancer

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Objective: We evaluated the prevalence of myocardial perfusion defects using myocardial perfusion imaging (MPI) after chemoradiation or radiation therapy (CRT/RT) in lung cancer patients and described their patterns in relation to tumor location.

Methods: MPI in 44 patients who received RT for lung cancer and 44 control patients were compared. The two groups were comparable in risk factors for coronary artery disease. Data regarding tumor stage and location, interval between CRT/RT and MPI, and mean radiation dose to the heart was collected. The level of radiation delivered to the affected segments of the left ventricle versus the normal segments was compared using the isodose lines on the simulation computed tomography.

Results: Considering all tumor locations, 8 patients (18%) demonstrated MPI defects after CRT/RT versus 9 (20%) in the controls. However, 7 of 18 patients (39%) with centrally located tumors in the CRT/RT group versus only 1 of 15 patients (7%) in the control group demonstrated MPI defect ($p = 0.04$). The defects in the CRT/RT group were in the anterior and septal segments while the defects were in different segments in the controls. The median interval between end of RT and MPI was 12.3 months. The affected segments in the CRT/RT group received a mean radiation dose of 39.6 versus 11.4 Gy ($p = 0.003$) to the normal segments.

Conclusions: CRT/RT to centrally located lung tumors tends to cause anterior/septal MPI defects. Abnormal MPI segments in the CRT/RT group have received significantly higher radiation than normal segments.

Key Words: Lung Cancer, Radiation therapy, Chemoradiation, Myocardial perfusion imaging.

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Multiple studies in patients with lymphoma or left breast cancer have demonstrated detrimental effects of radiotherapy (RT) on the heart.[1–6] Researchers have studied the effects of RT patients with these two particular types of cancer to evaluate the effects of RT because of the longer survival intervals after treatment which allowed for the long-term side effects of RT to manifest. However, investigators have demonstrated the early effects of RT using multiple imaging modalities.[7–9] For example, studies have found myocardial perfusion abnormalities using myocardial perfusion imaging (MPI) early after RT and even before the development of clinical symptoms.[10–14] The number of patients with such perfusion abnormalities usually increases as the interval after RT increases.[15] Furthermore, echocardiography has been used to assess the effects of radiation on the valves, pericardium, and myocardial contractility.[7,16] Both computed tomography (CT) and echocardiography are useful in evaluating the size and effects of pericardial effusions after RT.[17] Thus, different noninvasive imaging modalities have proven to be useful in early evaluation of the effects of RT on the heart.

Improvements in cancer therapy have resulted in prolonged survival after initial diagnosis of many cancers that were previously known to be lethal in short intervals. Additionally, screening and early detection of cancer have resulted in early initiation of therapy. Presently, patients with cancer tend to survive their disease long enough to experience the long-term side effects of cancer therapy. Lung cancer is one of the cancer types for which the 5-year survival rate has improved over the past decade.[18] Many patients diagnosed with lung cancer receive chemoradiotherapy (CRT) early in the course of their treatment. High-dose RT is usually delivered to the primary tumor and/or hilar lymph node metastases in close proximity to the heart. This is anticipated to cause myocardial perfusion abnormalities as seen using MPI. To our knowledge, the effects of CRT or RT on myocardial perfusion in patients with lung cancer have yet to be investigated adequately. There are no prior studies that described the expected patterns of MPI abnormalities with CRT or RT in patients with lung cancer. Therefore, in this study, we investigated the prevalence of myocardial perfusion abnormalities in patients with lung cancer who received CRT/RT and was compared with lung cancer patients who did not receive CRT/RT before MPI. We also investigated the relationship between primary lung tumor location and the pat-

terns of myocardial perfusion abnormalities in the patients who received CRT/RT.

PATIENTS AND METHODS

Upon approval of our study by the Institutional Review Board, a retrospective search of a prospectively collected database in the nuclear medicine department of MPI studies completed at our institution was performed. Data of 44 consecutive patients with lung cancer who underwent CRT/RT before MPI from March 2003 to May 2006 were extracted. The results of the MPI studies were compared with those in a control group of 44 consecutive patients with lung cancer who did not receive RT before MPI. The control group patients were extracted from the same data base and their MPI were performed between March to September of 2003. The patients in the CRT/RT and control groups were comparable in their demographic characteristics and lung tumor type. Patients for whom the interval between the end of CRT/RT and the initiation of MPI was less than 2 months were excluded since our previous experience demonstrated that most RT related abnormalities are unlikely to develop in such a short interval.[19] The patients' demographic data, tumor histology, tumor stage, interval between CRT/RT and MPI, RT technique, total radiation dose, mean radiation dose delivered to the heart were analyzed. Tumors medial to the mid clavicular line were classified as central and lateral to the mid clavicular line were classified as lateral in the lung. Tumors extending on both sides of the mid clavicular line were classified as both central and lateral in location. Most importantly, the locations of the primary lung tumors with or without central lymph node metastasis and RT planning fields were compared with the locations of myocardial perfusion abnormalities seen in MPI studies. The level of radiation delivered to the affected segments of the left ventricle (LV) versus the normal segments was compared using the isodose lines on the simulation CT for RT planning. The isodose line is a contour identifying the boundary of a region within which the dose is higher than the designated radiation dose level. Isodose lines demonstrate the distribution of the RT dose in 3-dimensions which correlated well with the 3-dimensional nature of MPI. Isodose lines containing the affected segments in myocardial perfusion images as well as the rest of the LV were recorded. Also, isodose lines encompassing the whole LV in patients with normal myocardial perfusion were recorded. This correlation of isodose lines with abnormal versus normal myocardial perfusion segments was performed to help identify the threshold RT dose above which ischemic changes occurred.

Similar data were collected for the control group except for the information related to CRT/RT since none of these patients received RT.

MPI was performed as part of routine standard-of-care studies for risk stratification before surgery in 43 patients, multiple risk factors for coronary artery disease (CAD) in 24 patients, symptoms of chest pain or dyspnea in 19 patient, for EKG abnormality in 1 patient and atrial fibrillation in another patient. MPI was performed using a dual-isotope protocol with 111 MBq (3 mCi) of thallium-201 injected intravenously before the acquisition of a rest single-photon emission computed tomography (SPECT) and 925–1110 MBq (25–30 mCi) of technetium-99m tetrofosmin injected at peak stress 30 minutes before a stress gated SPECT acquisition. Patients were stressed using adenosine, dobutamine, and exercise in 57, 16, and 15 patients, respectively. The rest and stress SPECT were acquired using a dual head gamma camera (Philips-Cardio 60) over 180 degrees arc, 20 sec/frame, 64 frames in a 64 × 64 matrix using a low energy all purpose collimator. The images were processed using filtered back projection with a butterworth filter at the order of 5 and frequency of 0.35 Nyquist. Gating was added to the stress SPECT images in eight bins over the cardiac cycle. The images are routinely interpreted by one out of five routine readers and was reread by an additional expert reader who was blinded to the locations of the lung tumors or the RT field or dose. Difference between the routine reader and the expert blinded reader was noted in only three patients in which the expert reader interpretation was considered for the data analysis. Perfusion abnormalities were identified using a 13-segment model of the LV. Perfusion abnormalities were qualitatively graded as scar; mild, moderate, or marked ischemia; or mixed mild, moderate or marked ischemia with scar. Functional information regarding left ventricular ejection fraction, end-diastolic volume, and end-systolic volume was also collected. The MPI findings for the CRT/RT group were visually correlated with the different RT isodose lines as seen on the simulation CT for RT planning used in these patients.

Statistical Analysis

Descriptive statistics were used to analyze the collected data. The Wilcoxon test was used to analyze significant differences in the continuous variables, such as in the functional results of the MPI studies. The Fisher's exact test was used to analyze differences in risk factors for CAD and the χ^2 test to compare the prevalence of myocardial perfusion abnormalities between the two patient groups. p-values less than 0.05 were considered statistically significant.

RESULTS

The demographics and lung cancer characteristics of the patients in the CRT/RT and control groups are listed in Table 1. Forty patients had CRT and four patients had RT only in the CRT/RT group. In the control group, 24 patients had chemotherapy. The two groups had similar distributions of risk factors for CAD except for hypertension, which was more prevalent in the control group than in the CRT/RT group (Table 2).

The mean total radiation dose ± SD (SD) delivered to the lung tumor in the CRT/RT group was 56.6 ± 9.6 Gy. Thirty-five patients underwent three-dimensional (3D) conformal RT, and nine patients underwent intensity-modulated RT (IMRT). The RT plans were available for review to obtain the mean radiation dose delivered to the heart in 39 patients in the CRT/RT group. The mean radiation dose ± SD delivered to the whole heart in this group was 18.3 ± 10.3 Gy. The mean interval between the end of RT and the MPI was 25.0 ± 2.5 months (median, 12.3 months). We did not observe a significant difference between the number of pa-

TABLE 1. Comparison of the Demographics of Lung Cancer Patients Who Were Treated with CRT/RT versus the Control Group

	CRT/RT Group (n = 44)	Control Group (n = 44)
Age (yr)	65.8 ± 9.4	69.0 ± 5.2
Sex (F:M)	22:22	20:24
Tumor type		
NSCLC	40	41
SCLC	4	3
Stage		
I	7	17[a]
II	0	5[a]
III a	14	12
III b	13	5
IV	8	6
Recurrence	2	0
Location		
LUL	12	14
LLL	5	5[a]
L hilum	4	1
RUL	15	6[a]
RML	1	1
RLL	6	16
R hilum	1	2

[a] One patient had two primary lung cancers.

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; LUL, left upper lobe; LLL, Left lower lobe; L, left; RUL, right upper lobe, RML, right middle lobe; RLL, right lower lobe; R, right; F, female; M, male.

TABLE 2. Prevalence of Risk Factors for CAD in the CRT/RT Group and the Control Group

Risk Factors for CAD	CRT/RT Group	Control Group	p
Diabetes mellitus	7	9	0.79
Hypertension	20	31	0.03
Smoking	43	36	0.11
Family history of CAD	28	30	0.82
Obesity	4	2	0.68
Dyslipidemia	19	14	0.38

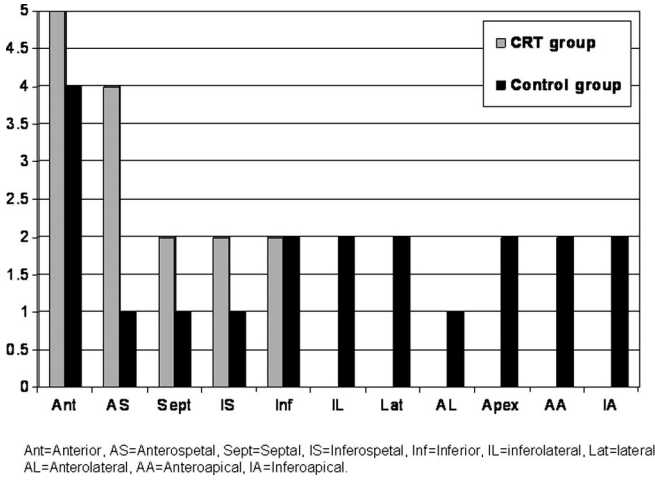
CRT/RT, chemoradiation/radiation therapy; CAD, coronary artery disease.

TABLE 3. Lung Cancer Tumor Location in the Patients with Abnormal versus Normal MPIs Who Received RT

	Abnormal MPI[a]		Normal MPI		
	Central	Both	Central	Lateral	Both
R apex	—	—	—	—	6
RUL	1	1	4	1	2
RML	—	—	1	—	—
RLL	1	—	—	1	4
L apex	—	—	—	—	4
LUL	3	—	4	5	—
LLL	1	—	1	3	—
R main bronchus	1	—	—	—	—

[a] None of the patients with abnormal MPI studies had a laterally located lung cancer.

R, right; RUL, right upper lobe, RML, right middle lobe; RLL, right lower lobe; L, left; LUL, left upper lobe; LLL, Left lower lobe; MPI, myocardial perfusion imaging; RT, radiation therapy.



Ant=Anterior, AS=Anterospetal, Sept=Septal, IS=Inferospetal, Inf=Inferior, IL=inferolateral, Lat=lateral, AL=Anterolateral, AA=Anteroapical, IA=Inferoapical.

FIGURE 1. The distribution of myocardial perfusion abnormalities in the left ventricular segments in patients in the chemoradiation/radiation therapy (CRT/RT) and control groups.

tients with myocardial perfusion abnormalities in the CRT/RT group and that in the control group (8 versus 9; p = 1.0) when all tumor locations were considered. However, seven of the eight patients with MPI abnormality in the CRT/RT group were in patients with centrally located tumors and particularly of the left lung (Table 3). Additionally, 7 of the 18 patients (39%) with centrally located lung cancer had MPI abnormalities in the CRT/RT group while only 1 of the 15 patients (7%) with centrally located cancer had MPI defect in the control group (p = 0.046). In the CRT/RT group, four patients had ischemia, two had scar, one had mixed scar and ischemia in the same segments, and one had scar and ischemia in different segments of the LV. In the control group, five patients had ischemia, two had scar, one had mixed scar and ischemia in the same segments, and one had scar and ischemia in different segments in the LV. Although the numbers of abnormalities in the two groups were not significantly different, the pattern of LV defects was consistently different. In the CRT/RT group, the anterior wall of the LV was abnormal in five patients, the anteroseptal/septal wall was abnormal in two patients, and the anteroseptal/apical wall was abnormal in one patient. In the control group, the abnormalities were distributed in almost all the different segments of the LV as demonstrated in Figure 1.

Seven of the eight patients in the CRT/RT group who had abnormal myocardial perfusion abnormalities received 3D conformal RT, whereas the remaining patient received IMRT. When correlated with the RT plans, the affected LV segments in the CRT/RT group received a mean radiation dose of 39.6 Gy while the normal segments received a mean radiation dose of 11.4 Gy (p = 0.003). Figure 2 demonstrates an example of a patient with left upper lung cancer and

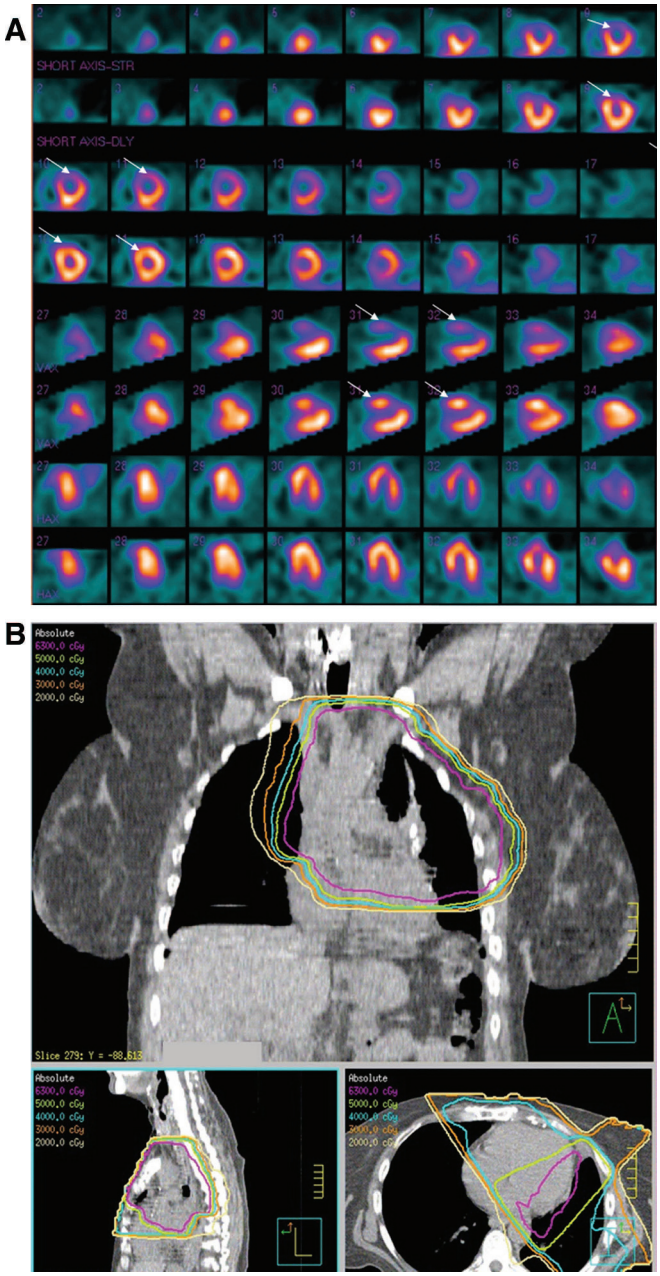


FIGURE 2. Myocardial perfusion images demonstrating anterior wall ischemia (arrows) (*A*) in a patient with left upper lung cancer who had 3D conformal radiation therapy as planned using simulation computed tomography (*B*).

anterior wall ischemia of the LV. All of the normal LV segments in the CRT group were encompassed by isodose lines of ≤20 Gy. An exception was noted in one patient with normal MPI in whom the whole heart was included evenly in high isodose lines of 40 to 50 Gy.

The mean left ventricular ejection fraction, end-diastolic volume, and end-systolic volume ± SD were 60.9 ± 14.6%, 71.6 ± 24.5 ml, and 30.2 ± 18.8 ml, respectively, in the CRT group and 64.8 ± 11.14% ($p = 0.19$), 77.5 ± 33.2 ml ($p = 0.69$), and 30.2 ± 23.1 ml ($p = 0.54$), respectively, in the control group. We observed no statistically significant differences in the functional data between the two groups.

DISCUSSION

Our study demonstrated that the prevalence of myocardial perfusion abnormalities in the patients with lung cancer who received CRT/RT, considering all tumor locations, is comparable to a control group of patients who did not receive RT (18% versus 20%, respectively). However, we noted consistent differences in the locations of myocardial perfusion abnormalities in the two groups, as patients who received CRT/RT had abnormalities in the anterior, anteroseptal and septal walls of the LV, whereas patients who did not receive RT had abnormalities in different walls of the LV. Also, 39% of the patients with centrally located tumors had MPI abnormality in the CRT/RT group versus 7% in the control group. This was statistically significant difference between the two groups in patients with centrally located tumors. Particularly, most of these patients had centrally located left lung cancer. This is probably due to the close proximity of these tumors to the heart. Interestingly, the patients who demonstrated anteroseptal and septal defects were the three patients who had centrally located right or right main bronchus lung cancer. This was probably related to the fact that the right ventricle is not visualized using MPI and that the septal and anteroseptal regions are the most medial portions of the LV involved in the RT field in patients with centrally located right lung tumors.

Our findings confirm a previously described increase in the prevalence of myocardial perfusion abnormalities in the inferior wall of the LV, in patients with distal esophageal cancer who received concurrent CRT (54%) compared with that in patients who did not receive CRT (16%).[19] In both patients with distal esophageal cancer and those with centrally located lung cancer or hilar metastases, the proximity of the tumor to the heart results in delivery of high radiation doses to the heart. Marks et al.[15] demonstrated that at 6, 12, 18, and 24 months after RT, 27%, 29%, 38%, and 42%, respectively, of patients with breast cancer had myocardial perfusion abnormalities. Our finding of 39% prevalence of MPI abnormalities in patients with centrally located tumors at a mean interval of follow-up after CRT/RT of 25 months (median 12.3 months) also are comparable to Marks et al. findings in breast cancer patients. The myocardial perfusion defects were also found to be associated with higher incidence of chest pain in breast cancer patients.[20] Harris et al.[21] have recently demonstrated an overall difference in mortality from cardiac causes in left-sided versus right-sided breast cancer patients using contemporary tangential beam techniques. Authors have also documented similar rates of myocardial perfusion abnormalities in patients with lymphoma who received RT.[8] The clinical implications of MPI defects seen is lung cancer patients have not been previously investigated and is the subject of ongoing research at our institution.

The literature is inconsistent regarding the etiology of myocardial perfusion abnormalities caused by RT. For example, Brosius et al.[22] documented proximal CAD in autopsy

specimens obtained from patients who received RT with fields that included the heart. Additionally, Girinsky et al.[23] observed a lower incidence of RT-related cardiac complications with shielding of the proximal coronary arteries during RT planning. Also Veinot et al.[24] have demonstrated pericardial coronary arteries lesions after RT by autopsy. Heidenreich et al.[8] also described the presence of coronary stenosis greater than 50% in 55% of patients with abnormal MPI and history of mediastinal irradiation and less than 50% in 22% of them. In contrast, Gyenes et al.[12] suggested that these perfusion abnormalities are probably caused by microvascular damage in the heart. An interesting case report by Letsas et al.[25] described a patient who experienced an acute myocardial infarction in the setting of normal coronary arteries 16 years after irradiation of the chest for the treatment of Hodgkin disease. Additionally, a recent case report by Hong et al.[9] described a patient with lymphoma who had a myocardial perfusion abnormality as detected using positron emission tomography but normal coronary arteries on a coronary CT angiogram. We have observed during this study and our previous study of patients with esophageal cancer sharp geometric demarcation between abnormal and normal myocardium in relation to the higher radiation isodose lines of 40 to 45 Gy. The myocardial perfusion defect pattern is similar to what is usually seen in bone, lung and brain scans in patients who undergo irradiation of these organs. This is supportive of the microvascular component of the damage. Thus, the etiology of myocardial defects is probably due to combination of radiation damage to both the epicardial coronary arteries and the microvasculature of the heart.

One patient in our study who received homogenous high radiation dose to the heart had normal myocardial perfusion. Since MPI demonstrates relative decreased perfusion to different segments of the LV, diffuse vascular involvement may not be apparent. This may be a limitation of MPI studies in such patients who receive homogeneous high radiation doses to the heart. This phenomenon would be similar to the previously described false negative results in patients with balanced three-vessel CAD.[26,27] Thus, we feel that the MPI results in this patient may have been a false-negative result because of the balanced diffuse effect of RT on the left ventricular vasculature. However, we do not have a supporting evidence to prove this hypothesis.

Since all of the detected myocardial perfusion abnormalities occurred in patients with centrally located lung tumors, vigilance in RT planning to spare the heart in such patients is necessary, especially when using 3D conformal RT. In our study, seven of eight patients in the CRT group who had myocardial perfusion abnormalities after RT underwent 3D conformal RT, whereas the eighth underwent IMRT. This suggests that patients with centrally located lung tumors may be better candidates for proton therapy, when available, since it is expected to deliver more targeted RT to the tumor with less damage to the surrounding normal organs.

One limitation of our study is the fact that it was retrospective with possible inaccurate documentation of the risk factors for CAD in both study groups. However, in all of the cases, our anesthesia and cardiology department collect the risk factors for CAD in a structured reporting format which helps more inclusive reporting system and more confidence in the data collected with less likelihood of omission of risk factors. Another limitation is the lack of use of attenuation correction for the MPI studies in our institution. However, the difference in location of MPI defects between the CRT/RT group and the control group is unlikely to be related or explained by attenuation artifacts since the distribution of males to females was comparable in the two study groups. The few number of abnormal MPI studies in both study groups may also represent a limitation in our study. Further validation of our results with large number of patients would add valuable information of the cardiac effects of CRT in lung cancer patients.

In conclusion, an association between centrally located lung cancers and anterior/septal MPI defects is demonstrated in our study. The affected MPI segments had a significantly higher radiation dose than normal segments in the CRT/RT group.

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