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Symptomatic cardiac toxicity is predicted by dosimetric and patient factors rather than changes in ^{18}F -FDG PET determination of myocardial activity after chemoradiotherapy for esophageal cancer

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Abstract

Purpose—To determine factors associated with symptomatic cardiac toxicity in patients with esophageal cancer treated with chemoradiotherapy.

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Material and Methods—We retrospectively evaluated 102 patients treated with chemoradiotherapy for locally advanced esophageal cancer. Our primary endpoint was symptomatic cardiac toxicity. Radiation dosimetry, patient demographic factors, and myocardial changes seen on ^{18}F -FDG PET were correlated with subsequent cardiac toxicity. Cardiac toxicity measured by RTOG and CTCAE v3.0 criteria was identified by chart review.

Results—During the follow up period, 12 patients were identified with treatment related cardiac toxicity, 6 of which were symptomatic. The mean heart V20 (79.7% vs. 67.2%, $p=0.05$), V30 (75.8% vs. 61.9%, $p=0.04$), and V40 (69.2% vs. 53.8%, $p=0.03$) were significantly higher in patients with symptomatic cardiac toxicity than those without. We found the threshold for symptomatic cardiac toxicity to be a V20, V30 and V40 above 70%, 65% and 60%, respectively. There was no correlation between change myocardial SUV on PET and cardiac toxicity, however, a greater proportion of women suffered symptomatic cardiac toxicity compared to men ($p=0.005$).

Conclusions—A correlation did not exist between percent change in myocardial SUV and cardiac toxicity. Patients with symptomatic cardiac toxicity received significantly greater mean V20, 30 and 40 values to the heart compared to asymptomatic patients. These data need validation in a larger independent data set.

Keywords

Chemoradiotherapy; Esophageal cancer; Cardiac Toxicity

Introduction

^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) scans are useful during the radiation therapy treatment planning process and as after treatment as a predictor of response and prognosis in patients with esophageal cancer undergoing chemoradiotherapy (CRT) [1–26]. Radiation therapy has a known potential to induce myocardial damage in patients receiving treatment for breast cancer and Hodgkin's disease depending upon dose and volume of heart irradiated [27–32]. In addition, nuclear medicine myocardium perfusion scans have been performed to assess radiotherapy-induced myocardial damage [30, 33–38]. Recently, ^{18}F -FDG PET scans have been used to evaluate radiation-induced damage to the lung, liver and heart in patients with esophageal cancer undergoing CRT [4, 39–41].

However, to date there exist only limited data determining whether pretreatment patient demographics, radiation dosimetry, and/or myocardial changes on PET can be predictive of subsequent symptomatic cardiac toxicity. Jingu and colleagues evaluated ^{18}F -FDG PET scans in patients with esophageal cancer treated with CRT performed at least 3 months after completion of therapy. They reported 20.3% of patients demonstrated a higher ^{18}F -FDG uptake in the basal myocardium within the irradiated fields as compared to myocardial ^{18}F -FDG uptake outside of the irradiated fields [41]. Pre-treatment ^{18}F -FDG PET scans were not obtained so comparison of pre- and post-therapy myocardial uptake could not be performed. Additionally, Wei and colleagues found the volume of the pericardium receiving 30 Gy or higher (V30) to be the only parameter significantly associated with risk of pericardial effusion on multivariate analysis [42].

The specific aims of this study were to correlate post-treatment symptomatic cardiac toxicity with change in ^{18}F -FDG myocardial uptake before and after CRT, pre-treatment patient demographics, and/or radiation dosimetry in a prospective cohort of patients with esophageal cancer treated with CRT.

Methods and materials

Patients

Between June 2002 and December 2007, 102 patients with biopsy proven squamous cell or adenocarcinoma of the esophagus presented for treatment at Fox Chase Cancer Center. Patients were treated initially with CRT. Patients suitable for surgical resection routinely underwent esophagectomy 4 to 6 weeks after completion of CRT. Patients treated initially with surgery or without radiation were excluded from this analysis. Forty-nine patients had only a single PET scan or did not have complete dose volume histogram (DVH) analysis of treatment leaving 53 eligible patients to correlate changes in myocardial ^{18}F -FDG PET uptake with cardiac toxicity. Additionally, 28 patients died prior to the 3 month follow-up, were treated palliative intent, or did not have complete DVH analysis of treatment leaving 74 patients eligible to correlate dosimetric and clinical factors with cardiac toxicity.

Chemotherapy

Chemotherapy regimens varied during the study period and were administered at the discretion of the treating medical oncologist. Regimens given concurrently with radiotherapy included; cisplatin and 5-fluorouracil (5-FU), 5-FU alone, 5-FU and paclitaxel, and paclitaxel alone. Eight patients received induction cisplatin ($75\text{mg}/\text{m}^2$ i.v.) and paclitaxel ($175\text{mg}/\text{m}^2$ i.v.) given in weeks 1 and 3. This was followed by cisplatin, paclitaxel, and 5-FU or oral capecitabine during radiotherapy. Two patients who were planned to receive concurrent chemotherapy were unable to do so due to comorbid illness. Please see Table 2 for full chemotherapy details and doses.

Radiotherapy

All patients underwent CT-simulation with intravenous contrast administration to those without contrast allergies and sufficient renal function. Patients were initially treated with anterior/posterior (AP) and posterior/anterior (PA) fields with 6 or 10 MV photon beams. An AP and two posterior oblique fields were incorporated into the treatment to limit the spinal cord to no more than 45 Gray (Gy). Customized blocks were used to protect normal tissue. Initially, no dose-volume constraints were placed on the heart during planning. After cardiac toxicity was noted early in the study period, we attempted to limit the volume of the heart receiving greater than 40 Gy to less than 60%, without sacrificing coverage to the planning target volume (PTV).

All patients had pretreatment PET-scan images fused with the CT-simulation images to aid in determination of the gross tumor volume (GTV). The GTV was also further modified by combining information from pretreatment endoscopic ultrasound, and diagnostic CT scan, and fused PET scan. The clinical target volume (CTV) was created by expanding the GTV 3.5 cm superiorly and inferiorly and 1.0 cm radially. The planning target volume (PTV) was created by expanding the CTV by 1.5 cm in all directions to account for daily set up error. Median prescription dose given was 50.4 Gy (range: 45 – 57.6 Gy) in 1.8 Gy fractions, which was prescribed to the isodose line covering the PTV.

^{18}F -FDG PET

Our institution's PET/CT procedures have been published previously [23]. A maximum standardized uptake value (SUV_{max}) was obtained from the cardiac septum, apex and lateral wall by a two nuclear medicine physicians individually (A.M. & J.Q.Y.) without knowledge of the clinical outcome.

Dosimetric analysis

The whole heart (WH-OAR) and left ventricle (LV-OAR) volumes were contoured prospectively at the time of treatment planning from the apex of the heart up to the origin of the take off of the great vessels to include the right auricular appendage. The LV-OAR was identified and outlined with the help of the fused ^{18}F -FDG PET-scan. The three dimensional (3D) dose distributions and dose-volume histograms (DVH) of the WH-OAR and LV-OAR were calculated from 3D conformal treatment plans. Relative volumes of the WH-OAR and LV-OAR treated to doses greater than 10–50 Gy (V10 through V50) were obtained from the DVH in 10 Gy increments.

Follow up

All patients underwent regular complete multidisciplinary follow up with the treating surgeon, medical oncologist, and radiation oncologist. Post-radiotherapy imaging (either CT or PET) was routinely performed 4–6 weeks after completion of treatment in conjunction with direct visualization, then at 3 month intervals for 2 years and 6 month intervals out to year 5.

If a pericardial effusion was seen on follow up imaging, pericardiocentesis was performed if the effusion was symptomatic or rapidly collecting. Aspirate was sent for cytology, to rule out malignant effusion. Small, asymptomatic effusions were not routinely tapped, and were assumed to be treatment related.

Patients with low grade toxicity were followed expectantly and referred to their primary care physician or cardiologist for management. Symptomatic complaints were fully evaluated with directed diagnostics, including echocardiogram, electrocardiogram, and/or rhythm monitoring at the discretion of the treating cardiologist. Thereafter, treatment included pericardial window or pacemaker placement, as appropriate.

Statistics

Cardiac toxicity as measured by Radiation Therapy Oncology Group (RTOG) late toxicity scoring and Common Toxicity Criteria Adverse Events (CTCAE) v3.0 was identified via retrospective chart review. Scales reviewed included cardiac ischemia, pericarditis, and arrhythmia. Patients with documented malignant pericardial effusions were censored as having no treatment related effusions, but were followed for other cardiac toxicity. The research project was reviewed and approved by the Fox Chase Cancer Center Institutional Review Board.

Wilcoxon test was used to determine an association between the percent change in SUV_{max} and the factors of: any RTOG or CTCAE v3.0 cardiac toxicity, sex, prior heart disease, diabetes, insulin use, smoking history or prior cardiac bypass/angioplasty [43]. Spearman correlation was used to determine association of WH-OAR V10-50, LV-OAR V10-50, days from completion of CRT to post-treatment PET, or age to any RTOG or CTCAE v3.0 cardiac toxicity [43]. Kaplan-Meier analysis was used to estimate the actuarial rate of both all and symptomatic cardiac toxicity.

Results

Patient specific characteristics are shown in Table 1. Twenty-six patients did not undergo surgery. The median follow-up for all patients was 10.7 months (range: 0.9 to 54.8). The median time to any cardiac toxicity was 4.2 (range: 1.2–22.6) months with the median time to symptomatic cardiac toxicity being 8.3 (range: 3–22.6) months. The median interval from end of treatment to post-treatment PET scan was 25 (range: 10–76) days. Twelve total

cardiac toxicities were identified, 6 of which were symptomatic. The 12-month actuarial incidence of any observed cardiac toxicity was 20.4%, and 8.5% when only symptomatic toxicities were considered. The number and intensity of cardiac events as measured by RTOG and CTCAE v3.0 is shown in Table 3. The types and grade of toxicity are depicted in Table 4. Six of the pericardial effusions were asymptomatic, CTCAE v3.0 Grade 1, and were detected on follow-up CT scans. All pericardial effusions, symptomatic or asymptomatic, are grade 3 toxicities in the RTOG system.

Fifty-three patients were eligible for analysis of change in pre- and post-CRT myocardial SUV_{max} . The median percent change in the lateral myocardial wall SUV_{max} was -18% (range: -90 to 362%), septum SUV_{max} -9% (range: -85 to 455%) and apex SUV_{max} -6% (range: -88 to 1110%). A significant SUV_{max} decrease was seen in the lateral myocardial wall ($p=0.009$) and the additive sum SUV_{max} of all 3 measured walls ($p=0.035$) between the pre- and post-chemoradiation ^{18}F -FDG PET-scans. Otherwise, none of the investigated variables correlated with percent change in septum, apex or lateral wall myocardial SUV_{max} uptake. The percent change in lateral wall, septum and apex myocardial SUV_{max} did not correlate or predict for cardiac toxicity.

Seventy-four patients were eligible for analysis of radiation dosimetry and cardiac toxicity. No significant correlation existed between WH-OAR or LV-OAR dosimetry and the presence of any cardiac toxicity. However, when only symptomatic cardiac toxicity was considered, a significant difference was noted in mean WH-OAR V20, V30 and V40 between those patients with and without symptomatic cardiac toxicity. The mean WH-OAR V20 in patients with symptomatic cardiac toxicity was 79.7% compared to 67.2% in patients without symptomatic cardiac toxicity ($p=0.05$). The mean WH-OAR V30 was 75.8% in patients with symptomatic cardiac toxicity compared to 61.9% in patients without symptomatic cardiac toxicity ($p=0.04$). The mean WH-OAR V40 was 69.2% compared to 53.8% ($p=0.03$) when comparing patients with and without a symptomatic cardiac toxicity. There was a 14%, 14%, and 15% probability of a symptomatic cardiac toxicity if the WH-OAR V20, V30 and V40 was greater than 70%, 65%, and 60%, respectively. Conversely, symptomatic cardiac toxicity was not observed in any patient if the WH-OAR V20, V30 and V40 was below 70%, 65% or 60%, respectively.

Patients undergoing surgery did not have a significant increase in any or symptomatic cardiac toxicity compared to patients not undergoing surgery. Four of 26 patients not undergoing surgery experienced an adverse cardiac event with only one being symptomatic. Eight of 46 patients undergoing surgery experienced a cardiac event with five being symptomatic.

No association was detected between prior heart disease, diabetes, insulin use, smoking history, or prior cardiac bypass or angioplasty and the development of any or symptomatic cardiac toxicity after treatment. Female patients were significantly more likely to develop any ($p=0.0046$) and symptomatic cardiac toxicity ($p=0.0013$). Female patients were older than males (mean: 70 vs. 62 years, $p=0.05$), but there were no significant difference between whole heart or left ventricle dosimetry on the basis of gender.

Discussion

Reports of the cardiotoxic effects of radiotherapy are well documented in patients with breast cancer and Hodgkin disease but to a lesser degree in recent reports detailing late radiation effects in patients with esophageal cancer receiving chemoradiotherapy. This may be a result of larger numbers of patients available for study and patients with breast cancer and Hodgkin disease surviving long enough to develop a late toxicity. Other authors have

reported cardiac toxicity in patients with esophageal cancer receiving radiotherapy or CRT [42, 44–46, 49–52]. These studies all have significant differences in the definition of cardiac toxicity, toxicity endpoints, radiation technique, definition of CT-determined heart and pericardial volumes for radiation dosimetry, chemotherapy, and use of surgery.

Martel and colleagues from the University of Michigan reported a 9% rate of nonmalignant pericardial effusions in 57 patients with esophageal cancer treated with pre-operative CRT on 3 consecutive clinical trials [44]. They defined the pericardial volume as a “rind” serving as the outer border of the previously contoured heart volume with the inner border automatically contoured 1 cm within the same volume. An upper anatomic pericardium level was not defined. All patients with pericardial effusion were treated on an institutional protocol giving 3.5 Gy fractions, and their results indicate a significant effect of the fractionation scheme, as well as biologically effective average and maximum pericardial doses in the development of pericardial effusion. Our study has no such fraction size confounders.

Recently, Wei et al. reported a crude rate of pericardial effusion of 27.7%, in 101 patients with inoperable esophageal cancer treated with CRT [42]. The heart was defined as extending from the inferior border of the right pulmonary artery through the apex of the heart and a “shell” extending 0.5 cm outward from the heart contours was used as a surrogate of the pericardium. Mean dose to the pericardium, pericardial V3 and V50, and heart volume treated to greater than 32–38 Gy were associated with an increased risk of pericardial effusion on univariate analysis. However, when multivariate analysis was performed, only the pericardial V30 was significantly associated with the risk of pericardial effusion.

As in the Martel and Wei studies, a proportion of our patients had asymptomatic pericardial effusions detected during post-treatment surveillance CT scans of the thorax. Six patients in this study, however, had symptomatic cardiac toxicity four of which were pericardial effusions. Additionally, one patient suffered a myocardial infarction, and another experienced sick sinus syndrome requiring a pacemaker. We observed a significant difference in the mean V20, V30 and V40 of the contoured whole heart between patients with and without these symptomatic cardiac toxicities. No such correlation was found for the left ventricular only contour, nor when asymptomatic effusions were included in the analysis.

We can speculate that low radiation doses to partial heart volumes may cause minimal inflammation of the pericardium resulting in an asymptomatic, clinically insignificant pericardial effusion. Conversely it may require larger volumes radiated to higher doses to result in a symptomatic cardiac toxicity. This is an important distinction to make, and may explain why we did not see a difference in mean dose between patients with and without any cardiac toxicity but why we did see a significantly higher mean V20, V30 and V40 in patients with symptomatic cardiac toxicity. Left ventricular V20, V30 and V40 was not found to be associated with any cardiac toxicity. A longer follow up interval may be required to demonstrate cardiac toxicity related to left ventricular irradiation, such as a reduced ejection fraction.

Standard contouring definitions for heart, pericardium and left ventricle do not exist, and all reports to date have contoured the heart and pericardium differently. We chose to contour the entire heart since we were investigating all cardiac toxicities rather than pericardial effusions exclusively. A number of assumptions were made to locate the pericardium in past reports and we had concerns regarding the actual location of the pericardium as represented on a static treatment planning CT scan because of both cardiac and respiratory motion. In

addition, the patient populations of the three studies have likewise differed. Martel et al. included patients undergoing surgery, while Wei et al. only included inoperable patients. In the present study, we include both operable and inoperable patients.

There exists considerable heterogeneity in the current literature as to the determination of cardiac toxicity after chemoradiotherapy for esophageal cancer. Previous reports did not employ a standard definition of cardiac toxicity. Two authors utilized no grading system for late toxicity [42,50]. Four authors used the RTOG/EORTC scoring system [45–46, 51–52], one used the Late Effects Normal Tissue (LENT) scoring system [44], and one used the toxicity criteria of the Japan Society for Cancer Therapy [45]. We employed two different grading systems to simultaneously utilize a frequently used scale (RTOG/EORTC) and to separate by symptomatic and asymptomatic toxicity, using the CTCAE v3.0. It should be noted that at least one Grade 5 cardiac toxicity was noted in 4 of the 9 studies listed [45–46, 51–52], and that total radiation doses of 60 Gy or higher were used in each of these 4 trials.

Interestingly, female patients had a higher incidence of any and symptomatic cardiac toxicity. None of the previously published series investigated patient gender as a variable in evaluating cardiac toxicity in patients treated with CRT. However, Wang, et al. reported female gender to be significantly associated with an increased incidence of post-operative pulmonary complications in patients with esophageal cancer treated with neoadjuvant CRT followed by surgery on univariate, but not multivariate analysis [47]. Further study is needed to determine the etiology of cardiac toxicity in this subgroup as this may have therapeutic implications in the future.

Post-treatment change in maximum myocardial ^{18}F -FDG uptake failed to predict for cardiac toxicity in this study. It has been determined that the use of pre-treatment FDG-PET can modify radiotherapy treatment planning volumes in esophageal cancer [1] and enhance normal tissue sparing in other thoracic tumors [53]. Additionally, tumor metabolic response to therapy as measured by FDG-PET has been shown to be predictive and prognostic of patient outcome in a number of gastrointestinal sites [54]. Furthermore, increased post-therapy SUV_{max} in lung parenchyma can predict for increased incidence of radiation-induced lung toxicity in patients with non-small cell lung cancer [55]. Unfortunately, the uptake of FDG in cardiovascular tissue is unpredictable and heterogeneous. Increased SUV has been reported in the setting of inflammatory cardiovascular disease such as myocarditis and pericarditis [56]. Radiation has been associated with volume-dependent perfusion defects and wall motion abnormalities in women with breast cancer treated with tangential radiation fields [33, 48]. Though none of those patients experienced a documented myocardial infarction or congestive failure, further study is ongoing to better define the long-term functional consequences from thoracic CRT. Jingu et al. reported that 20.3% of patients treated with radiotherapy for esophageal cancer demonstrated a high FDG uptake in the myocardium corresponding to the irradiated fields on PET scans obtained a median of 9.25 months after completion of radiotherapy. Pretreatment PET was unavailable for study, so comparison was made to out of field myocardium. Of the 14 patients with high SUV, 8 consented for further work-up with 7 having abnormalities on advanced imaging and/or cardiac symptoms. Conversely, we generally found a decrease in maximum FDG uptake when directly comparing the pre- and post-treatment PET scans routinely taken 1 month after completion of radiotherapy. Additionally we found no evidence that this decrease in SUV_{max} correlated with cardiac toxicity. The reasons for these differing results are unclear, but we may speculate that the relative latency to PET scan likely played a role. Further study is needed.

Limitations certainly exist with this study. The treatment received by the entire cohort was fairly heterogeneous in terms of total radiation dose, chemotherapy regimens, and candidacy

for surgical resection. Although a single radiation oncologist was responsible for all heart and left ventricular contours, variation was sure to exist. Additionally, the heart is a mobile structure and its location may vary both interfraction and intrafraction relative to the planning CT scan, though all studies of this type would suffer from the same limitation. Given the structured, comprehensive, and multidisciplinary follow-up that each patient received, we believe that our prospectively collected toxicity data is robust. However, it is certainly possible that events went unrecorded, particularly among those with asymptomatic toxicity. Additionally, cardiac toxicity was grouped together as a single entity, however it is unlikely that all cardiac toxicities share a common radiation induced pathophysiology. In a larger cohort, it may be possible to observe dosimetric limits for distinct heart volumes, such as the LAD or left ventricular wall for individual toxicity outcomes. Because of the above limitations, the whole heart V20, V30 and V40 values reported above for symptomatic cardiac events in our patients will need validation by an independent data set with a large number of clinical events.

Conclusion

A significant difference in the radiation dosimetric parameters of V20, V30 and V40 was noted between patients with and without symptomatic cardiac toxicity. In our cohort, we found the no symptomatic cardiac toxicity when the whole heart V20, V30 and V40 was kept below 70%, 65% or 60%, respectively. Left ventricular dosimetry and therapy induced changes in myocardial ^{18}F -FDG uptake failed to predict for cardiac toxicity. Female patients had a higher incidence of any and symptomatic cardiac toxicity, though they represented a minority in our patient population. While these findings are clinically important, validation via an independent data set with standardized parameters needs to be performed to further inform radiation oncologists to the avoidance of cardiac toxicity in patients with esophageal cancer who receive aggressive multimodality treatment regimens.

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Table 1**Pretreatment Patient Demographics**

Sex	
Male	65
Female	9
Age	
Median	62 (range: 37–87)
Tumor Location	
Middle	11
Lower	30
Gastroesophageal Junction	33
Histology	
Adenocarcinoma	65
Squamous cell carcinoma	9
Stage	
IIA	11
IIB	4
III	42
IVA	10
IVB	1
Unknown	6
Pre-existing Heart Disease	
Yes	42
No	32
Diabetes	
Yes	17
No	57
Insulin	
Yes	4
No	70
Smoking	
Yes	58
No	16
History of Bypass or angioplasty	
Yes	10
No	64

Table 2**Concurrent Chemotherapy Details and Doses**

	<i>n</i> (%)
No induction chemotherapy given	
Cisplatin (75mg/m ² i.v. days 1 and 20) and 5-FU (1000mg/m ² /day continuous infusion for 96–120 hours weeks 1 and 5 during radiation)	55 (74)
5-FU only (225 mg/m ² continuous infusion daily during radiation)	7 (9)
5-FU (225 mg/m ² continuous infusion daily during radiation) & Taxol (50 mg/m ² i.v. weekly during radiation)	1 (1)
Taxol (50 mg/m ² i.v. weekly during radiation)	1 (1)
Following induction chemotherapy	
Paclitaxel (50mg/m ² i.v.), cisplatin (25mg/m ² i.v.), 5-FU (200 mg/m ² /day continuous infusion 7 days a week during radiation)	7 (9)
Capectabine (825 mg/m ² orally b.i.d. during radiation)	1 (1)
None	2 (3)

Table 3

Cardiac toxicity as graded by RTOG and CTCAE v3.0

<i>Patients</i>	
RTOG Cardiac Toxicity Grade	
Grade 1	0
Grade 2	0
Grade 3	9
Grade 4	3
CTCAE v3.0	
Grade 1	6
Grade 2	0
Grade 3	5
Grade 4	1

RTOG-Radiation Therapy Oncology Group; CTCAE-Common Toxicity Criteria Adverse Events

Table 4

Cardiac Toxicity by RTOG and CTCAE v3.0 Grade

	Myocardial Infarction	Pericardial Effusion	Sick Sinus Syndrome
RTOG Grade			
3	1	7	1
4	0	3	0
CTCAE v3.0 Grade			
1	0	6	0
2	0	0	0
3	1	3	1
4	0	1	0

RTOG-Radiation Therapy Oncology Group; CTCAE-Common Toxicity Criteria Adverse Events