Cardiovascular concerns from radiation therapy and other radiation exposure


Hassan Tariq, MD, Eric E. Harrison, MD

Department of Cardiology, Morsani School of Medicine, University of South Florida, Tampa, FL, US

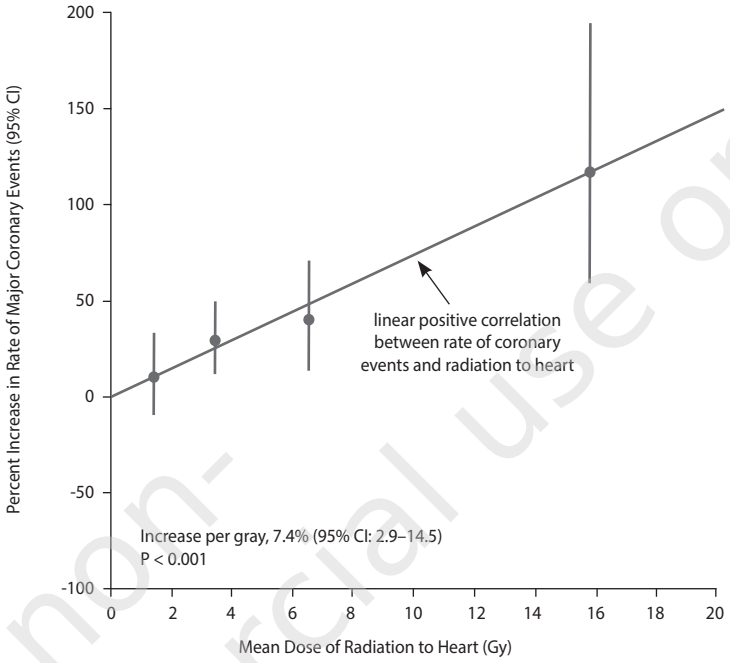
Received: 8.02.2016. Accepted: 22.02.2016.

This session began at 1 p.m. Thursday, October 15, 2015 following a breakout for lunch. The leadoff presenter was **Dr. Gary Freedman** from the University of Pennsylvania. Dr. Freedman is associate professor of Radiation Oncology with his practice limited to breast cancer. Although he practices in Philadelphia he enjoys a long commute so that he can live in rural Pennsylvania where he enjoys hiking. He is an avid gamer who was eagerly awaiting the release of "Fallout" on November 4.
Dr. Freedman led off his presentation with the now classical figure about the rate of major coronary events according to mean radiation dose to the heart from Sarah Darby MD et al. (fig. 1) [1].

He further illustrates this point by relating the radiation dose to heart in particular eras with relative cardiovascular (CV) risk. From 1958 to 2001, in the era of heart radiation without the availability of computed tomography (CT) planning, the mean radiation dose to the heart was 660 centigray (cGy). This translated to an increase of 7.4 % in relative risk of CV disease for each increase in gray (Gy) radiation. To put this radiation dose in perspective, a cardiac catheterization gives a mean radiation dose to heart of 250 cGy whereas an angioplasty gives 640 cGy [2].

Correspondence:
Eric E. Harrison, MD
Fellow of ACC, AHA, SCAI, ACP
Department of Cardiology
Morsani School of Medicine
University of South Florida
Tampa, Florida
e-mail: eeharrison253@hotmail.com

FIGURE 1.
Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart (modified [1]).



Improvements in focused radiation over time have decreased collateral damage to the heart and there by lowered CV mortality. Before 1975, radiation exposure was associated with an increase of 7% in CV mortality [3]. Between 1964 and 1986, radiation exposure translated to a 3–4% increase in CV mortality and the fields encompassed large volumes of the heart [4]. As per the Surveillance, Epidemiology and End Results (SEER) program data from 1973 to 1992, the CV mortality related to radiation dropped to 2–3% [5]. Data from 1977 to 1994 showed no overall significant difference in mortality between left- and right-sided irradiated patients but a higher rate of myocardial infarctions (MIs) with left breast irradiated patients [6]. A meta-analysis of data from 1976 to 1999 showed that radiation therapy (RT) after breast-conserving therapy resulted in a gain of 1% loss of survival [7].

More recent data shows that in a patient without CV disease risk factors, a 300 cGy mean radiation dose increases the risk of CAD from 1.9% to 2.4% by age 80 [1]. Conversely, in patients with one CV disease risk factor, the risk of CAD jumps from 3.4% to 4.1% after exposure to radiation [1]. In the current treatment era of focused and low-cumulative radiation, the absolute risk for CV disease from radiation exposure has been reduced to about 0.5% to 1% [8]. Current radiation planning with three-dimensional (3D) CT simulation reveals that in 80% of cases, less than 3% of heart volume is irradiated [9].

Instead of clinical trials involving invasive coronary angiography or evaluating mortality assessment over 10 to 15 years, short--term observations of lab markers (e.g. troponin), CT coronary calcium scoring, or myocardial strain (maybe even T1 or T2 cardiac magnetic resonance imaging [MRI], comment of the mini-reviewers) may be observed.

But what is more important: whole-heart or artery dose? In the Swedish breast cancer cohort with RT and subsequent coronary angiography, the highest anatomical location of coronary artery disease (CAD) was in the mid and distal left anterior descending and distal diagonal vessels [10].

Modern 3D CT radiation planning encompasses accurate targeting and avoiding the heart with a mean radiation dose to the heart of 165–173 cGy. Prone positioning allow for better results with only 98 cGy dose to the heart and deep inspiration breath holding brings the radiation dose down to 98 cGy. Meanwhile techniques utilizing the Bragg's physics of proton beam therapy peak with results in mean radiation exposure to the heart of 80–108 cGy.

Dr. Freedman proposed future research with the primary endpoint of major CV events involving pre-radiation risk factor evaluation and randomization to proton vs. photon therapy in non-metastatic breast cancer patients receiving comprehensive nodal radiation.

Dr. Anju Nohria from Brigham and Women's Hospital in Boston, MA spoke on "Autonomic dysfunction in patients treated with mediastinal or neck radiation". She started the presentation with data from van Nimwegen et al. highlighting the increase in CV disease incidence from mediastinal radiation therapy with and without anthracycline therapy [11]. Such evidence has led to consensus statements defining patients at high-risk for radiation-induced heart disease and proposing the screening for CV disease post-radiation exposure. For example, the guidelines suggest use of non-invasive stress testing to detect CAD 5 to 10 years after RT [12].

In keeping with the guidelines, non-invasive stress testing and echocardiography are offered at Dr. Nohria's survivorship clinic for surveillance of CAD in cancer patients after radiation exposure. Her study of 263 Hodgkin's lymphoma (HL) survivors has yielded information to suggest impaired cardiac autonomic function as a long-term outcome of mediastinal radiation [13]. In comparison to age-, sex-, and CV risk score-matched controls, she reported an increase in resting heart rate (HR), abnormal HR recovery with cessation of exercise, chronotropic incompetence, and decrease in exercise duration in HL patients. The incidence of autonomic dysfunction was found to increase with time from and dosage of radiation. Finally, an increase in mortality was reported over a three-year follow-up period with abnormal HR recovery. Her data is in agreement with current literature suggesting exercise parameters of increase in resting HR, abnormal HR recovery, chronotropic incompetence (CI), and decrease in exercise duration correlate with an increase in CV and all-cause mortality.

The presentation was concluded by highlighting her current research aimed at the use of ivabradine to lower HR in HL patients and assess their autonomic function and quality of life. Dr. Nohria called out for further research to understand the mechanism behind autonomic dysfunction secondary to chest irradiation and more importantly to search for modalities of restoring this imbalance in hopes to potentially improve functional capacity and/or survival.

Dr. Ronald G. Schwartz from University of Rochester Medical Center in Rochester, NY spoke on "Radionuclide Ventriculography (RNA): Safety and Proven Clinical Effectiveness to Manage Chemotherapy and Radiotherapy Risks of Heart Failure (HF)". He started the presentation with the synopsis that screening patients with baseline ejection fraction (EF)-based strategies for monitoring anthracycline cardiotoxicity can markedly affect the outcome of HF. Radiation risk of cardiac radionuclide studies cannot be meaningfully demonstrated because diagnostic evaluation relies on only low-dose (less than 100 millisieverts) exposure. Dr. Schwartz indicated that lack of optimal diagnostic evaluation due to radiation controversy may prove to be harmful to cancer patients with high residual risk of cardiac mortality. Anthracyclines are highly-effective anti-neoplastic therapies with dose-dependent cardiotoxicity leading to HF. Patient-centered approach focusing on the benefits of monitoring anthracycline cardiotoxicity and the theoretical yet unsubstantiated risk of diagnostic (low-dose) radiation needs to be taken. The 2003 guidelines of American College of Cardiology (ACC)/American Heart Association (AHA)/American Society of Nuclear Cardiology (ASNC) recommend the use of RNA for longitudinal quantitative assessment of left ventricular (LV) dysfunction during therapy with cardiotoxic drugs (class 1A evidence) [14]. There is extensive literature emphasizing the diagnostic accuracy of RNA relative to contrast ventriculography, cardiac MRI, and electron-beam CT. Dose-related incidence of cardiotoxicity led to early recommendations to limit radiation dose during diagnostic evaluation that are used in some current protocols. However, it has been reported that radiation dose alone cannot predict development of HF. The serial decline in LVEF following doxorubicin therapy can be monitored by RNA and this can help ensure the safe use of this anti-neoplastic medication in patients. The Yale study evaluated 1487 patients over 7-year period and identified 282 high-risk patients in 3 groups: (A) large decline in LVEF from normal; (B) abnormal baseline LVEF, and (C) high dose (> 450 mg/m^2) doxorubicin (4). Guidelines for monitoring anthracycline cardiotoxicity were established by the study and their use led to a 10-fold increase in survival probability of cancer patients treated with doxorubicin [15]. Clinical HF was improved in 87% of patients with medical therapy and no death was reported in the high-risk population. Several risk modifiers have been identified that influence RNA follow-up of cancer patients treated with doxorubicin.

Dr. Schwartz then switched gears to talk about myocardial perfusion imaging using gated single-photon emission CT (G-SPECT). The interest in this approach was fueled by previous observations that calculation of end-systolic volume index (ESVI) by contrast ventriculography predicts the probability of adverse CV outcomes in CAD patients. His work demonstrated that G-SPECT correlates well with first pass ventriculography for the calculation of end-systolic and end-diastolic volumes. A gender-specific difference in adverse CV outcomes was identified. Women had a much more rapid increase in adverse events as their ESVI increased and EF decreased. He briefly mentioned that there is variability with echocardiography in the ability to

monitor cardiotoxicity of chemotherapy and guidelines for monitoring with this technique should be followed carefully.

In conclusion, he reported radionuclide myocardial perfusion imaging can provide validated, accurate and unique information for management of CAD patients at risk for adverse events. The cancer risk of radiation exposure from RNA must be compared to the much higher risk of immediate major CV events from cardiotoxicity of anti-neoplastic drugs. A patient-centered approach defining the optimal benefit-to-risk strategy for use of nuclear cardiology must be taken which mandates adherence to the guidelines developed and endorsed by ACC, AHA, ASNC and Society of Nuclear Medicine.

Acknowledgements

The presented report is the summary of the session 3 of the **Global Cardio-Oncology Summit**, organized in Nashville, Tennessee, US (October, 15–16th, 2015).

References

1. Darby SC, Ewertz M, McGale P et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368(11): 987-998.
2. Frazier TH, Richardson JB, Fabré VC, Callen JP. Fluoroscopy-induced chronic radiation skin injury: a disease perhaps often overlooked. Arch Dermatol 2007; 143(5): 637-640.
3. Cuzick J, Stewart H, Rutqvist L et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994; 12(3): 447-453.
4. McGale P, Taylor C, Correa C et al.; EBCTCG (Early Breast Cancer Trialists' Collaborative Group): Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014; 383(9935): 2127-2135.
5. Paszat LF, Mackillop WJ, Groome PA et al. Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. J Clin Oncol 1998; 16(8): 2625-2631.
6. Harris EE, Correa C, Hwang WT et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol 2006; 24(25): 4100-4106.
7. Darby S, McGale P, Correa C et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011; 378(9804): 1707-1716.
8. Berry JD, Dyer A, Cai X et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012; 366(4): 321-329.
9. Das IJ, Cheng EC, Freedman G, Fowble B. Lung and heart dose volume analyses with CT simulator in radiation treatment of breast cancer. Int J Radiat Oncol Biol Phys 1998; 42(1): 11-19.
10. Nilsson G, Holmberg L, Garmo H et al. Distribution of coronary artery stenosis after radiation for breast cancer. J Clin Oncol 2012; 30(4): 380-386.
11. van Nimwegen FA., Schaapveld M, Janus CP et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015; 175(6): 1007-1017.
12. Lancellotti P, Nkomo VT, Badano LP et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2013; 26(9): 1013-1032.
13. Groarke JD, Tanguturi VK, Hainer J et al. Abnormal exercise response in long-term survivors of hodgkin lymphoma treated with thoracic irradiation: evidence of cardiac autonomic dysfunction and impact on outcomes. J Am Coll Cardiol 2015; 65(6): 573-583.
14. Klocke FJ, Baird MG, Lorell BH et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). Circulation 2003; 108(11): 1404-1418.
15. Schwartz RG, McKenzie WB, Alexander J et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med 1987; 82(6): 1109-1118.