Lung Cancer Radiation May Increase the Risk of Major Adverse Cardiac Events

“In this day and age, no cancer patient undergoing chest radiation should fail to see a cardio-oncologist.”
– Guilherme H. Oliveira, MD, MBA

A new retrospective study of patients with locally advanced non-small cell lung cancer (NSCLC) appearing in the Journal of the American College of Cardiology (doi:10.1016/j.jacc.2019.03.500) concludes that cardiac radiation dose exposure is an independent predictor of the incidence of major adverse cardiac events (MACE) and all-cause mortality (ACM).

“What we’re seeing now, especially with immunotherapy and other advances in cancer treatments, is that many lung cancer patients are living longer,” says Raymond H. Mak, MD, a coauthor of the study and a thoracic radiation oncologist at the Dana-Farber Cancer Institute and Brigham and Women’s Hospital in Boston, Massachusetts. “So it’s more important than ever to focus more on how to minimize the cardiac risks years after treating patients.” Dr. Mak, who also is senior physician and disease center leader in radiation oncology and thoracic oncology as well as an assistant professor of radiation oncology at Harvard Medical School in Cambridge, Massachusetts, points to recent clinical trials that report 5-year survival rates of 15% to 20% and median survivals of greater than 2 years for patients with stage III NSCLC.

Although previous research has examined the link between radiotherapy and heart disease, Dr. Mak says earlier studies of patients with NSCLC were smaller and used varying endpoints and inconsistent cardiac risk assessments. “Our study focused on MACE, which, as an endpoint, we believe has greater value for cardiologists.”

The primary objective of this study was to examine a large cohort of patients with locally advanced NSCLC who were treated with thoracic radiotherapy to determine whether cardiac radiation dose exposure increased the risk of American College of Cardiology/American Heart Association–defined MACE (cardiac death, unstable angina, myocardial infarction), heart failure hospitalization or urgent visit, and coronary revascularization) and ACM. The study adjusted for traditional lung cancer and cardiovascular (CV) prognostic factors, including preexisting coronary heart disease (CHD).

Study Details

The researchers analyzed data and outcomes for 748 patients with NSCLC who were treated with thoracic radiotherapy at the Dana-Farber/Brigham and Women’s Cancer Center and the Dana-Farber/Brigham and Women’s Cancer Center at Milford Regional Hospital between November 30, 1998 and January 27, 2014. Mean heart dose (MHD) was calculated and defined for every subject as the mean radiation dose (in grays [Gy]) delivered to the whole heart (including the pericardium) by the completion of radiotherapy.

The authors discovered that after follow-ups of just greater than 20 months, a total of 77 patients (10.3%) experienced MACE; a total of 28 patients developed a myocardial infarction, 28 had a heart failure event, 27 had a cardiac-specific death, and 20 required coronary revascularization.

Researchers observed a higher risk of MACE in CHD-positive patients compared with patients without CHD, and in analyses of both CHD groups combined they observed a significant increase in the risk of MACE in patients with increasing MHD (adjusted hazards ratio, 1.05/Gy; 95% CI, 1.02-1.08/Gy; P < .001). It is interesting to note that the research team found a significant interaction between MHD and CHD: MHD was found to be significantly associated with MACE and with ACM.

KEY POINTS

• “Our study focused on MACE, which, as an endpoint, we believe has greater value for cardiologists.”

• Researchers observed an increased risk of cardiac events with greater cardiac radiation dose exposure, especially for patients without a history of previous heart disease.
in CHD-negative patients, but not in those with preexisting CHD.

Among CHD-negative patients, the hazard ratio for treatment with MHD of \( \geq 10 \text{ Gy} \) (compared with \( <10 \text{ Gy} \)) was 3.01, with 2-year cumulative incidence estimates of 3.5% and 1.1%, respectively \((P = .025)\). Similarly, the hazard ratio for \( \geq 10 \text{ Gy} \) (compared with \( <10 \text{ Gy} \)) was 1.34, with 2-year cumulative mortality estimates of 52.2% and 40.0%, respectively \((P = .014)\).

A total of 533 patients died (71.3%). Of those deaths, 357 were from lung cancer (67.0%), 41 were from known noncardiac causes (7.7%), and 27 were from cardiac causes (5.1%). Among the 27 cardiac deaths, 17 of 268 deaths (6.3%) occurred in patients with CHD compared with 10 of 480 deaths (2.1%) in patients without CHD.

**Study Results**

Dr. Mak says this study advances understanding of the link between CHD and cardiac radiation dose exposure and hopefully will help to change national guidelines regarding radiotherapy planning to inform cardiologists, primary care physicians, and cardiologists. Moreover, Dr. Mak adds that he and his colleagues currently are collaborating with their cardiology counterparts to explore early interventions to lower the risk of cardiac injury from radiotherapy.

Susan F. Dent, MD, a medical oncologist, professor of medicine, and associate director of breast cancer clinical research at the Duke Cancer Institute in Durham, North Carolina, says that although there is a large volume of literature discussing cancer therapy-related cardiac dysfunction in survivors of breast cancer and hematological malignancies (especially non-Hodgkin lymphoma), to her knowledge little has been written about those patients with advanced NSCLC. “This is likely due to the competing risks of cancer-related death. With respect to chest radiation, the impact of this treatment modality [on survivors of breast cancer or lymphoma] is not usually seen for at least a decade after completion of cancer therapy. Patients with lung cancer are now living longer—leading to an increasing awareness of the potential detrimental impact of cancer therapy (including radiation) on CV health. This study opens up a new area of clinical inquiry: assessment and management of CV risk factors before, during, and following cancer therapy for those individuals with unresectable/locally advanced NSCLC.”

Dr. Dent added that ageing, smoking, diet, and alcohol are examples of shared risk factors for the development of both cancer and CV disease. “So, when developing cancer treatment plans, attention should be paid to optimization of these risk factors, ideally permitting the oncologists to offer the most effective cancer therapy without compromising CV health.”

Dr. Dent, who also is an executive officer of the International Cardiologist Society, says that despite the abundance of data regarding the CV toxicity of cancer treatments in patients with breast and hematological malignancies, the majority of these patients do not have adequate CV risk assessments before initiating cancer therapy. “Education is needed for all health care providers involved in the treatment of oncology patients around the importance of CV risk assessment. Groups such as the National Comprehensive Cancer Network can advise health care professionals on best practices through their guidelines. Organizations such as the American Society of Clinical Oncology, American College of Cardiology, American Heart Association, and European Society of Cardiology can promote best practices for CV risk assessment in this patient population.”

In an accompanying commentary in the *Journal of the American College of Cardiology* (doi:10.1016/j.jacc.2019.04.011), Guilherme H. Oliveira, MD, MBA, director of the Advanced Heart Failure and Transplant Center and the oncocardiology program at University Hospitals Cleveland Medical Center in Cleveland, Ohio, commended the researchers for their diligence in uncovering the presence or absence of CHD, calculating individual Framingham Risk Scores to establish CV risk profiles, and assessing individual radiation doses and calculated heart doses for each patient.

“In summary,” writes Dr. Oliveira, “[They] provide us with the data on which to build an evidence-based cardiovascular approach to lung cancer patients—and perhaps any patient—receiving chest radiation. Based on their findings, these patients should be aggressively screened for CHD and, if present, mean heart dose should be minimized at all costs because no dose is totally safe.”

“The message is clear,” he concludes. “In this day and age, no cancer patient undergoing chest radiation should fail to see a cardio-oncologist.”

“We will not completely spare the heart from radiation exposure,” says Dr. Mak. “What we need to study is how radiation exposure affects not just the heart as a whole, but how it affects the coronary arteries, valves, muscles, and other substructures and combines with baseline risk factors to produce cardiac events, so we can
personalize each patient’s treatment plan to the safest amount of radiation to minimize risk.” He notes that the research team recommends that a much lower cardiac radiotherapy dose limit be considered for patients than given in current national guideline recommendations: 10 Gy instead of 20 Gy.

Dr. Oliveira agrees. “For patients without preexisting heart disease, the Framingham Risk Score should be calculated and mitigated, and the mean heart dose should be kept to under 10 Gy,” he writes.

doi:10.3322/caac.21581