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Outcomes After Percutaneous Coronary Intervention With Stents in Patients Treated With Thoracic External Beam Radiation for Cancer

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ABSTRACT

OBJECTIVES The aim of this study was to assess outcomes after percutaneous coronary intervention (PCI) with stents in patients treated with thoracic external beam radiation therapy (EBRT).

BACKGROUND Thoracic EBRT for cancer is associated with long-term cardiotoxic sequelae. The impact of EBRT on patients requiring coronary stents is unclear.

METHODS We analyzed outcomes after PCI in cancer survivors treated with curative thoracic EBRT before and after stenting between 1998 and 2012. Reference groups were propensity-matched cohorts with stenting but no EBRT. Primary endpoint was target lesion revascularization (TLR), a clinical surrogate for restenosis. Secondary endpoints included myocardial infarction (MI) and cardiac and overall mortality.

RESULTS We identified 115 patients treated with EBRT a median 3.6 years *after* stenting (group A) and 45 patients treated with EBRT a median 2.2 years *before* stenting (group B). Long-term mean TLR rates in group A (3.2 vs. 6.6%; hazard ratio: 0.6; 95% confidence interval: 0.2 to 1.6; $p = 0.31$) and group B (9.2 vs. 9.7%; hazard ratio: 1.2; 95% confidence interval: 0.4 to 3.4; $p = 0.79$) were similar to rates in corresponding control patients (group A: 1,390 control patients; group B: 439 control patients). Three years post-PCI, group A had higher overall mortality (48.6% vs. 13.9%; $p < 0.001$) but not MI (4.8% vs. 4.3%; $p = 0.93$) or cardiac mortality (2.3% vs. 3.6%; $p = 0.66$) rates versus control patients. There were no significant differences in MI, cardiac, or overall mortality rates in group B.

CONCLUSIONS Thoracic EBRT is not associated with increased stent failure rates when used before or after PCI. A history of PCI should not preclude the use of curative thoracic EBRT in cancer patients or vice versa. Optimal treatment of cancer should be the goal. (J Am Coll Cardiol Intv 2014;7:1412–20) © 2014 by the American College of Cardiology Foundation.

As the prevalence and survival of both coronary artery disease (CAD) and cancer continue to increase among the aging population, the 2 diseases often coexist in the same individual. External beam radiation therapy (EBRT) is a cornerstone of cancer therapy; however, when used for certain thoracic malignancies (e.g., breast, lung, Hodgkin and non-Hodgkin lymphoma, esophagus), it results in a substantial amount of cardiac exposure. The adverse cardiovascular impact of thoracic EBRT is well established and includes coronary atherosclerosis, restrictive cardiomyopathy, constrictive pericarditis, and valvular heart disease. Percutaneous coronary intervention (PCI) using stents, performed in the vast majority, has become the predominant mode of revascularization. Thus, in many patients

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with an initial diagnosis of CAD, cancer develops, requiring EBRT. Conversely, many cancer survivors who received EBRT subsequently require PCI for symptomatic CAD.

Despite the deleterious impact of EBRT on the heart and concerns regarding impaired vascular healing, radiation brachytherapy was used in the past as a treatment for coronary restenosis with bare-metal stents (BMS) (1,2). However, long-term follow-up demonstrated a delayed risk of stent failure (3,4). This observation raises the possibility that EBRT may adversely affect outcomes in patients with coronary stents, but there is a paucity of data on the subject. Thus, the aim of this study was to assess clinical outcomes after PCI with stents in cancer patients treated with EBRT before or after the coronary revascularization.

METHODS

STUDY POPULATION. In this retrospective analysis, patients referred to the Mayo Clinic in Rochester, Minnesota, for curative thoracic EBRT for the treatment of malignancy between March 1998 and November 2012 who were also treated with PCI at our institution during the same time interval, either before or after EBRT, were included. The EBRT-treated population was restricted to malignancies that would result in significant cardiac exposure. These patients were then cross-referenced with the Mayo Clinic PCI database. The patients were divided into 2 groups: those who had PCI *before* EBRT (group A) and those who had PCI *after* EBRT (group B). Two separate control groups of propensity-matched patients who had PCI but no EBRT were identified for comparison. The study was approved by the Mayo Clinic's Institutional Review Board.

PCI PROCEDURE. The Mayo Clinic PCI registry includes demographic, clinical, angiographic, and procedural data. Immediate and in-hospital events are recorded, and each patient is surveyed by telephone contact by trained research coordinators using a standardized questionnaire at 6 months, 1 year, and then annually after the procedure. All adverse events are confirmed by reviewing the medical records of the patients followed at our institution and by contacting the patients' physicians and reviewing the hospital records of patients followed elsewhere.

Only patients who had successful PCI with at least 1 BMS or drug-eluting stent (DES) were included. All patients received dual-antiplatelet therapy for a minimal duration of 1 month for a BMS and 12 months in those treated with a DES. In the absence of an allergy or marked intolerance, lifelong aspirin therapy was recommended.

RADIATION THERAPY. All patients had a biopsy-confirmed or radiographic (early-stage non-small cell lung cancer) diagnosis of malignancy and received EBRT with a curative intent. The malignancies included cancers of the lung (small cell or non-small cell), breast, thymus, gastrointestinal tract (including the biliary tree, stomach, esophagus, and pancreas), and lymphoma. The majority of patients had a cancer above the diaphragm. The TNM staging was assigned and defined according to the American Joint Committee on Cancer *Cancer Staging Manual, Sixth Edition* (5). The cancers were staged from I to IVA (stage IVA for esophageal carcinoma is considered locally advanced and potentially curable), with none of the cancers having M1 staging (proven metastasis at initial diagnosis, usually noncurable by combined modalities including radiation). The non-Hodgkin lymphoma patients received a dose ranging from 35 to 70 Gy, and the 3 Hodgkin patients received total radiation doses of 24, 24, and 30.6 Gy, respectively. All EBRT simulation plans were performed with computed tomography imaging. A radiation oncologist (T.T.S.) reviewed each individual dosimetric plan and verified cardiac involvement by EBRT. Fifteen cases of stereotactic body radiation therapy (all for early-stage lung cancers) and 11 cases of intensity-modulated radiotherapy (a more modern radiation technique) were included.

CARDIAC CLINICAL OUTCOMES. The primary outcome of this study was target lesion revascularization (TLR), a surrogate for clinically significant stent stenosis and defined as any attempted percutaneous or surgical revascularization of the target lesion at any time after the initial procedure. Secondary outcomes included MI, cardiac mortality, and all-cause mortality. MI was diagnosed in the presence of 2 of the following 3 criteria: 1) typical chest pain for at least 20 min; 2) increase in creatine kinase (or the myocardial band fraction) >2 times normal; and 3) a new Q-wave on an electrocardiogram. Deaths were considered cardiac if they were due to MI, sudden death (within 1 h of cardiac symptoms), or other cardiac causes (e.g., congestive heart failure, arrhythmia).

STATISTICAL ANALYSIS. Continuous variables are summarized as mean ± SD unless otherwise noted; discrete variables are summarized as frequency (percentage). For both groups A and B, a propensity score was developed to predict case membership

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)
CAD = coronary artery disease
DES = drug-eluting stent(s)
EBRT = external beam radiation therapy
IQR = interquartile range
MI = myocardial infarction
PCI = percutaneous coronary intervention
TLR = target lesion revascularization