Long-Term Mortality in Patients With Radiation-Associated Coronary Artery Disease Treated With Percutaneous Coronary Intervention

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Background—The incidence and predictors of long-term mortality after percutaneous coronary intervention (PCI) for radiation-associated coronary artery disease are unknown.

Methods and Results—In this observational study of 314 patients (age, 65.2±11.4 years; 233 [74%] women) treated with PCI, 157 patients with previous external beam radiation therapy (XRT) were matched 1:1 with 157 comparison patients with atherosclerotic coronary artery disease without previous XRT, based on age, sex, lesion artery, and PCI type. The primary end point was all-cause mortality, and the secondary end point was cardiovascular mortality. After follow-up of 6.6±5.5 years, there were 101 deaths; 59 in the XRT group and 42 in the comparison group (P=0.04). On Cox proportional hazards multivariable survival analysis, previous XRT remained an independent predictor of all-cause mortality (hazard ratio [HR] 1.85; 95% confidence interval [CI], 1.21–2.85; P=0.004) and cardiovascular mortality (HR, 1.70; 95% CI, 1.06–2.89; P=0.03). Additional independent predictors of increased all-cause mortality included balloon angioplasty or bare-metal stent placement compared with drug-eluting stent placement (HR, 2.50; 95% CI, 1.61–3.97; P<0.0001), SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score of ≥11 (the sample median; HR, 1.99; 95% CI, 1.32–3.04; P<0.001), New York Heart Association functional class ≥3 (HR, 1.83; 95% CI, 1.15–2.91; P=0.012), history of smoking (HR, 1.88; 95% CI, 1.10–3.09; P=0.022), and age ≥65 years (HR, 1.70; 95% CI, 1.07–2.07; P=0.024).

Conclusions—Compared with patients with typical atherosclerotic coronary artery disease, patients with radiation-associated coronary artery disease are at higher risk for mortality after PCI. Previous XRT exposure is independently associated with increased all-cause and cardiovascular mortality in patients treated with PCI. **(*Circ Cardiovasc Interv*. 2016;9:e003483. DOI: 10.1161/CIRCINTERVENTIONS.115.003483.)**

Key Words: coronary artery disease ■ mortality ■ percutaneous coronary intervention ■ radiation oncology ■ survival

External beam radiation therapy (XRT) is a common treatment for thoracic malignancy, yet it is associated with many adverse cardiovascular effects, including accelerated coronary artery disease (CAD), valvular heart disease, constrictive pericarditis, and others.[1–5] Radiation-associated CAD is a poorly understood process thought to have a unique pathophysiology separate from standard atherosclerotic CAD.[1,2] Certain small studies suggest the XRT exposure may predispose to left main trunk (LMT) and ostial coronary artery stenoses[2]; however, the true distribution of CAD in such patients has not been explored in a large study to date.

There is limited evidence available to guide the clinician on the optimal revascularization strategy of radiation-associated CAD.[6] As a result, these patients are usually treated in a standard fashion, similar to those with atherosclerotic CAD. However, it is unclear whether usual therapeutic strategies should be extrapolated to this patient population, or whether specific interventional or surgical bypass strategies should be preferred. Illustrating this, in a recent study, we demonstrated that patients with radiation-associated cardiac disease (coronary and valvular disease) have a worse prognosis after cardiovascular surgery when compared with age-matched controls. In that study, XRT was shown to be an independent predictor of increased mortality, including those patients undergoing isolated coronary artery bypass grafting (CABG).[7] Although a few small studies have suggested that patients with radiation-associated CAD may have worse outcomes after percutaneous coronary intervention (PCI),[8–10] these studies have generally been underpowered and limited in follow-up duration and scope. Thus, long-term outcomes in patients with radiation-associated CAD treated with PCI are not yet well known. Given the paucity of evidence available to guide decision making in these patients, we conducted an observational cohort study to (1) quantify the incidence of short- and long-term all-cause and

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WHAT IS KNOWN

- External beam radiation therapy is associated with advanced coronary artery disease with a different pathophysiology than atherosclerotic coronary artery disease.
- The incidence and predictors of long-term mortality after percutaneous coronary intervention in these patients is not known.

WHAT THE STUDY ADDS

- This is the first study to establish previous external beam radiation therapy exposure as an independent risk factor for all-cause and cardiovascular mortality after percutaneous coronary intervention.
- Additional risk factors for increased long-term mortality in this patient population include balloon angioplasty or bare-metal stenting compared with drug-eluting stenting, elevated SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score, New York Heat Association Functional class ≥3, and age ≥65 years.

cardiovascular mortality in patients with radiation-associated CAD treated with PCI and (2) compare this with age- and sex-matched atherosclerotic controls treated with PCI.

Methods

Study Design

The current study was an observational cohort study of 314 consecutive patients who underwent PCI at a tertiary care center between January 2000 and December 2012. Institutional review board approval was obtained before data collection. The study population consisted of 2 equally matched groups (an XRT group and a comparison group). The XRT group contained 157 patients with radiation-associated CAD, identified by a history of documented malignancy requiring chest XRT (Table I in the Data Supplement), that subsequently developed CAD significant enough to require PCI. Patients had either documentation of a normal stress test, normal coronary angiography, or had few risk factors for CAD and no previous documentation of CAD before XRT. The formal diagnosis of radiation-associated CAD was made after a thorough clinical evaluation by both an experienced cardiologist and oncologist. The type of malignancy, location of XRT, total dose of XRT, and date of last dose of XRT were also collected when available. The comparison group consisted of 157 patients with atherosclerotic CAD (no previous XRT exposure), each matched in a 1:1 fashion to a patient in the XRT group. Each patient was fully matched based on the following parameters: age within 5 years, sex, target artery during PCI, and type of PCI performed (ie, balloon angioplasty [BA], bare-metal stent [BMS], or drug-eluting stent [BMS]).

Clinical Data

Clinical data were manually retrieved from each patient's electronic medical record or paper chart, when applicable. Baseline patient characteristics including demographics, vital signs, past medical history, oncological history, and common laboratory values prior to PCI were collected. Data were obtained as close to the date of PCI as possible (typically within 1 month). Medication use at the time of PCI was ascertained by electronic medical record review, as well as review of the individual PCI reports for periprocedural medication administration, as described below.

Angiographic Analysis

Details on each patient's coronary anatomy and each PCI procedure(s) performed were obtained from the institutional diagnostic coronary angiography and PCI databases. These databases are standardized repositories of baseline patient characteristics, description of coronary anatomy, and procedural details for each PCI procedure. Data were obtained to determine PCI lesion location and lesion severity (ie, A, B, or C type).[11] The presence of calcification, eccentricity, bifurcation or trifurcation anatomy, distal disease, and overall procedural success was also recorded. Periprocedural medication use was collected, including aspirin, $P2Y_{12}$ inhibitor therapy, anticoagulation (unfractionated heparin, low-molecular weight heparin, or bivalirudin), glycoprotein IIb/IIIa inhibitors, β-blockers, and statins.

To confirm the angiographic findings reported in the PCI reports, each film was individually rereviewed, and quantitative coronary angiography was performed by an experienced author who was blinded to the clinical and outcomes data at the time. The STYNAX score for each patient was calculated during visualization of the angiogram.[12]

Follow-Up and Outcomes

The beginning of follow-up was considered the date of PCI, and the primary end point was all-cause mortality. Data on death and survival were obtained from the medical record, from the US Social Security Death Index,[13] or Ohio Death Index. The secondary end point was cardiovascular mortality. Cause of death was discerned from chart review or telephone follow-up. Cardiovascular mortality was defined as any death caused by cardiac arrest, myocardial infarction, arrhythmia, heart failure, or any other cardiovascular cause. In addition, if the cause of death could not be discerned, this was also categorized as a cardiovascular in cause unless the patient's proximal history strongly suggested a noncardiovascular cause.[14] A separate analysis utilizing only definitive cardiovascular deaths as the end point is included in a supplement.

Statistical Analysis

Patient and procedural characteristics were stratified by XRT exposure and reported as mean (SD) if approximately parametrically distributed, and median (interquartile range) if nonparametrically distributed. Categorical variables were reported as n (% of total n). When appropriate, continuous variables were divided into 2 groups based on the median for dichotomous analyses. Differences in baseline and procedural characteristics between matched groups were assessed with Student paired *t* test or repeated measures ANOVA (for parametric variables) and the Wilcoxon signed-rank test (for nonparametric variables). Differences in the distribution of categorical variables were compared using conditional logistic regression stratified by matched pair.

Univariate Cox proportional hazards analysis was performed to determine predictors of all-cause and cardiovascular mortality. Multivariable analysis ignoring matched pairs was performed first to describe the impact of the matched variables and XRT exposure on mortality. Subsequently, conditional Cox proportional hazards analysis stratified by matched pair was performed to discern if prior XRT exposure remained an independent predictor of mortality. Multivariable models for each end point were built using a univariate screen with stepwise inclusion of variables with the highest hazard ratios (HRs), prioritizing variables statistically significant ($P<0.05$) and those thought to be most biologically important to the outcome, avoiding collinearity and overfitting (a 10 event: 1 variable ratio was utilized). Cox proportional hazard results are reported as HR with 95% confidence intervals (CI). Cumulative survival probabilities as a function of time were obtained via the Kaplan–Meier method, and event curves for XRT and comparison groups were compared using the log-rank test. Significance was determined at $P<0.05$. Statistical analysis was performed utilizing JMP Pro 11 (SAS Institute Inc, Cary, NC), R version 3.1.0, and SPSS version 11.5 (SPSS Inc, Chicago, IL).

Table 1. Clinical Characteristics of the Study Population

Variable	XRT (n=157)	Comparison (n=157)	*P* Value
Baseline characteristics			
Age, y, mean (SD)	65.2 (11.2)	65.2 (11.5)	0.891
Female sex, n (%)	117 (74)	116 (75)	0.997
BMI, kg/m^2, median (IQR)	26.8 (23.5–31.3)	29.4 (25.4–35.6)	0.178
Hypertension, n (%)†	95 (61)	75 (48)	0.027*
Hyperlipidemia, n (%)‡	91 (58)	76 (48)	0.077
CHF (history of), n (%)§	40 (25)	21 (13)	0.011*
Severe valvular disease, n (%)			
Aortic stenosis	7 (5)	4 (3)	0.108
Aortic insufficiency	0 (0)	1 (2)	0.037*
Mitral regurgitation	5 (3)	3 (2)	0.003*
Mitral stenosis	1 (1)	1 (1)	0.741
Diabetes mellitus, n (%)	50 (32)	49 (31)	0.910
CKD (stage III-V), n (%)	20 (13)	11 (7)	0.100
Atrial fibrillation, n (%)	43 (27)	18 (11)	<0.001*
Peripheral arterial disease, n (%)	20 (13)	15 (10)	0.371
Smoking (current or past), n (%)	25 (16)	11 (7)	0.020*
COPD, n (%)	37 (24)	21 (13)	0.026*
Previous MI, n (%)	15 (10)	9 (6)	0.187
Prior CABG, n (%)	0 (0)	1 (3)	0.997
Indication for PCI			0.216
Stable angina	37 (24)	43 (27)	
Acute coronary syndrome	86 (55)	91 (58)	
Unstable angina	45 (29)	67 (43)	
NSTEMI	30 (13)	13 (8)	
STEMI	37 (24)	43 (27)	
Atypical symptoms	34 (22)	23 (15)	
Laboratory values, mg/dL			
Creatinine, median (IQR)	0.9 (0.7–1.2)	0.9 (0.8–1.3)	0.524
Hematocrit, mean (SD)	37.6 (4.9)	38.9 (5.4)	0.574
Low-density lipoprotein, mean (SD)	104 (37)	109 (54)	0.789

BMI indicates body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and XRT, external beam radiation therapy.

*Statistical significance at $P<0.05$.

†The use of any blood pressure medication (β-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, thiazide, calcium channel blocker, or nitrate).

‡The use of any lipid-lowering medication or low-density lipoprotein ≥130 mg/dL.

§Median left ventricular ejection fraction was 35% (IQR, 25%–40%) among those with CHF.

Results

Baseline, Anatomic, and Procedural Characteristics

Baseline clinical characteristics are shown in Table 1. The patient population was relatively young (mean age, 65.2±11.4 years), most were women (233 [74%]), and approximately one third were diabetic. There were no clinically significant differences between the XRT and the comparison groups. The indications for PCI were similar in each group (most patients underwent PCI for an acute coronary syndrome, n=117 [56%]). The breakdown of previous malignancies and radiation doses in the radiation-associated CAD group was as follows: breast cancer (96 [61%], 50–60 Gy), lung cancer (24 [15%], 60 Gy), Hodgkin lymphoma (21 [14%], 40–45 Gy), non-Hodgkin lymphoma (16 [10%], 40–45 Gy), and others (28 [17%], 40–45 Gy). The average time from XRT to PCI was 13±10 years and 19% received cardiotoxic chemotherapy. A full breakdown of malignancies by group is provided in Table I in the Data Supplement.

The distribution of CAD in the study population is provided in Table 2. Overall, there was a similar distribution of CAD in the XRT and comparison groups. There was a trend toward more multivessel disease in the comparison group although this did not reach significance. The proportion of patients with severe LMT stenosis was low; however, approximately one third of patients had either an LMT or ostial coronary artery stenosis. The median SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score was 11 (interquartile range, 6–15) and average was 11.0±6.2, likely reflecting that patients with LMT lesions, ostial coronary artery stenoses, and elevated SYNTAX scores were referred to CABG as advised by current guidelines.

Procedural details on lesion characteristics, type of PCI performed, and periprocedural medication use are also included in Table 2. Procedural success was achieved in 100% of patients in both the XRT and the comparison groups. The left anterior descending was the most common artery to undergo PCI, followed by the right coronary artery. Patients in the XRT group tended to have fewer stents placed than in the comparison group (1.5±0.9 versus 2.6±1.5 stents, respectively; $P<0.001$).

Overall, 25 (8%) patients had BA only, 125 (39%) patients had BMS, and 167 (53%) patients had drug-eluting stenting (DES). Lesion characteristics were similar between groups although patients in the XRT group had a higher proportion of more complex B2/C lesions (71% versus 36%, respectively; $P<0.001$).

All-Cause Mortality During Long-Term Follow-Up

During an average follow-up duration of 6.6±5.5 years after PCI, there were 101 deaths (32% of all patients died). Of the 101 deaths, 59 (59%) were in the XRT group and 42 (42%) were in the comparison group (38% of XRT patients died versus 27% of comparison patients; $P=0.04$). To first evaluate whether the variables in the matching criteria (age, sex, type of PCI, and lesion location) were predictors of all-cause mortality, univariate Cox proportional hazards analysis was performed for the variables in Tables 1 and 2, ignoring match status. These results are provided in Table II in the Data Supplement. The variables included in the final multivariable model are included in Table 3. In unmatched analysis,

Table 2. Distribution of CAD and Procedural Characteristics

Variable	XRT (n=157)	Comparison (n=157)	*P* Value
Distribution of CAD			
No. of vessels†			0.009*
1 vessel	80 (51)	69 (44)	
2 vessels	60 (38)	56 (36)	
≥3 vessels	17 (11)	32 (20)	
Multivessel‡	77 (49)	88 (56)	0.097
LMT stenosis	4 (6)	5 (8)	0.997
LMT or any ostial stenosis	21 (33)	20 (32)	0.876
SYNTAX score, median (IQR)	9 (6–15)	10 (6–15)	0.270
Target vessel of PCI, n (%)			
LMT	6 (4)	10 (6)	0.341
Left anterior descending	81 (52)	109 (69)	0.005*
Left circumflex	39 (25)	59 (37)	0.019*
Right coronary artery	60 (38)	83 (53)	0.091
PCI type, n (%)			
Bare-metal stent	67 (43)	72 (46)	0.257
Drug-eluting stent	82 (52)	84 (54)	0.670
Balloon angioplasty only	8 (5)	8 (5)	1.00
Lesion characteristics			
No. of stents placed	1.5 (0.9)	2.6 (1.5)	<0.001*
Length, mm, mean (SD)	14.0 (7.4)	13.0 (6.8)	0.551
Diameter, mm mean (SD)	3.1 (0.6)	3.0 (0.5)	0.048*
Post-PCI % stenosis, mean (SD)	3 (14)	3 (9)	0.500
Heavy calcification, n (%)	46 (29)	56 (36)	0.533
Eccentric lesion, n (%)	67 (43)	68 (43)	0.912
Bifurcation lesion, n (%)	30 (19)	41 (26)	0.127
Lesion complexity, n (%)			
A/B1	46 (29)	101 (64)	<0.001*
B2/C	111 (71)	56 (36)	<0.001*
Periprocedural medications, n (%)			
Aspirin	154 (98)	157 (100)	0.997
$P2Y_{12}$ inhibition	146 (93)	131 (83)	0.008*
Glycoprotein IIb/IIIa inhibition	50 (32)	67 (43)	0.029*
Heparin (UFH or LMWH)	84 (54)	65 (41)	0.028*
Bivalirudin	94 (60)	71 (45)	0.007*
Any anticoagulant	157 (100)	152 (97)	0.998
β-blockade	131 (83)	111 (71)	0.010*
ACE inhibitor or ARB	69 (44)	75 (48)	0.492
Statin	99 (63)	118 (75)	0.020*
Calcium channel blocker	26 (17)	22 (14)	0.528
Nitrate	74 (47)	38 (60)	0.124

Ramus intermedius lesions included in total for left circumflex. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; IQR, interquartile range; LMT, left main trunk; LMWH, low-molecular weight heparin; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; UFH, unfractionated heparin; and XRT, external beam radiation therapy.

*Statistical significance at $P<0.05$.

†Number of coronary arteries with severe (>70%) stenosis.

‡≥2 vessels with severe stenosis.

previous XRT exposure remained an independent predictor of all-cause mortality (adjusted HR, 1.85; 95% CI, 1.21–2.85; $P=0.004$) after multivariable adjustment. Additional independent predictors of all-cause mortality included PCI type (BA or BMS placement; adjusted HR, 2.50; 95% CI, 1.61–3.97; $P<0.0001$), SYNTAX score of ≥11 (sample median; adjusted HR, 1.99; 95% CI, 1.32–3.04; $P<0.001$), New York Heart Association (NYHA) class ≥3 (adjusted HR, 1.83; 95% CI, 1.15–2.91; $P=0.012$), current or previous smoking (adjusted HR, 1.88; 95% CI, 1.10–3.09; $P=0.022$), and age ≥65 years (adjusted HR, 1.70; 95% CI, 1.07–2.75; $P=0.024$; Table 3). On analysis of χ^2, previous XRT exposure added incremental prognostic utility in this multivariable model, which included clinical characteristics, SYNTAX score of ≥11 (sample

Table 3. Multivariable Cox Proportional Hazard Model for All-Cause Mortality

Variable	Hazard Ratio (95% CI)	*P* Value
Balloon angioplasty or BMS placement	2.50 (1.61–3.97)	<0.0001*
SYNTAX score ≥11 (median)	1.99 (1.32–3.04)	<0.001*
XRT exposure	1.85 (1.21–2.85)	0.004*
NYHA class ≥3 (at time of PCI)	1.83 (1.15–2.91)	0.012*
Current or previous smoking	1.88 (1.10–3.09)	0.022*
Age ≥65 y	1.70 (1.07–2.75)	0.024*
Diabetes mellitus (insulin dependent)	1.55 (0.89–2.61)	0.119
Sex (male)	1.20 (0.74–1.91)	0.459
COPD	1.13 (0.67–1.85)	0.630
Chronic renal insufficiency†	1.09 (0.55–1.96)	0.797
Overall model	…	<0.0001*

Model does not account for matching. Please see text for results from the matched model. BMS indicates bare-metal stent; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; and XRT, external beam radiation therapy.

*Significance at $P<0.05$.

†Creatinine ≥2.0 at time of PCI or documented history of at least stage III chronic kidney disease.

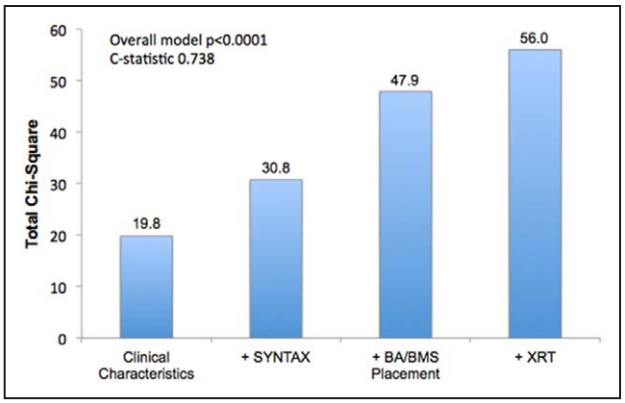

Figure 1. Overall model χ^2 with stepwise addition of variables. The addition of external beam radiation therapy (XRT) exposure added a significant benefit to the overall multivariable model χ^2 when combined with clinical characteristics, SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score (stratified at ≥11), and percutaneous coronary intervention (PCI) type. Clinical characteristics included age (stratified at ≥65 years), sex, current or previous smoking, chronic kidney disease, diabetes mellitus (insulin dependent), chronic obstructive pulmonary disease, and New York Heart Association class at time of PCI (stratified at ≥3). Unmatched model used for this comparison. BA/BMS indicates balloon angioplasty/bare-mental stenting.

median), and type of stent placed (Figure 1). There was no interaction between XRT exposure and PCI type (*P*=0.289).

To account for matching status, a multivariable conditional Cox proportional hazards model was built stratified by matched group. This model was adjusted for XRT exposure, SYNTAX score of ≥11, atrial fibrillation, chronic kidney disease, NYHA class ≥3, and insulin-dependent diabetes mellitus. Previous XRT exposure was the only significant independent predictor of mortality (adjusted HR, 2.02; 95% CI, 1.08–3.78; *P*=0.028).

Similarly, the long-term cumulative probability of all-cause mortality was significantly greater in patients with previous XRT by Kaplan–Meier analysis (*P*=0.0009; Figure 2A). Differences in mortality were further compared across subgroups (Table 4). Patients with a history of smoking (current or prior) had a greater probability of all-cause mortality regardless of previous XRT exposure (*P*<0.05 for all comparisons). Patents aged ≥65 years and those with insulin-dependent diabetes mellitus had greater all-cause mortality in the comparison group (*P*<0.05 for all comparisons), but not in the XRT group. Women had a greater probability of all-cause mortality in the comparison group; however, mortality was greater among men in the XRT group (*P*<0.05 for both comparisons). Patients with previous XRT exposure and a NYHA class ≥3 heart failure at the time of PCI had greater mortality than all other groups (*P*<0.0001).

Regarding angiographic variables, patients with a SYNTAX score of at least the sample median of 11 had greater all-cause mortality in both the XRT and the comparison groups (Table 4; Figure 3; *P*<0.05 for both comparisons). Patients in the XRT group with a SYNTAX score of <11 had similar mortality as patients in the comparison group with a SYNTAX score of ≥11 (Figure 3; *P*=0.049).

The probability of mortality was significantly greater in patients previously treated with XRT after BA/BMS placement than those treated after DES placement (Figure 4; *P*=0.0006). This difference was not observed in the comparison group. Furthermore, patients in the XRT group with DES placement had a similar probability of mortality as patients in the comparison group.

Cardiovascular Mortality During Long-Term Follow-Up

Cardiovascular mortality occurred in 69 (22%) patients. Of the 69 cardiovascular mortalities, 37 (54%) occurred in the XRT group and 32 (46%) in the comparison group. Furthermore, in the XRT group, the cause of death was determined to be cardiovascular in 63% of patients (n=37), and malignancy or other causes in 37% of patients (n=20; n=17 caused by malignancy, n=2 caused by respiratory failure, n=1 caused by sepsis). On Kaplan–Meier analysis, the cumulative probability of cardiovascular mortality was greater in the XRT group (*P*=0.045; Figure 2B). Similarly, the cumulative probability of cardiovascular mortality was highest in patients with previous XRT exposure and NYHA functional class ≥3 (*P*<0.0001), SYNTAX score of ≥11 (*P*=0.006), and BA or BMS placement (*P*=0.035; Figure I in the Data Supplement). In unmatched analysis, after multivariable adjustment for age, sex, NYHA functional class at time of PCI ≥3, SYNTAX score, and PCI type, previous XRT exposure remained an independent predictor of cardiovascular mortality (adjusted HR, 1.7; 95% CI, 1.06–2.89; *P*=0.03). In matched analysis, after adjustment for variables significant on a univariate screen (heart failure and insulin-dependent diabetes mellitus) plus SYNTAX score, XRT exposure remained a significant independent predictor of cardiovascular mortality (adjusted HR, 2.07; 95% CI, 1.01–4.26; *P*=0.047).

Discussion

In this cohort study of long-term outcomes after PCI, patients with radiation-associated CAD had significantly higher rates

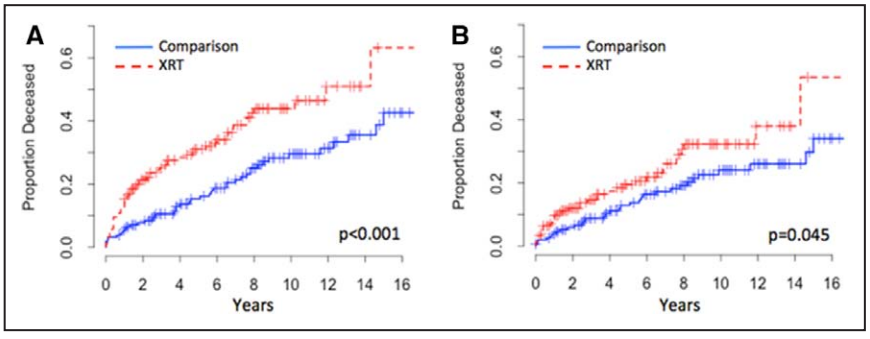

Figure 2. Kaplan–Meier analysis demonstrating that after percutaneous coronary intervention, both all-cause mortality (**A**) and cardiovascular mortality (**B**) were greater among patients with previous external beam radiation therapy (XRT) exposure as a cause of coronary artery disease when compared with atherosclerotic control patients.

Table 4. All-Cause Mortality Stratified by XRT Exposure, Separated by Subgroup

Variable	All Patients (n=101), n/n (%)	XRT Group (n=59), n/n (%)	Comparison Group (n=42), n/n (%)
Age, y			
<65	31/137 (23)*	22/68 (32)	9/69 (13)*
≥65	70/177 (40)*	37/89 (42)	33/88 (38)*
Sex			
Male	29/81 (36)	23/41 (56)*	6/40 (15)*
Female	72/133 (54)	36/116 (31)*	36/117 (31)*
Diabetes mellitus†			
Yes	21/60 (35)*	14/29 (48)*	7/31 (23)
No	80/154 (52)*	45/128 (35)*	35/126 (28)
Chronic kidney disease‡			
Yes	12/31 (39)	9/20 (45)	3/11 (27)
No	89/183 (49)	50/137 (36)	39/146 (27)
Atrial fibrillation			
Yes	21/61 (34)	19/43 (44)	2/18 (11)
No	80/253 (32)	40/114 (35)	40/139 (29)
Smoking, current or previous			
Yes	21/38 (55)*	16/25 (64)*	5/11 (45)*
No	80/278 (29)*	43/132 (33)*	37/146 (25)*
NYHA class at time of PCI			
<3	58/214 (27)*	27/97 (28)*	31/117 (27)
≥3	43/100 (43)*	32/60 (53)*	11/40 (28)
PCI type			
BA/BMS	70/150 (47)*	41/75 (55)*	29/75 (39)
DES	31/164 (19)*	18/82 (22)*	13/82 (16)
SYNTAX score (median)			
<11	39/162 (24)*	23/83 (28)*	16/79 (20)*
≥11	62/152 (41)*	36/74 (49)*	26/78 (33)*

BA/BMS indicates balloon angioplasty/bare-mental stenting; DES, drug-eluting stenting; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; and XRT, external beam radiation therapy.

*Significance at log-rank $P<0.05$ on Kaplan–Meier analysis. Multivariable Cox proportional hazards analysis including each variable provided in Table 3.

†Insulin-dependent diabetes mellitus.

‡Creatinine >2.0 at the time of PCI or documented history of chronic kidney disease stage ≥3.

of short- and long-term mortality than patients in a comparison group. This was observed in both unmatched multivariable analyses and in analyses after matching for age, sex, lesion location, and type of PCI performed. After a robust multivariable adjustment, previous XRT exposure remained an independent predictor of increased long-term all-cause mortality in unmatched comparisons (adjusted HR, 1.99; 95% CI, 1.21–2.85) and in cardiovascular mortality (adjusted HR, 1.7; 95% CI, 1.06–2.89). Similar results for all-cause and cardiovascular mortality were observed after accounting for matching. To the best of our knowledge, this is the first study to quantify the risk associated with previous XRT exposure and mortality after PCI. Furthermore, our results are supportive of the premise that cardiovascular death is common among patients with malignancy who initially survive XRT (ie, radiation survivors), particularly those previously treated with thoracic radiation that have developed concomitant CAD requiring PCI.

When stratified by the type of PCI, patients treated with BMS or BA were at particularly high risk for both all-cause and cardiovascular mortality in the XRT group, but not in the comparison group (Figure 4). There was a brisk separation in the Kaplan–Meier mortality curves within the first 2 years after PCI, but from 2 years onward, the slopes of the mortality curves seem similar (Figure 4). Thus, there may be an early mortality hazard associated with BA or BMS placement compared with DES placement in patients with previous XRT exposure, but not in patients with typical atherosclerotic CAD. The reasons for this are unclear, and this association does not prove causation between PCI type and mortality. Indeed, it is possible that patients selected for BA or BMS placement had comorbidities that precluded DES placement, such as bleeding issues or upcoming surgeries, which we were unable to fully control for in our study. However, given our data, it may be reasonable to consider DES in patients with previous XRT whenever possible. Our results suggest that patients with previous XRT exposure treated with PCI may behave differently during long-term follow-up than patients with atherosclerotic CAD and are at elevated risk of adverse outcomes.

Even when stratified at a relatively low SYNTAX score of ≥11, patients in the XRT group had particularly high mortality rates during follow-up compared with patients in all other groups (Figure 3), even after multivariable adjustment. Our results support subanalyses from several large clinical trials that demonstrate even modest elevations in SYNTAX may predict mortality and other adverse cardiac events across a range of settings.[15–17] SYNTAX score may be a particularly useful tool in predicting mortality in patients with radiation-associated CAD treated with PCI.

In our study, approximately one third of patients had LMT or ostial coronary artery disease, consistent with previous studies that suggest a high prevalence of ostial CAD in patients with radiation-associated CAD.[2,7,18] As ours was a population of patients selected for PCI, our cohort did not include patients who underwent CABG or patients with asymptomatic CAD. Thus, the true prevalence of ostial CAD in patients with radiation-associated CAD is likely higher than observed in this PCI-only population. In addition, although valvular heart disease is a known complication of XRT,[1,19] in our sample, few patients had moderate or severe valvular pathology. This is likely because that at our institution, these patients are routinely selected for combined valve replacement surgery and CABG rather than PCI. Furthermore, an NYHA class ≥3 was associated with increased mortality in the XRT group, but not in the comparison group (Table 4). A potential explanation for this is that certain patients in the XRT group received anthracycline chemotherapy, which in addition to XRT exposure may cause cardiomyopathy.

Our group has previously reported that certain features may be potential predictors of adverse outcomes in patients

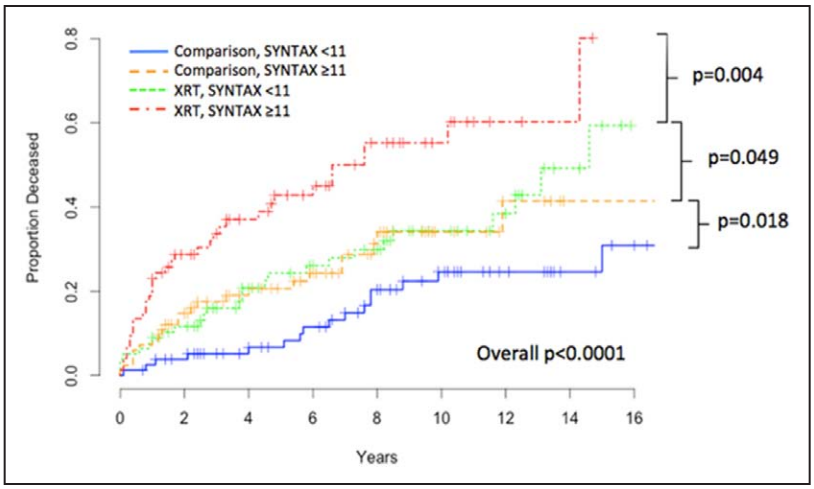

Figure 3. Kaplan–Meier analysis demonstrating that patients with both previous external beam radiation therapy (XRT) exposure and SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores at or above the median of 11 had greater all-cause mortality than XRT patients with SYNTAX scores <11, or patients without XRT exposure, regardless of SYNTAX score.

with radiation-associated cardiac disease.[7,20–22] We have previously demonstrated that previous XRT exposure was an independent risk factor for increased long-term mortality in patients undergoing cardiac surgery, including isolated CABG and combined CABG and valvular surgery.[7] We found that long-term mortality in patients with radiation-associated CAD undergoing isolated CABG may approach 46%,[7] whereas in the current study, we found long-term mortality after PCI to be 38% overall, up to 55% in patients treated with BA or BMS and 22% in patients treated with DES. These results seem to validate that alternative treatment strategies may be warranted in patients with previous XRT exposure requiring cardiac surgery.[19,23–25] There has not yet been a study directly comparing outcomes in patients with radiation-associated CAD treated with CABG or PCI, and thus, the optimal revascularization strategy in this patient population remains uncertain.

Previous studies of patients with radiation-associated CAD treated with PCI have been limited by small sample sizes, and results have differed across studies. Illustrating this, in a case–control study of 41 patients with radiation-associated CAD matched to 81 age- and comorbidity-matched control patients treated with stenting, there was no difference in myocardial infarction, target lesion revascularization, or major adverse cardiovascular events between groups.[8] However, patients in the radiation-associated CAD group did have an increase in both all-cause mortality (HR, 4.2; 95% CI, 1.8–9.5; *P*=0.0006) and cardiac mortality (HR, 4.2; 95% CI, 1.0–17.0; *P*=0.0451), consistent with the results of the current study. In a separate small study of 15 patients with radiation-associated CAD, previous XRT was found to be an independent predictor of coronary restenosis (odds ratio, 21.7; 95% CI, 4.7–100.9; *P*<0.001).[9] In contrast to these results, a more recent analysis by Liang et al[10] found that XRT was not associated with increased target lesion revascularization whether administered before or after stenting, and that among the 45 patients with previous XRT and subsequent stenting, there was no difference in subsequent myocardial infarction, cardiac mortality, or all-cause mortality. However, a separate analysis of 76 patients with radiation-associated CAD suggested, there may be a dose-dependent effect of thoracic XRT on subsequent cardiac-event–free survival.[26] A recent, large study of 1713 survivors of Hodgkin lymphoma, among whom 429 were treated with XRT, found that patients treated with both chemotherapy and XRT had the greatest incidence of cardiovascular disease.[5] Although our results are consistent with the findings in this study, long-term and cardiovascular mortality were not specifically reported, and outcomes after PCI were not evaluated. Thus, our current study adds to this study, and is of particular importance, as to our knowledge, this is the largest study of PCI outcomes in patients with

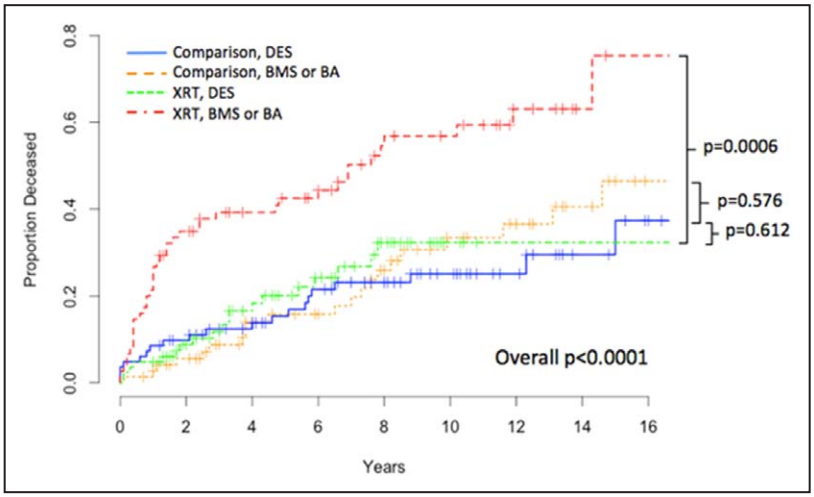

Figure 4. Kaplan–Meier analysis demonstrating that mortality was similar in the comparison group regardless of percutaneous coronary intervention type, but that among patients in the external beam radiation therapy (XRT) group, those who had balloon angioplasty/bare-mental stenting (BA/BMS) placement had greater mortality than patients treated with drug-eluting stenting (DES).

radiation-associated CAD to date and helps clarify the discrepancies observed between other smaller studies.[27]

The present study had certain limitations. This was a large study conducted in a quaternary care hospital system, and results may not be generalizable to all patients with radiation-associated CAD treated with PCI. In addition, our comparison group was a group of patients matched to the XRT patients based on age, sex, target lesion location, and type of PCI, and thus may not represent the general CAD population. Furthermore, patients were paired based on age, sex, target lesion location, and type of PCI, rather than their overall distribution of CAD to facilitate matching. As such, patients in the comparison group were permitted to have additional lesions beyond their matched counterpart in the XRT group. Although there was a trend toward more multivessel CAD and more stents placed in the comparison group, the XRT group still did worse when compared with the comparison group. In addition, we chose all-cause mortality as our primary end point as it is considered more objective and unbiased than cardiovascular mortality for this reason.[13,28] Furthermore, we utilized the Social Security Death Index given its superior specificity and potential less bias then the National Death Index,[13] supplemented with individual medical record review and patient telephone calls, where appropriate. In addition, there was some heterogeneity in PCI reporting, especially early in the study period, which is likely the reason for a lower-than-expected proportion of patients on anticoagulation and $P2Y_{12}$ therapy during PCI. Furthermore, data on the exact radiation doses or laterality of XRT were not available on all patients, and thus we were unable to perform analyses of whether these were associated with outcomes. Because randomized controlled trials will be difficult to perform in patients with radiation-associated CAD, a prospective registry may be useful to address these issues in the future.

Conclusions

Patients with radiation-associated CAD are at high risk for short- and long-term mortality after treatment with PCI. Previous XRT exposure is an independent predictor of increased mortality in this patient population. Among patients with radiation-associated CAD, an elevated SYNTAX score and BA or BMS placement are independently associated with increased mortality. Although this does not prove causation between PCI type and mortality, in patients with radiation-associated CAD, it may be reasonable to consider for DES placement whenever possible. Additional studies are needed to determine the optimal revascularization strategy in this patient population. Such studies may identify which angiographic characteristics are most predictive of cardiovascular events among patients with previous XRT, and how PCI outcomes compare with CABG outcomes in this patient population.

Disclosures

None.

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Long-Term Mortality in Patients With Radiation-Associated Coronary Artery Disease Treated With Percutaneous Coronary Intervention

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Supplemental Material

Supplemental Table 1. Frequency and types of malignancy in the study population.

Variable	XRT Group n=157	Comparison Group n=157	P-value
Type of malignancy, n (%)			
Breast cancer	96 (61)	6 (4)	<0.001*
Lung cancer	15 (24)	2 (1)	<0.001
Hodgkin's lymphoma	21 (14)	0 (0)	<0.001*
Non-Hodgkin's lymphoma	16 (10)	2 (1)	0.006*
Skin caner	11 (7)	6 (4)	0.232
Leukemia	1 (0)	0 (0)	1.000
Other cancer	16 (10)	20 (13)	0.494
Any malignancy	100 (157)	36 (23)	<0.001*

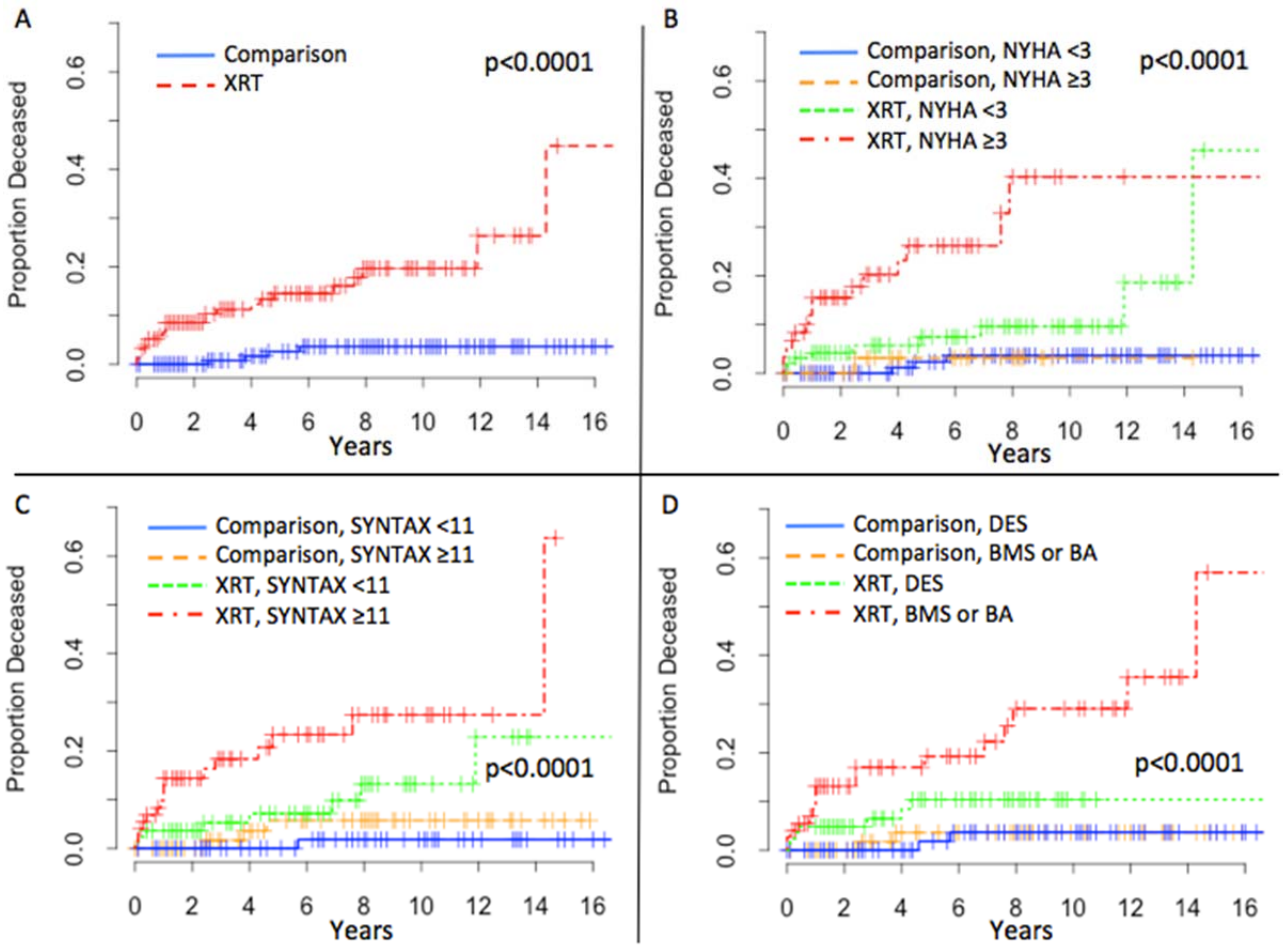
Patients may have had more than one type of malignancy; totals are not summative across types. Other cancer types predominantly included esophageal cancer and prostate cancer.
* Denotes significance at $p < 0.05$. Abbreviations: XRT, external beam radiation therapy.

Supplemental Table 2. Univariate Cox proportional hazard analysis for all-cause mortality.

Variable	Hazard Ratio (95% CI)	ChiSquare	P-value
Baseline Characteristics			
XRT exposure	1.94 (1.31 – 2.94)	10.81	0.001*
Age	1.04 (1.02 – 1.06)	14.91	0.0001*
Age ≥ 65	1.98 (1.31 – 3.06)	10.72	0.001*
Male gender	1.14 (0.73 – 1.75)	0.39	0.533
Body Mass Index, kg/m^2	0.93 (0.90 – 0.97)	11.46	0.0001*
Hypertension†	1.29 (0.84 – 1.96)	1.42	0.234
Hyperlipidemia‡	1.01 (0.67 – 1.52)	0.002	0.962
Congestive heart failure (history of)	2.17 (1.39 – 3.31)	10.89	0.001*
Diabetes mellitus (insulin dependent)	1.82 (1.08 – 2.91)	5.06	0.024*
Chronic kidney disease	1.33 (0.69 – 2.33)	0.80	0.371
Atrial fibrillation	1.29 (0.78 – 2.05)	1.04	0.307
Peripheral arterial disease	0.85 (0.41 – 1.56)	0.25	0.615
Smoking, current or prior	2.75 (1.65 – 4.39)	13.69	0.0002*
COPD	1.40 (0.85 – 2.21)	1.79	0.181
Prior myocardial infarction	2.63 (1.26 – 4.94)	6.32	0.012*
Indication for PCI and Symptoms			
Acute coronary syndrome	1.44 (0.96 – 2.18)	3.16	0.076
NYHA class at time of PCI	1.30 (1.14 – 1.48)	15.22	<0.0001*
NYHA class ≥ 3	2.31 (1.52 – 3.45)	15.44	<0.0001*
Coronary Anatomy Characteristics			
Multi-vessel§	1.23 (0.83 – 1.83)	1.05	0.305
LMT or any ostial stenosis	1.25 (0.75 – 1.98)	0.76	0.383
SYNTAX score	1.05 (1.02 – 1.08)	9.87	0.0017*
SYNTAX score ≥ 11 (median)	2.07 (1.39 – 3.12)	13.02	0.0003*
PCI Characteristics			
Balloon angioplasty or BMS placement	2.05 (1.34 – 3.19)	11.31	0.0001*
Large lesion diameter (>3.0 mm)‖	1.28 (0.84 – 2.01)	1.33	0.249
Long lesion length (>20 mm)‖	1.06 (0.67 – 1.63)	0.07	0.797
Calcification (at least moderate)‖	2.33 (1.51 – 3.30)	15.71	<0.0001*
Eccentric lesion‖	1.11 (0.75 – 1.65)	0.27	0.602
Bifurcation or trifurcation lesion‖	0.72 (0.43 – 1.16)	1.80	0.185
Complex lesion (B2/C)‖	1.20 (0.81 – 1.79)	0.82	0.366
Periprocedural Medications			
Aspirin	1.00 (0.22 – 17.68)	0.000	0.998
$P2Y_{12}$ inhibition	1.00 (0.60 – 1.74)	0.001	0.992
Glycoprotein IIb/IIIa inhibition	0.82 (0.55 – 1.23)	0.901	0.342
Any anticoagulant	1.50 (0.46 – 9.15)	0.362	0.548
Beta-Blockade	0.81 (0.53 – 1.26)	0.897	0.344
ACE inhibitor or ARB	0.98 (0.65 – 1.46)	0.012	0.912
Statin	0.74 (0.50 – 1.11)	2.17	0.141

Hazard ratios for continuous variables are per unit change in regressor. * Denotes significance at $p < 0.05$. † Use of any anti-hypertensive medication or documented history in chart. ‡ Use of any lipid lowering medication or LDL ≥ 130 mg/dl. § More than 1 vessel with severe (≥ 70%) stenosis. ‖ Incorporated into SYNTAX score. Abbreviations: CI, confidence interval; XRT, external beam radiation therapy; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; NYHA, New York Heart Association; LMT, left main trunk; BMS, bare-metal stent; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Supplemental Figure. Definite cardiovascular mortality in XRT and comparison patients, across subgroups.



Kaplan-Meier analysis demonstrating that after percutaneous coronary intervention, the cumulative probability of definite cardiovascular mortality was greater in patients with prior XRT exposure compared to atherosclerotic control patients (Panel A). Similar findings were seen when stratified by NYHA class (Panel B), SYNTAX score (Panel C), and PCI type (Panel D). Only deaths due to a definite cardiovascular cause were included (deaths due to an uncertain cause were excluded in this analysis). XRT, external beam radiation therapy; NYHA, New York Heart Association; DES, drug-eluting stent; BMS, bare metal stent; BA, balloon angioplasty; PCI, percutaneous coronary intervention.