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

Jackson J. Liang, DO,* Terence T. Sio, MD, MS,† Joshua P. Slusser, BS,‡ Ryan J. Lennon, MS,‡ Robert C. Miller, MD,† Gurpreet Sandhu, MD,§ Abhiram Prasad, MD‖

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

From the *Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; †Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; ‡Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; §Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; and ‖Cardiovascular Sciences, St. George's, University of London, London, United Kingdom. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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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

TABLE 1 Baseline Demographic and Clinical Characteristics, Presenting Characteristics at the Time of PCI, and Medications at Hospital Discharge After PCI

	PCI Before EBRT (n = 115)	Control Patients (n = 1,930)	p Value	EBRT Before PCI (n = 45)	Control Patients (n = 439)	p Value
Age, yrs	66.1 ± 9.5	66.3 ± 9.5	0.59	70.2 ± 9.7	70.2 ± 9.6	0.81
Male	50 (43)	839 (43)	*	16 (36)	156 (36)	*
Body mass index, kg/m^2	29.4 ± 5.9	29.5 ± 6.2	0.76	29.7 ± 6.8	29.4 ± 5.9	0.78
Lifelong nonsmoker	34 (30)	554 (29)	0.96	17 (40)	183 (42)	0.84
Congestive heart failure	6 (5)	67 (4)	0.63	8 (18)	79 (18)	0.95
Diabetes mellitus	25 (22)	349 (18)	0.27	9 (20)	106 (24)	0.72
Hypertension	81 (74)	1,209 (65)	0.036	34 (76)	323 (77)	0.71
Hyperlipidemia	66 (65)	1,187 (68)	0.70	32 (73)	308 (74)	0.97
History of myocardial infarction	20 (18)	307 (16)	0.68	7 (16)	74 (17)	0.86
History of PCI	15 (13)	249 (13)	0.93	6 (13)	44 (10)	0.72
History of coronary artery bypass grafting	10 (9)	154 (8)	0.77	2 (4)	31 (7)	0.47
Peripheral vascular disease	14 (12)	186 (10)	0.34	5 (11)	43 (10)	0.65
History of stroke or TIA	9 (8)	107 (6)	0.33	5 (11)	46 (11)	0.96
Moderate to severe renal disease	3 (3)	51 (3)	0.85	2 (4)	21 (5)	0.82
Characteristics at the time of PCI						
Pre-procedural shock	2 (2)	58 (3)	0.37	3 (7)	14 (3)	0.79
Unstable angina	73 (63)	1,212 (63)	0.98	23 (51)	208 (47)	0.54
Left ventricular ejection fraction, %			0.84			0.62
>40	60 (52)	995 (52)		19 (42)	196 (45)	
<40	8 (7)	115 (6)		6 (13)	45 (10)	
Unknown	47 (41)	820 (42)		20 (44)	197 (45)	
No. of diseased vessels			0.32			0.044
1	37 (34)	670 (37)		11 (26)	140 (34)	
2	40 (37)	704 (38)		16 (38)	161 (39)	
3	31 (28)	427 (23)		15 (36)	100 (24)	
Multivessel disease	73 (66)	1,155 (62)	0.52	31 (74)	270 (64)	0.19
Thrombus in any lesion	38 (34)	691 (37)	0.49	15 (36)	157 (39)	0.90
Bifurcation in any lesion	14 (13)	241 (13)	0.87	7 (17)	71 (17)	1.00
Ostial lesion	16 (17)	264 (17)	0.88	9 (25)	70 (18)	0.21
Pre-PCI TIMI flow 0 or 1 any lesion	24 (28)	341 (24)	0.38	8 (22)	100 (26)	0.51
Urgency of PCI			0.11			0.85
Elective	48 (42)	653 (34)		14 (31)	139 (32)	
Urgent	48 (42)	889 (46)		17 (38)	160 (36)	
Emergent	19 (17)	388 (20)		14 (31)	141 (32)	
Total no. of vessels treated			0.58			0.42
1	102 (89)	1,738 (90)		40 (89)	376 (86)	
2	11 (10)	177 (9)		5 (11)	59 (13)	
3	2 (2)	16 (1)		0 (0)	4 (1)	
Total no. of stents placed	1.6 ± 0.8	1.5 ± 0.8	0.67	1.5 ± 0.8	1.5 ± 0.9	0.92
Drug-eluting stent use	31 (27)	502 (26)	0.69	27 (60)	263 (60)	1.00
PCI native LAD	46 (40)	721 (37)	0.52	19 (42)	211 (48)	0.58
PCI native LMCA	4 (3)	31 (2)	0.29	0 (0)	0 (0)	–
PCI native RCA	52 (45)	902 (47)	0.75	17 (38)	186 (42)	0.32
PCI native left circumflex	27 (23)	417 (22)	0.69	14 (31)	108 (24)	0.31
PCI vein graft	2 (2)	52 (3)	0.44	0 (0)	2 (0)	0.56
Procedural success	115 (100)	1,907 (99)	0.10	44 (98)	437 (99)	0.26
Post-PCI TIMI flow 3 in all lesions	108 (96)	1,815 (97)	0.34	43 (96)	409 (96)	0.93

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versus control membership. The propensity score was modeled using logistic regression, using covariates different between the patients and the control patients pool at the 0.25 significance level. The date of PCI and discharge medications were also included in the model, regardless of the p value. A greedy matching algorithm was used to match control patients with patients with the following restrictions on the control patient to be matched to a patient: propensity score must be within one-fourth of the propensity score SD of the patient, age must be within 5 years, exact match on sex, and PCI date within 2 years

TABLE 1 Continued

	PCI Before EBRT (n = 115)	Control Patients (n = 1,930)	p Value	EBRT Before PCI (n = 45)	Control Patients (n = 439)	p Value
Medications at discharge after PCI						
Aspirin	112 (97)	1,883 (98)	0.79	41 (95)	426 (98)	0.49
Thienopyridine	113 (98)	1,910 (99)	0.38	43 (96)	436 (99)	0.045
Lipid-lowering agent	86 (75)	1,460 (76)	0.72	34 (77)	352 (81)	0.76
ACE inhibitor	41 (36)	674 (35)	0.90	19 (43)	202 (46)	0.83
Beta-blocker	87 (76)	1,463 (76)	1.00	36 (82)	388 (89)	0.37

Values are n (%) or mean ± SD. *There was no p value for male sex because the matching algorithm forced a perfect match between the groups.

ACE = angiotensin-converting enzyme; EBRT = external beam radiation therapy; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction.

of the patient. For patients with EBRT after PCI, control patients had to survive at least as long as the length of time from the patient's PCI to the EBRT date. As many as 20 control patients could be matched per case. Summary statistics were weighted so that each set of control patients for a particular case contributed as much weight as any other set of matched control patients. Stratified logistic regression was used to compare differences between patients and control patients, with each case/control(s) set constituting separate strata. Time-to-event variables were compared between the 2 groups using a Cox regression model, with separate strata for each patient/control patient(s) set.

RESULTS

There were 13,508 patients treated with thoracic EBRT involving the heart during the study period. Cross-referencing these patients with the Mayo Clinic PCI database resulted in a total of 334 patients who underwent both EBRT and coronary artery stenting at our institution from 1998 to 2012. After excluding duplicate patients, those in whom EBRT was for palliative intent (n = 7), those with no or incomplete follow-up (n = 87), as well as those for whom we could not find appropriate matched control patients (n = 80), a total of 160 patients were ultimately selected for analysis.

OUTCOMES IN PATIENTS RECEIVING EBRT AFTER PCI. Of the 160 patients identified, 115 had PCI *before* receiving curative thoracic EBRT for cancer (group A) with a median interval between the 2 events of 3.6 (interquartile range [IQR]: 4.9; [Q1,Q3] = 1.7 to 6.5) years. These patients were compared with a propensity-matched control patient cohort of 1,930 patients without previous EBRT. Baseline clinical, angiographic, and procedural characteristics at the time of PCI (Table 1) were similar between the EBRT-treated group and control patients, with the exception of a higher rate of hypertension in the EBRT group (74% vs. 65%, p = 0.04). Medication use was similar between groups.

During a median follow-up period of 2.1 years (IQR: 3.3; [Q1,Q3] = 1.0 to 4.3 years), TLR rates were similar between the 2 groups (3-year rate: EBRT, 3.2%; control patients, 6.6%; p = 0.31) (Figure 1A, Table 2). There were no significant differences in rates of MI (4.8% vs. 4.3%, p = 0.93) (Figure 1B) or cardiac death (2.3% vs. 3.6%, p = 0.66) (Figure 1C). As expected, the cohort of cancer patients treated with EBRT after PCI had a significantly higher all-cause mortality rate as demonstrated by Kaplan-Meier survival estimate (48.6% vs. 13.9%, p < 0.001) (Figure 1D) compared with controls.

The matching of stent type (DES vs. BMS) between patients and control patients was similar in the majority (83%) of patients (based on weighted controls). Among the cohort of 115 EBRT-treated patients, there was no significant correlation between the primary outcome TLR and the EBRT-PCI interval (p = 0.63) or stent type (DES vs. BMS) (p = 0.37).

OUTCOMES IN PATIENTS WHO REQUIRED PCI AFTER EBRT. A total of 45 cancer survivors were treated with PCI at a median of 2.2 (IQR: 4.5; [Q1,Q3] = 0.6 to 5.1) years *after* EBRT (group B). Compared with 439 matched control patients without previous EBRT, baseline characteristics and discharge medications were similar (Table 1).

Table 2 summarizes the clinical outcomes in group B. Overall, after a median of 3.1 years of follow-up (IQR: 3.5; Q1,Q3 = 1.5 to 5.1), rates of TLR (3-year rate: EBRT patients, 9.2%; control patients, 9.7%; p = 0.79 (Figure 2A), MI (4.6% vs. 9.3%, p = 0.66) (Figure 2B), cardiac death (6.8% vs. 3.4%; p = 0.30) (Figure 2C), and all-cause death (27.4% vs. 22.0%) (p = 0.35) (Figure 2D) were similar between both groups.

The type of stent used (DES or BMS) in the patients treated with stenting after EBRT matched 100% of

the time with the control patients. Among the cohort of 45 EBRT-treated patients, there was no significant correlation between the interval between EBRT-PCI ($p = 0.59$) or stent type (DES vs. BMS) ($p = 0.88$) with the primary outcome TLR.

DISCUSSION

The major and novel finding of this study of patients with concomitant CAD treated with PCI and cancer requiring thoracic EBRT is that the latter is not associated with increased rates of stent failure. This is important given the otherwise well-known deleterious cardiac side effects of thoracic EBRT.

RADIATION THERAPY AS *TREATMENT* FOR CAD. Intracoronary radiotherapy has previously been used as an adjunctive therapeutic option in the management of patients with CAD treated with PCI. Animal studies have demonstrated that intravascular radiotherapy may reduce restenosis after balloon injury by inhibiting neointimal formation (6) and preventing late adventitial fibrosis (7). Adjunctive coronary brachytherapy was once the preferred therapy for in-stent restenosis to prevent recurrence in patients with BMS (8,9). However, long-term follow-up of intracoronary brachytherapy confirmed a risk of delayed stent failure, and hence, this approach is no longer used (3,4).

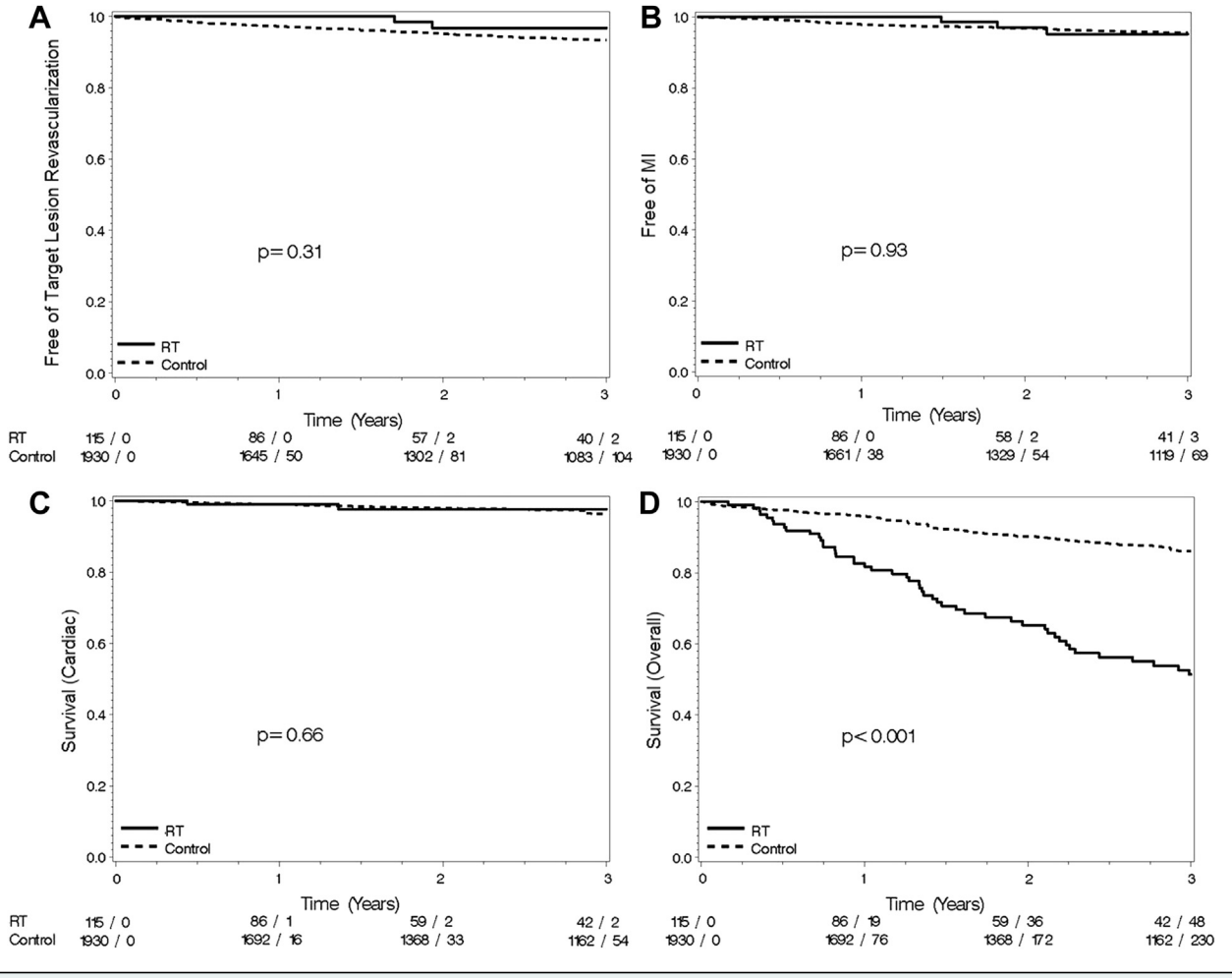

FIGURE 1 Three-Year Outcomes After External Beam Radiation Therapy in Patients With Previous Stenting (Group A)

Kaplan-Meier survival curves demonstrating freedom from target lesion revascularization **(A)**, freedom from myocardial infarction (MI) **(B)**, cardiac survival **(C)**, and overall survival **(D)**. RT = radiation therapy.

The effect of EBRT on vascular stents remains unclear. Animal and human studies have found variable effects of EBRT on preventing stenosis in coronary and noncoronary arteries after arterial injury and stenting. Some studies have reported a dose-dependent inhibitory effect of EBRT on the development of intimal hyperplasia after balloon injury to animal carotid arteries (10,11). Conversely, other studies have demonstrated increased neointimal formation in the coronary and iliac arteries with low-dose (<16 Gy) EBRT, possibly due to up-regulation of extracellular matrix expression (12,13). Contrarily, Verheye et al. (14) reported a beneficial effect of high-dose (21 Gy) EBRT on pig hearts immediately after BMS implantation, resulting in a significant increase in lumen area and reduction in neointima formation. In another study in pigs, coronary EBRT resulted in increased neointimal and adventitial collagen compared with intracoronary radiotherapy, and focal interstitial necrosis in the adjacent myocardium was only seen in the EBRT-treated pigs (15). Prospective studies examining the effect of EBRT have not been performed with human coronary artery stents, but EBRT has been shown to decrease rates of restenosis in human peripheral arterial stents (16,17).

EBRT *AFTER* STENTING FOR CAD. In the present study, we demonstrate no increase in clinically significant in-stent restenosis or stent thrombosis in patients who are treated with EBRT, as evidenced by similar rates of TLR, MI, and cardiac mortality. Previous human and animal studies examining the effects of EBRT after angioplasty and stenting involved EBRT treatment immediately after the arterial intervention, and therefore the findings cannot be extrapolated to patients who are treated with EBRT months or years after stenting. To our knowledge, our study is the first to examine the effect of delayed EBRT in patients with coronary artery stents.

In current practice, radiation oncologists do not typically alter the radiation doses or treatment plans based on the presence or location of coronary artery stents, and our results are reassuring in that the indiscriminate use of EBRT without using coronary artery-sparing techniques in these patients does not place them at increased risk of worse long-term cardiac outcomes. As expected, the patients with EBRT in our study had worse overall survival compared with the non-EBRT group. Because cardiac mortality remained unchanged, this increased noncardiac mortality is likely attributed to the underlying malignancy for which patients received the EBRT. Based on our results, clinicians need not be as concerned about the stent-toxic effects of EBRT and should instead aim to treat the underlying malignancy as the priority.

TABLE 2 Primary and Secondary Outcomes After PCI and EBRT

	Stent Before EBRT (n = 115)	Control Patients (n = 1,930)	p Value	EBRT Before Stent (n = 45)	Control Patients (n = 439)	p Value
TLR			0.31			0.79
30 days	0 (0)	9 (0.5)		0 (0)	1 (0.2)	
180 days	0 (0)	31 (1.7)		4 (9.2)	24 (5.7)	
270 days	0 (0)	41 (2.2)		4 (9.2)	26 (6.0)	
1 yr	0 (0)	50 (2.7)		4 (9.2)	28 (6.5)	
2 yrs	2 (3.2)	81 (4.8)		4 (9.2)	35 (8.6)	
3 yrs	2 (3.2)	104 (6.6)		4 (9.2)	38 (9.7)	
Myocardial infarction			0.93			0.66
30 days	0 (0)	3 (0.1)		0 (0)	7 (1.6)	
180 days	0 (0)	14 (0.8)		2 (4.6)	25 (5.7)	
270 days	0 (0)	27 (1.5)		2 (4.6)	26 (6.1)	
1 yr	0 (0)	38 (2.1)		2 (4.6)	27 (6.2)	
2 yrs	2 (3.0)	54 (3.2)		2 (4.6)	36 (8.7)	
3 yrs	3 (4.8)	69 (4.3)		2 (4.6)	38 (9.3)	
Cardiac mortality			0.66			0.30
30 days	0 (0)	0 (0)		1 (2.2)	2 (0.4)	
180 days	1 (1.0)	7 (0.4)		2 (4.4)	5 (1.2)	
270 days	1 (1.0)	13 (0.7)		3 (6.8)	5 (1.2)	
1 yr	1 (1.0)	16 (0.9)		3 (6.8)	6 (1.3)	
2 yrs	2 (2.3)	33 (2.0)		3 (6.8)	8 (2.0)	
3 yrs	2 (2.3)	54 (3.6)		3 (6.8)	12 (3.4)	
Overall mortality			<0.001			0.35
30 days	0 (0)	13 (0.7)		1 (2.2)	4 (0.9)	
180 days	7 (6.3)	45 (2.4)		3 (6.7)	15 (3.4)	
270 days	12 (10.9)	63 (3.3)		5 (11.1)	21 (4.7)	
1 yr	19 (17.4)	78 (4.1)		6 (13.3)	25 (5.7)	
2 yrs	36 (34.7)	172 (9.8)		11 (24.4)	74 (17.9)	
3 yrs	48 (48.6)	230 (13.9)		12 (27.4)	88 (22.0)	

Values are n (%).
TLR = target lesion revascularization; other abbreviations as in Table 1.

EBRT *BEFORE* STENTING. The outcomes after coronary artery stenting in cancer survivors previously treated with EBRT were reported in 2 previous studies (18,19). Dubois et al. (18) reported in their retrospective study that patients with previous thoracic EBRT for lymphoma, lung, or breast cancer who later underwent coronary artery stenting had higher rates of all-cause (hazard ratio: 4.2, p = 0.0006) and cardiac (hazard ratio: 4.2, p = 0.00451) mortality. However, similar to our findings, they saw no significant difference in clinical presentation for in-stent restenosis, with similar rates of TLR, acute MI, and stent thrombosis in those previously treated with EBRT. As such, it is unlikely that the increased cardiac or all-cause mortality is directly related to stent failure. Rather, the presence of underlying malignancy was a likely confounding factor for the higher all-cause mortality rate, and the previous use of cardiotoxic

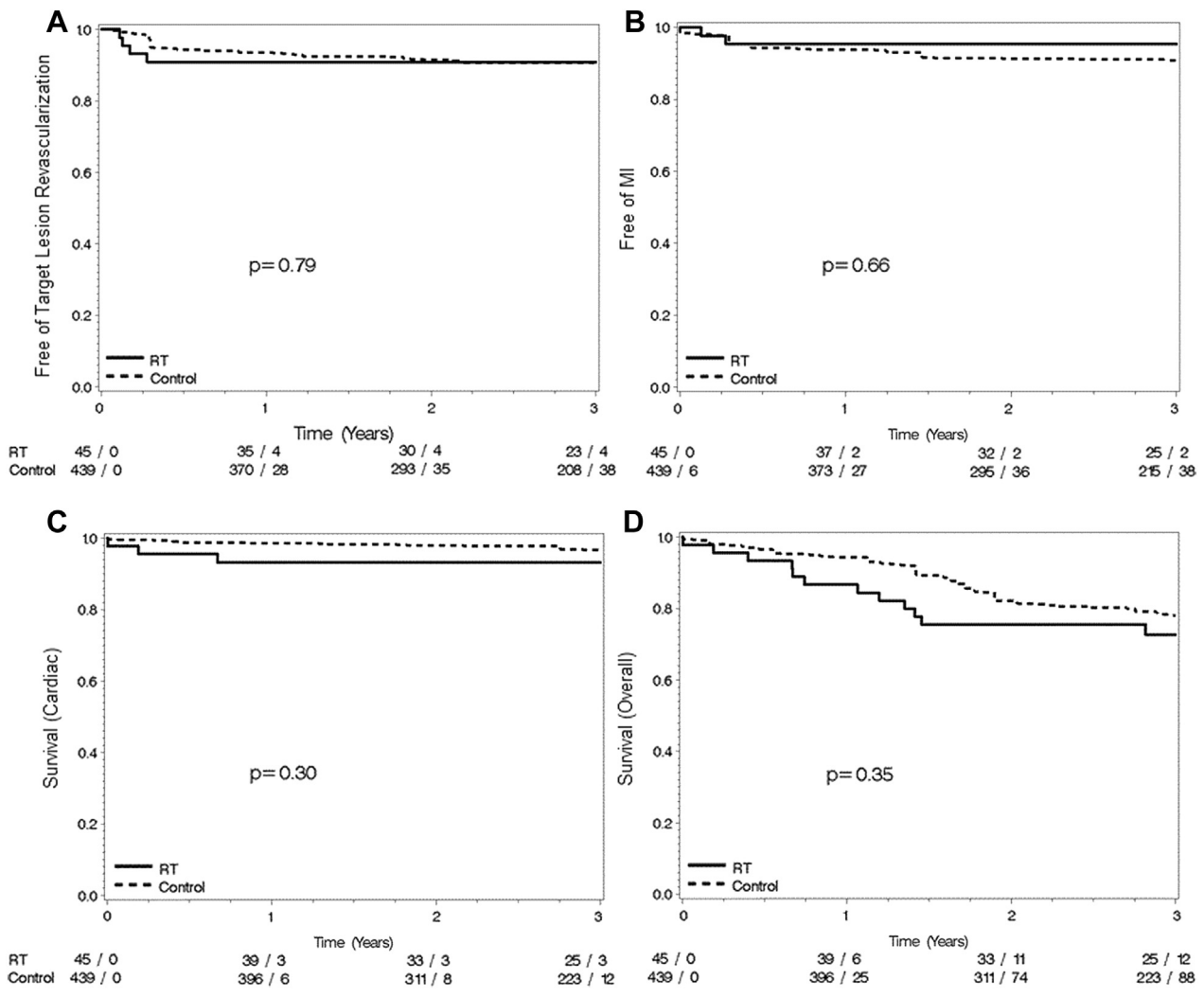

FIGURE 2 Three-Year Outcomes After Percutaneous Coronary Intervention and Stenting in Patients With Previous Thoracic External Beam Radiation Therapy (Group B)

Kaplan-Meier survival curves demonstrating freedom from target lesion revascularization **(A)**, freedom from MI **(B)**, cardiac survival **(C)**, and overall survival **(D)**. Abbreviations as in Figure 1.

chemotherapeutic agents including anthracyclines may have contributed to the higher rates of cardiac mortality.

In a retrospective analysis, Schomig et al. (19) reported a smaller cases series of patients who underwent coronary stenting using BMS and underwent follow-up coronary angiography after 6 months. They compared rates of angiographic restenosis in 14 lymphoma survivors who had received previous EBRT versus 6 lymphoma survivors who had never received EBRT, and 10,032 control patients with no history of lymphoma. Angiographic stent restenosis occurred more frequently in the lymphoma survivors with previous EBRT (85.7%) compared with those with lymphoma and no EBRT (16.7%) and those with no history of lymphoma or EBRT (25.5%) (19). In contrast to the results of our study as well as those reported of the aforementioned study by Dubois et al. (18), the rates of TLR reported by Schomig et al. (19) were higher in the EBRT group (66.6% vs. 14.2% and 18.0%, $p < 0.001$), a finding possibly attributed to the oculostenotic reflex or angiographically versus clinically driven TLR (18). Moreover, in contrast to our investigation, the study by Schomig et al. (19) had a

smaller sample size, was limited to a single type of malignancy, and had an unmatched control group. Thus, based on the data available to date, it is likely that previous EBRT does not increase stent failure in the broader population of patients with thoracic malignancies but may predispose to subclinical restenosis.

STUDY LIMITATIONS. Due to the retrospective design of our study, our results should be considered exploratory and hypothesis generating. It is important to note that although all patients in our study underwent *both* PCI and EBRT within a 14-year study period, radiation cardiotoxicity including CAD may occur decades after the initial EBRT treatment course. For example, 1 study demonstrated that the median time to diagnosis of CAD in Hodgkin lymphoma survivors after EBRT was 15.8 years (20). As such, our results may not be applicable to those patients with long intervals between EBRT and PCI, as our EBRT-treated cohort may have had preexisting CAD before the EBRT, and plaque quality may be different than in those with CAD attributed solely to EBRT. Future studies with longer EBRT-PCI intervals would be helpful to elucidate whether rates of stent failure differ in those patients. For the patient-control patient comparisons in both EBRT groups, the case populations were inherently different compared with the controls because they all had treated or active malignancy, which was not always the case in the controls. The presence of malignancy and use of cardiotoxic chemotherapy may have been confounders when analyzing outcomes in our analysis. We included a small number of patients treated with intensity-modulated radiotherapy and stereotactic body radiation therapy, 2 increasingly used EBRT techniques that are thought to better spare the heart and lungs. The long-term cardiotoxic effects of these 2 techniques have not been well studied and merit further investigation. Finally, the small sample sizes and low event rates (except for all-cause mortality) in our patient cohorts were a limitation as well, and there was inadequate power to identify whether EBRT resulted in differential effects on stent failure rates based on stent type (DES vs. BMS).

CONCLUSIONS

Our findings suggest that treatment with thoracic EBRT does not increase the risk of the development of clinically significant stent failure in patients with cancer who are treated with coronary artery stents either before or after EBRT. EBRT need not be withheld in patients with coronary stents, and the use of coronary artery-sparing EBRT in these patients appears to be unnecessary. The emphasis in these patients should be on eradicating the underlying malignancy. In addition, PCI with stents may be safely used as a treatment option for CAD in cancer survivors previously treated with EBRT. This is highlighted by the fact that patients with radiation-associated heart disease have increased long-term mortality after cardiac surgery, and some investigators have suggested that alternative treatment strategies may be more appropriate (21).

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Abhiram Prasad, Cardiovascular Sciences Research Centre, St. George's, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom. E-mail: a.prasad@sgul.ac.uk.

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