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Original Research

Intracoronary Brachytherapy for Drug-Eluting Stent Restenosis: Outcomes and Clinical Correlates

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ABSTRACT

Background: This study aimed to report outcomes of intracoronary brachytherapy (ICBT) in treating drug-eluting stent (DES) in-stent restenosis (ISR) and identify correlated factors.

Methods: Patients who underwent ICBT for DES ISR from 2010 to 2021 were included in this single-institution retrospective PCI registry. Patients were treated with balloon angioplasty, laser atherectomy, and/or rotational atherectomy, followed by ICBT at a dose of 18.4-25 Gy delivered at the site of ISR with dose determined by the reference vessel size. The primary outcome was 3-year target lesion failure rate (TLF). Secondary end points were 1-year TLF, target lesion revascularization (TLR), all-cause mortality, and cardiac mortality.

Results: In total, 330 consecutive patients presented with 345 treated lesions; 70% were male, age was 66 ± 11 years, 55% were diabetic patients, 62% underwent previous bypass surgery, and 89% were placed with at least 2 stent layers at the treated site. The rate of TLF was 18% at 1 year and 46% at 3 years. All-cause mortality and cardiac mortality rates were 19.8% and 12.3% at 3 years. The number of stent layers was associated with 3-year TLF (1 layer, 33.3%; 2 layers, 47.0%, >3 layers, 60.2%; $P = .045$). Diabetes, repeat ICBT, final percent stenosis, lesion length, and intravascular imaging use were not correlated with the primary outcome. Lower ICBT dose ($P = .035$) and restenosis <1 year from previous percutaneous coronary intervention ($P = .044$) were correlated with early (1-year) TLF.

Conclusion: ICBT for recurrent DES ISR provided low recurrence rates at 1 year, which increased substantially by 3 years. Outcomes were most closely correlated with the number of stent layers, but early restenosis and lower ICBT dose adversely affected early TLF.

Introduction

Drug-eluting stents (DES) are the treatment of choice for coronary stenting; however, injury and mechanical, biological, and patient-specific factors may lead to neointimal proliferation or neoatherosclerosis, with resultant in-stent restenosis (ISR).[1] ISR causes recurrence of ischemic symptoms, often necessitating further treatment, and is the cause of approximately 10% of percutaneous coronary interventions (PCIs) performed in the United States.[2] Five-year ISR rates for second-generation drug-eluting stents are estimated at 5% to 6%.[3] Recurrent ISR is more problematic, with repeat failure rates of 12% to 14% in low-risk lesions and up to 41% at 1 year for ≥3 stent layers.[4]

Current US guidelines recommend treatment of ISR with placement of a DES (class 1, LOE A).[5] If multiple stent layers are present or the target vessel is not favorable for repeat DES, coronary artery bypass graft surgery (class IIa, LOE C) or brachytherapy (class IIb, LOE B) can be considered.[5] Intracoronary brachytherapy (ICBT) involves temporarily implanted radiation sources delivering very high radiation doses at the site of the source.[6] Although ICBT is not currently the preferred therapy

Abbreviations: BMS, bare metal stent; DAPT, dual antiplatelet therapy; DCB, drug-coated balloon; DES, drug-eluting stent; DS, diameter stenosis; ICBT, intracoronary brachytherapy; ISR, in-stent restenosis; PCI, percutaneous coronary intervention; TLF, target lesion failure; TLR, target lesion revascularization.

Keywords: drug-eluting stent restenosis; in-stent restenosis; intracoronary brachytherapy.

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Table 1. Baseline characteristics of patients treated with ICBT for recurrent DES ISR (N = 330).

Characteristic	Value
Age, y	66 ± 11
Acute MI at presentation	20.9%
Diabetes	54.5%
Dialysis	4.2%
LVEF, %	55 (range 43-66)
Male sex	70.3%
Previous CABG	62.0%
Current smoker	8.9%
Peripheral vascular disease	24.1%
Race (self-described)	
White	86.2%
Black	6.2%
Other	7.6%
No. of ISR	3.1 ± 1.5

Values are given as mean ± SD, percentage, or median (IQR).
CABG, coronary artery bypass graft; DES, drug-eluting stent; ICBT, intracoronary brachytherapy; ISR, in-stent restenosis; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

for single-layer ISR, it remains a safe and feasible option for treating recurrent multilayer ISR or ISR where repeat DES is not optimal (eg, small vessel size and bifurcation).[7,8] European guidelines recommend using a second-generation DES or a drug-coated balloon (DCB), with preference for DCB, if there are at least 2 stent layers; they do not make any recommendation involving ICBT for recurrent restenosis, likely because of lack of widespread availability of the modality.[9] DCB are not included in the American guidelines as they are not yet approved for use.

Intracoronary brachytherapy was introduced in 1994 and modulates vascular biology by delaying or disrupting the formation of neointima and inducing vessel remodeling, effects that are often maintained at the 2-year follow-up.[10–12] This is accomplished directly

Table 2. Lesion and treatment characteristics.

Characteristic	Value
Days to ISR	284 (20-765)
No. ISR recurrences	3 (1-5)
Stent layers	2 (1-3)
Previous ICBT at target	9.8%
Angiography	
Reference vessel diameter, mm	2.95 ± 0.56
Percentage of diameter stenosis preintervention	74 ± 19
Chronic total occlusion	9.3%
Lesion length, mm	37 ± 23
Percentage of diameter stenosis postintervention	34 ± 15
Vessel	
Left main	5.3%
Left anterior descending	29.4%
Left circumflex	26.4%
Right coronary artery	28.9%
Saphenous vein graft	12.3%
Treatment	
Intravascular imaging	37.4%
Laser atherectomy	47.9%
Rotational atherectomy	6.5%
Cutting balloon	40.3%
Noncompliant balloon	100.0%
Brachy, 23 Gy	70.8%
Second-generation P_2Y_{12} at discharge	29.9%
Cilostazol at discharge	6.4%
Statin at discharge	89.5%
Sirolimus at discharge	0.8%
Warfarin at discharge	7.0%
Direct oral anticoagulant at discharge	5.9%

Values are given as mean ± SD, percentage, or median (IQR).
ICBT, intracoronary brachytherapy; ISR, in-stent restenosis.

Table 3. Clinical outcomes at 1, 2, and 3 years.

	1-Year rate	2-Year rate	3-Year rate
TLF, %	17.7	31.1	45.8
TLR, %	17.5	29.3	41.7
All-cause mortality, %	6.2	14.4	21.5
Cardiac mortality, %	3.6	8.2	12.3

Values are given in percentages.
TLF, target lesion failure; TLR, target lesion revascularization.

by damaging key components of the cell cycle and indirectly by generating free radicals that trigger apoptosis.[12] ICBT was approved for use in the United States based on favorable outcomes in multiple randomized trials with bare metal stent (BMS) restenosis[13,14] but fell out of favor after studies showed reduced restenosis with first-generation DESs.[15] There are no randomized control trials comparing ICBT with other therapies for the treatment of DES ISR, but one retrospective cohort study found lower major adverse cardiac outcome rates at 8 months compared with repeat DES in treating DES ISR,[16] whereas another prospective study showed favorable 1-year major adverse cardiac outcome rates for ICBT compared with those for non-ICBT (including but not limited to repeat DES) for recurrent DES ISR.[17]

There are no substantial reports of long-term follow-up of ICBT-treated patients in the current era. Available data include a 2021 meta-analysis by Megaly et al,[18] showing that treatment of recurrent DES ISR with ICBT was associated with a 29.2% incidence of TVR during 2 years follow-up. Another study showed restenosis rates with the placement of a second layer of DES were 10% to 20% and with balloon angioplasty alone were 44.6% at 9 to 12 months of follow-up.[19] Many studies have noted a late catch-up phenomenon, in which low failure rates at earlier time points increase substantially at later time points.[7,12,13,20,21]

Previously cited risk factors for ISR include smoking, hypertension, type 2 diabetes, chronic kidney disease, Thrombolysis in Myocardial Infarction score, the type of stent, low inflating stent pressure, multistenting, number of coronary artery lesions, unstable angina, location in the left anterior descending artery, stent diameter ≤3.0 mm, and stent length >20.0 mm.[22,23] There are very limited data about risk factors for recurrent restenosis after ICBT. One study found ICBT failure in treating ISR was associated with ostial location of the target lesion and lower post-treatment luminal diameter.[21]

Many of the existing studies of ICBT include mostly BMS ISR or single-layer DES ISR, or they fail to report the number of stent layers. Because DES is now the predominant strategy for the treatment of stable and unstable coronary lesions, data are needed in this specific population. This study aimed to report the clinical outcomes and correlates in our DES ISR population treated with ICBT.

Methods

Study population

This study included patients with recurrent anginal symptoms or ischemia demonstrated by noninvasive testing from a single-center PCI registry (IRB 16-1102) for patients with stable angina, unstable angina/non–ST-elevation MI, or ST-elevation myocardial infarction (MI) were treated with ICBT between 2010 and 2021. Only patients whose innermost stent layer was DES were included. For those with multiple lesions, only the first treated lesion was included in the analysis. Patients from outside of the United States were excluded owing to absent or incomplete follow-up data.

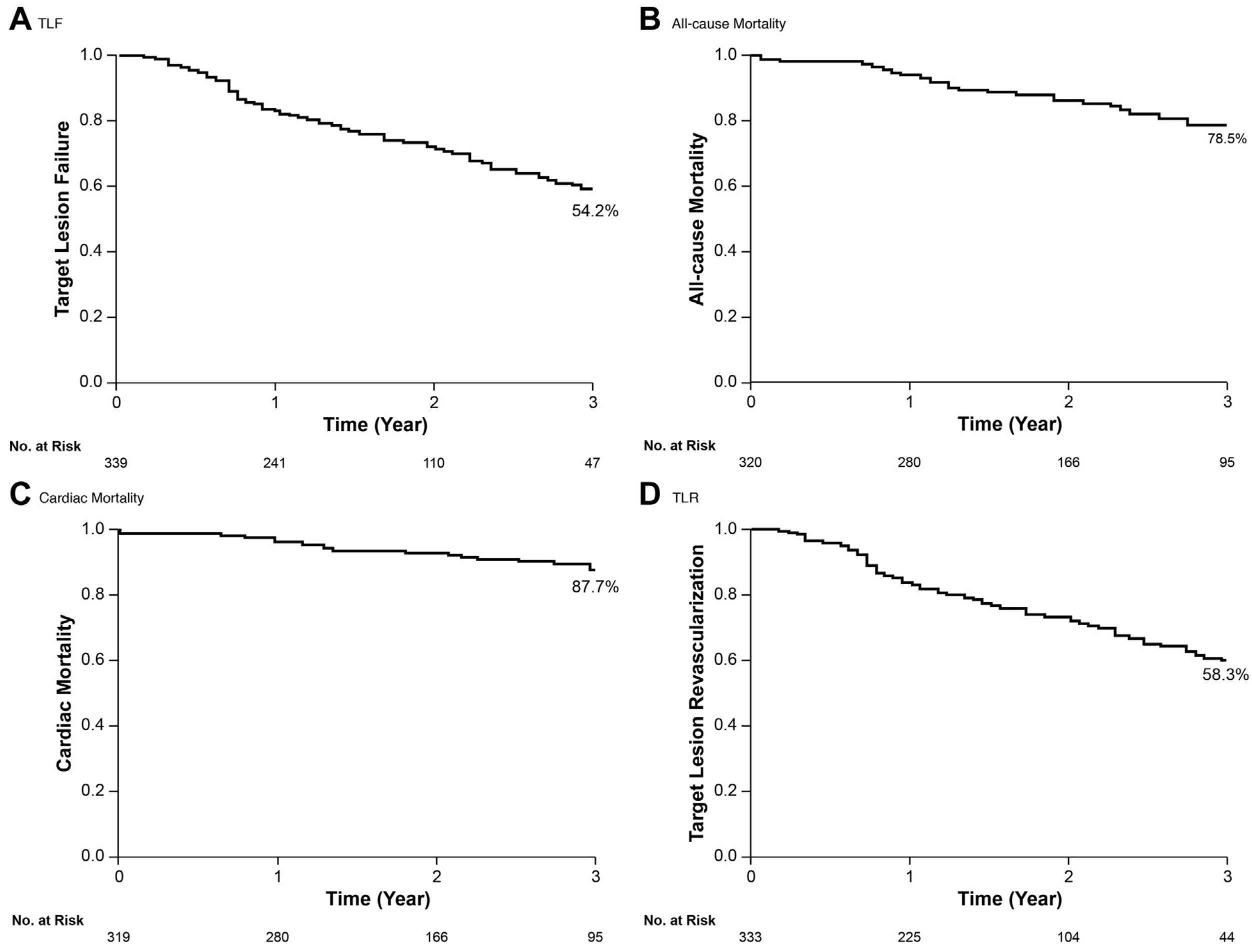


Figure 1.
Kaplan-Meier estimates: (**A**) target lesion failure; (**B**) all-cause mortality; (**C**) cardiac mortality; and (**D**) target lesion revascularization.

Baseline demographic, clinical, and procedural data

Baseline demographics, clinical characteristics, and procedural information were collected from the registry using standardized computerized entry forms with data input by trained cardiology fellows or staff.

Procedural details

All patients were either on dual antiplatelet therapy (DAPT) or received loading doses of DAPT before the procedure and were maintained on heparin for the procedure duration. Arterial access was obtained through the femoral, brachial, or radial artery. Strategy for pretreatment was determined by the operator and included plain old balloon angioplasty, cutting/scoring balloon angioplasty, and laser or rotational atherectomy. Debulking was typically undertaken when it was not felt adequate luminal gain could be made with balloon angioplasty alone. Intravascular imaging was used at the operator's discretion. After pretreatment, ICBT was delivered using the 40.0-mm Novoste Beta-Cath system (Best Vascular). The target vessel was prescribed a dose of 18.4 Gy (vessel diameter ≤3.35 mm) or 23 Gy (vessel diameter >3.35 mm) delivered 2.0 mm from source center at the site of ISR. After March 2015, the standard dose was changed institutionally to 23 Gy (small vessel) or 25 Gy (large vessel) at a depth of 2.0 mm from the center of the source based on the reference vessel diameter. This was based on anecdotal evidence of greater efficacy with higher doses reported by others (Ron Waksman, personal communication). For this analysis, the 18.4/23-Gy doses were considered low dose and the 23/25 Gy as high dose. A margin of 10.0 mm from both ends of the source was allowed to ensure adequate edge coverage; longer lesions were treated with overlapping dwells. Post-radiation stenting was avoided unless necessary for technical success. All patients were maintained on DAPT after the procedure.

Quantitative Coronary Angiographic Analysis

The quantitative coronary angiographic analysis was performed on all angiograms using CAAS version 8.1 (Pie Medical Imaging B.V.). Pretreatment and posttreatment diameter stenosis (DS), lesion length, and reference vessel diameter were obtained.

Clinical end points and definitions

The primary outcome was 3-year target lesion failure rate (TLF), which comprises cardiac death, target lesion revascularization (TLR), target vessel occlusion without revascularization, or target vessel MI. TLR was defined as percutaneous revascularization for stenosis within a stent or within 5.0 mm proximal or distal to the stent. Secondary end points included TLF rate at 1 year, all-cause mortality, and cardiac mortality.

Follow-up

Data management and analyses were performed by research staff. Clinical follow-up data were recorded by research staff to determine

Table 4. Association between outcome and clinical characteristics.

Correlate	3-Year TLF		1-Year TLF	
	HR, 95% CI	*P*	HR, 95% CI	*P*
Number of stent layers	1.39 (0.25-1.53)	.045	1.27 (0.06-2.33)	.28
Saphenous vein graft target	1.53 (0.27-2.81)	.10	1.30 (−0.13 to 2.73)	.48
Time to treated ISR (<1 y)	1.40 (0.12-2.68)	.18	2.01 (0.59-3.42)	.044[a]
Diabetes	1.29 (0.07-2.51)	.21	1.18 (0.87-2.51)	.54
IVUS/OCT	0.85 (−0.39 to 2.09)	.44	0.83 (−0.49 to 2.15)	.50
Radiation dose (low dose vs high dose)	0.98 (0.07-2.03)	.66	0.89 (0.02-1.76)	.035[a]
Final percentage of diameter stenosis	1.00 (0.94-1.06)	.70	1.00 (0.91-1.09)	.79
Previous ICBT	1.11 (0.72-2.50)	.75	1.34 (0.80-2.88)	.46
Occluded target	1.10 (−0.35 to 2.55)	.80	1.27 (−0.33 to 2.87)	.58
Reference vessel diameter	1.04 (−0.14 to 2.22)	.80	0.77 (−0.49 to 2.03)	.26
End-stage renal disease	0.88 (−0.78 to 2.55)	.81	0.65 (−1.40 to 2.70)	.55
Debulking	0.97 (−0.25 to 2.19)	.86	1.03 (−0.28 to 2.34)	.91
Patient sex	0.98 (−0.26 to 2.22)	.93	0.63 (−0.68 to 1.94)	.09
Lesion length	1.00 (−0.04 to 2.04)	.99	1.00 (−0.06 to 2.06)	.76

ICBT, intracoronary brachytherapy; ISR, in-stent restenosis; IVUS, intravascular ultrasound; OCT, optical coherence tomography; TLF, target lesion failure.
[a] Cox multivariable analysis: dose, $P = .046$; time < 12 mo, $P = .052$.

post-ICBT events through the electronic medical record documentation of hospitalizations, office visits, and phone visits. Direct phone calls to the patient/family were made when electronic medical record documentation was incomplete.

Statistical analysis

Analyses were performed using IBM SPSS version 26 and SYSTAT version 13. Patient characteristics are described as mean ± SD, median and interquartile range, or percentage, as appropriate. Kaplan-Meier and Cox logistic regression analyses were used to describe the rate of TLF and determine its correlates, with $P \leq .05$ considered significant and $.05 < P < .10$ considered a trend. The variables were prespecified based on previous studies and limited in number to avoid overmodeling; they included debulking, diabetes, end-stage renal disease, final DS percentage, lesion length, number of stent layers, occluded target, patient sex, previous ICBT, radiation dose (low dose vs high dose), reference vessel diameter, saphenous vein graft target, intravascular imaging use, and time to treatment of ISR (>1 year vs <1 year). Model assumptions were assessed with Schoenfeld residuals.

Results

Baseline characteristics

In total, there were 330 consecutive patients (Table 1). The mean age was 66 ± 11 years, and 70.3% were male. Most of the patients presented with advanced coronary disease with preserved ejection fraction; 62% with previous coronary bypass surgery, and 54.5% with diabetes. The most common clinical presentations were stable angina and unstable angina, and 20.9% presented with acute MI.

Lesion characteristics/procedural data

In total, 345 lesions were treated (Table 2). When known, the mean time to ISR from the last failed DES implantation was 284 days. Of the 285 patients with known number of stent layers, 88.5% had at least 2 stent layers at the target lesion: 11.5% had 1 stent, 59.3% had 2 stents, and 83 had 3 or more stent layers. The median number of ISR recurrences was 3, and 9.8% had received previous radiation at the lesion. The most common sites treated were the left anterior descending artery (29.4%) and left circumflex artery (26.4%); 12.3% of the treated lesions were located within a venous bypass graft.

Treatment before ICBT routinely involved high pressure noncompliant balloons, often after debulking with laser or rotational atherectomy and/or cutting balloon angioplasty. Postprocedural angiograms showed reduction of stenosis, from mean stenosis of 74% ± 19% to 34% ± 15%. Most lesions received at least 23 Gy (70.8%), with 262 lesions longer than 20 mm requiring overlapping dwells.

All patients were maintained on DAPT after the procedure, with 92.5% on DAPT at 1 year, 86.0% at 2 years, and 75.4% at 3 years.

Clinical outcomes

The rate of TLF was 17.7% at 1 year and 45.8% at 3 years; TLR rate was 17.5% at 1 year and 41.7% at 3 years (Table 3); cardiac mortality rose from 3.6% at 1 year to 12.3% at 3 years; and overall mortality was 6.2% and 21.5%, respectively (Figure 1, Central Illustration). Target vessel MI and stent thrombosis rates were 3.8% at 3 years.

Clinical variable correlations

A Cox analysis on 13 preselected clinical variables yielded statistically significant correlation between number of stent layers and 3-year TLF (HR = 1.39, $P = .045$) (Table 4, Central Illustration). The rates of 3-year TLF were 33.3%, 47.0%, and 60.2% for 1, 2, and 3 or more stents, respectively. Both lower radiation dose and lower time to ISR recurrence (time to treated ISR) were correlated with 1-year TLF but not at 3 years. TLF trended higher if the target lesion was within a vein graft ($P = .097$). Final percentage of DS of the target lesion, debulking, and intravascular imaging use were not correlated with TLF at 1 year or at 3 years. There was a trend toward increased TLF in women at 1 year but not at 3 years. Figure 2 shows the survival curves for cohorts stratified by selected variables.

Discussion

This study is one of the largest series reporting long-term outcomes for patients with recurrent DES ISR, including a very high proportion of long and multilayer ISR, and we report a comprehensive evaluation of possible covariates and their relationship with outcomes. Our follow-up period of 3 years is longer relative to other contemporary cohort studies comparing ICBT outcomes with other treatment outcomes.[18,24,25] The use of quantitative coronary angiographic analysis in the determination of DS adds diagnostic rigor when compared with other studies. The key findings include the safety and feasibility of ICBT for recurrent DES ISR,

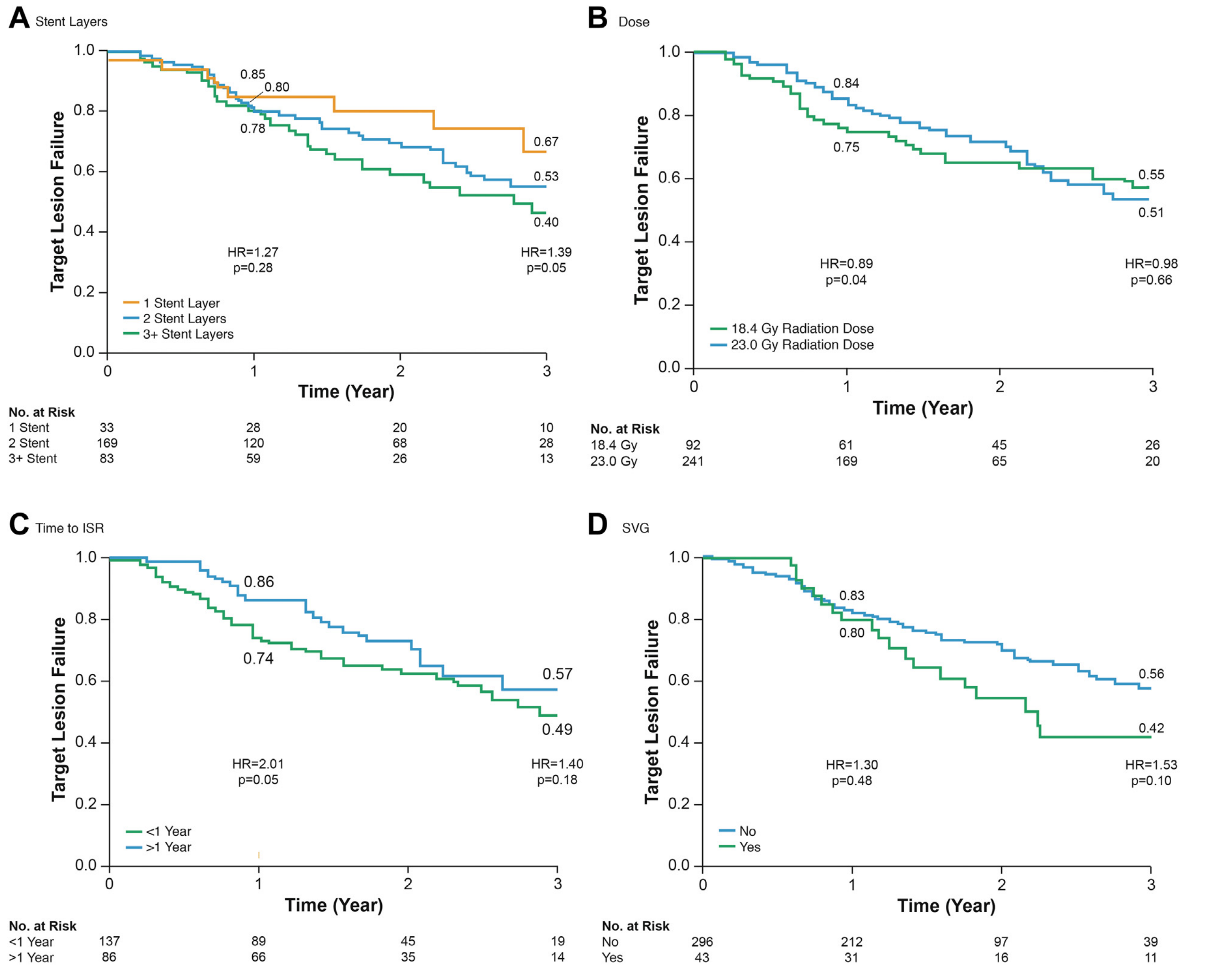


Figure 2.

Kaplan-Meier estimates stratified by the following: (**A**) number of stent layers; (**B**) radiation dose; (**C**) time to in-stent restenosis; and (**D**) target lesion location within a saphenous vein graft.

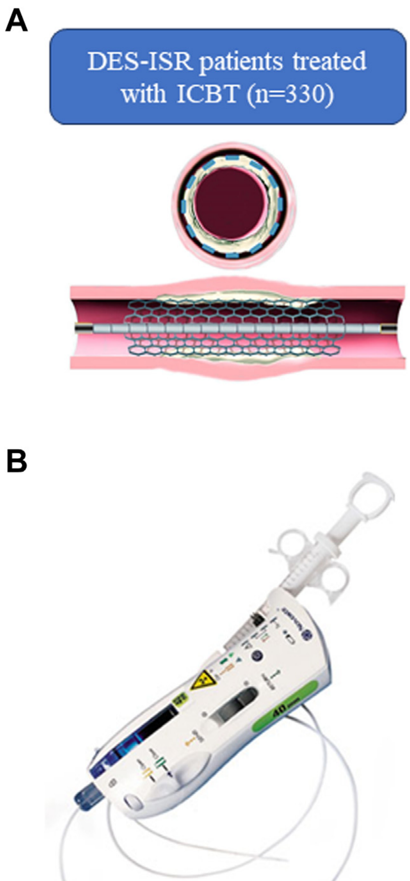
long-term outcomes in a complex patient population, and the identification of patient and treatment factors correlated with a ICBT treatment failure.

Intracoronary brachytherapy was approved based on data from BMS restenosis, but randomized data are lacking in DES restenosis.[10,11] Negi et al[24] demonstrated the safety and efficacy of ICBT for recurrent DES ISR in a single-institutional retrospective study, and Mangione et al[25] reported outcomes of ICBT in treating recurrent DES ISR, finding a 1-year TLR of 24%. A meta-analysis by Megaly et al[26] reported long-term outcomes of ICBT treatment of recurrent DES ISR, finding a TLR and TLF incidence of 18.9% and 20.1% at 1 year. In addition, an observational study by Maluenda et al[27] suggested ICBT may be comparable with repeat DES and balloon angioplasty alone in treating initial DES ISR.

The ICBT failure rates in this study were comparable with those of previously published rates, although our patient population tended to have more advanced disease, with high rates of coronary artery bypass grafting, multiple stent layers, and longer lesions than in most previous studies. Rates of stent thrombosis were low, which is reassuring given previous concerns of stent thrombosis related to ICBT. The observed TLF of 18% at 1 year in this study is better than rates >40% reported for balloon angioplasty and similar to the 10% to 20% for repeat DES.[16] This is particularly encouraging given the high rate of multilayer DES in this study that may limit the use of repeat DES. Moreover, this study demonstrated that TLF was correlated with increasing stent layers, which has important implications for management.

Many risk factors have been elucidated for ISR in general,[19,28,29] but there is a dearth of knowledge of risk factors for failure of ICBT in recurrent ISR. Of the variables tested for association with TLF, only the number of stent layers remained significant at 3 years. Given the lack of correlation between final percentage of stenosis, debulking, and use of intravascular imaging with 3 year TLF in this study, it seems unlikely that increased stent layers act primarily through a mechanical effect; rather, the multiple restenosis more likely reflects an adverse biologic substrate. Moreover, it is possible that vascular inflammation caused by aggressive lesion modification or debulking before irradiation triggers a proliferative response that offsets the luminal patency gained. The very poor outcomes with 3 layers suggest that ICBT should be offered before placing a third stent layer, and in fact, these data suggest there may be merit in studying the use of ICBT in comparison with other treatment options at the time of first restenosis.

The beneficial effect of higher radiation dose on early outcomes has not been previously published. This finding suggests that increased dose is better in the short term by improving suppression of neointimal proliferation but that the effect of brachytherapy is likely time-limited. The



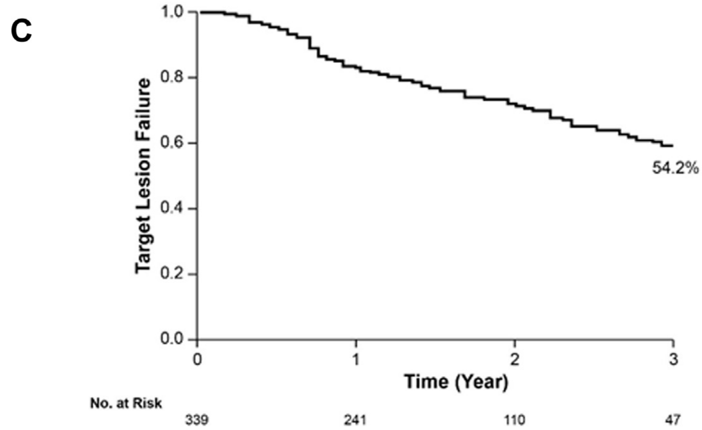


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Table 4: Association between Outcome and Clinical Characteristics

Correlate	3-year TLF		1-year TLF	
	HR, 95% CI	p	HR, 95% CI	p
# Stent layers	1.39 (0.25-1.53)	0.045	1.27 (0.06-2.33)	0.28
SVG target	1.53 (0.27-2.81)	0.10	1.30 (-0.13-2.73)	0.48
Time to treated ISR (<1 year)	1.40 (0.12-2.68)	0.18	2.01 (0.59-3.42)	0.044*
Diabetes	1.29 (0.07-2.51)	0.21	1.18 (0.87-2.51)	0.54
IVUS/OCT	0.85 (-0.39-2.09)	0.44	0.83 (-0.49-2.15)	0.50
Radiation dose (low dose vs high dose)	0.98 (0.07-2.03)	0.66	0.89 (0.02-1.76)	0.035*
Final % diameter stenosis	1.00 (0.94-1.06)	0.70	1.00 (0.91-1.09)	0.79
Prior ICBT	1.11 (0.72-2.50)	0.75	1.34 (0.80-2.88)	0.46
Occluded target	1.10 (-0.35-2.55)	0.80	1.27 (-0.33-2.87)	0.58
Reference vessel diameter	1.04 (-0.14-2.22)	0.80	0.77 (-0.49-2.03)	0.26
ESRD	0.88 (-0.78-2.55)	0.81	0.65 (-1.40-2.70)	0.55
Debulking	0.97 (-0.25-2.19)	0.86	1.03 (-0.28-2.34)	0.91
Patient sex	0.98 (-0.26-2.22)	0.93	0.63 (-0.68-1.94)	0.09
Lesion length	1.00 (-0.04-2.04)	0.99	1.00 (-0.06-2.06)	0.76

Central Illustration.
(**A**) Illustration of β-rail brachytherapy catheter within stented segment. (**B**) Novoste Beta-Cath system (Best Vascular). (**C**) Kaplan-Meier estimates of target lesion failure over time. (**D**) Association between outcome and clinical characteristics. DES, drug-eluting stent; ICBT, intracoronary brachytherapy; ISR, in-stent restenosis.

fact that patients with previous ICBT at the target lesion did not have increased TLF suggests that repeat ICBT may be safe and efficacious, but very few patients underwent more than 2 treatments. The adverse effect of shorter time to restenosis on 1-year TLF likely underscores the importance of a biologic predisposition toward restenosis.

Limitations

This study was limited by its retrospective nature, absence of a control group for comparison, variability among operator pretreatment strategies, and lack of availability of some pretreatment variables that might ideally have been captured. In addition, the duration of DAPT in our population was longer than standard and may have mitigated against stent thrombosis.

Conclusion

Recurrent DES ISR remains a challenge to treat, but this study demonstrates that ICBT is a safe, feasible option in one of the largest published cohorts. Our novel analysis of correlated clinical variables suggests a possible biological predisposition for repeated treatment failure. TLF was most influenced by number of stent layers, without clear effects of baseline patient characteristics, final DS, debulking, or use of intravascular imaging. Future work should include prospective double-blinded randomized control studies comparing ICBT with DCB in multilayer ISR, which has shown promise in this population, testing of combination therapies, and evaluation of the utility of higher dose or repeat brachytherapy dosing at set time intervals on outcomes in ISR treated with brachytherapy.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement and patient consent

This study was approved by the institutional review board at the Cleveland Clinic Foundation and has adhered to relevant ethical guidelines. No patient consent was required because all data were retrospective.

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