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Quantitative Angiographic Methods for Appropriate End-Point Analysis, Edge-Effect Evaluation, and Prediction of Recurrent Restenosis After Coronary Brachytherapy With Gamma Irradiation

Alexandra J. Lansky, MD,* George Dangas, MD, FACC,* Roxana Mehran, MD, FACC,* Kartik J. Desai, MD,* Gary S. Mintz, MD, FACC,† Hongsheng Wu, PHD,† Martin Fahy, MSC,* Gregg W. Stone, MD, FACC,* Ron Waksman, MD, FACC,† Martin B. Leon, MD, FACC*

New York, New York, and Washington, D.C.

OBJECTIVES The study was done to investigate the relationship between clinical restenosis and the relative angiographic location of the recurrent restenotic lesion, after treatment of in-stent restenosis with vascular brachytherapy in the Washington Radiation for In-Stent Restenosis Trial (WRIST).

BACKGROUND Intracoronary radiation therapy reduces recurrence of in-stent restenosis. We investigated the above objective in patients enrolled in WRIST.

METHODS The WRIST study randomized 130 patients to double-blinded therapy with gamma irradiation (iridium-192 [^{192}Ir]) versus placebo after interventional treatment of diffuse in-stent restenosis. After the intervention and at follow-up, three vessel segments were individually analyzed with quantitative coronary angiography: 1) the "stent," 2) the "radiation ribbon," and 3) the "ribbon+margin" segment (including 5 mm on either end of the injured or radiation-ribbon segment). Receiver operator curves (ROC) were used to assess the value of the follow-up percent diameter stenosis (DS) for each of the three analyzed segments in predicting target vessel revascularization (TVR).

RESULTS ^{192}Ir reduced recurrent restenosis (23.7% vs. 60.7%, $p < 0.001$) and the length of recurrent restenosis (8.99 ± 4.34 mm vs. 17.54 ± 10.48 mm, $p < 0.001$) at follow-up compared to placebo. Isolated stent edge (3.4%) and ribbon edge (1.7%) restenoses were infrequent in both groups. The best angiographic surrogate of TVR was the 50% follow-up DS obtained from the ribbon+margin analysis (ROC area 0.806).

CONCLUSIONS In WRIST, not only was ^{192}Ir therapy effective in reducing restenosis, but it also reduced the lesion length of treatment failures by 50%, and it was not associated with edge proliferation. The restenosis rate obtained from the vessel segment *inclusive* of the dose fall-off zones was the best correlate of TVR and should become a standard analysis site in all vascular brachytherapy trials. (J Am Coll Cardiol 2002;39:274–80) © 2002 by the American College of Cardiology

The angiographic evaluation of brachytherapy trials has become more challenging due to the extended length of the segments receiving therapy, the multiple associated landmarks (lesion, balloon injury, stent, and radiation delivery), and the fact that recurrent stenosis may theoretically occur at any location spanning the stent, the radiation delivery catheter, or its dose fall-off edges. A better understanding of the luminal changes that occur after vascular brachytherapy is necessary to optimize radiation prescription and delivery techniques. To that end, we reviewed the quantitative angiographic methods and results of the Washington Radiation for In-Stent Restenosis Trial (WRIST) (1). The specific aims of this angiographic substudy were: 1) to define the segment landmarks used in the angiographic analysis, 2) to determine the location, pattern and predictors of treatment failures, and 3) to determine the best angiographic correlate of clinical revascularization in patients undergoing vascular brachytherapy.

METHODS

Patient population and procedure. Between March 1997 and December 1998, a total of 130 consecutive patients with native vessel (n = 100) or saphenous vein graft (n = 30) stent restenosis were assigned to treatment with iridium-192 (^{192}Ir) or to placebo in the WRIST study. Patients were included in this study if they had a single in-stent restenotic lesion up to 47 mm in length in a 3.0- to 5.0-mm vessel. The procedural details of WRIST have been published in detail elsewhere (1). After successful intervention, patients were randomly assigned to treatment with either ^{192}Ir or placebo. Discrete lesions were treated with a 19- or 23-mm-long ribbon containing five or seven 3-mm sources; longer lesions were treated with a 35-mm, 51-mm, or 55-mm ribbon containing nine, thirteen, or fifteen 3-mm seeds (Best Medical International, Springfield, Virginia). The ribbons were precisely positioned to span the treated lesion. The mean dwell time was 21.7 min, sufficient to deliver 15

From the *Cardiovascular Research Foundation and Lenox Hill Heart and Vascular Institute, New York, New York, and the †Departments of Internal Medicine (Cardiology Divisions) of the Washington Hospital Center, Washington, D.C. This study was supported in part by a grant from Cordis.

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Abbreviations and Acronyms

DS	=	diameter stenosis
^{192}Ir	=	iridium-192
MLD	=	minimal lumen diameter
RD	=	reference diameter
ROC	=	receiver operator curve
TVR	=	target vessel revascularization
WRIST	=	Washington Radiation for In-Stent Restenosis Trial

Gy to a target site 2 mm from the source surface for 3.0- to 4.0-mm vessels, and 24 Gy for >4.0-mm vessels. After removal of the ribbon, cineangiography was repeated to document the absence of complications. Follow-up was obtained at six months.

Angiographic analysis. All procedural and follow-up cineangiograms were analyzed independently by observers who were blinded to the treatment strategy. Standard morphologic criteria were used to characterize baseline lesion complexity (2) and identify the occurrence of angiographic complications (3). Lesion length was determined by the "shoulder-to-shoulder" extent of obstruction both at baseline and at follow-up.

Quantitative coronary angiography (QCA) was performed sequentially at baseline, after intervention and at follow-up, using the CMS-GFT algorithm (MEDIS, Leiden, The Netherlands) guided by the analyst's drawing of the arterial segment and its side branches, demonstrating the precise location of the baseline stenosis, the stent, and the radiation delivery ribbon (Fig. 1) (4). The minimal lumen diameter (MLD) and the mean reference diameter (RD), obtained from averaging a 5-mm segment proximal and distal to the final ribbon or injured+margin location, were used for calculations of %DS [diameter stenosis] = [(1 − MLD/RD) × 100].

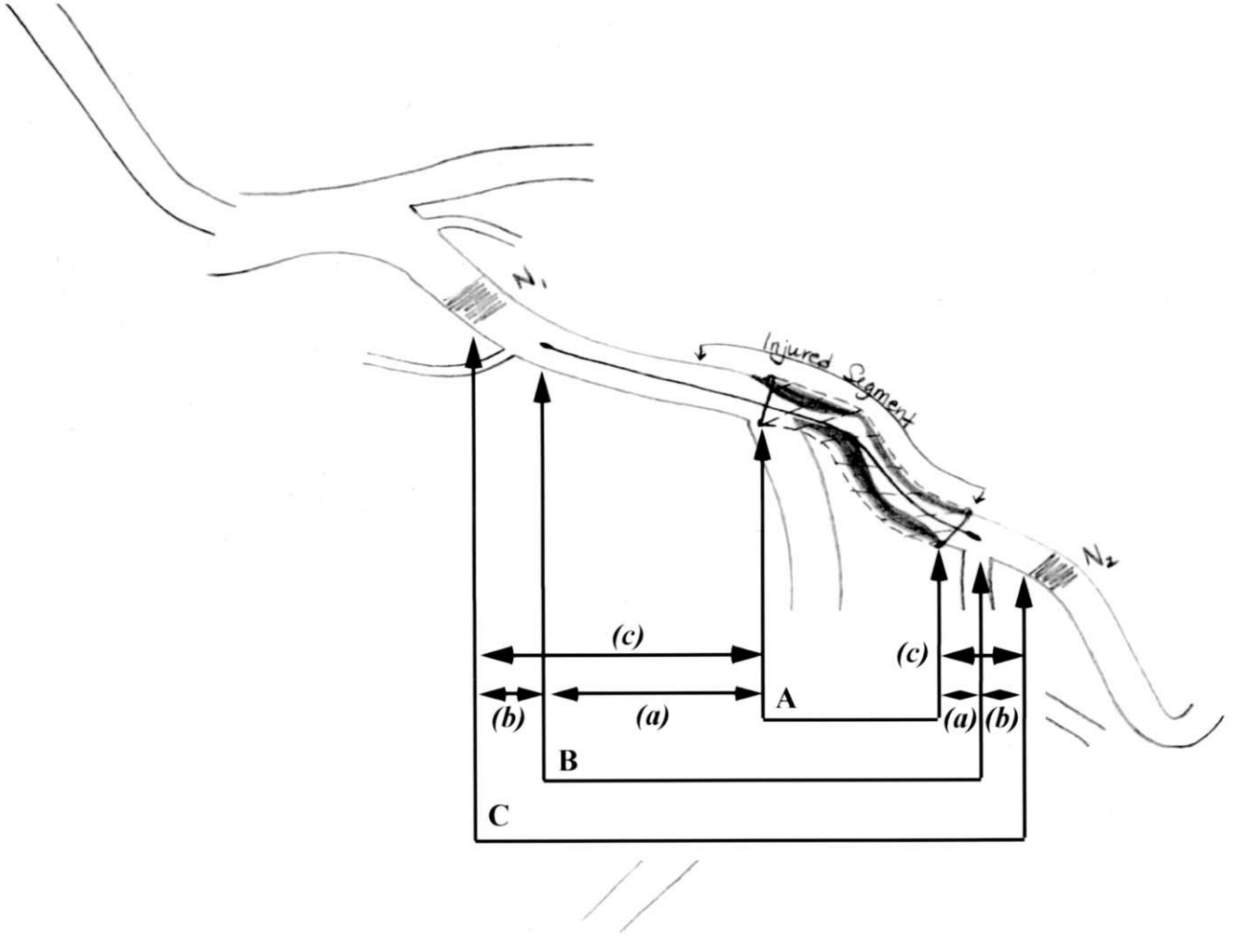

Figure 1. Schematic representation of the stent, ribbon, and ribbon+margin segment analysis. **A (arrows)** represented the axial length of the stent analysis after the procedure; **B (arrows)** represented the ribbon analysis; **C (arrows)** represented the ribbon+margin analysis including approximately 5 mm of margins beyond the ribbon (includes any injury). The three analyses at follow-up enabled definition of **(a)** restenosis at the margin of the stent within the radiated segment [(ribbon restenosis) − (stent restenosis)], **(b)** restenosis at the margin of the radiation ribbon [(ribbon + margin restenosis) − (ribbon restenosis)], and **(c)** restenosis beyond the stent margin [(ribbon + margin restenosis) − (stent restenosis)]. Five-millimeter segments of proximal and distal reference diameters are averaged to estimate the reference vessel diameter.

After final treatment and at follow-up, three separate analyses were performed: 1) a "stent" analysis, which identified the MLD within the axial stent length; 2) a "ribbon" analysis, which identified the MLD within the segment spanning the radiation delivery ribbon; and 3) a "ribbon+margin" analysis, which identified the MLD in the segment spanning the ribbon *and* including a 5-mm margin proximal and distal to the ribbon or injured zone (Fig. 1). An MLD of 0.0 was imputed in the presence of a total occlusion at baseline or at follow-up. *Acute gain* was defined as the change in the MLD from baseline to the final procedural angiogram; *late loss* was defined as the change in MLD from the final to the follow-up angiogram. The *arithmetic loss index* was defined as (late loss)/(acute gain). Binary restenosis was defined as a >50% DS at follow-up. The three analyses at follow-up enabled definition of (a) restenosis at the margin of the stent within the radiated segment [(ribbon restenosis) − (stent restenosis)], (b) restenosis at the margin of the radiation ribbon [(ribbon + margin restenosis) − (ribbon restenosis)], and (c) restenosis beyond the stent margin [(ribbon + margin restenosis) [(ribbon + margin restenosis) − (stent restenosis)] (Fig. 1).

Statistical analysis. Continuous variables are presented as mean ± SD; ordinal variables are presented as frequencies. Comparison between continuous variables was performed using the Student *t* test; comparisons between ordinal variables were performed using chi-square or the Fisher exact test, when indicated. A $p < 0.05$ was considered significant. Paired statistical tests were used for comparing different analysis segments within each treatment group. Paired *t* tests were used for continuous variables, and the McNemar test was used for categorical variables. The Bonferroni adjustment was used to control for multiple comparisons. Receiver operator curves (ROC) were used to assess the value of the follow-up percent DS obtained using the three different segments analyzed (stent, ribbon, and ribbon+margin) in predicting clinically driven target vessel revascularization (TVR). Multivariable logistic regression analyses were performed to identify clinical and angiographic predictors of restenosis in all patients enrolled in WRIST and those patients randomized to radiation therapy. Binary stepwise multivariate logistic regression analysis utilized p values of 0.10 for entry and 0.20 for removal. A two-tailed p value < 0.05 was considered significant.

RESULTS

Lesion characteristics. Baseline and follow-up angiograms technically suitable for quantitative angiographic analysis were available in 128 and in 117 of 130 patients, respectively. Treated lesion location and baseline complexity were similar in the ^{192}Ir and placebo groups (1). Patients with American College of Cardiology/American Heart Association (ACC/AHA) B2 and C lesion complexity (63%), and mean lesion length (20.5 ± 10.5 mm), were similarly distributed in the two groups. The mean seed to lesion length ratio was 1.82 ± 0.87. After the final procedure, dissections remained in 18.8% of ^{192}Ir and 12.5% of placebo patients ($p = 0.33$). No late angiographic complications related to radiation treatment, such as the development of aneuryms or arterial constriction, were observed. All dissections remaining at the final procedure were healed at follow-up. The follow-up lesion length was significantly longer in placebo compared to ^{192}Ir-treated patients (17.54 ± 10.48 mm vs. 8.99 ± 4.34 mm; $p < 0.0001$).

Table 1. Quantitative Angiographic Results

	^{192}Iridium	Placebo	p Value
No. of patients	64	64	
Reference (mm)			
Baseline	2.71 ± 0.53	2.72 ± 0.56	0.908
Final	2.79 ± 0.50	2.85 ± 0.50	0.544
Follow-up	2.90 ± 0.52	2.87 ± 0.58	0.788
MLD (mm)			
Baseline	0.94 ± 0.42	0.81 ± 0.42	0.074
Final			
Stent	2.23 ± 0.52*	2.25 ± 0.50*	0.851
Ribbon	2.00 ± 0.68	2.10 ± 0.51	0.336
Lesion (ribbon+margin)	2.00 ± 0.47	2.05 ± 0.42	0.514
Follow-up			
Stent	2.01 ± 0.93*	1.24 ± 0.77†	<0.0001
Ribbon	1.72 ± 0.95	1.14 ± 0.86	0.0008
Lesion (ribbon+margin)	1.70 ± 0.78	1.20 ± 0.75	0.0007
% Stenosis			
Baseline	65.2 ± 14.3	70.4 ± 14.6	0.0471
Final			
Stent	19.8 ± 15.2*	20.5 ± 14.8*	0.799
Ribbon	28.4 ± 22.9	26.2 ± 12.0	0.5120
Lesion (ribbon+margin)	28.3 ± 11.9	27.3 ± 12.0	0.631
Follow-up			
Stent	30.1 ± 30.0*	57.9 ± 22.0†	0.0001
Ribbon	41.5 ± 30.5	60.7 ± 24.6	0.0003
Lesion (ribbon+margin)	42.1 ± 23.3	59.3 ± 20.1	<0.0001

A single culprit lesion is reported for each patient.
*$p < 0.001$ for comparison of stent versus ribbon and stent versus ribbon+margin; †$p < 0.05$ for comparison of stent versus ribbon and stent versus ribbon+margin.

Quantitative angiographic results. Quantitative angiographic findings are in Tables 1 and 2. Reference vessel diameters and the postprocedure stent, ribbon or ribbon+margin MLDs were similar for both ^{192}Ir and placebo-treated patients. At follow-up the stent, ribbon and ribbon+margin MLD values were significantly larger in ^{192}Ir-treated patients ($p < 0.001$ for all). The distribution of follow-up MLDs for the stent analysis demonstrated a near bimodal distribution with systematically larger MLDs with iridium therapy. For the ribbon+margin analysis, the distribution of follow-up MLDs, although demonstrating more overlap, still had systematically larger MLDs with ^{192}Ir therapy compared to placebo (Fig. 2).

The ^{192}Ir-treated patients had a lower late loss and loss index compared to placebo-treated patients regardless of the vessel segment analyzed ($p < 0.001$) (Table 2). Unlike placebo patients, ^{192}Ir patients had a significantly lower late loss within the stent than within the ribbon or the ribbon+margin ($p < 0.001$ for both comparisons); accord-

Table 2. Serial Changes in Lumen Dimensions

	^{192}Iridium	Placebo	p Value
Acute gain (mm)			
Stent	1.29 ± 0.53†	1.44 ± 0.53†	0.1072
Ribbon	1.06 ± 1.75	1.29 ± 0.50	0.0396
Lesion (ribbon+margin)	1.06 ± 0.50	1.25 ± 0.48	0.0334
Late loss (mm)			
Stent	0.24 ± 0.84	1.00 ± 0.69†	<0.0001
Ribbon	0.28 ± 0.73	0.88 ± 0.64	<0.0001
Lesion (ribbon+margin)	0.32 ± 0.70	0.84 ± 0.70	0.0001
Loss index (Arithmetic)			
Stent	0.18 ± 0.73‡	0.70 ± 0.46	0.0001
Ribbon	0.26 ± 0.12	0.58 ± 0.15	0.0001
Lesion (ribbon+margin)	0.29 ± 0.70	0.60 ± 0.92	0.0468
Restenosis rate (%)			
Stent	12 (20.3)*	32 (57.1)	<0.001
Ribbon	13 (22.4)	33 (60.0)	<0.001
Lesion (ribbon+margin)	14 (23.7)	34 (60.7)	<0.001
Stent margin only	2 (3.4)	2 (3.4)	NS
Ribbon margin only	1 (1.7)	1 (1.7)	NS
Irradiated stent margin	1 (1.7)	1 (1.7)	NS

*p = 0.0832 for comparison of stent versus ribbon; †p < 0.001 for comparison of stent versus ribbon and stent versus ribbon+margin; ‡p = 0.223 for comparison of stent versus ribbon+margin.

ingly, the loss index within the stent was lower than within the ribbon+margin segment (p = 0.0223).

Edge restenosis after gamma radiation. Compared with placebo patients, ^{192}Ir-treated patients had lower stent restenosis rates (p < 0.001), ribbon restenosis (p < 0.001) and ribbon+margin segment restenosis rates (p < 0.001). Isolated stent margin restenosis occurred in only 3.4% of lesions, and isolated ribbon margin restenosis occurred in 1.7% of treated lesions. There was no significant increase or reduction in the restenosis rate with ^{192}Ir therapy at the stent margin (3.4% radiation vs. 3.4% placebo; p = 0.5) or at the ribbon margin only (1.7% radiation vs. 1.7% placebo, p = 0.6). Ribbon or stent edge restenosis was unrelated to the extent of coverage of the stent edges with seeds. A total of four patients in the iridium group had inadequate coverage of both the proximal (mean of two seeds) and the distal edge (mean of three seeds) of the stent with active seeds. Restenosis did not occur in any of these patients. In the two patients with stent edge restenosis including the patient with restenosis at the edge of the radiation delivery catheter, there was extensive coverage of the proximal and distal edge areas by 6 and 10 seeds, respectively.

Predictors of recurrent angiographic restenosis. In the overall WRIST population, univariate predictors of restenosis included ^{192}Ir therapy, lesion length, baseline MLD, lesion complexity, final ribbon MLD, and reference diameter, but only three factors were independently predictive of restenosis: 1) ^{192}Ir therapy (OR [odds ratio] 0.175, 95% CI [confidence interval] 0.064–0.476, p = 0.0006); 2) increasing lesion length (per mm) (OR 1.073, 95% CI [1.017–1.133], p = 0.01); and 3) increasing reference vessel size (per mm) (OR 0.339, 95% CI [0.115–0.995], p = 0.049). Among patients who received ^{192}Ir therapy only, univariate predictors included lesion length, RD, final ribbon MLD, ostial location, and left anterior descending coronary artery (LAD) location, but only increasing lesion length (per mm) (OR 1.133, 95% CI [1.032–1.245], p = 0.0091), ostial location (OR 16.32, 95% CI [1.94–137.32], p = 0.01020) and LAD location (OR 12.37, 95% CI [1.76–86.92], p = 0.0115) were significant independent predictors of restenosis by multivariate analysis.

Figure 3 describes the relationship between initial lesion length and the probability of restenosis within the in-stent segment, the stent edge segment and the entire treated (ribbon+margins) segment. It is evident that the relationship between these two parameters is different at the stent

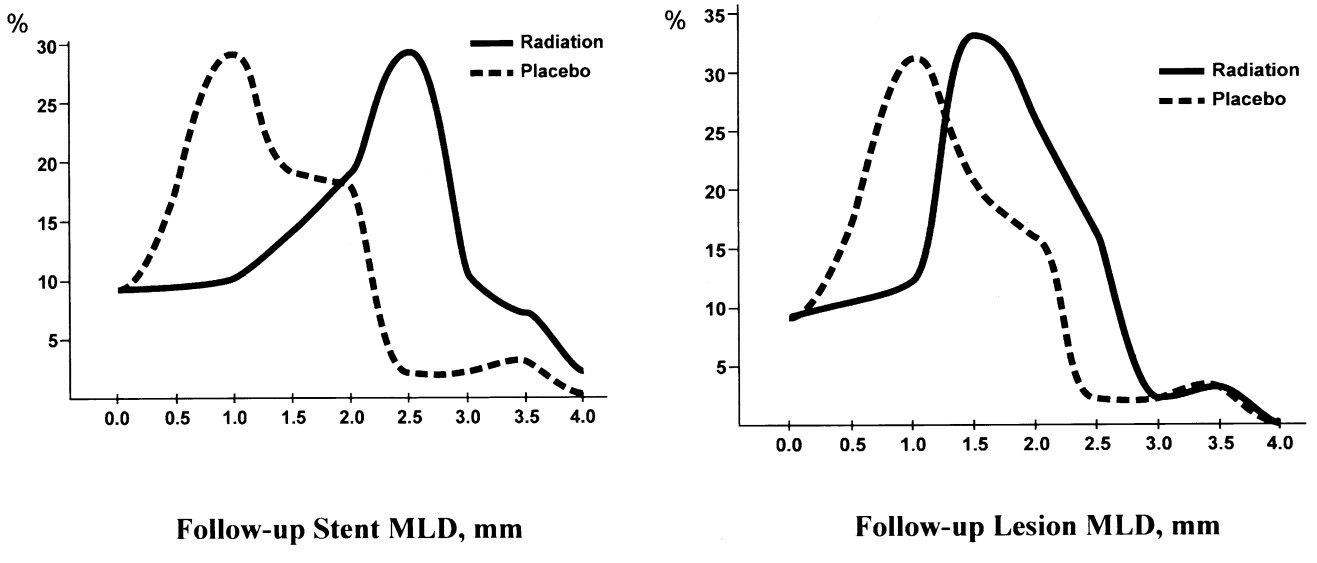

Figure 2. Frequency of minimal lumen diameters (MLDs) at follow-up demonstrating a bimodal distribution of the iridium and placebo groups using the stent MLD compared to a near-normal distribution of the iridium and placebo groups using the ribbon+margin MLD.

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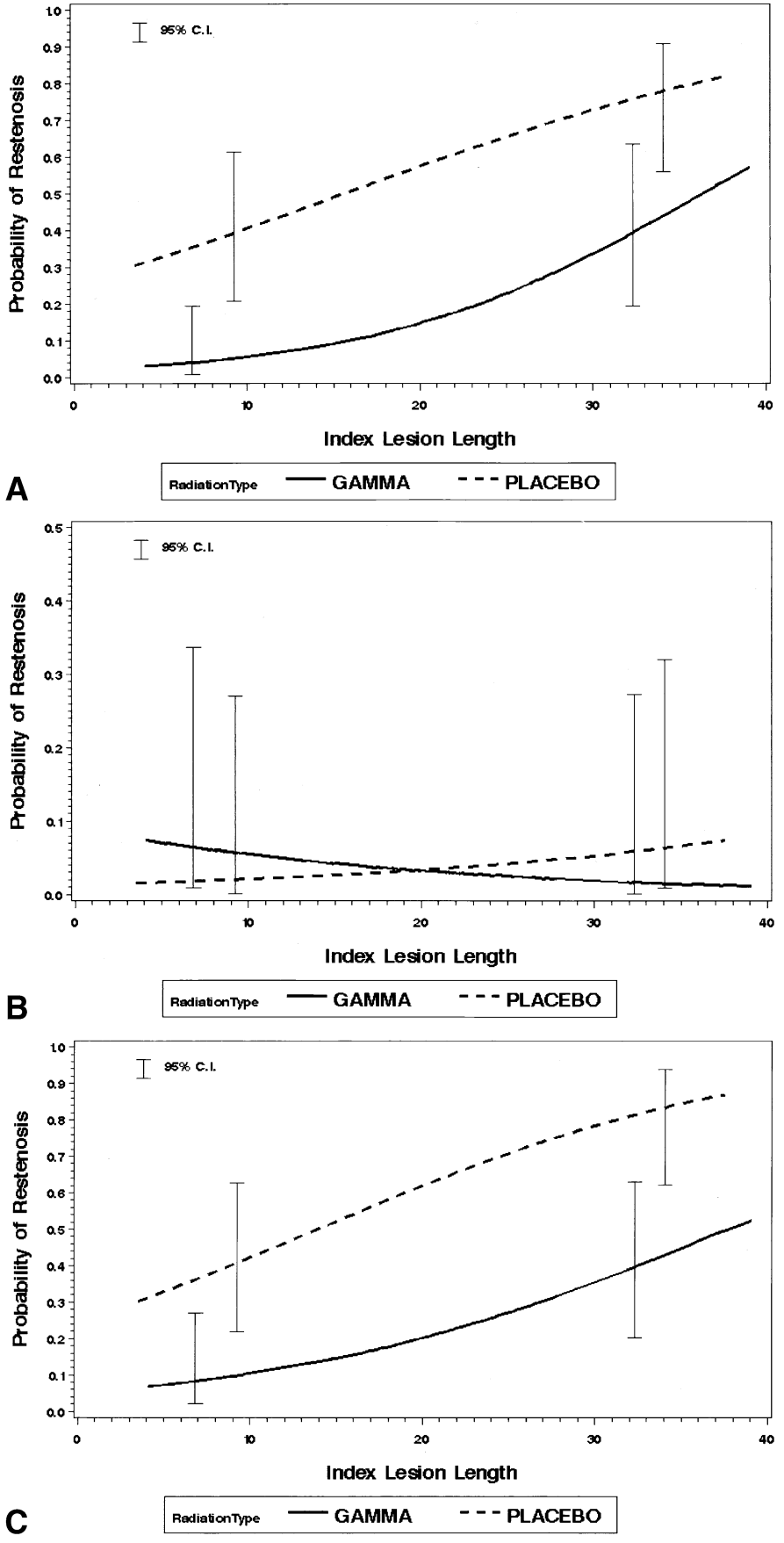
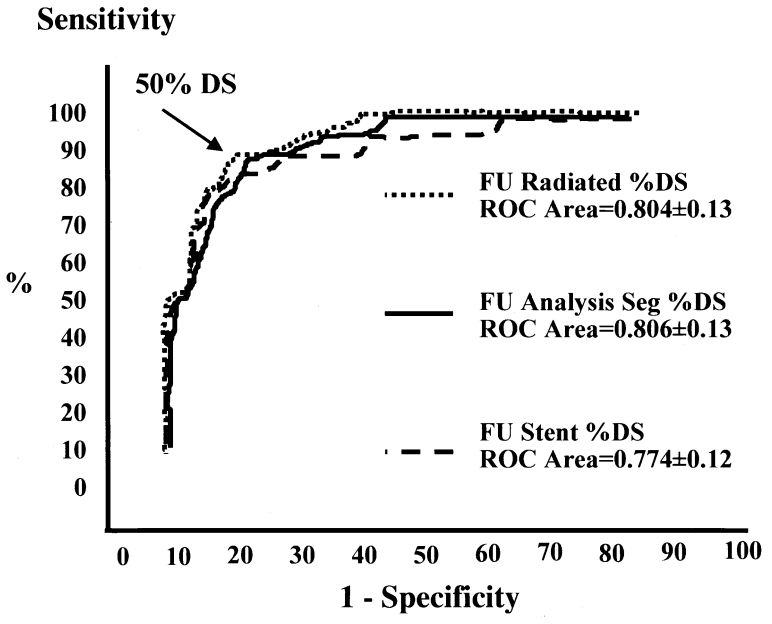


Figure 3. Probability of recurrent restenosis according to the initial lesion length. Restenoses within the stent **(A)**, the stent edges **(B)** and the entire treated segment (ribbon+margins, **C**) are analyzed separately.



	Sensitivity	Specificity	Area ± SE	p Value
Follow-up stent % DS >50%	64.29%	89.19%	0.774 ± 0.121	< 0.001
Follow-up ribbon % DS >50%	66.07%	87.84%	0.804 ± 0.130	< 0.001
Follow-up ribbon+margin% DS >50%	67.86%	86.49%	0.806 ± 0.130	< 0.001

Figure 4. Receiver operator curves of the follow-up percent diameter stenosis (DS) for the stent, ribbon, and ribbon+margin analyses to determine the best surrogate of target vessel revascularization. A follow-up 50% DS obtained from the ribbon or the ribbon+margin analyses had the highest combined sensitivity and specificity for target lesion revascularization. FU = follow-up; ROC = receiver operator curve.

edges depending on treatment allocation. Stent edge restenosis is generally low, and it appears to be more frequent in shorter lesions treated with radiation, and in longer lesions treated with placebo. For any given lesion length, restenosis within the stent and within the entire treated segment is lower with radiation than with placebo and is increasing with increasing initial lesion length in both groups.

Angiographic correlates of target lesion revascularization. The follow-up percent DS obtained from the three angiographic analyses, including the stent, the ribbon and the ribbon+margin segments, correlated with clinically driven target lesion revascularization (Fig. 4). Although no significant differences were found among the tested angiographic variables, the one with the highest combined sensitivity and specificity for predicting clinically driven TVR was the binary restenosis rate (>50% DS) obtained from the ribbon+margin analysis segment (ROC area = 0.806, $p < 0.001$), compared to the ribbon analysis segment (ROC area = 0.804 ± 0.130, $p < 0.001$) or the stent analysis (ROC area = 0.774 ± 0.121, $p < 0.001$).

DISCUSSION

Important differences exist in the early and late angiographic findings after treatment of in-stent restenosis with gamma radiation in WRIST, depending on whether the angiographic measurements were made within the stent, irradiated or irradiated+margin segments. The greatest angiographic benefit from ^{192}Ir was obtained within the stent segment, as evident by the lower restenosis rate and the lower loss index compared to the other two segments encompassing the irradiated segment, including the margins. Both stent edge restenosis and ribbon edge restenosis were infrequent after gamma radiation, and no different than with placebo; thus iridium therapy had no apparent proliferative edge effect. In addition to the reduction in restenosis, ^{192}Ir also resulted in a more focal pattern of restenosis among treatment failure. Despite the low frequency of edge restenosis after gamma radiation in WRIST, the angiographic analysis encompassing the irradiated+margin segment was the strongest correlate of TVR. These findings underscore the importance of systematically including the angiographic outcome of the radiation ribbon and its margins in the angiographic analysis of brachytherapy trials.

Restenosis and the "edge effect" after ^{192}Ir brachytherapy. In the SCRIPPS trial (5,6), treatment of patients with ^{192}Ir reduced the angiographic restenosis within the stent by 79% (8.3% vs. 39.3%; $p = 0.010$) and at the margin of the stent by 42% (8.3% vs. 14.3%, $p = 0.503$). In WRIST, the greatest reduction in restenosis was also within the stent (20.3% vs. 57.1%, $p < 0.001$), while both stent margin restenosis (3.4%) and ribbon margin restenosis (1.7%) were trivial and the same for ^{192}Ir and placebo patients.

The frequency distribution of the follow-up MLD based on the ribbon+margin analysis further supports the absence of a significant "edge effect" after gamma radiation in the WRIST trial, because the follow-up MLD values were systematically larger with ^{192}Ir therapy compared to placebo (Fig. 2). In addition, the longer length of radiation delivery seeds used to cover the stent margins in this study (mean radiation seed length over lesion length ratio >1.8) had no apparent detrimental effects on the adjacent nonstented arterial segments at six months.

Pattern of in-stent restenosis after ^{192}Ir brachytherapy. Consistent with the previous SCRIPPS trial (5), ^{192}Ir therapy in WRIST was the strongest protective predictor of binary restenosis. Furthermore, when recurrent restenosis occurred, angiographic lesions were significantly shorter (more frequently focal) after ^{192}Ir therapy compared to placebo. Thus, in cases of treatment failure, ^{192}Ir appears to alter the pattern of in-stent restenosis, with an increase of focal patterns (7). Because the angiographic pattern of in-stent restenosis is the predominant predictor of long-term clinical outcome (7), this observation may be of clinical importance. Not only does ^{192}Ir therapy produce fewer failures than placebo, but radiation failures (more frequently focal pattern) may have better prognosis than placebo failures (more frequently diffuse pattern).

Among patients assigned to ^{192}Ir therapy, similar high-risk lesion and procedural characteristics as seen in non-brachytherapy trials were predictive of restenosis, including lesion length, ostial lesions, and LAD location.

Angiographic and clinical restenosis in vascular brachytherapy trials. Binary restenosis has been used as a surrogate of TVR in assessing the effectiveness of new devices in interventional cardiology. In the WRIST study, despite the low frequency of edge restenosis, the best predictor of TVR was the binary restenosis rate obtained from the ribbon+margin and the ribbon analysis (Fig. 4). This may be due to the apparent shift in follow-up MLD away from the original lesion site (evidenced by the follow-up MLD being smaller within the ribbon+margin than within the stent segment) in ^{192}Ir-treated patients, a phenomenon previously reported elsewhere (8). Therefore, selecting an adequate length of analysis in the angiographic assessment of vascular brachytherapy trials is particularly relevant the greater the concern or frequency of edge restenosis. A comprehensive segment of analysis that encompasses any zone of injury, the radiation delivery device, and its dose fall-off zones is necessary in the surrogate evaluation of this new therapeutic modality.

Study limitations. First, despite using side branches and other anatomic landmarks, the relative radiolucency of some stents make precise localization of the stent within the artery somewhat problematic for angiographic analysis, as well as for precise positioning of ^{192}Ir seeds within the stent at the time of intervention. Second, although the injured area was an integral part of the ribbon+margin analysis, the zones of injury were not independently assessed in the present study, which may have provided further insight into another potential cause of vascular brachytherapy failure. Finally, a systematic analysis of the dose fall-off zones to more precisely quantify the "edge effect" in all patients was not performed.

Conclusions. The efficacy of ^{192}Ir therapy appears to extend beyond the overall reduction in restenosis, also altering the pattern of treatment failures to a more focal restenosis pattern, which may have a better prognosis than the diffuse placebo failures. Based on the radiation prescription techniques used in WRIST, a proliferative effect related to dose fall-off at the edge of the source was not demonstrated. Despite infrequent "edge" restenosis in WRIST, the appropriate angiographic surrogate end point in this and other vascular brachytherapy trials where "edge effect" is of concern should assess the luminal changes of the full extent of the arterial segment exposed to radiation inclusive of dose fall-off margins.

Reprint requests and correspondence: Dr. Alexandra J. Lansky, Cardiovascular Research Foundation, 55 East 59th St., 6th Floor, New York, NY 10022. E-mail: alansky@crf.org.

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