Edge Stenosis and Geographical Miss Following Intracoronary Gamma Radiation Therapy for In-Stent Restenosis

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OBJECTIVES We sought to determine the relationship between geographical miss (GM) and edge restenosis (ERS) following intracoronary radiation therapy.

BACKGROUND Edge restenosis may be a limitation of intracoronary irradiation to prevent in-stent restenosis (ISR). Inadequate radiation source coverage of the injured segment (GM) has been proposed as a cause of ERS. We studied the relationship between GM and ERS following 192Ir treatment of ISR.

METHODS There were 100 patients with native vessel ISR in WRIST (Washington Radiation for In-Stent Restenosis Trial), in which patients with ISR were first treated with conventional techniques and then randomized to gamma irradiation (192Ir) or placebo. Geographical miss was defined as segments proximal or distal to the treated lesion that were subjected to injury during primary intervention but were not covered by the radiation source.

RESULTS Geographical miss was documented in 56 of 164 edges (34%). Edge restenosis was noted at eight of 80 radiated edges and in four of 84 placebo edges. In the irradiated group, ERS was observed in 21% of edges with GM and in 4% of edges without GM (p = 0.035). In contrast, in the placebo group, ERS was observed in only 7% of edges with GM and in 4% of edges without GM (p = NS). The late edge lumen loss was higher in the irradiated group with GM as compared to placebo with GM (0.74 ± 0.57 vs. 0.41 ± 0.50 mm, p = 0.016).

CONCLUSIONS Edge restenosis following gamma irradiation treatment of ISR is related to GM: a mismatch between the segment of artery injured during the primary catheter-based intervention and the length of the radiation source. (J Am Coll Cardiol 2001;37:1026–30) © 2001 by the American College of Cardiology

In-stent restenosis (ISR) has become an important clinical problem because of the exponential increase in the use of intracoronary stents (1,2). Adjunctive intracoronary radiation therapy (IRT) using both beta and gamma emitters has been shown to reduce the recurrence rate of ISR (3–6). However, a common pattern of recurrent edge restenosis (ERS) is found in patients with IRT failure (7). Edge restenosis was initially observed with the use of radioactive 32P stents (activities of 3–20 mCi) (8–10) and more recently with the use of catheter-based systems (7,11).

The exact mechanisms of ERS are still under investigation. It has been proposed, however, that low dose radiation may stimulate proliferation at the edge of the treatment zone, which is injured during primary intervention (9,12–14). Failure at the edge of a treatment zone has been described in radiation oncology reports (15) and the term geographical miss (GM), that is, inadequate coverage of the diseased segment, has been applied.

The purpose of the current study was to determine the relationship between GM and ERS following gamma irradiation treatment for ISR.

METHODS

Patients and procedure. The Washington Radiation for In-Stent restenosis Trial (WRIST) was a placebo-controlled protocol in which patients with ISR were first treated with conventional catheter-based techniques and then randomized to receive either gamma irradiation (192Ir) or placebo (dummy seeds). There were 100 patients with native vessel ISR. Patients without angiographic follow-up or with total occlusions at follow-up were excluded. Angiographic analysis was available in 42 patients from the irradiated group and 44 patients from the placebo group.

The details of WRIST have been presented elsewhere (6). In brief, angiographic entry criteria included diameter stenosis (DS) ≥50% in vessels 3 to 5 mm in diameter with lesion lengths <47mm treated successfully (<30% residual stenosis without complications). Devices used during the primary intervention included balloon, ablative devices (ex-cimer laser angioplasty [spectranetics], or rotational atherectomy [SCIMED]), additional stents or a combination thereof. All procedural steps were documented angiographically. Following the primary intervention, patients were randomly assigned to receive a nylon ribbon (0.003 in. diameter) containing either placebo or 192Ir seeds (Best Medical International, Springfield, Virginia); sources contained five, nine or 13 seeds that covered 19, 36 and 51 mm, respectively. The prescribed dose was 15 Gy to a distance of...
Definitions and angiographic analysis. Intracoronary nitroglycerin (200 μg) was administered before each angiogram. Cineangiograms at follow-up were acquired using the same projections of the procedural angiograms. All procedural and follow-up cineangiograms were analyzed at the Washington Hospital Center Angiographic Core Laboratory by observers blinded to the treatment strategy. Cine frames were selected at the end-diastolic phase from the two sharpest and most severe projections of the stenosis before and after the procedure and at six-month follow-up. Quantitative angiographic analysis was performed with the CMS-GFT system (Medis) (16). The contrast-filled catheter was used for image calibration (17).

The overall angiographic results from WRIST have previously been reported (6). The minimal lumen diameter (MLD) at each edge was measured. Acute edge lumen gain was defined as the change of MLD at each edge from pre- to postintervention; late edge lumen loss was defined as the change of MLD at the edges from postintervention to follow-up at six months.

The investigators attempted to angiographically document all the steps of the intervention, including the position of the radiation to determine whether the edge of the radiated segment was injured. Edge restenosis was defined as a follow-up DS ≥50% occurring ≤5 mm proximal or distal to the last seed of the radiation source (Fig. 1). Geographic miss was defined as segments proximal or distal to the treated lesion that were subjected to injury during balloon inflation or new stent implantation but were not covered by the last seeds of the radiation source.

Statistical analysis. Continuous variables are presented as mean ± SD; ordinal variables are presented as frequencies. A comparison between continuous variables was performed using the Student t test with the Bonferroni correction for multiple comparisons. Comparisons between ordinal variables were performed using the chi-square or Fisher exact test. In order to control the within-patient effects, a generalized estimation equation modeling analysis, using patients as subjects, was performed. A p value <0.05 was considered significant.

RESULTS

Eighty-six irradiated coronary arteries and 172 edges (two edges per irradiated segment) in 86 patients were eligible for the study. However, eight edges were excluded because of the ostial location of the proximal end of the source in the right coronary artery. Thus, 164 edges were analyzed. Overall, GM was documented in 56 of 164 edges (34%). In the irradiated group, GM was observed in 28 of 80 (35%) edges induced by balloon dilation (n = 17) or additional stent implantation (n = 11). Geographic miss in the placebo group was observed in 28 of 84 (33%) edges induced by balloon dilation (n = 18) or stent implantation (n = 10). The frequency of GM was similar among the proximal and distal segments in the irradiated and placebo groups. Edge restenosis was noted at eight of 80 radiated edges (two proximal, four distal, and one both proximal and distal) and in four of 84 placebo edges (two proximal and two distal).

The relationship between GM and ERS is shown in Table 1. In the irradiated group, ERS was observed in 21% of edges with GM and in 4% of edges without GM (p = 0.035). In contrast, in the placebo group ERS was observed in only 7% of edges with GM and in 4% of edges without GM (p = NS). Generalized estimation equation analysis, which was used to account for within-patient effect, showed that in radiation-treated patients the probability of ERS depended on the GM (p = 0.021), but not on distal/ proximal lesion location (p = 0.397). For the placebo-treated patients, the probability of ERS did not depend on either GM (p = 0.481) or lesion location (p = 0.971).

Quantitative angiographic analysis of the 164 edges is presented in Table 2. The preintervention, postintervention and follow-up reference diameters were similar in all four


**DISCUSSION**

The current study identifies edge restenosis as a cause of failure in using $^{192}$Ir brachytherapy to prevent recurrent ISR. Although the mechanism of ERS remains unclear, it occurred in 21% of edges in which the $^{192}$Ir source did not adequately cover the entire segment of artery injured during the primary catheter-based treatment of ISR (Fig. 2). This is the definition of GM (15).

**Frequency of ERS.** The incidence of ERS after initial stent implantation without radiation has been reported to be between 5% and 10% (18,19). The incidence of ERS after treatment of in-stent restenotic lesions without radiation is less clear; reports vary from 15.3% in the placebo group of the SCRIPPS (Scripps Coronary Radiation to Prevent Proliferation Post-Stenting) trial (3,20) to only 3% to 4% in the control arms of WRIST (6) and GAMMA 1 (21).

The first reports of ERS following brachytherapy were related to the use of the $^{32}$P-radioactive stent (8–10). In these patients ERS was seen four to six months after implantation and was located at or near the margins of the stent. The pronounced ERS in these patients has been called the “candy-wraper” effect (10). Conversely, in SCRIPPS, a randomized, placebo-controlled, clinical trial similar to WRIST, the frequency of stent margin restenosis with $^{192}$Ir was similar to placebo (3,20). The major effect of gamma irradiation appeared to be the reduction of in-stent neoointimal tissue.

The current study addressed the question whether gamma irradiation treatment of ISR is associated with an increased incidence of edge effect. In the current analysis, the incidence of ESR in the $^{192}$Ir arm was 10.0% and 4.7% in the placebo arm. This difference did not reach statistical significance, as it may be because the event rate was low. However, when more sensitive angiographic indices were analyzed (i.e., late edge lumen loss and follow-up edge MLD), gamma irradiation had a negative impact on stent edge lumen dimensions compared with placebo. This increased late edge lumen loss and the smaller follow-up edge MLD after brachytherapy indicate that the edge effect after gamma irradiation is not simply an illusion due to the absence of neoointimal formation within the length of the stent (as suggested by the SCRIPPS trial) (3).

**Table 2.** Quantitative Angiographic Edge Analysis

<table>
<thead>
<tr>
<th></th>
<th>$^{192}$Ir</th>
<th>Placebo</th>
<th>$^{192}$Ir vs. Placebo</th>
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<tbody>
<tr>
<td></td>
<td>GM (+)</td>
<td>GM (−)</td>
<td>p Value</td>
</tr>
<tr>
<td>Preintervention (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter</td>
<td>2.57 ± 0.42</td>
<td>2.64 ± 0.45</td>
<td>NS</td>
</tr>
<tr>
<td>Edge MLD</td>
<td>2.01 ± 0.38</td>
<td>2.08 ± 0.37</td>
<td>NS</td>
</tr>
<tr>
<td>Postintervention (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter</td>
<td>2.68 ± 0.41</td>
<td>2.72 ± 0.44</td>
<td>NS</td>
</tr>
<tr>
<td>Edge MLD</td>
<td>2.34 ± 0.47</td>
<td>2.09 ± 0.38</td>
<td>0.0065</td>
</tr>
<tr>
<td>Follow-up (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter</td>
<td>2.63 ± 0.39</td>
<td>2.65 ± 0.44</td>
<td>NS</td>
</tr>
<tr>
<td>Edge MLD</td>
<td>1.60 ± 0.51</td>
<td>1.96 ± 0.48</td>
<td>0.0023</td>
</tr>
<tr>
<td>Changes of luminal diameter (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute edge lumen gain</td>
<td>0.33 ± 0.20</td>
<td>0.01 ± 0.30</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Late edge lumen loss</td>
<td>0.74 ± 0.57</td>
<td>0.13 ± 0.42</td>
<td>&lt; 0.0001</td>
</tr>
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GM = geographical miss; MLD = minimal lumen diameter; NS = not specified.
GM and edge stenosis. The current study also addressed the question of whether GM contributes to ERS following gamma irradiation treatment for ISR. The concept of GM has been adopted from the field of radiation oncology to explain treatment failure due to inadequate doses delivered to the tumor margins (15). When applied to lesions treated with brachytherapy, GM refers to those cases in which there was a mismatch between the length of the radiation source and the length of the segment of the coronary artery injured by the primary interventional procedure. There are two potential causes of this mismatch: inadequate 192Ir source length or overly aggressive primary intervention. At the time that patients were enrolled into the current study, there were few data concerning the “edge effects” of brachytherapy. Therefore, no measures were taken to minimize the potential problem of inadequately covering the artery’s entire segment injured during primary intervention. Although the radiation protocol mandated source coverage of at least 5 mm proximal and distal to the end of each lesion, up to 34% of the treated arteries had GM. In contrast, the current analysis contains substantial evidence of overly aggressive primary intervention. In both the 192Ir and placebo groups, the acute edge lumen gain and postintervention edge MLD were larger in lesions with GM, which was built into the definition because a treated edge would no doubt be larger than an untreated edge. In addition, in some of these cases GM was a result of additional post-brachytherapy catheter-based intervention in order to optimize the acute angiographic results. The increased late edge lumen loss in the placebo versus the placebo without GM probably reflects this increased injury.

Possible mechanism of ERS. The precise mechanism of ERS is not well understood. Serial intravascular ultrasound studies indicate that it is a combination of neointimal proliferation, negative remodeling (9,11) and/or longitudinal plaque displacement (22,23).

In the 32P-emitting stent, the candy-wrapper effect is mostly a result of neointimal proliferation (24). After 32P beta irradiation plus nonradioactive stent implantation, ERS is caused by neointimal proliferation in lesions without GM and negative remodeling in lesions with GM (25).

Depending on the source, ERS can be explained simply as a fall in dose to the point where it is inadequate to inhibit the restenosis process. However, others have suggested that low doses in fact stimulate neointimal formation at segments subjected to trauma (9,11). Weinberger et al. (26) reported a dose-dependent effect using intracoronary 192Ir radiation prior to overstretch injury in the pig model; there was a significant stimulatory effect at 10 Gy and a marked reduction of neointima formation at >15 Gy. In this study, the finding that the late edge lumen loss in the treated GM edges is greater than that in untreated GM edges, leading to a significant difference in edge MLD, indicates this is not a passive phenomenon but an active phenomenon. This paradoxical stimulation of neointimal formation at a lower than therapeutic dose is a problem confronting vascular radiation therapy in general.

Limitations. This study contains a number of limitations. First, the number of patients that were treated and subsequently developed ERS was too small to detect differences for the binary restenosis. However, when more sensitive angiographic indices were analyzed (i.e., late edge lumen loss and follow-up edge MLD), radiation clearly had a negative impact on edge lumen dimensions compared with placebo. Second, radiation dose clearly falls off at the last seed in the ribbon (3 mm) detected a 25% decrease in the cumulative dose compared with a seed in the center of the ribbon. However, because the therapeutic window is unknown, we elected to consider GM beyond the last seed when it was clear that there was no sufficient therapeutic dose at the injured segment. Third, it is possible that not all injured segments were captured with the use of ablative devices. This analysis is therefore limited to the documented injury performed by balloon inflation. Nevertheless, this study did not detect any device-specific contribution to the incidence of edge effect.

Conclusions and clinical implications. Edge restenosis following gamma irradiation treatment of ISR is related to GM: a mismatch between the segment of artery injured during the primary catheter-based intervention and the length of the radiation source. This suggests that careful
attention to the distribution of the treatment, confining it to the stenosed segment with maximal coverage of the treated segment with radiation sources, should be taken in order to avoid ERS.

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REFERENCES