Intravascular Ultrasound Assessment of the Mechanisms and Results of Brachytherapy

Gary S. Mintz, MD; Neil J. Weissman, MD; Peter J. Fitzgerald, MD, PhD

Serial intravascular ultrasound (IVUS) studies have shown that restenosis in nonstented lesions and late lumen loss in reference segments contiguous with both stented and nonstented lesions is a balance between arterial remodeling and neointimal hyperplasia. Conversely, in-stent restenosis (ISR) is neointimal hyperplasia. The present review focuses on lessons learned from IVUS about mechanisms of brachytherapy in preventing or treating restenosis.

Most brachytherapy studies have included IVUS analyses, but to various degrees and with various methodologies. In some studies—eg, the Washington Radiation for In-stent Restenosis (WRIST) trials—serial (postirradiation and follow-up) IVUS was performed in the majority of patients. In other trials, IVUS was usually a site-specific substudy in small numbers of patients (Table 1). These studies assessed only the short-term (typically 6 to 9 months) effects of brachytherapy.

**Methodological Considerations**

IVUS should be performed with motorized transducer pullback, and volumetric as well as mean cross-sectional area (CSA) analysis should be reported. Because lesion lengths vary among trials, longer lesions may have larger stent, lumen, and neointimal volumes. Therefore, mean planar analysis (in which measured volumes are normalized for lesion length) may be a preferable way to compare different studies.

Understanding lesion effects is more straightforward than understanding edge effects. (1) Edge analysis was not performed in all studies (Table 1). (2) Some studies combined proximal and distal edges and analyzed them together; others analyzed proximal and distal edges separately. (3) Edge analysis requires a larger sample size because of the wider range of possible responses. (4) It may be hard to determine the relationship between the source, the injured segment, and the IVUS images to assess geographical miss. Angiographic guidance may work in stented lesions; even in stented lesions (which are often radiolucent), however, meticulous comparison of IVUS and angiographic studies is necessary. (5) Some studies reported volumetric (or mean planar) analysis; others reported CSA analysis millimeter by millimeter over the length of the segment. This requires very careful "registration" of serial (postirradiation and follow-up) images. (6) Most studies analyze 5-mm-long edge segments; yet, the "edge effect" may be more than 5 mm from the edge of the stent or lesion. To properly understand the incidence and mechanism of edge effects, protocols must be designed to image the entire irradiated (not just stented) length plus at least 5 to 10 mm proximal and distal to the irradiated segment.

**Radiation in Nonstented Lesions**

The earliest clinical studies combined γ-radiation and balloon angioplasty. These studies, however, did not collect serial IVUS data.

The data on β-irradiation of nonstented lesions are limited to 2 published reports from the Beta Energy Restenosis Trial (BERT). The first study showed no change in lesion external elastic membrane (EEM), lumen, or plaque-plus-media (P&M) CSA from after irradiation to follow-up. In this report, only 1 image slice per lesion was studied, the location of this image slice was not specified, and edges were not analyzed. The second study was an extensive and detailed serial (ECG-gated) volumetric analysis of 30-mm-long lesions and contiguous 5-mm-long edges. At the lesion, there was significant positive remodeling (an increase in EEM volume) that was roughly equal to the increase in P&M volume; as a result, lumen volume remained unchanged. These "beneficial" effects on remodeling, however, did not extend to the edges, where there was an increase in P&M but no positive remodeling, resulting in lumen loss (Table 2). The different conclusions in these 2 reports may be related to the significant differences in methodology.

In another report from BERT, the irradiated segment (but not the edges) was analyzed in 2-mm-long subsegments. There were 3 independent predictors of the absolute P&M volume at follow-up: plaque volume after irradiation, minimum effective dose delivered to 90% of the adventitia, and the type of plaque (hard versus soft). There was wide variability, however, in the calculated minimum effective dose delivered to 90% of adventitia: 26.2% of the subsegments received <4 Gy, 32.5% received 4.0 to 5.9 Gy, 22.8% received 6.0 to 7.9 Gy, 13.6% received 8.0 to 9.9 Gy, and 4.9% received ≥10 Gy. The authors concluded that the

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minimum effective dose was 4 Gy, because subsegments that received >4 Gy demonstrated a significantly smaller increase in P&M volume than those that received <4 Gy \((P<0.01)\). This analysis, however, assumed that adjacent subsegments behaved independently with regard to ∆EEM, ∆P&M, and ∆lumen, an assumption that may not be valid.

### Radiation Followed by Stenting

Data on the use of β-irradiation before de novo stenting comes from 2 sources. In BERT, crossover to stent implantation was permitted in clinically significant dissections or residual stenosis >30%\(^a\). At follow-up, the in-stent intimal hyperplasia (IH) volume measured \(7±7 \text{ mm}^3\), less than in historical controls and similar to other brachytherapy trials. The edge effect in the stent crossover lesions was similar to the edge effect in the nonstented lesions in BERT (see above).

The Proliferation Reduction with Vascular Energy Trial (PREVENT) was a trial of intracoronary radiation with \(^{32}\)P, a β-emitting source, in patients with ISR \(n=25\), restenosis after PTCA \(n=7\), and de novo lesions treated with stents \(n=64\) or balloon angioplasty \(n=9\).\(^7\) Patients were randomized to placebo \(n=25\) or to 1 of 3 dose schedules. The IVUS analysis was limited primarily to the patients who received stents. Within the stented segment, there was an increase in IH volume in irradiated patients that was less than in placebo patients. An analysis of 40 stent edges in 23 patients showed a decrease in EEM (but no change in plaque), resulting in a decrease in lumen dimensions.\(^9\) There was geographic miss in 30 of 40 edges; in 77% of these 30 edges, negative remodeling was the dominant cause of edge lumen loss. Conversely, in the 10 edges with adequate radiation coverage, negative remodeling was seen in only 20%, and the main mechanism of edge lumen loss was IH (Table 2).

### ISR Treated With γ-Irradiation

Extensive data show that brachytherapy reduces recurrent ISR. The first report was the Coronary Radiation to Inhibit Intimal Proliferation Post Stenting (SCRIPPS) Trial, in which most of the lesions were ISR lesions.\(^10\) The distance from the center of the IVUS catheter (assumed to be the position of the radiation source) to the leading edge of the adventitia (the target) was used to determine the dose prescription. At follow-up, the increases in mean IH CSA (Table 3) and volume \((16±23 \text{ vs } 45±39 \text{ mm}^3)\) were smaller in \(192\)Ir patients than in placebo patients \((P=0.01 \text{ for both comparisons})\). There was no edge analysis in SCRIPPS, because edge effects were underrecognized at that time, and the edges were not imaged.

The WRIST Trial specifically addressed treatment of ISR.\(^11\) The dose prescription was 15 Gy at 2 mm from the source. At follow-up, the minimal lumen CSA was larger in the \(192\)Ir group than the placebo group \((P=0.0001\), Table 3\). There was a smaller increase in IH volume \((4±33 \text{ vs } 65±65 \text{ mm}^3, P<0.0001)\) and mean IH CSA \((P<0.0001\), Table 3\) in the \(192\)Ir group than in placebo. Of note, more than

### TABLE 1. IVUS Analyses in Various Brachytherapy Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients in IVUS Study</th>
<th>Isotope</th>
<th>IVUS Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCRIPPS</td>
<td>18 18</td>
<td>(^{192})Ir</td>
<td>X X</td>
</tr>
<tr>
<td>WRIST</td>
<td>47 50</td>
<td>(^{192})Ir</td>
<td>X X</td>
</tr>
<tr>
<td>Long WRIST</td>
<td>30 34</td>
<td>(^{192})Ir</td>
<td>X</td>
</tr>
<tr>
<td>High-Dose Long WRIST</td>
<td>25</td>
<td>(^{192})Ir</td>
<td>X</td>
</tr>
<tr>
<td>Gamma-1</td>
<td>37 33</td>
<td>(^{192})Ir</td>
<td>X X</td>
</tr>
<tr>
<td>Beta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BERT, PTCA lesions</td>
<td>21</td>
<td>(^{90})Sr/(^{90})Y</td>
<td>X X</td>
</tr>
<tr>
<td>BERT, stented lesions</td>
<td>17</td>
<td>(^{90})Sr/(^{90})Y</td>
<td>X X</td>
</tr>
<tr>
<td>PREVENT</td>
<td>30 10</td>
<td>(^{32})P</td>
<td>X X</td>
</tr>
<tr>
<td>Beta WRIST</td>
<td>25</td>
<td>(^{90})Y</td>
<td>X</td>
</tr>
<tr>
<td>START</td>
<td>24 16</td>
<td>(^{90})Sr/(^{90})Y</td>
<td>X X</td>
</tr>
</tbody>
</table>

### TABLE 2. Summary of IVUS Findings of the Effects of Brachytherapy on Nonstented Segments

<table>
<thead>
<tr>
<th>Remodeling (\Delta)EEM</th>
<th>Remodeling (\Delta)P&amp;M</th>
<th>Remodeling (\Delta)lumen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ 0 0</td>
<td>+ 0 0</td>
</tr>
</tbody>
</table>

PTCA + β-irradiation (BERT): Lesion X X X
Edges X X X

β-irradiation + stenting (BERT): Edges X X X

β-irradiation + stenting (PREVENT): Edge restenosis with geographic miss X X X

γ-Irradiation: Edge restenosis with geographic miss X X X
Radiated but uninjured reference segments X X X
half of the lesions had a reduction in IH between radiation and follow-up.

Edge Effects in WRIST

There were no significant overall differences in ΔEEM, Δlumen, or ΔP&M in 192Ir versus placebo patients. Distal edge recurrence was noted, however, in 8 γ-irradiated patients. These patients were compared with 21 irradiated patients with no recurrence. Lesions with distal edge recurrence had (1) a greater decrease in distal lumen CSA (−3.0±1.2 versus −0.7±1.0 mm², P=0.0002), (2) no change in distal EEM CSA (−0.2±0.5 mm²) versus an increase in distal EEM CSA of 1.0±0.9 mm² in non-edge recurrence lesions (P=0.0047), and (3) a greater increase in distal P&M CSA (2.9±1.2 versus 1.7±0.6 mm², P=0.0103). In addition, lesions with distal edge recurrence had a significant increase in mean intrastent IH, but the decrease in lumen CSA and the increase in IH CSA were more pronounced closer to the distal edge of the stent. These findings suggested that edge recurrence after γ-irradiation was part of diffuse treatment failure.

In 6 of 8 distal edge recurrence lesions, there was evidence of geographical miss (versus 4 of 21 nonrecurring lesions, P=0.0046). Lesions with geographical miss had a greater decrease in lumen CSA because there was no change in EEM CSA (versus an increase in EEM CSA in lesions with adequate coverage); the increase in ΔP&M CSA was similar in both groups. Thus, as in BERT and PREVENT, edge lumen loss appeared to be related to remodeling, which appeared to be related to inadequate coverage of injured edge segments.

Impact of Brachytherapy on Reference Segments

One proposed solution to edge effects was to radiate longer segments. To determine the short-term safety of this approach, the effect of brachytherapy on irradiated but uninjured reference segments was analyzed. There was an increase in P&M CSA in both the 192Ir and placebo patients. In the 192Ir group, however, there was an increase in EEM CSA, whereas in the placebo group, there was a decrease in EEM CSA. Consequently, there was no change in lumen CSA in the 192Ir group, whereas in the placebo group, there was a decrease in lumen area. Thus, as in other studies noted above, brachytherapy promoted positive remodeling to prevent lumen loss despite an increase in plaque mass.

Effect of Lesion Length on Effectiveness of Brachytherapy

“Long WRIST” was a double-blind, placebo-controlled trial of brachytherapy in long, diffuse native artery ISR (length, 36 to 80 mm). The dose prescription was identical to that in WRIST. In placebo patients, the increases in IH CSA (Table 3) and volumes (120±81 versus 35±76 mm³) were significantly greater in irradiated patients (P<0.0001 for both comparisons).

In an attempt to understand the impact of lesion length on treatment of ISR, irradiated Long WRIST lesions were compared with irradiated native artery WRIST lesions. Postintervention stent areas were larger in WRIST (8.9±2.5 mm²) than in Long WRIST (7.6±2.5 mm², P=0.0274). In particular, minimum stent CSA in Long WRIST measured only 5.2±1.0 mm². Serial IVUS documented reduced efficacy of brachytherapy in long, diffuse ISR lesions. There was (1) a significant decrease in mean lumen CSA and a significant increase in mean IH CSA in Long WRIST but not in WRIST patients; (2) a much greater increase in maximum IH CSA in Long WRIST versus WRIST; (3) a ratio of maximum to minimum follow-up IH CSA of 7.7±13.6 in Long WRIST versus 2.9±1.3 in WRIST, indicating a greater heterogeneity in neointimal recurrence in Long WRIST; and (4) a follow-up minimum lumen area of 2.9±1.0 mm² in Long WRIST versus 4.2±2.0 mm² in WRIST, P=0.0015.

The maximum and minimum distances from the IVUS catheter to the EEM were then measured as an index of the source-to-target distance. The maximum source-to-target distance was greater in Long WRIST than in WRIST (4.0±0.7 versus 2.8±0.4 mm, P<0.0001), and it correlated directly with ISR length (r=0.547, P<0.0001). Importantly, Δminimum lumen CSA, Δmaximum IH CSA, and the ratio of maximum to minimum follow-up IH CSA all correlated with the maximum source-to-target distance. This indicated that the greater heterogeneity in the neointimal response in Long WRIST lesions was related to a greater variability in lesion geometry and source eccentricity.

This suggested 2 possible solutions to the long lesion problem: improving the dose homogeneity via centering (see below) or increasing the dose prescription. To test the second solution, a group of 25 patients with long, diffuse ISR lesions...
were then treated with a higher dose (18 Gy at 2 mm from the source). At follow-up, the minimum lumen CSA was larger in the high-dose group (4.0±1.4 versus 2.9±1.0 mm², \(P=0.0009\), Table 3).

**Gamma-1 Trial**
The Gamma-1 Trial was a multicenter study of \(\gamma\)-irradiation treatment of ISR. The dose prescription was similar to that in SCRIPPS. The IVUS substudy was performed in 4 centers. At follow-up, the increase in IH volume (28±37 versus 50±40 mm³, \(P=0.0352\)) and the increase in IH CSA (Table 3) were less in the \(^{192}\)Ir versus placebo patients. Follow-up minimum lumen area was larger and the area stenosis (33±32% versus 55±38%, \(P=0.0124\)) smaller in the \(^{192}\)Ir patients. The lack of an edge effect that was observed in WRIST was substantiated in Gamma-1.16

**IVUS Dosimetry**
Two studies (SCRIPPS and Gamma-1) used IVUS dosimetry; the others did not. The results of fixed dosimetry were similar to those of IVUS dosimetry, which brings into question the need for IVUS guidance for dosimetric calculations.

**Centering**
Although uniform dosing of the adventitia may be desirable, it probably is not possible because it requires the source to be centered within the artery. Two parameters determine centering within the artery: (1) centering the source within the lumen and (2) P&M eccentricity. These 2 factors may be additive (to exaggerate dose heterogeneity) or they may cancel each other. There is a greater possibility that these 2 factors are additive in longer lesions, as was suggested by the comparison of Long WRIST with WRIST lesions.15 Calculations indicate that centering a source within the lumen (eliminating the first of these 2 factors) should improve dose homogeneity for both \(\gamma\)- and \(\beta\)-emitters, but especially for \(\beta\)-emitters.17,18

**\(\beta\)-Irradiation Treatment of ISR**
Beta WRIST was a registry; there was no actual control group. The source was a \(^{90}\)Y wire that was inserted into a segmented centering balloon delivery catheter. The prescribed dose was 20.6 Gy at 1 mm from the surface of the balloon. The results were compared with those of the placebo group in WRIST. In treated patients, there was an increase in IH volume (102±53 to 118±61 mm³) and a decrease in lumen volume (189±83 to 165±105 mm³), but these changes were significantly less than in WRIST placebo patients (Table 3).19

Stents and Radiation Therapy (START)20 was a randomized trial comparing the same brachytherapy system as used in BERT (hydraulic delivery of \(^{89}\)Sr\(^{90}\)Y seeds) with placebo in the treatment of ISR. The findings were similar to the \(\gamma\)-emitter studies, with no change in the IH CSA in the treated group and a significant increase in the IH CSA in the placebo group (Table 3).

**Radiation-Emitting Stents**
A number of analyses have looked at \(^{32}\)P-emitting stents6,21–25; dose findings from Milan, core laboratory analysis of the global Isostent experience, and analyses from the Thoraxcenter. All 3 reached the same conclusion: increasing activity decreased in-stent IH CSA assessed at 6 months. There are 2 main limitations of \(^{32}\)P-emitting stents: the "candy-wrapper" effect and late "catch-up."

**Candy-Wrapper Effect**
The Isostent experience illustrates the importance of the analysis plan in understanding edge effects. When analyzed millimeter by millimeter, there was a profound, focal, and sharply demarcated lumen loss peaking \(\approx 1\) mm outside the edge of the \(\beta\)-emitting stent resulting from a focal increase in neointimal tissue.21,22,24 Conversely, when 5-mm-long segments proximal and distal to the stent edges were analyzed as a volume, the conclusion was quite different: (1) a decrease in lumen volume, (2) a decrease in EEM volume, but (3) no significant change in P&M volume.6

Two modifications were tried. Creation of cold ends (25-mm stent length with 15-mm long, 3- to 24-\(\mu\)Ci, \(\beta\)-emitting centers and 5-mm-long nonemitting ends) broadened the peak of the edge effect, shifted the peak IH response within the body of the stents, and caused more in-stent neointima.25 Conversely, hot ends appeared to attenuate the edge effect but were associated with 6 cases of late stent malapposition. Although there was no significant increase in mean EEM CSA in the “hot-ends cases,” late stent malapposition was associated with positive remodeling, emphasizing the importance of looking at individual cases, not just at the entire cohort. One previous study showed no increase in EEM within the length of the \(^{32}\)P-\(\beta\)-emitting stent in either the low-activity (0.75 to 1.5 \(\mu\)Ci) or high-activity (6.0 to 12.0 \(\mu\)Ci) group.6 The activity of the 18-mm-long hot-ends Isostent, however, was \(\approx 8\) \(\mu\)Ci within the 14-mm body (0.57 \(\mu\)Ci/mm) and \(\approx 10\) \(\mu\)Ci at the 2 mm ends combined (2.6 \(\mu\)Ci/mm); the total activity (\(\approx 18\) \(\mu\)Ci) was more than that of the previously noted high-activity group.

**Late Catch-Up**
In a recent report, between 6 and 12 months there was a significant increase in IH volume, from 18.2±12.6 to 27.9±12.0 mm³ (\(P=0.001\)), mainly in the mid and distal portions of the stent. There was no change in edge lumen volume during this time period.26 Although the volume of neointimal tissue was less at 12 months than in nonbrachytherapy studies, such as the Heparin Infusion Prior to Stenting trial (40.5 mm³),27 the late increase is disturbing.

**IVUS Complications of Brachytherapy**
The impact of brachytherapy on the healing of postangioplasty dissections was reported in BERT. In one study, IVUS dissections were seen in 16 of 22 patients (73%); at follow-up, 6 had no evidence of healing, and 2 had partial healing. The calculated dose was similar in healed and unhealed dissections.28 In another report, post-PTCA and 6-month follow-up IVUS studies of 94 patients in the MultiVitamins and Probucol (MVP) trial were compared with 26 patients in BERT.29 Of the 28 patients with post-PTCA dissections in MVP, all but 1 had healed; of the 16 patients with post-PTCA dissections in BERT, 7 had not healed (\(P<0.0002\)).
A second potential complication is late stent–vessel wall malapposition, an effect of exaggerated positive remodeling in the absence of neointimal hyperplasia. In Gamma-1, late malapposition was seen in only 1 patient; that patient was in the placebo group. In START, there was 1 documented case in the irradiated group and none in the placebo group. In hot-ends Isostent, there were 6 cases. Positive remodeling and neointima inhibition, the combination that appears to lead to late malapposition, are dose related.

A third potential complication is the “black hole” phenomenon: echolucent neointimal tissue. This has been seen after both γ- and β-emitters, after β-emitting stents, in patients with and without stents, and in patients with ISR. Directional atherectomy has been performed in 4 patients; specimens showed large myxoid areas with interspersed smooth muscle cells that were scattered in an extracellular matrix containing proteoglycan. The clinical implications of this finding, however, are not known.

As noted, none of these observations are unique to brachytherapy; however, they occur with increased frequency in irradiated patients. Despite the suggestion that these complications may contribute to late thrombosis, none of these patients developed late thrombosis, and no patient with late thrombosis had IVUS imaging. Thus, it is unclear whether any of these observations should be called a true complication. It is important, however, that these terms be defined carefully and used consistently. For example, the term “black hole”—echolucent neointimal tissue—is sometimes confused with the gaps between stent and vessel wall, ie, late malapposition.

What Have We Learned?
Methodology is important to understanding the mechanisms of brachytherapy, especially edge effects. IVUS substudies with small numbers of patients have the power to show significant in-lesion or in-stent treatment efficacy. Larger numbers of patients, however, are necessary to assess edge effects. It is important to look at individual cases, not only mean changes in EEM, lumen, P&M, and IH volume or CSA.

The mechanisms of brachytherapy in PTCA, stenting, and treatment of ISR are dose related: (1) decreased neointimal hyperplasia, (2) positive remodeling in PTCA-treated lesions, and (3) either no effect or positive remodeling along irradiated edges and uninjured reference segments. At the edges, where the dose is less, and especially in the presence of geographical miss, there is a combination of increased neointimal hyperplasia and either absence of positive remodeling or frank negative remodeling that contributes to lumen loss.

The findings in β-emitting stents are idiosyncratic and very different. There is a dose-related decrease in intrastent neointima. The candy-wrapper effect is primarily a focal exaggeration of IH accumulation at the edge of the stent. The late catch-up in neointimal proliferation needs to be studied in other settings.

Unusual IVUS observations, such as unhealed dissections, late malapposition (also a manifestation of radiation-induced positive remodeling), and the black hole, are worrisome, but their exact clinical consequence is unknown.

All of these findings are lessons to be remembered in the new era of drug-eluting stents.

References

Keywords: ultrasonics ■ stents ■ restenosis ■ remodeling ■ radioisotopes
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