Serial Intravascular Ultrasound Analysis of the Impact of Lesion Length on the Efficacy of Intracoronary γ-Irradiation for Preventing Recurrent In-Stent Restenosis

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Background—The relation between lesion length and effectiveness of brachytherapy is not well studied.

Methods and Results—We compared serial (postintervention and follow-up) intravascular ultrasound findings in 66 patients with native coronary artery in-stent restenosis (ISR) who were treated with 192Ir (15 Gy delivered 2 mm away from the radiation source). Patients were enrolled in the Washington Radiation for In-Stent Restenosis Trial (WRIST; ISR length, 10 to 47 mm; n=36) or Long WRIST (ISR length, 36 to 80 mm; n=30). External elastic membrane, stent, lumen, and intimal hyperplasia (IH; stent minus lumen) areas and source-to-target (intravascular ultrasound catheter to external elastic membrane) distances were measured. Postintervention stent areas were larger in WRIST and smaller in Long WRIST patients (P<0.0001). At follow-up, maximum IH area significantly increased in both WRIST and Long WRIST patients (P<0.0001 for both), but this increase was greater in Long WRIST patients (P=0.0006). Similarly, minimum lumen cross-sectional area significantly decreased in both WRIST and Long WRIST patients (P<0.05 and P<0.0001, respectively), but this decrease was more pronounced in Long WRIST patients (P=0.0057). The maximum source-to-target distance was longer in Long WRIST than in WRIST, and it correlated directly with ISR length (r=0.547, P<0.0001). Overall, the change in minimum lumen area and the change in maximum IH area correlated with the maximum source-to-target distance (r=0.352, P=0.0038 and r=0.523, P<0.0001 for WRIST and Long WRIST, respectively). The variability (maximum/minimum) in IH area at follow-up also correlated with the maximum source-to-target distance (r=0.378, P<0.0001).

Conclusions—Brachytherapy may be less effective in longer ISR lesions because of the greater variability and longer source-to-target distances in diffuse ISR. (Circulation. 2001;103:188-191.)

Key Words: stents ■ restenosis ■ imaging

In-stent restenosis (ISR) is a significant clinical problem; treatment remains unsatisfactory, with high recurrence.1–10 A number of studies have identified risk factors associated with recurrence, especially ISR length.1–10 Recently, endovascular radiation has emerged as a promising adjunct therapy for the treatment of ISR.11,12

The present study used serial (postirradiation and follow-up) intravascular ultrasound (IVUS) imaging to analyze the impact of lesion length on recurrent neointimal hyperplasia after γ-radiation treatment of native ISR. In particular, the current analysis compares the 192Ir-treated patients from 2 randomized, placebo-controlled clinical trials that used identical dose prescriptions: the Washington Radiation In-Stent Restenosis Trial (WRIST) included ISR lesions 10 to 47 mm long, and Long WRIST included lesions 36 to 80 mm long.

Methods

Patient Population
The study population included 36 patients with native artery ISR from WRIST and 30 patients with native coronary artery ISR from Long WRIST; all patients were treated with radiation. Although these were randomized, placebo-controlled trials, only patients randomized to receive radiation were included in the current analysis. After primary interventional procedures, such as rotational atherectomy (SCIMED/BSC), excimer laser angioplasty (Spectranetics), additional stent implantation, balloon angioplasty, or a combination of treatments, patients were treated with γ-irradiation. The same radiation dose prescription and delivery system was used in both studies. A 5-F, closed-end, noncentering catheter was used to deliver the 192Ir (15 Gy delivered 2 mm radially distant from the radiation source). There was no difference in dwell time between the 2 groups (20.4±3.1 minutes for Long WRIST versus 21.5±3.2 minutes for WRIST, P=0.14). These patients represent the entire cohort of native artery lesions in WRIST and Long WRIST for which postirradiation and follow-up IVUS imaging is available.

IVUS Imaging and Analysis
IVUS imaging was performed after the administration of 200 μg of intracoronary nitroglycerine using SCIMED/BSC equipment and automated transducer pullback (0.5 mm/s) through a stationary imaging sheath. IVUS imaging was performed immediately after and 6 months after irradiation.11,14 External elastic membrane (EEM), stent, and lumen boundaries were identified. Stent, lumen, and
intimal hyperplasia (IH; stent minus lumen) cross-sectional areas (CSAs) were measured every 1 mm for WRIST lesions and every 2 mm for Long WRIST lesions (Tape Measure, Indec Systems) according to standard protocols. Stent length was measured using motorized transducer pullback \[\text{length} = (\text{number of seconds}) \times (0.5 \text{ mm/second})\]. In addition, the maximum and minimum distances from the center of the IVUS catheter to the EEM were measured (Figure 1); this reflected source-to-target distances. Source eccentricity was determined by dividing the maximum IVUS catheter-to-EEM distance by the minimum distance. The axial variability in IH reaccumulation was calculated as the maximum follow-up IH CSA divided by the minimum CSA.

**Statistical Analysis**
Statistical analysis was performed using Statview 4.5 (SAS Institute). Continuous variables are presented as mean $\pm$ 1SD and compared using paired or unpaired Student’s t tests or regression analysis. Categorical variables are presented as frequencies and compared using $\chi^2$ statistics.

**Results**
Baseline patient and lesion characteristics and primary treatments are shown in Table 1. Long WRIST lesions were more often located in the right coronary artery and were more often treated with additional stents.

**Postintervention IVUS Results**
IVUS results are shown in Table 2. ISR lesion length was 26.0 $\pm$ 12.2 mm in WRIST and 55.1 $\pm$ 13.4 mm in Long WRIST.

Postintervention stent areas were larger in WRIST and smaller in Long WRIST. This is consistent with the trend for EEM CSA to be larger in WRIST lesions (15.0 $\pm$ 3.7 mm$^2$ versus 13.6 $\pm$ 2.7 mm$^2$ for WRIST versus Long WRIST, $P$ = 0.078). In particular, minimum stent CSA in Long WRIST measured only 5.2 $\pm$ 1.0 mm$^2$.

Postintervention lumen CSAs were similar in both groups. There was less residual neointimal tissue in Long WRIST lesions; this may be related to the smaller stent areas and the greater use of additional stents in this group.

**Serial IVUS Results**
At follow-up, mean lumen areas significantly decreased in Long WRIST but not WRIST patients. Mean IH CSA significantly increased in Long WRIST patients but not in WRIST patients. This resulted in a smaller follow-up mean lumen area in Long WRIST patients (Table 2).

There was a significant decrease in minimum lumen CSA and a significant increase in maximum IH CSA in both WRIST and Long WRIST patients at follow-up, but these changes were more pronounced in Long WRIST patients (Table 2). Minimum lumen area was smaller in Long WRIST patients.

The ratio of maximum to minimum follow-up IH CSA was 7.7 $\pm$ 13.6 in Long WRIST lesions and 2.9 $\pm$ 1.3 in WRIST lesions. This indicated a greater heterogeneity in neointimal recurrence over the length of the ISR lesion in Long WRIST.

**Impact of Lesion Geometry**
To analyze the impact of lesion geometry on the response to radiation, the maximum and minimum distances from the IVUS catheter to the EEM were measured as an index of the source-to-target distance. The maximum source-to-target distance was greater in Long WRIST than in WRIST (Table 2), and the maximum source-to-target distance correlated directly with ISR length ($r = 0.547$, $P < 0.0001$; Figure 2). No patient in WRIST had an IVUS source-to-target distance $\geq 4.0$ mm, but 43% of the patients in Long WRIST did ($P < 0.0001$).

When IVUS results were compared with the source-to-target distances, the change in minimum lumen area and the change in maximum IH area correlated with the maximum source-to-target distance ($r = 0.352$, $P = 0.0038$ and $r = 0.523$, $P < 0.0001$, respectively; Figure 2). The variability in neointimal reaccumulation (maximum/minimum follow-up IH CSA) also correlated with the maximum source-to-target distance ($r = 0.378$, $P < 0.0001$). This suggested that the greater heterogeneity in the neointimal response present in Long WRIST lesions was related to lesion geometry.

**Figure 1.** IVUS analysis of source-to-target measurements. The maximum and minimum distances from IVUS catheter to EEM in this image are indicated (arrows).

**Table 1.** Patient, Lesion, and Procedural Data

<table>
<thead>
<tr>
<th>Lesion location</th>
<th>WRIST</th>
<th>Long WRIST</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>8.0</td>
<td>10.7</td>
<td>0.7</td>
</tr>
<tr>
<td>LAD</td>
<td>38.0</td>
<td>25.0</td>
<td>0.24</td>
</tr>
<tr>
<td>LCX</td>
<td>26.0</td>
<td>10.7</td>
<td>0.10</td>
</tr>
<tr>
<td>RCA</td>
<td>28.0</td>
<td>53.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetics, %</td>
<td>38.0</td>
<td>42.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Device use, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotational atherectomy</td>
<td>58.0</td>
<td>71.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Excimer laser angioplasty</td>
<td>18.0</td>
<td>21.4</td>
<td>0.71</td>
</tr>
<tr>
<td>Additional stents</td>
<td>42.0</td>
<td>78.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LM indicates left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex artery; and RCA, right coronary artery.
Discussion

The findings in the current study indicate that brachytherapy using a fixed dose of 15 Gy at 2 mm from the source is less effective in longer ISR lesions. There was greater lumen loss and more neointimal hyperplasia in Long WRIST than in WRIST patients.

The influence of lesion length on recurrence after brachytherapy is not well understood. The findings in the current study indicate that longer ISR lesions are associated with (1) smaller stent sizes, (2) greater source eccentricity within the artery, and (3) longer source-to-target distances (measured by the distance from the IVUS catheter to the EEM). Because source-to-target distances determine the dose delivered to the adventitia, focal areas within longer ISR lesions would have received a lower dose, resulting in a greater heterogeneity of the neointimal response. The increase in maximum IH and decrease in minimum lumen CSA both correlated with the maximum source-to-target distance; the maximum source-to-target distance, in turn, correlated with ISR length. Previous IVUS brachytherapy studies indicated that to be effective, a minimum dose must be delivered to the adventitia.15

Source eccentricity and source-to-target distances have the following 2 anatomic components: (1) plaque mass and plaque eccentricity and (2) the location of the source within the lumen. Previous studies have shown a relationship between plaque eccentricity and lesion length.16 The current study indicates that a similar relationship exists between the location of the IVUS catheter within the lumen and lesion length. The longer the lesion, the greater the variability in cross-sectional geometry. Higher radiation doses or centering may improve the homogeneity of the actual dosing of the adventitia.

Finally, longer lesions had smaller stents. Smaller stent areas might magnify the increased amount and greater variability of recurrent neointimal hyperplasia.13

Limitations

Follow-up was limited to 6 months. The analysis assumes that the source was located at the same position as the IVUS catheter. Analysis was limited to the stent length and did not include the stent margins. More patients in the Long WRIST group received new stents, which might have stimulated additional intimal hyperplasia. The current analysis includes

Table 2. Serial IVUS Analysis

<table>
<thead>
<tr>
<th></th>
<th>Wrist</th>
<th>Long Wrist</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent length, mm</td>
<td>26.0±12.2</td>
<td>55.1±13.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postirradiation measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean stent area, mm²</td>
<td>8.9±2.5</td>
<td>7.6±2.5</td>
<td>0.0274</td>
</tr>
<tr>
<td>Mean lumen area, mm²</td>
<td>6.5±1.9</td>
<td>5.9±1.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean IH area, mm²</td>
<td>2.5±1.5</td>
<td>1.8±1.7</td>
<td>0.055</td>
</tr>
<tr>
<td>Minimum stent area, mm²</td>
<td>7.6±2.1</td>
<td>5.2±1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minimum lumen area, mm²</td>
<td>4.7±1.6</td>
<td>4.2±1.3</td>
<td>0.081</td>
</tr>
<tr>
<td>Source eccentricity</td>
<td>1.9±0.3</td>
<td>3.3±0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Follow-up (6 months) measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean stent area, mm²</td>
<td>6.3±2.1</td>
<td>5.3±1.7†</td>
<td>0.0284</td>
</tr>
<tr>
<td>Mean IH area, mm²</td>
<td>2.6±1.3</td>
<td>2.4±2.0†</td>
<td>0.6</td>
</tr>
<tr>
<td>Minimum lumen area, mm²</td>
<td>4.2±2.0‡</td>
<td>2.9±1.0‡</td>
<td>0.0015</td>
</tr>
<tr>
<td>Maximum IH area, mm²</td>
<td>5.2±1.8‡</td>
<td>4.9±2.2‡</td>
<td>0.54</td>
</tr>
<tr>
<td>Change in measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean stent area, mm²</td>
<td>-0.1±1.2</td>
<td>-0.6±1.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean IH area, mm²</td>
<td>0.1±1.0</td>
<td>0.6±1.1</td>
<td>0.0356</td>
</tr>
<tr>
<td>Maximum IH area, mm²</td>
<td>-0.6±1.7</td>
<td>-1.4±1.6</td>
<td>0.0567</td>
</tr>
<tr>
<td>Minimum catheter-to-EEM distance, mm</td>
<td>1.85±0.33</td>
<td>1.31±0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum catheter-to-EEM distance, mm</td>
<td>2.8±0.35</td>
<td>4.0±0.67</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.05, †P<0.01, ‡P<0.0001 vs postirradiation.

Figure 2. Left, Maximum source-to-target (IVUS catheter-to-EEM) distances were correlated with ISR lesion lengths in entire cohort (r=0.547, P<0.0001). Right, Maximum follow-up IH CSA was correlated with source-to-target distance (r=0.523, P<0.0001). ○ indicates WRIST lesions; X, Long WRIST lesions.
only patients who had IVUS imaging both immediately after irradiation and at follow-up.

**Conclusions**

Brachytherapy is less effective in longer ISR lesions because of the greater variability and longer source-to-target distances in diffuse ISR.

**References**

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_Circulation_. 2001;103:188-191
doi: 10.1161/01.CIR.103.2.188

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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