Safety of Intracoronary \( \gamma \)-Radiation on Uninjured Reference Segments During the First 6 Months After Treatment of In-Stent Restenosis

A Serial Intravascular Ultrasound Study

Javed M. Ahmed, MD; Gary S. Mintz, MD; Ron Waksman, MD; Neil J. Weissman, MD; Roxana Mehran, MD; Augusto D. Pichard, MD; Lowell F. Satler, MD; Kenneth M. Kent, MD, PhD; Martin B. Leon, MD

Background—The effects of endovascular irradiation on uninjured reference segments during the treatment of in-stent restenosis are unknown.

Methods and Results—In the Washington Radiation for In-Stent restenosis Trial (WRIST), patients with in-stent restenosis were first treated with conventional catheter-based techniques and then randomized (blinded) to receive either \( \gamma \)-irradiation (\( ^{192}\text{Ir} \)) or a placebo (dummy seeds). We identified all patients in whom the active (n = 19) or dummy seeds (n = 19) extended >10 mm proximal and distal to the in-stent restenosis lesion. Serial (postirradiation and follow-up) external elastic membrane (EEM), lumen, and plaque and media (EEM–lumen) areas were measured (using intravascular ultrasound) every 1 mm over 5-mm-long reference segments that were 6 to 10 mm proximal and distal to the in-stent restenosis lesion. During follow-up, a similar small increase occurred in the plaque and media area in the proximal and distal reference segments in both \( ^{192}\text{Ir} \) and placebo patients. However, in the \( ^{192}\text{Ir} \) patients, an increase in both proximal and distal EEM area occurred; as a result, no change in lumen area occurred. Conversely, in the placebo patients, the proximal reference EEM area decreased, and no change occurred in the distal reference EEM area; this contributed to a decrease in lumen area.

Conclusions—There was no evidence of a deleterious effect of \( \gamma \)-irradiation on angiographically normal uninjured reference segments in the first 6 months after the treatment of in-stent restenosis. (Circulation. 2000;101:2227-2230.)

Key Words: restenosis ■ ultrasonics ■ radioisotopes

Randomized, placebo-controlled clinical trials have shown that adjunct brachytherapy reduces recurrent in-stent restenosis after primary catheter-based intervention.\(^1,2\) However, concerns about brachytherapy still include late thrombosis, edge effects, aneurysm formation, and the occurrence of premature atherosclerosis.\(^3,4\) The need to cover the entire treated area to avoid “geographical miss” and edge effects and the limited selection of \( ^{192}\text{Ir} \) source lengths has resulted in the use of longer radioactive seed trains. As a result, angiographically normal (and unintervened) reference segments are often exposed to \( \gamma \)-irradiation. The safety of this approach is not known.

The current report used serial (postirradiation and follow-up) intravascular ultrasound (IVUS) to assess the response to ionizing radiation of the angiographically normal but (by IVUS) “pathologically abnormal” reference segments that were not injured during the primary catheter-based treatment of in-stent restenosis.

Methods

Patient Population

In the Washington Radiation In-Stent restenosis Trial (WRIST), patients with in-stent restenosis were first treated with conventional catheter-based techniques and then randomized (blinded) to receive either \( \gamma \)-irradiation (\( ^{192}\text{Ir} \), Best Industries) or a placebo (dummy seeds). All index angiograms and serial IVUS from native artery WRIST patients were screened. We identified all patients in whom active (n = 19) or dummy seeds (n = 19) extended >10 mm proximal and distal to the in-stent restenosis lesion to cover arterial reference segments that were \( \geq 5 \) mm long and that were not injured during the intervention. Initial interventions included rotational atherectomy (SciMed/Boston Scientific Corporation, n = 24), excimer laser angioplasty (Spectranetics, n = 4), additional stent implantation (n = 10), balloon angioplasty (n = 3), or a combination of the techniques. Sites of intervention at each step were documented angiographically.

The seeds were delivered through 5-French closed-end, noncentering catheters. Dwell time (22.4 ± 4.2 minutes) was calculated to deliver 15 Gy at 2 mm from the source. Angiographic and IVUS studies were performed after the administration of 200 \( \mu \)g of intracoronary nitroglycerin. IVUS imaging was performed after the...
dwell time and at follow-up using a commercial scanner (SciMed/Boston Scientific) and motorized pullback (at 0.5 mm/s) of a mechanically rotating transducer (40 or 30 MHz) through a stationary imaging sheath.

**IVUS Analysis**

External elastic membrane (EEM), lumen, and plaque and media (P&M = EEM − lumen) areas and the plaque burden (P&M area/EEM area) were measured using computerized planimetry (TapeMeasure, Indec Systems) according to validated and published protocols.5–8 IVUS analysis was limited to 5-mm-long reference segments that were 6 to 10 mm proximal and 6 to 10 mm distal to the in-stent restenosis lesion. The first 5 mm were skipped to ensure that only the uninjured reference segment was analyzed. Measurements were made every 1 mm and averaged.

**Statistical Analysis**

Statistical analysis was performed using StatView 4.5 (SAS Institute). Data are presented as mean ± SD. Continuous variables were compared using a paired or unpaired Student’s t test or ANOVA for repeated measures.

**Results**

**Baseline Findings**

None of the reference segments were normal; the minimal plaque burden was 0.37. Proximal reference postintervention EEM, lumen, and P&M areas were larger in 192Ir versus control arteries; however, because of the small numbers, these differences did not reach significance (Table: $P = 0.056$, $P = 0.18$, and $P = 0.16$, respectively). Distal reference postintervention EEM, lumen, and P&M areas were similar in both groups (Table: $P = 0.9$, $P = 0.8$, $P = 0.8$, respectively). Plaque burdens were also similar (Table).

**Serial Findings**

During follow-up, a similar small increase occurred in P&M area in the proximal and distal reference segments in both 192Ir and control patients (Table and Figure 1). However, changes in EEM differed significantly. In 192Ir patients, both the proximal and distal EEM areas increased; as a result, no change occurred in proximal or distal lumen area. Conversely, in the control patients, proximal reference EEM area decreased, but no change occurred in distal reference EEM.

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**Figure 1.** In the proximal reference artery, an increase in P&M area occurred in both 192Ir (0.7 ±1.1 mm²) and placebo (0.6 ±0.9 mm²) patients; these increases were similar ($P = 0.4$). In the 192Ir group, EEM area increased (0.5 ±0.6 mm²), whereas in the placebo group, EEM area decreased (−0.6 ±0.7 mm²; $P < 0.0001$ vs 192Ir). Thus, no significant decrease occurred in lumen area in the 192Ir group (−0.2 ±1.4 mm²); however, in the placebo group, lumen area did significantly decrease (−1.2 ±1.1 mm²; $P = 0.0002$ vs 192Ir). In the distal reference artery, an increase in P&M area occurred in both the 192Ir (1.0 ±1.0 mm²) and placebo groups (0.9 ±0.9 mm²); these increases were similar ($P = 0.5$). In the 192Ir group, EEM area increased (1.0 ±1.1 mm²), whereas in the placebo group, EEM area slightly decreased (−0.4 ±1.1 mm²; $P < 0.0001$ vs 192Ir). As a result, in the 192Ir group, no change occurred in lumen area (−1.2 ±1.1 mm²; $P < 0.0001$ vs 192Ir). CSA indicates cross-sectional area.

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area; as a result, both proximal and distal reference lumen areas decreased (Table and Figure 1).

When the individual image slices were compared, these changes did not vary along the length of the reference segment (Figure 2). No difference existed in IVUS measurements according to the primary device used.

Discussion
The current study failed to detect a deleterious effect of γ-irradiation on uninjured, reference segments in the first 6 months after irradiation. Mild progression of disease (increased P&M area) occurred in both irradiated and placebo arteries. However, the increased P&M area in the controls was not accompanied by positive remodeling (increase in EEM); as a result, lumen dimensions decreased. Conversely, γ-irradiation seemed to induce positive remodeling, so the increase in P&M area had little impact on lumen dimensions.

Angiographic reference segments in the current study were not normal. Histopathologic studies have indicated that an enlargement of the diseased arterial wall occurs to compensate for atherosclerotic plaque accumulation.9,10 Previous IVUS studies of reference segments after catheter-based interventions have shown a combination of increased P&M area (after nonstent intervention), intimal hyperplasia (after stent implantation), and either negative or an absence of positive remodeling.2,8 Conversely, other studies have demonstrated positive remodeling after brachytherapy.11–14 In the Beta Energy Restenosis Trial (BERT), as in the current study, β-irradiation prevented lumen loss, not by reducing neointimal hyperplasia, but by promoting positive remodeling.13

Limitations
Follow-up was limited to 6 months. Atherosclerosis as a complication of external irradiation has been reported >5 years after treatment.15–18 Thus, longer follow-up of brachytherapy patients will be necessary. However, external-beam irradiation delivers larger doses of radiation than brachytherapy, and most of the patients in this report were treated at an age when their coronary arteries were probably not atherosclerotic.

Reference segments in the current study were diseased. The impact of brachytherapy on normal reference segments cannot be determined. The increase in P&M area was small.

Although the current report includes all patients with native artery WRIST lesions in whom seeds extended >10 mm proximal and distal to the in-stent restenosis lesion, only 38 of 100 lesions fit this criterion, which might have introduced selection bias. The number studied may have been too few to detect an effect; we calculated a 12.7% possibility of not detecting a decrease in lumen area in the 192Ir group (P<0.05).

Conclusions
In the first 6 months after the treatment of in-stent restenosis, γ-irradiation does not seem to injure angiographically normal reference segments. Instead, γ-irradiation seems to promote positive remodeling.

Acknowledgment
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References


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