Catheterization and Cardiovascular Interventions 63:208–214 (2004)

Late Intravascular Ultrasound Findings of Patients Treated With Brachytherapy for Diffuse In-Stent Restenosis

Myeong-Ki Hong,[1] MD, PhD, Gary S. Mintz,[2] MD, Cheol Whan Lee,[1] MD, PhD, Young-Hak Kim,[1] MD, Seung-Whan Lee,[1] MD, Dae-Hyuk Moon,[3] MD, PhD, Seung-Jun Oh,[3] PhD, Jong-Min Song,[1] MD, PhD, Ki-Hoon Han,[1] MD, Duk-Hyun Kang,[1] MD, PhD, Jae-Kwan Song,[1] MD, PhD, Jae-Joong Kim,[1] MD, PhD, Seong-Wook Park,[1*] MD, PhD, and Seung-Jung Park,[1] MD, PhD

This study aimed at evaluating long-term (24-month) effects of β-irradiation (^{188}Re-MAG$_3$-filled balloon) using intravascular ultrasound (IVUS) in patients with in-stent restenosis (ISR). Long-term effects of β-irradiation on intimal hyperplasia (IH) within the stented segment and vessel and lumen dimensions of nonstented adjacent segments in patients with ISR have not been sufficiently evaluated. Two-year follow-up IVUS was performed in 30 patients with patent ISR segments at 6-month follow-up angiography. Serial IVUS images were acquired at five equidistant intrastent sites and at three different reference segment sites. IH burden (%) was defined as 100 × (IH/stent area). Mean intrastent IH area and IH burden significantly increased between 6 and 24 months, from 2.1 ± 1.1 to 2.6 ± 1.4 mm^2 ($P < 0.001$) and from 26% ± 10% to 33% ± 14% ($P < 0.001$), respectively. There was a significant decrease of mean external elastic membrane (from 10.1 ± 3.9 to 9.7 ± 3.9 mm^2; $P = 0.015$) and lumen area (from 5.6 ± 2.3 to 5.1 ± 2.3 mm^2; $P = 0.021$) within distal reference segments between 6 and 24 months. Target lesion revascularization (TLR) was performed in six patients (20%) between 6 and 24 months after β-irradiation therapy. There were no significant differences between TLR and non-TLR groups except for a smaller minimum lumen area at 24 months in the TLR group. Because of a small amount of late loss between 6 and 24 months, most irradiated ISR vessel segments remained stable for up to 2 years. However, quantitative evidence of late catch-up was evident in most patients and was significantly associated with 24-month TLR in some patients. *Catheter Cardiovasc Interv 2004;63:208–214.*

Key words: restenosis; radiation; ultrasonics

[1]Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea
[2]Cardiovascular Research Foundation, New York, New York
[3]Department of Nuclear Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Grant sponsor: the Interdisciplinary Research Program of the Korean Science and Engineering Foundation (KOSEF); Grant number: 1999-2-206-001-3; Grant sponsor: Korea Institute of Science and Technology Evaluation and Planning; Grant sponsor: Ministry of Science and Technology, Korea Government, through the National Nuclear Technology Program; Grant sponsor: Cardiovascular Research Foundation, Seoul, South Korea.

*Correspondence to: Dr. Seong-Wook Park, Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-2dong, Songpa-gu, Seoul, 138-736, South Korea.
E-mail: swpark@amc.seoul.kr

Received 11 December 2003; Revision accepted 16 April 2004

DOI 10.1002/ccd.20118
Published online in Wiley InterScience (www.interscience.wiley.com).

INTRODUCTION

Studies of intracoronary brachytherapy in patients with in-stent restenosis (ISR) demonstrated a reduction of 6-month angiographic restenosis and 9-month target lesion revascularization (TLR) compared with control groups [1–6]. This was supported by 6-month follow-up intravascular ultrasound (IVUS) studies that also showed a significant inhibition of intimal hyperplasia (IH), the cause of first-time and recurrent ISR [7–9]. Our reports of β-irradiation ISR treatment with ^{188}Re-MAG$_3$-filled balloon showed similar results [3,9]. Recently, clinical and angiographic studies have demonstrated long-term ($\geq$ 2-year) effectiveness of brachytherapy [10–12]. Late thrombosis and restenosis, which occurred beyond 6 months after intracoronary brachytherapy, were also reported [1,4,13,14]. However, there is little long-term IVUS data beyond 6 months on the effectiveness of brachytherapy in ISR. One report of patients with non-ISR lesions treated with a radioactive stent showed suppression of IH at 6 months, but late catch-up at 12 months [15]. Therefore, the objective of the current study was to use serial (postirradiation and 6- and 24-month follow-up) IVUS to evaluate the long-term (24-month) effectiveness after β-radiation therapy using ^{188}Re-MAG$_3$-filled balloon in patients with diffuse ISR.

MATERIALS AND METHODS

Study Population

β-irradiation therapy with a ^{188}Re-MAG$_3$-filled balloon was performed for patients with diffuse ISR (lesion length $>$ 10 mm, diameter stenosis $>$ 50%) [3]. Inclusion criteria were diffuse ISR in a native coronary artery with angina, demonstrable objective myocardial ischemia, and written informed consent. Exclusion criteria were acute myocardial infarction within 72 hr, poor renal function, pregnancy, contraindication to antiplatelet therapy, and concomitant serious disease with an expected survival of $<$ 2 years. Our institutional review board approved this study. The angiographic follow-up was requested at 6 months in all patients who underwent intracoronary radiation therapy. Seventy-five patients were enrolled in this study; 73 patients underwent 6-month angiography. Among patients with 6-month angiograms, 2-year follow-up study was performed in 34 selected patients. Among patients with 6-month angiograms, 2-year angiographic follow-up study was performed in 34 selected patients who showed patent irradiation segments at 6 months, did not require TLR at 6 months, and gave their written informed consent to participate in a 2-year follow-up study at the time of the 6-month follow-up. Any major adverse cardiac events and typical chest pain did not occur in these selected patients between 6- and 24-month follow-up. Among these 34 patients, late total occlusion of a distal part of the irradiated segment occurred in two patients (5.9%) at 2-year follow-up. Because IVUS catheter did not pass through the totally occluded lesion, 2-year follow-up IVUS images were not acquired. Both late total occlusion patients were asymptomatic and had a negative exercise test; both were treated medically. Two additional patients were excluded from IVUS analysis because of poor image quality in one patient and a mismatching of IVUS images between 6- and 24-month studies in one patient. The irradiated segment in these two patients was patent at 2-year follow-up. Therefore, 30 patients were included in this 2-year IVUS analysis.

Radiation Delivery System, Dosimetry, and Procedure

The methods of brachytherapy were described in detail in a previous report [3]. The delivery system was a ^{188}Re-MAG$_3$-filled angioplasty balloon. Liquid ^{188}Re is a high-energy β-emitter that is available daily from a ^{188}W/^{188}Re generator (Oak Ridge National Laboratory, Oak Ridge, TN). From the dosimetry data, the irradiation time was calculated to deliver 15 Gy at 1.0 mm deep into the vessel wall from the balloon/artery interface [3]. To avoid geographic miss, irradiation was performed to cover the proximal and distal nonstented injured segments as well as the proximal and distal uninjured margins by $>$ 5 mm.

All the patients were pretreated with aspirin 200 mg/day, ticlopidine 500 mg/day, and cilostazol 200 mg/day for 2 days. Ticlopidine was given for 1 month, but aspirin and cilostazol were administered for more than 6 months after irradiation [3].

IVUS Imaging Protocol

Postirradiation and 6- and 24-month follow-up IVUS studies were performed in identical fashion. Intracoronary 0.2 mg nitroglycerin was administered. The ultrasound catheter was advanced approximately 10 mm beyond the lesion site, and an imaging run was performed from beyond the lesion site to the aorto-ostial junction. The studies were performed with a commercially available system (Boston Scientific/Cardiovascular Imaging System, San Jose, CA); this system used a 30 MHz single-element beveled transducer mounted on the end of a flexible shaft and rotated at 1,800 rpm within a 3.2 Fr short-monorail imaging sheath. With this system, the transducer was withdrawn automatically at 0.5 mm/sec to perform the imaging sequence. Ultrasound studies were recorded on a 0.5″ high-resolution s-VHS tape for offline analysis. The postirradiation IVUS imaging run was the final step in the intervention procedure. At 6- and

24-month follow-up, IVUS imaging was performed before any subsequent intervention.

Quantitative Coronary Angiographic (QCA) Analysis

Coronary angiography was performed after the administration of 0.2 mg intracoronary nitroglycerin. Using the guiding catheter for magnification calibration and an online QCA system (Ancor V2.0, Siemens, Germany), the minimal luminal diameter (MLD) was measured. QCA measurements of the MLD within 5 mm beyond irradiated segments were performed before and after intervention and at 6- and 24-month follow-up from diastolic frames in a single matched view showing the smallest luminal diameter. Reference diameter was selected from user-defined segments proximal and distal to the lesion. Lesion length was determined by the shoulder-to-shoulder extent of narrowing in the view with the least amount of foreshortening.

Quantitative IVUS Measurements

Measurements were performed according the American College of Cardiology clinical expert consensus document on standards for acquisition, measurement, and reporting of IVUS studies [16] by the investigator who was blinded to clinical and angiographic data. Measurements included external elastic membrane (EEM), stent, lumen, plaque and media (P&M = EEM − lumen), and IH (stent − lumen) cross-sectional areas (CSA). IH burden (%) was defined as 100 × (IH/stent CSA).

On playback of the postirradiation and 6- and 24-month follow-up IVUS studies, matching image slices were acquired at three different sites of the nonstented adjacent segment at 1, 2, and 4 mm from the stent margin and at five equidistant sites within the stented segment (Fig. 1). Mean proximal reference, intrastent, and distal reference values are reported. In practice, the 6-month follow-up target slices were first analyzed; then the distance from each target slice to the closest identifiable axial landmark (i.e., stent edge) was measured (using seconds or frames of videotape). Finally, this distance was used to identify the corresponding slices on the postirradiation and 24-month IVUS studies. Vascular and perivascular markings were also used to confirm image slice identification. When necessary, the analysis was done side by side and the imaging runs were studied frame by frame to ensure that matching image slices were measured. The minimum lumen CSA was also determined.

Statistical Analysis

Categorical data are presented as frequencies. Continuous data are presented as mean ± SD. Comparison was performed with paired and nonpaired Student's *t*-test, Fisher's exact test, and ANOVA with repeated measures using the Bonferroni correction for post hoc analyses. P value < 0.05 was considered statistically significant.

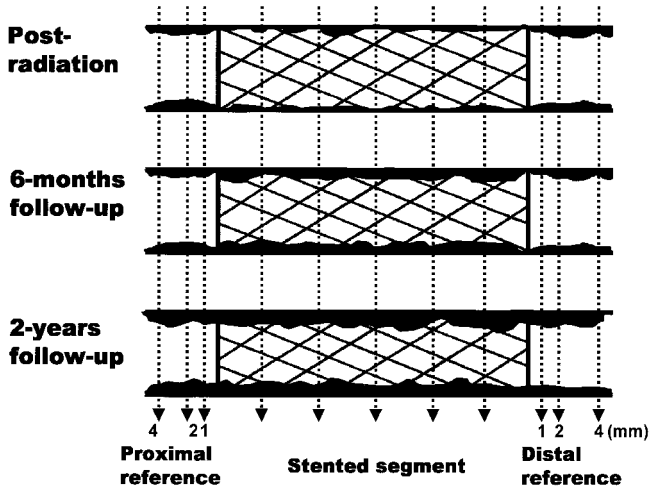

Fig. 1. Matching (postintervention and 6- and 24-month follow-up) IVUS image slices were acquired at three different sites of the nonstented adjacent segment (at 1, 2, and 4 mm from the stent margin) and at five equidistant sites within the stented segment.

TABLE I. Baseline Clinical Characteristics

	TLR	Non-TLR	*P*
Number of patients	6	24	
Age (years)	51 ± 9	52 ± 9	0.3
Men	4 (67%)	17 (71%)	0.6
Systemic hypertension	1 (17%)	13 (54%)	0.12
Diabetes mellitus	1 (17%)	9 (38%)	0.3
Hypercholesterolemia (≥ 240 mg/dl)	1 (17%)	6 (25%)	0.6
Cigarette smoking	3 (50%)	11 (46%)	0.6
History of previous myocardial infarction	1 (17%)	5 (21%)	0.7
Clinical presentation			0.4
Stable angina	1 (17%)	8 (33%)	
Unstable angina	5 (83%)	16 (67%)	

RESULTS

The initial and long-term angiographic follow-up was performed at a mean of 6.1 ± 1.2 and 24.0 ± 2.8 months after the index procedure, respectively. Angiographically, restenosis (diameter stenosis > 50%) occurred in eight patients between 6 and 24 months after β-irradiation therapy. The location of the restenosis was the edge of irradiation in two patients and within the irradiated segment in six patients. Six out of these eight restenosis patients (20%) underwent TLR; TLR was not performed in the remaining two patients because of the intermediate degree of stenosis and absence of symptoms. Baseline clinical characteristics and QCA measurements between

TABLE II. QCA Measurements

	TLR	Non-TLR	*P*
Number of lesions	6	24	
Mean lesion length (mm)	24.1 ± 11.9	19.0 ± 7.4	0.2
Reference vessel diameter (mm)	2.7 ± 0.2	2.9 ± 0.5	0.2
Minimal lumen diameter (mm)			
Preintervention	0.4 ± 0.4	0.7 ± 0.6	0.15
Postintervention	2.5 ± 0.3	2.7 ± 0.5	0.3
6-month follow-up	2.2 ± 0.7	2.5 ± 0.5	0.2
2-year follow-up	1.0 ± 0.5	1.9 ± 0.6	0.003

TABLE III. Serial IVUS Data

	Postradiation	6 months	2 years	*P* ANOVA
Distal segment				
Mean EEM CSA (mm^2)	9.7 ± 3.7	10.1 ± 3.9	9.7 ± 3.9	0.016
Mean lumen CSA (mm^2)	5.3 ± 2.1	5.6 ± 2.3	5.1 ± 2.3	0.029
Mean P&M CSA (mm^2)	4.4 ± 1.9	4.6 ± 1.9	4.6 ± 2.0	0.10
Stented segment				
Mean stent CSA (mm^2)	8.1 ± 2.3	8.1 ± 2.4	8.1 ± 2.3	0.7
Mean lumen CSA (mm^2)	6.3 ± 2.1	6.0 ± 2.1	5.5 ± 2.2	< 0.001
Mean IH CSA (mm^2)	1.8 ± 0.8	2.1 ± 1.1	2.6 ± 1.4	< 0.001
Mean IH burden (%)	23 ± 8	26 ± 10	33 ± 14	< 0.001
Proximal segment				
Mean EEM CSA (mm^2)	15.5 ± 3.2	15.7 ± 3.1	15.4 ± 3.3	0.082
Mean lumen CSA (mm^2)	7.9 ± 3.1	8.1 ± 3.0	7.7 ± 3.3	0.12
Mean P&M CSA (mm^2)	7.6 ± 2.4	7.6 ± 2.3	7.7 ± 2.6	0.5

patients with and without TLR are shown in Tables I and II, respectively. MLD progressively decreased from 2.7 ± 0.5 mm at postintervention to 2.3 ± 0.7 mm at 6-month follow-up to 1.7 ± 0.7 mm at 2-year follow-up (ANOVA $P < 0.001$); the MLD at 24 months was significantly smaller than that at 6 months ($P = 0.003$).

IVUS Results

Serial IVUS findings are presented in Table III. In the stented segment, there was no change in stent CSA. There was a trend for an increase in IH CSA at 6 months ($P = 0.14$ vs. postirradiation) and a significant increase at 24 months ($P < 0.001$ vs. 6 months follow-up). This resulted in a trend for a decrease in lumen CSA at 6 months ($P = 0.11$) and a significant decrease in lumen CSA at 24 months ($P < 0.001$ vs. 6-month follow-up). The IH burden (IH/stent CSA) measured 23% ± 8% postirradiation, 26% ± 10% at 6 months ($P = 0.10$ vs. postirradiation), and 33% ± 14% at 24-month follow-up ($P < 0.001$ vs. 6-month follow-up).

In the distal nonstented segment, there was an increase in EEM CSA at 6 months and a decrease in EEM CSA at 24 months (both $P < 0.05$). The decrease in EEM CSA at 24 months was accompanied by a decrease in lumen CSA ($P < 0.05$ vs. 6-month follow-up). In the proximal nonstented segment, there was no change in EEM or lumen CSA at 6 months, but a trend for a decrease in EEM CSA and lumen CSA from 6 to 24 months ($P = 0.17$ and $P = 0.19$, respectively). There were no significant changes in P&M CSA between 6 and 24 months in either the proximal or the distal nonstented adjacent segments.

IVUS findings between patients with and without TLR are shown in Table IV. There was no significant difference of IVUS measurement from irradiation to 6-month follow-up between the two groups except for a smaller minimum lumen CSA at 24 months in the TLR group. Figure 2 showed the ΔIH CSA between postirradiation and 6 months and that between postirradiation and 24 months.

DISCUSSION

The current study demonstrated late catch-up occurred in both stented and nonstented adjacent segments in asymptomatic patients between 6 and 24 months after intracoronary brachytherapy. The main mechanism of late lumen loss between 6 and 24 months was IH proliferation within the stented segment and vessel shrinkage rather than plaque proliferation in the nonstented adjacent segment. The irradiated ISR vessel segment remained stable for up to 2 years in most patients. However, significant late catch-up was associated with late TLR in some patients between 6 and 24 months after irradiation.

TABLE IV. IVUS Findings Between Patients With and Without TLR

	TLR	Non-TLR	*P*
Postradiation			
Distal segment			
Mean EEM CSA (mm^2)	8.8 ± 2.3	9.9 ± 4.0	0.4
Mean lumen CSA (mm^2)	4.9 ± 0.7	5.4 ± 2.3	0.4
Mean P&M CSA (mm^2)	3.8 ± 1.6	4.5 ± 2.0	0.5
Stented segment			
Mean stent CSA (mm^2)	7.5 ± 0.6	8.3 ± 2.6	0.5
Mean lumen CSA (mm^2)	5.8 ± 0.9	6.4 ± 2.3	0.3
Mean IH CSA (mm^2)	1.7 ± 0.7	1.9 ± 0.8	0.6
Mean IH burden (%)	23 ± 9	23 ± 8	1.0
Proximal segment			
Mean EEM CSA (mm^2)	14.9 ± 4.9	15.7 ± 2.9	0.8
Mean lumen CSA (mm^2)	8.6 ± 3.9	7.8 ± 3.1	0.8
Mean P&M CSA (mm^2)	6.3 ± 1.1	7.8 ± 2.5	0.11
Minimal lumen CSA	4.5 ± 0.5	4.9 ± 2.1	0.4
6-month follow-up			
Distal segment			
Mean EEM CSA (mm^2)	9.6 ± 2.5	10.3 ± 4.1	0.6
Mean lumen CSA (mm^2)	5.5 ± 1.4	5.6 ± 2.4	0.9
Mean P&M CSA (mm^2)	4.1 ± 1.3	4.7 ± 2.0	0.4
Stented segment			
Mean stent CSA (mm^2)	7.5 ± 0.6	8.3 ± 2.6	0.5
Mean lumen CSA (mm^2)	5.7 ± 0.9	6.1 ± 2.3	0.5
Mean IH CSA (mm^2)	1.8 ± 0.5	2.1 ± 1.2	0.3
Mean IH burden (%)	24 ± 8	26 ± 10	0.6
Proximal segment			
Mean EEM CSA (mm^2)	15.0 ± 4.8	15.8 ± 2.8	0.8
Mean lumen CSA (mm^2)	8.6 ± 3.8	8.1 ± 2.9	0.8
Mean P&M CSA (mm^2)	6.4 ± 1.5	7.7 ± 2.4	0.2
Minimal lumen CSA	4.5 ± 1.1	4.6 ± 2.2	0.8
24-month follow-up			
Distal segment			
Mean EEM CSA (mm^2)	8.7 ± 2.5	9.9 ± 4.1	0.4
Mean lumen CSA (mm^2)	4.4 ± 1.5	5.2 ± 2.4	0.4
Mean P&M CSA (mm^2)	4.2 ± 1.1	4.7 ± 2.1	0.5
Stented segment			
Mean stent CSA (mm^2)	7.5 ± 0.6	8.3 ± 2.6	0.5
Mean lumen CSA (mm^2)	4.8 ± 1.6	5.7 ± 2.3	0.3
Mean IH CSA (mm^2)	2.6 ± 1.2	2.6 ± 1.5	1.0
Mean IH burden (%)	36 ± 19	32 ± 13	0.6
Proximal segment			
Mean EEM CSA (mm^2)	14.3 ± 5.5	15.7 ± 2.8	0.7
Mean lumen CSA (mm^2)	8.0 ± 4.1	7.7 ± 3.2	0.9
Mean P&M CSA (mm^2)	6.3 ± 2.2	8.0 ± 2.6	0.2
Minimal lumen CSA	2.2 ± 1.0	4.0 ± 1.9	0.003

In conventional stenting of de novo lesions, restenosis or renarrowing of MLD usually occurred within 6 months after stenting. In patients who were restenosis-free at 6 months after de novo stenting, late catch-up rarely occurred after 6 months [17]. However, in radioactive stent implantation into de novo lesions, late progression of IH was observed from 6 months to 1 year in a 1-year IVUS follow-up study. This suggests that with brachytherapy, IH proliferation is delayed rather than prevented [15].

In ISR lesions treated with intracoronary brachytherapy, several studies showed late catch-up: occurrence of TLR and decrease in QCA MLD between 6 and 24 months [10,12]. However, there are no published data to evaluate long-term (≥ 2-year) changes of IH using serial IVUS in ISR lesions. The current IVUS study in the ISR lesions treated with intracoronary brachytherapy showed late catch-up in most patients as well as TLR in six patients (20%), a progressive decrease in QCA MLD and IVUS minimum lumen CSA.

Our previous IVUS studies showed that β-irradiation therapy inhibits IH proliferation within the stented segment and promotes positive remodeling in nonstented adjacent segments at 6-month follow-up [9,18]. The cur-

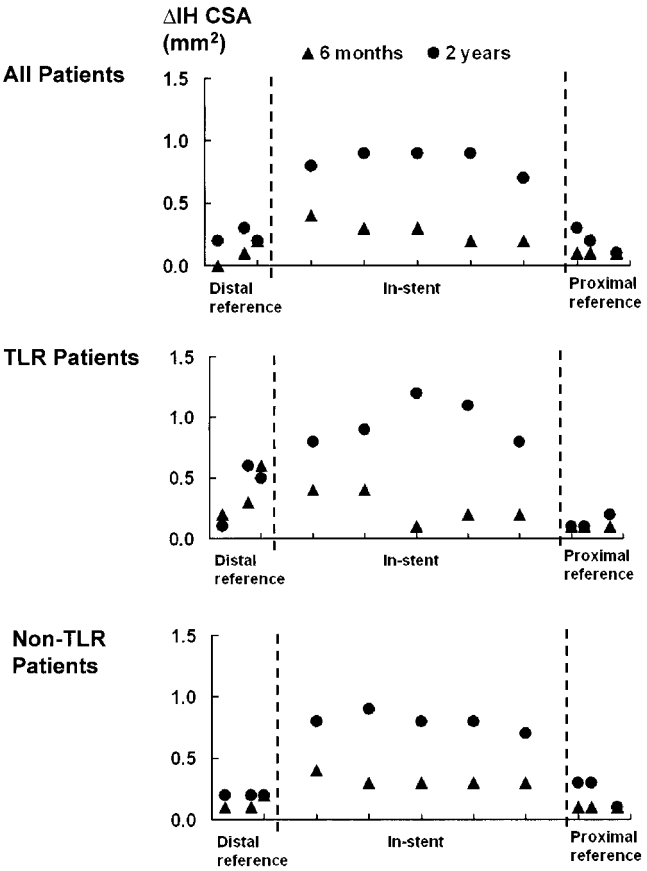

Fig. 2. The ΔIH CSA between postirradiation and 6 months (triangles) and that between postirradiation and 24 months (circles) are shown in the total cohort of 30 patients as well as in patients who did require TLR (n = 6) between 6 and 24 months and those who did not (non-TLR, n = 24).

rent study demonstrated that at 2 years, there is reappearance of IH proliferation within the stented segment and vessel shrinkage in the nonstented adjacent segment. Thus, there is a biphasic remodeling responses of the nonstented reference segment: initial vessel enlargement at 6 months [18] and late vessel shrinkage at 2 years. This biphasic remodeling response was more prominent in the distal compared to the proximal reference segment; this may be partly related to dosing since the distal segment is smaller than the proximal segment. A biphasic remodeling response has been reported in other nonstented interventional environments [19].

Several clinical and angiographic studies demonstrated long-term (≥ 2-year) safety and efficacy of intracoronary brachytherapy [10,12]. The current study also showed long-term safety and efficacy in most patients. Overall, the amount of late loss between 6 and 24 months was small; mean IH burden in the stented segment rose from 26% ± 10% to 33% ± 14%, and mean lumen CSA in the proximal and distal nonstented adjacent segment decreased from 8.0 ± 3.0 to 7.5 ± 3.2 mm^2 and from 5.6 ± 2.3 to 5.0 ± 2.3 mm^2, respectively. However, in patients with late TLR and restenosis, serial IVUS studies showed more IH proliferation and a greater lumen loss at 24 months. Previous study suggested that a larger radiation dose is associated with a longer delay in the restenosis process [20]. The radiation dose in the current study was 15 Gy at 1.0 mm deep into the vessel wall. Longer-term (> 2-year) follow-up IVUS study may be needed to evaluate the exact timing of plateau phase or cessation of this late catch-up phenomenon. In addition, one previous study has shown that radiation failure is associated with a heterogeneous increase in IH manifested quantitatively as a greater decrease in minimum lumen area than an increase in IH volume or mean IH area [21].

Late stent thrombosis is a new phenomenon occurring as a complication of vascular brachytherapy. Among the early trials, the rate of late thrombosis was reported to be 5.3–9.2% [1,4,13,14]. Predictors of late thrombosis are placement of a new stent and in-stent restenosis lesion length [14]. Previous study reported that 6 months of clopidogrel reduces the rate of late thrombosis after γ-irradiation to 2.5% compared with only 1 month of clopidogrel for patients with ISR treated with γ-radiation [22]. Recent study showed that 12 months of clopidogrel is superior to 6 months in reducing overall major cardiac events and TLR [23]. All 34 patients in this study received ticlopidine for 1 month and both aspirin and cilostazol during the 2-year follow-up period [3]. No reimbursement of clopidogrel in insurance system of our country resulted in the use of cilostazol instead of clopidogrel. No late thrombosis, which was associated with major adverse cardiac events and typical chest pain, occurred during the 2-year follow-up period. Two patients with late total occlusion of the distal segment who were excluded from this IVUS analysis were asymptomatic. Therefore, these two patients might have had an exaggerated manifestation of the late catch-up phenomenon.

Study Limitations

This study has several limitations. First, the number of patient was relatively small and perhaps insufficient to determine any predictors of radiation failure between 6 and 24 months. Second, 2-year follow-up IVUS was performed in only a selected group of patients. However, the current study demonstrated the quantitative evidence of late catch-up between 6 and 24 months after intracoronary brachytherapy even in asymptomatic patients. Third, this study was performed with β-radiation therapy with a ^{188}Re-MAG_3-filled balloon and a radiation dosage of 15 Gy. Thus, the results of the present study cannot be compared to those of the other studies using different

radiation sources, radiation dosage, and delivery methods. Fourth, there were no control patients.

Because of a small amount of late loss between 6 and 24 months, most irradiated ISR vessel segments remained stable for up to 2 years. However, quantitative evidence of late catch-up was present in most patients and was significantly associated with 24-month TLR in some patients.

REFERENCES

1. Waksman R, White LR, Chan RC, Bass BG, Geirlach L, Mintz GS, Satler LF, Mehran R, Serruys PW, Lansky AJ, Fitzgerald P, Bhargava B, Kent KM, Pichard AD, Leon MB. Intracoronary γ-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation 2000;101:2165–2171.
2. Waksman R, Bhargava B, White LR, Chan RC, Mehran R, Lansky AJ, Mintz GS, Satler LF, Pichard AD, Leon MB, Kent KM. Intracoronary β-radiation therapy inhibits recurrence of in-stent restenosis. Circulation 2000;101:1895–1898.
3. Park SW, Hong MK, Moon DH, Oh SJ, Lee CW, Kim JJ, Park SJ. Treatment of diffuse in-stent restenosis with rotational atherectomy followed by radiation therapy with a rhenium-188-mercaptoacetyltriglycine-filled balloon. J Am Coll Cardiol 2001;38:631–637.
4. Leon MB, Teirstein PS, Moses JW, Tripuraneni P, Lansky AJ, Jani S, Wong SC, Fish D, Ellis S, Holmes DR, Kerieakes D, Kuntz RA. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med 2001; 344:250–256.
5. Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L, for the INHIBIT investigators. Use of localised intracoronary radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. Lancet 2002;359:551–557.
6. Popma JJ, Suntharalingam M, Lansky AJ, Heuser RR, Speiser B, Teirstein PS, Massullo V, Bass T, Henderson R, Silber S, von Rottkay P, Bonan R, Ho KKL, Osattin A, Kuntz RA, for the Stents and Radiation Therapy (START) investigators. Randomized trial of 90Sr/90Y radiation versus placebo control for treatment of in-stent restenosis. Circulation 2002;106:1090–1096.
7. Bhargava B, Mintz GS, Mehran R, Lansky AJ, Weissman NJ, Walsh C, Chan RC, Waksman R. Serial volumetric intravascular ultrasound analysis of the efficacy of beta irradiation in preventing recurrent in-stent restenosis. Am J Cardiol 2000;85:651–653.
8. Mintz GS, Weissman NJ, Teirstein PS, Ellis SG, Waksman R, Russo RJ, Moussa I, Tripuraneni P, Jani S, Kobayashi Y, Giorgianni JA, Pappas C, Kuntz RA, Moses J, Leon MB. Effect of intracoronary γ-radiation therapy on in-stent restenosis: an intravascular ultrasound analysis from the gamma-1 study. Circulation 2000;102:2915–2918.
9. Hong MK, Park SW, Moon DH, Oh SJ, Lee CW, Rhee KS, Sun F, Song JM, Kang DH, Song JK, Kim JJ, Park SJ. Intravascular ultrasound analysis of beta radiation therapy for diffuse in-stent restenosis to inhibit intimal hyperplasia. Catheter Cardiovasc Interv 2001;54:169–173.
10. Waksman R, Ajani AE, White RL, Pinnow E, Mehran R, Bui AB, Deible R, Gruberg L, Mintz GS, Satler LF, Pichard AD, Kent KM, Lindsay J. Two-year follow-up after beta and gamma intracoronary radiation therapy for patients with diffuse in-stent restenosis. Am J Cardiol 2001;88:425–428.
11. Grise MA, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Cloutier DA, Leon MB, Tripuraneni P, Teirstein PS. Five-year clinical follow-up after intracoronary radiation: Results of a randomized clinical trial. Circulation 2002; 105:2737–2740.
12. Teirstein PS, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Sirkin K, Cloutier DA, Leon MB, Tripuraneni P. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation 2000;101:360–365.
13. Maehara A, Mintz GS, Weissman NJ, Bui AB, Castagna MT, Ajani AE, Pichard AD, Satler LF, Suddath WO, Kent KM, Yang N, Chan R, White L, Waksman R. Late thrombosis after gamma-brachytherapy. Catheter Cardiovasc Interv 2003;58:455–458.
14. Waksman R, Bhargava B, Mintz GS, Mehran R, Lansky AJ, Satler LF, Pichard AD, Kent KM, Leon MB. Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis. J Am Coll Cardiol 2000;36:65–68.
15. Kay IP, Wardeh AJ, Kozuma K. Foley DP, Knook AHM, Thury A, Sianos G, van der Giessen WJ, Levendag PC, Serruys PW. Radioactive stents delay but do not prevent in-stent neointimal hyperplasia. Circulation 2001;103:14–17.
16. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG. ACC Clinical Expert Consensus Document on Standards for the acquisition, measurement and reporting of intravascular ultrasound studies: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001;37:1478–1492.
17. Kimura T, Yokoi H, Nakagawa Y, Tamura T, Kaburagi S, Sawada Y, Sato Y, Yokoi H, Hamasaki N, Nosaka H, Nobuyoshi M. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med 1996;334:561–566.
18. Hong MK, Park SW, Moon DH, Oh SJ, Lee CW, Kim YH, Lee JW, Song JM, Kang DH, Song JK, Kim JJ, Park SJ. Intravascular ultrasound analysis of nonstented adjacent segments in diffuse in-stent restenosis treated with radiation therapy with a rhenium-188-filled balloon. Catheter Cardiovasc Interv 2003;58:428–433.
19. Kimura T, Kaburagi S, Tamura T, Yokoi H, Nakagawa Y, Yokoi H, Hamasaki N, Nosaka H, Nobuyoshi M, Mintz GS, Popma JJ, Leon MB. Remodeling of human coronary arteries undergoing coronary angioplasty or atherectomy. Circulation 1997;96:475–483.
20. Brenner DJ, Miller RC, Hall EJ. The biology of intravascular irradiation. Int J Radiat Oncol Biol Phys 1996;36:805–810.
21. Ahmed JM, Mintz GS, Waksman R, Neil J. Weissman, Leiboff B, Pichard AD, Satler LF, Kent KM, Leon MB. Serial intravascular ultrasound analysis of the impact of lesion length on the efficacy of intracoronary gamma irradiation for preventing recurrent in-stent restenosis. Circulation 2001;103:188–191.
22. Waksman R, Ajani AE, White RL, Pinnow E, Dieble R, Bui AB, Taaffe M, Gruberg L, Mintz GS, Satler LF, Pichard AD, Kent KM, Lindsay J. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary γ-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial Plus 6 Months of Clopidogrel (WRIST PLUS). Circulation 2001; 103:2332–2335.
23. Waksman R, Ajani AE, Pinnow E, Cheneau E, Leborgne L, Dieble R, Bui AB, Satler LF, Pichard AD, Kent KM, Lindsay J. Twelve versus six months of clopidogrel to reduce major cardiac events in patients undergoing γ-radiation therapy for in-stent restenosis: Washington Radiation for In-Stent restenosis Trial (WRIST) 12 versus WRIST PLUS. Circulation 2002;106:776–778.