Incidence and predictors of late recurrence after β-radiation therapy with a ^{188}Re-MAG$_3$–filled balloon for diffuse in-stent restenosis

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Background The long-term fate of patent irradiated segments at 6 months after β-radiation therapy has not been sufficiently evaluated.

Methods Two-year follow-up angiography was performed in 52 patients with patent irradiated segments at 6 months after β-radiation with a rhenium 188–mercaptoacetyltriglycine–filled balloon for diffuse in-stent restenosis. We evaluated late recurrence (LR) and its predictors after β-radiation.

Results Late recurrence at 2 years after radiation was observed in 10 (19.2%) of 52 patients. The minimal lumen diameter (MLD) progressively decreased, from 2.67 ± 0.44 mm at postprocedure to 2.42 ± 0.53 mm at 6 months to 2.09 ± 0.75 mm at 2 years (P = .001). In the 42 patients without LR, the MLD decreased from postprocedure (2.74 ± 0.43 mm) to 6 months (2.44 ± 0.54 mm; P = .006), but did not change between 6 months and 2 years (2.35 ± 0.49 mm, P = .13). In the LR group, the MLD was unchanged from postprocedure (2.33 ± 0.29 mm) to 6 months (2.30 ± 0.43 mm; P = .81), but decreased significantly between 6 months and 2 years (1.02 ± 0.75 mm, P = .001). Multivariate analysis identified postprocedural MLD as an independent predictor of LR (odds ratio 0.025, 95% CI 0.007-0.94, P = .04). Late target lesion revascularization was performed in 6 patients (11.5%) between 6 months and 2 years after radiation.

Conclusion Although LR after radiation was observed in some patients, irradiated segments remained stable for up to 2 years in most patients. Smaller postprocedural MLD, followed by delayed late loss between 6 months and 2 years, was associated with LR. (Am Heart J 2006;151:158-63.)

In patients with in-stent restenosis (ISR), intracoronary brachytherapy has demonstrated a dramatic reduction of angiographic restenosis and target lesion revascularization.[1-3] We have previously shown that β-radiation using a rhenium 188 (^{188}Re)–mercaptoacetyltriglycine (MAG_3)–filled balloon for diffuse ISR improved clinical and angiographic outcomes.[4] Although intracoronary brachytherapy has resulted in long-term (≥2 years) effectiveness,[5-9] late recurrence (LR), or so-called late catch-up, has been shown to reduce the long-term effectiveness of this procedure. However, information regarding the incidence of LR and the long-term natural history of an irradiated segment after brachytherapy has been limited because of the small number of follow-up patients, which ranged from 21 to 26.[5,8] We therefore prospectively evaluated the long-term angiographic (24 months) restenosis of patent irradiated segments at 6-month follow-up angiography and its predictors after β-radiation therapy with a ^{188}Re-MAG$_3$–filled balloon for diffuse ISR (lesion length >10 mm) of 52 patients.

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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%).[4] 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 hours, poor renal function (serum creatinine >3.0 mg/dL), pregnancy, contraindication to antiplatelet therapy, and concomitant serious disease with an expected survival of <2 years. Our institutional review board approved this study.

Table I. Baseline clinical characteristics of study patients

	Total (n = 52)	LR (−) (n = 42)	LR (+) (n = 10)	*P*
Male/female	42/10	35/7	7/3	.38
Age (y)	56.4 ± 10.1	56.7 ± 10.7	55.0 ± 6.9	.63
Risk factors				
Hypertension	24 (46.2%)	19 (45.2%)	5 (50.0%)	.79
Hypercholesterolemia (>200 mg/dl)	14 (26.9%)	12 (37.5%)	2 (25.0%)	.69
Smoking	22 (42.3%)	18 (42.9%)	4 (40.0%)	1.0
Diabetes mellitus	10 (19.2%)	8 (19.0%)	2 (20.0%)	1.0
Prior myocardial infarction	6 (11.5%)	4 (9.5%)	2 (20.0%)	.32
Left ventricular ejection fraction, %	60.0 ± 8.6	59.9 ± 8.7	60.1 ± 8.6	.58
Clinical presentation				.40
Stable angina	32 (61.5%)	27 (64.3%)	5 (50.0%)	
Unstable angina	20 (38.5%)	15 (35.7%)	5 (50.0%)	

One hundred and thirty-seven consecutive patients with diffuse ISR were prospectively enrolled in this study. Repeat coronary angiography was requested 6 months and 2 years after radiation, or earlier if clinically indicated; 120 patients underwent 6-month angiography. Among the latter, 90 patients had patent irradiated segments. From them, we performed 2-year follow-up on 52 selected patients who showed patent irradiation segments at 6 months and did not require target lesion revascularization; all of these patients provided written informed consent to participate in a 2-year follow-up.

Radiation delivery system, dosimetry, and procedure

The methods of brachytherapy have been described in detail previously.[4] The delivery system was a ^{188}Re-MAG$_3$–filled angioplasty balloon. Liquid ^{188}Re is a high-energy β-emitter available daily from a ^{188}W/^{188}Re generator (Oak Ridge National Laboratory, Oak Ridge, Tenn). From the dosimetry data, the irradiation time was calculated to deliver 15 Gy from the balloon/artery interface 1.0 mm deep into the vessel wall.[4] 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 patients were pretreated for 2 days with aspirin (200 mg/day), ticlopidine (500 mg/day), and cilostazol (200 mg/day). After irradiation, ticlopidine was continued for 1 month, whereas aspirin and cilostazol were continued indefinitely.

Quantitative coronary angiographic analysis

Coronary angiography was performed after the administration of 0.2 mg intracoronary nitroglycerin. The minimal luminal diameter (MLD) was measured using a guiding catheter for magnification calibration and an on-line quantitative coronary angiographic (QCA) system (ANCOR V2.0, Siemens, Germany). Quantitative coronary angiographic measurements of the MLD of the 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. The reference vessel, defined as the vessel segment 5 mm proximal and distal to the radiation sources, was also compared. Lesion length was determined by the "shoulder-to-shoulder" extent of narrowing in the view with the least amount of foreshortening.

Clinical follow-up

All patients were evaluated clinically during outpatient visits 1, 3, and 6 months after radiation therapy, and every 4 months thereafter. Major adverse cardiac events, including death, nonfatal myocardial infarction, and target lesion revascularization, were evaluated. Myocardial infarction was diagnosed when cardiac enzymes were elevated threefold or greater, with chest pain lasting at least 30 minutes, or with the appearance of new electrocardiographic changes. The angiographic incidence of LR at 2 years (diameter stenosis ≥50%) was evaluated by QCA. The clinical outcomes were compared between patients with (n = 52) and without (n = 38) 2-year follow-up angiogram who had patent irradiated segments at 6-month angiographic follow-up.

Statistical analysis

Categorical data are presented as frequencies. Continuous data are presented as mean ± SD. Comparison was performed using the paired Student *t* test, the χ^2 or Fisher's exact test, and 1-way analysis of variance with repeated measures using the Bonferroni correction for post hoc analyses. A *P* value <.05 was considered statistically significant. Rates of event-free survival were determined by Kaplan-Meier analysis. To evaluate the predictors of LR, clinical and angiographic parameters were compared in patients with and without LR.

Results

Baseline characteristics

Baseline characteristics of 52 study patients are shown in Table I. The clinical presentations were unstable angina in 61.5% and stable angina in 38.5%. The risk factors included hypertension in 46.2%, diabetes mellitus in 19.2%, hypercholesterolemia in 26.9%, and current smoking in 42.3%. The mean left ventricular ejection fraction was 60.0% ± 8.6 %. Baseline clinical

Table II. Angiographic and procedural data

	Total (n = 52)	LR (–) (n = 42)	LR (+) (n = 10)	*P*
Lesion length (mm)	24.09 ± 10.48	22.38 ± 9.56	31.10 ± 11.69	.01
Reference vessel size (mm)	2.88 ± 0.42	2.93 ± 0.45	2.71 ± 0.19	.02
Treatment before radiation				.41
Rotational atherectomy	28 (53.8%)	21 (50%)	7 (70.0%)	
Balloon angioplasty	20 (38.5%)	17 (40.5)	3 (30.0%)	
Cutting balloon angioplasty	4 (7.7%)	4 (9.5%)	0	
Artery treated				.26
Left anterior descending artery	34 (65.4%)	27 (64.3%)	7 (70.%)	
Left circumflex artery	8 (15.4%)	8 (19.0%)	0	
Right coronary artery	10 (19.2%)	7 (16.7%)	3 (30.0%)	
Radiation therapy				
Irradiated segment length (mm)	34.40 ± 4.94	33.45 ± 4.95	38.40 ± 2.07	.003
Overlap of balloon	8 (15.4%)	6 (14.3%)	2 (20%)	.64
Fractionation	9 (17.3%)	8 (19.0%)	1 (10.0%)	.67
Exposure time (s)	169.5 ± 53.3	167.5 ± 54.6	178.5 ± 49.2	.63
Additional stenting	2 (4.8%)	2 (4.8%)	0	1.0
Diameter stenosis				
Before intervention	78.32 ± 13.69	77.05 ± 13.02	83.49 ± 15.82	.18
Postprocedure	7.19 ± 12.26	5.63 ± 11.88	13.57 ± 12.31	.07
At 6 mo	15.33 ± 15.38	15.35 ± 18.31	15.23 ± 13.75	.98
At 2 y	26.71 ± 28.43	18.13 ± 21.14	61.91 ± 28.13	.0001
Minimal lumen diameter (mm)				
Before intervention	0.63 ± 0.42	0.67 ± 0.41	0.43 ± 0.40	.09
Postprocedure	2.67 ± 0.44	2.74 ± 0.43	2.33 ± 0.29	.002
At 6 mo	2.42 ± 0.53	2.44 ± 0.54	2.30 ± 0.43	.43
At 2 y	2.09 ± 0.75	2.35 ± 0.49	1.02 ± 0.75	.0001
6-mo follow-up				
Acute gain	2.03 ± 0.50	2.06 ± 0.50	1.89 ± 0.48	.33
Late loss	0.23 ± 0.59	0.28 ± 0.62	0.03 ± 0.39	.23
Late loss index	0.09 ± 0.28	0.12 ± 0.29	0.01 ± 0.22	.29
2-y vs 6-mo follow-up				
Late loss	0.32 ± 0.69	0.09 ± 0.41	1.27 ± 0.83	.0001
Late loss index	0.10 ± 0.38	0.04 ± 0.31	0.54 ± 0.36	.0001
2-y follow-up vs postprocedure				
Late loss	0.57 ± 0.74	0.39 ± 0.65	1.30 ± 0.68	.0001
Late loss index	0.21 ± 0.30	0.12 ± 0.22	0.57 ± 0.32	.0001

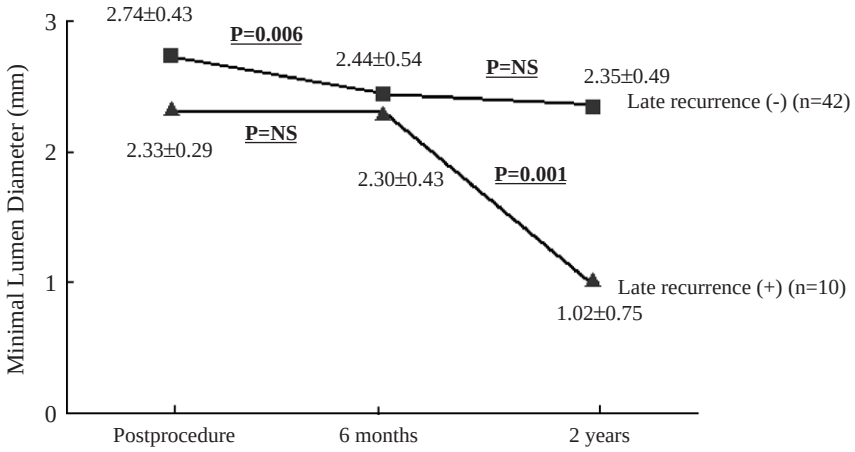
characteristics were similar in patients with and without LR. Mean lengths of the lesion and irradiation segment were 24.09 ± 10.48 mm and 34.40 ± 4.94 mm, respectively (Table II).

Angiographic analysis

Six-month follow-up angiography was performed at 6.1 ± 2.0 months, whereas 2-year follow-up angiography was obtained at 23.6 ± 6.2 months, after radiation therapy. At the 2-year follow-up, LR had occurred in 10 patients (19.2%), with the restenosis located at the edge of the irradiated segment in 2 patients and within the irradiated segment in 8 patients. The pattern of restenosis included 3 diffuse ISRs, 2 focal ISRs, 2 edge restenoses, and 3 total occlusions. Three patients who had total occlusion did not show any clinical symptoms of acute coronary syndrome. Although detailed angiographic analysis revealed that geographic miss was present in 60% of irradiated margin at the time of index procedure, the edge restenosis at 2-year follow-up in 2 patients occurred in the irradiated edges which were not associated with geographic miss.

Quantitative coronary angiographic data were analyzed in the 52 patients who underwent 6-month and 2-year follow-up angiography. The overall MLD progressively decreased, from 2.67 ± 0.44 mm at postprocedure, to 2.42 ± 0.53 mm at 6 months, and to 2.09 ± 0.75 mm at 2 years (P = .001). Minimal lumen diameter decreased in 26 patients (50%), increased in 13 patients (25%), and was unaltered in 13 patients (25%) between the 6-month and 2-year angiograms. There was no significant change in reference vessel diameter between the 6-month (2.88 ± 0.42 mm) and 2-year (2.81 ± 0.43 mm) angiograms (P = .57). In patients without LR, the MLD significantly decreased from postprocedure (2.74 ± 0.43 mm) to 6 months (2.44 ± 0.54 mm; P = .006), but did not change significantly between 6 months and 2 years (2.35 ±

Figure 1



Serial changes of minimal lumen diameter in patients with or without late recurrence.

Table III. Long-term clinical outcomes

	Total (n = 52)	LR (−) (n = 42)	LR (+) (n = 10)	*P*
Mean follow-up duration (mo)	44.2 ± 9.3	43.7 ± 9.7	45.9 ± 7.8	.512
Myocardial infarction	0	0	0	1.0
Death	0	0	0	1.0
Target lesion revascularization	6 (11.5%)	0	6 (60%)	.000
Repeat intervention	4 (7.7%)	0	4 (40%)	
Bypass surgery	2 (3.8%)	0	2 (20%)	

0.49 mm; P = .13) (Figure 1). In patients with LR, the MLD was unchanged between postprocedure (2.33 ± 0.29 mm) and 6 months (2.30 ± 0.43 mm, P = .81), but decreased significantly between 6 months and 2 years (1.02 ± 0.75 mm, P = .001) (Figure 1). The late loss from 6 months to 2 years in irradiated segment was uniform for both large (reference vessel size ≥3.0 mm, n = 20) and small vessel (reference vessel size <3.0 mm, n = 32) in our study (0.43 ± 0.63 mm in large vessel vs 0.26 ± 0.72 mm in small vessel, P = .38). No aneurysm formation was observed between the 6-month and 2-year angiograms.

Clinical follow-up

Clinical follow-up was obtained in all 52 patients, with a mean follow-up period of 44.2 ± 9.3 months. Angiographically, restenosis (diameter stenosis >50%) occurred in 10 patients (19.2%) between 6 and 24 months after β-irradiation therapy. Six of these patients (11.5%) required target lesion revascularization, which was accomplished with optimal balloon angioplasty (n = 1), cutting balloon angioplasty (n = 3), or bypass surgery (n = 2) (Table III). The remaining 4 patients with LR did not undergo target lesion revascularization because of the intermediate degree of stenosis and absence of symptoms. None of these patients, however, suffered from myocardial infarction, late thrombosis, or death from any cause during the follow-up period. The rate of 40-month survival without major adverse cardiac events (death, nonfatal myocardial infarction and target lesion revascularization) was 87.9 ± 4.7%. Five patients (9.6%) required percutaneous interventions of a nontarget vessel because of progression of disease during follow-up.

Among 38 patients without 2-year angiogram who had patent irradiated segment at 6-month angiographic follow-up, one patient (2.6%) died of cancer and another patient (2.6%) received late target lesion revascularization during a mean follow-up period of 47.2 ± 10.5 months. None of these patients suffered from myocardial infarction or stent thrombosis during the follow-up period. The long-term clinical outcomes were similar between patients with and without 2-year follow-up angiogram, in terms of death (0% vs 2.6%, P = .416), target lesion revascularization (11.5% vs 2.6%, P = .231), and major adverse cardiac events (11.5% vs 5.3%, P = .459).

Predictors of late recurrence

On univariate analysis, mean lengths of the lesion and irradiation segment were longer in patients with LR than those without LR. The patients with LR had a smaller reference vessel and postprocedural MLD than those without LR (Table II). Multivariate analysis was performed to determine the independent predictors of LR after brachytherapy. The following variables were tested (all with $P < .2$ in univariate analysis): lesion length, reference vessel size, irradiated segment length, preintervention diameter stenosis, postprocedural diameter stenosis, preintervention MLD, and postprocedural MLD. On multivariate analysis, postprocedural MLD was an independent predictor of LR (odds ratio 0.025, 95% CI 0.007-0.94, $P = .04$).

Discussion

The major findings of this study are as follows: (1) LR occurred in nearly 20% of patients between 6 and 24 months after intracoronary brachytherapy, but the irradiated ISR vessel segment remained stable for up to 2 years in most patients; (2) LR was associated with smaller postprocedural MLD than in patients without LR, followed by marked late loss between 6 months and 2 years; and (3) intracoronary brachytherapy with β-radiation using a ^{188}Re-MAG$_3$–filled balloon for diffuse ISR appears to be safe in terms of long-term clinical outcome, without significant side effects related to radiation.

Intracoronary brachytherapy is a promising therapy for preventing restenosis in diffuse ISR, with reductions in restenosis rate and maintenance of benefits observed up to 5 years later.[5-9] Long-term (≥2 years) angiographic follow-up, however, showed occurrence of late target lesion revascularization, which may be associated with LR, and a decrease in MLD by QCA between 6 and 36 months.[5,8] However, as data regarding long-term angiographic (≥2 years) outcomes of brachytherapy were limited by the small number of patients studied, which ranged from 21 to 26,[5,8] the natural history of irradiated segments has not been sufficiently evaluated. To our knowledge, the current study is the first to investigate the incidence and predictors of LR in patients who underwent 6-month and 2-year angiographic follow-up study after β-radiation therapy.

In this present study, the overall MLD by QCA decreased between 6 months and 2 years, and LR was observed in nearly 20%, findings which are similar to those previously reported.[5,8] Our results suggest delayed neointima formation after irradiation. It was previously reported that increased radiation dose was associated with a longer delay in the restenosis process.[10] The radiation dose we used was 15 Gy at 1.0 mm deep into the vessel wall. Longer-term (>2 years) follow-up study may be required to evaluate the true incidence of this LR phenomenon.

In 42 patients without LR, the MLD between postprocedure and 6 months significantly decreased but was unchanged between 6 months and 2 years. In the LR group, however, the MLD was unchanged over the first 6 months, but decreased significantly between 6 months and 2 years. These findings suggest that the irradiated segments have a different period of restenosis process in patients with LR compared to those without LR, with the former showing negligible intimal hyperplasia within 6 months and marked delayed intimal growth between 6 months and 2 years. Whereas the irradiated segments in patients without LR had a significant intimal hyperplasia within 6 months and were stable between 6 months and 2 years. Therefore, the current study demonstrated that transient cessation and resumption of intimal hyperplasia over 2 years occurred in some patients, which usually was associated with LR, but most amount of intimal hyperplasia occurring after radiation therapy developed within 6 months in other patients, and there was no continued intimal hyperplasia beyond 6 months. However, until now, there were no data regarding angiographic or clinical predictors of LR after radiation therapy. In the current study, reference vessel size was smaller in the LR group. In the circumstance of the same diameter stenosis, a smaller vessel usually had a shorter source-to-adventitia distance than a larger vessel, which may make possible the delivery of more homogeneous and exact radiation energy to the target tissue, thus effectively preventing intimal hyperplasia within the first 6 months, which is a plausible explanation for our results that the patients with LR had a minimal late loss of 0.03 at 6 months, compared to late loss of 0.28 at 6 months in those without LR. Our findings were similar to those reported earlier, in which brachytherapy was shown to be more efficacious in preventing angiographic restenosis in smaller vessels.[11] This earlier study, however, did not evaluate the change of irradiated segments beyond 6 months. After the traditional restenosis period, radiation would no longer freeze postprocedural angiographic results, leading to exaggerated intimal growth in the LR group. On the basis of our results, brachytherapy has more beneficial effects in inhibiting intimal hyperplasia in relatively small vessel within the traditional restenosis period, but thereafter, the beneficial effects vanish with time. Previous report suggested that prevention of cellular division was the dominant mechanism of radiation action in reducing and delaying restenosis.[12] The possible cause of LR after brachytherapy, therefore, would be later activation of cellular proliferation after the initial inhibition of most but not all of the dividing cells that would otherwise cause restenosis within 6 months. Our findings suggest that nearly complete suppression of cellular division within 6 months might trigger significant reaccumula-

tion of neointima. However, the reason why the significant delayed intimal growth between 6 months and 2 years that caused LR occurred in the selected patients remains unknown.

The patients with LR had a smaller reference vessel size and postprocedural MLD than those without LR, and postprocedural MLD was identified as an independent predictor of LR. In the current study, brachytherapy allowed significant neointimal hyperplasia between postprocedure and 2 years, resulting in progressive decrease in overall MLD, although no further decrease in MLD occurred beyond 6 months in patients without LR. Furthermore, the late loss from 6 months to 2 years uniformly occurred for both large and small vessel. Considering the uniform late loss from 6 months to 2 years in all the irradiated segments in conjunction with postprocedural MLD as the independent predictor of LR, smaller vessels would be associated with a high risk of LR at 2-year follow-up compared to larger vessels.

Long-term concerns of intracoronary brachytherapy on irradiated segments include aneurysm formation and late thrombosis. We observed no incidence of late angiographic aneurysm formation, but we did find 3 late total occlusions at 2-year follow-up. Late total occlusion represents either late exaggerated intimal hyperplasia or late thrombotic complication. The latter has been associated with early discontinuation of antiplatelet therapy and additional new stent implantation at the time of radiation therapy.[13,14] Intracoronary thrombosis may present clinically as acute coronary syndrome. Of the 3 patients with total occlusion at 2 years, however, none had any clinical symptoms of angina or acute coronary syndrome. Moreover, aspirin and cilostazol were administered indefinitely in all of the study patients, suggesting that the late total occlusions observed here may be a manifestation of delayed progressive intimal hyperplasia after intracoronary brachytherapy. These findings indicate that late thrombotic occlusion may be prevented by prolonged antiplatelet therapy,[14] but the optimal duration of this treatment remains to be determined.

In conclusion, LR after brachytherapy usually occurs in patients with smaller postprocedural MLD in conjunction with small intimal hyperplasia within 6 months and significant intimal hyperplasia between 6 months and 2 years. Although LR related to target lesion revascularization may occur between 6 and 24 months after β-radiation, long-term angiographic benefits of intracoronary brachytherapy with β-irradiation using a ^{188}Re-MAG$_3$–filled balloon for diffuse ISR are believed to be sustained for up to 2 years.

Limitations of this study need to be addressed. First, although we enrolled a larger patient population than in previous studies, we included a relatively small number of patients. In addition, 2-year follow-up angiography was performed in only a selected group of patients, who may not be representative of the true restenosis rate at 2 years. Furthermore, we performed β-radiation using a ^{188}Re-MAG$_3$–filled balloon. We cannot, therefore, compare our results with those of other studies using different kinds of radiation sources, delivery methods, and interventional devices.

References

1. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med 1997;336:1697-703.
2. Waksman R, Bhargava B, White L, et al. Intracoronary β-radiation therapy inhibits recurrence of in-stent restenosis. Circulation 2000;101:1895-8.
3. Waksman R, White RL, Chan RC, et al. Intracoronary γ-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation 2000;101:2165-71.
4. Park SW, Hong MK, Moon DH, et al. 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;38:631-7.
5. Teirstein PS, Massullo V, Jani S, et al. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation 2000;101:360-5.
6. Grise MA, Massullo V, Jani S, et al. Five-year clinical follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation 2002;105:2737-40.
7. Waksman R, Ajani AE, White RL, et al. Two-year follow-up after beta and gamma intracoronary radiation therapy for patients with diffuse in-stent restenosis. Am J Cardiol 2001;88:425-8.
8. Meerkin D, Joyal M, Tardif JC, et al. Two-year angiographic follow-up of intracoronary Sr90 therapy for restenosis prevention after balloon angioplasty. Circulation 2002;106:539-43.
9. Waksman R, Ajani AE, White RL, et al. Five-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. Circulation 2004;109:340-4.
10. Brenner DJ, Miller RC, Hall EJ. The radiobiology of intravascular irradiation. Int J Radiat Oncol Biol Phys 1996;36:805-10.
11. Ajani AE, Waksman R, Cha DH, et al. The impact of lesion length and reference vessel diameter on angiographic restenosis and target vessel revascularization in treating in-stent restenosis with radiation. J Am Coll Cardiol 2002;39:1290-6.
12. Brenner DJ, Miller RC. Long-term efficacy of intracoronary irradiation in inhibiting in-stent restenosis. Circulation 2001;103:1330-2.
13. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med 2001;344:250-6.
14. Waksman R, Ajani AE, White RL, et al. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS). Circulation 2001;103:2332-5.