Three-Year Clinical Follow-up Results of Intracoronary Radiation Therapy Using a Rhenium-188-Diethylene-Triamine-Penta-Acetic-Acid-Filled Balloon System

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Background  Intracoronary radiation therapy (IRT) prevents recurrent in-stent restenosis, but its long-term safety and efficacy remain uncertain. In the present study, the long-term clinical outcome of IRT using the rhenium-188 (188Re)-filled balloon system was evaluated.

Methods and Results  After successful catheter-based treatment of either a de novo or restenotic lesion, 187 patients were randomly assigned to either the radiation (N=104) or the control (N=83) group. The 188Re-filled balloon system was designed to deliver 17.6 Gy to 1.0-mm tissue depth. Angiographic restenosis was significantly reduced with IRT at 9 months (18.9% vs 45.9%, p<0.001), but the incidence of major adverse cardiac events (MACE) including death, myocardial infarction, and target-vessel revascularization (TVR) by 3 years showed no difference. Lack of clinical benefit might be related to TVR caused by geographic miss (6/22, 28.6%), balloon-induced unhealed dissection (3/22, 13.6%) and late thrombosis (2/22, 9.1%). In the restenotic subgroup (N=39), the MACE rate within 3 years was significantly reduced with IRT (14.3% vs 54.5%, p=0.01).

Conclusions  IRT using the 188Re-filled balloon system is safe and technically feasible. Although IRT failed to show favorable outcomes for de novo lesion, the clinical benefits for restenotic lesions seem durable for 3 years. Furthermore, preventing geographic miss and dissection might improve long-term outcomes.  

Key Words: Angioplasty; Radioisotopes; Restenosis

Restenosis after percutaneous coronary intervention is the most problematic issue for interventional cardiology and the main mechanisms are excessive neointimal formation, extracellular matrix synthesis, and negative vessel remodeling in response to balloon injury. Stent implantation has led to a 30–50% decrease in the rate of restenosis, with good clinical results. Coronary stenting reduces restenosis primarily by preventing the constrictive remodeling and elastic recoil of the artery, but it fails to inhibit neointimal proliferation. Thus, a new technique that could prevent neointimal hyperplasia would be of great clinical benefit. Intracoronary radiation therapy (IRT) has been introduced to decrease the exaggerated response to injury and it is believed that IRT is not only effective in treating in-stent restenosis (ISR), but also prevents its recurrence.

IRT using the rhenium-188 (188Re)-filled balloon system is attractive because it has the advantages of self-centering and ease to use. Several clinical trials have shown that IRT using the 188Re-filled balloon system is safe and effective in treating coronary artery disease, but its long-term safety and efficacy remains uncertain. The objective of the present study was to evaluate the long-term clinical outcome of IRT using the 188Re-filled balloon system in treating de novo or restenotic lesions.

Methods

Study Patients  The Seoul National University Hospital Post-Angioplasty Rhenium (SPARE) trial was designed as a prospective, randomized, case-controlled trial. The purpose of this trial was to evaluate the safety and efficacy of 188Re source irradiation following angioplasty in patients with de novo or restenotic lesions of native coronary arteries. For the inclusion criteria to be met, the diameter of the vessel had to be between 2.5 and 4.0 mm, and the lesion length had to be shorter than 20 mm. Patients were excluded if there was a history of recent myocardial infarction (<4 weeks), an ostial lesion, a bifurcation lesion that required intervention for both branches, an angiographic thrombus, pregnancy, contraindication to antiplatelet therapy, or concomitant serious disease with an expected survival of less than 2 years. Patients underwent clinical and angiographic follow-up at 9 months and clinical follow-up at 3 years. The study protocol was approved by the Institutional Review Board of the Seoul National University Hospital before the initiation of the study. Informed consent was obtained from all participants.
Radiation Delivery System and Dosimetry

188Re is a high-energy ß-emitter with a maximal energy of 2.12 MeV and is available daily as 188Re-perhrenate solution from the 188W/188Re generator (Oak Ridge National Laboratory, Oak Ridge, TN, USA), and it has a half-life of 17 h. 188Re was concentrated up to 5,550 MBq/ml with a simple ion exchange column-based method and was successfully used to label diethylene triamine penta-acetic acid (DTPA). 188Re-DTPA is rapidly excreted via the kidneys in the event of the material leaking into the systemic circulation. 188Re-DTPA was mixed with ionic contrast agent (Hexabrix; Guerbet, France) to make the final iodine concentration reach 5% (vol/vol). Before this clinical trial, we performed detailed in vitro studies to evaluate the dosimetry of a liquid 188Re-DTPA-filled angioplasty balloon system. The distribution of dose around the angioplasty balloon was estimated by the Monte Carlo simulation using the EGS4 code. Fifty % of the energy was deposited in the first millimeter of the vessel wall next to the balloon’s surface. The calculated absorbed dose of radiation agreed with the one measured by the film dosimetry, which was performed using a water phantom, with errors ranging from 9.4% to 17%. From the dosimetric data, the irradiation time was calculated to deliver 17.6 Gy at a depth of 1.0 mm into the vessel wall from the balloon – artery interface depending on the size of the balloon and the actual radioactivity of the 188Re-DTPA solution.

Radiation Therapy Procedure

All patients were pretreated with 100 mg of aspirin daily and patients with implanted stents also received ticlopidine 250 mg bid or 75 mg of clopidogrel daily after the loading dose for at least 4 weeks. Systemic anticoagulation was achieved by an initial bolus dose of 10,000 U of intravenous heparin, with additional heparin given to maintain an activated clotting time of greater than 300s during the procedure. Angioplasty was performed in the standard fashion. Following successful angioplasty with or without stenting, patients were randomly assigned to either the radiation or the control group. Irradiation was performed with the 188Re-DTPA-filled conventional angioplasty balloon system. For irradiation, a conventional angioplasty balloon of the same diameter as the vessel, but at least 10 mm more in length, was selected to cover the proximal and distal uninjured segments. The balloon-traumatized area was identified by contrast injection with the deflated balloon in place and the same level of inspiration, giving the exact positions of the proximal and distal markers within the vessel. The 188Re-DTPA-filled syringe and a conventional in-deflator device were connected to the balloon by a 3-port coronary manifold. After complete removal of air from the balloon, the 188Re-DTPA solution was introduced into the balloon catheter and inflation was maintained at the nominal pressure. Fractionation was allowed in case of severe angina or significant hemodynamic changes; in that event, the balloon was deflated for at least 1 min and was left in place across the target lesion to avoid shifting of the balloon and to minimize radiation exposure to other areas.

Quantitative Coronary Angiography (QCA)

Coronary angiograms were analyzed using an on-line QCA system (Quantaor QCA, version 4.0, Pie Medical Imaging, the Netherlands). Angiographic measurements were made during diastole after the administration of intracoronary nitroglycerin, using the guiding catheter for magnification calibration. The irradiated segments and both edges were analyzed by QCA before and after intervention and also at follow-up. QCA measurements were performed in single, matched views showing the smallest luminal diameter. Angiographic restenosis was defined as a diameter stenosis of 50% or greater at follow-up.

Definitions

The irradiated segment was defined as the area encompassed by the proximal and distal radiopaque balloon markers. The edges of the irradiated segment were defined as the 5-mm long segments proximal and distal to the angiographic location of the proximal and distal markers of the radiation balloon. Geographic miss (GM) was defined when there was not sufficient coverage (>5 mm beyond the balloon-traumatized segment) with irradiation.

Primary and Secondary Endpoints

All patients were clinically evaluated during an office visit at 1 month and then every 1–2 months after radiation therapy. Repeat coronary angiography was performed at 9 months after irradiation, or earlier if clinically indicated. Major adverse cardiac events (MACE), including death, myocardial infarction, and repeat revascularization, were evaluated. The primary endpoint was the angiographic incidence of restenosis by QCA at 9 months. The secondary end point was the occurrence of any MACE during the follow-up period. Myocardial infarction was diagnosed when cardiac enzymes were elevated 3-fold or greater, with chest pain lasting more than 30 min, or with the appearance of new electrocardiographic changes.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows 10.0 (SPSS Inc, Chicago, ILL, USA). Continuous variables are expressed as mean ± 1 SD, and were compared by unpaired Student’s t-test. Discrete variables were expressed as counts and percentages, and the chi-square or the Fisher’s exact test were used to compare proportions. All statistical analyses were 2-tailed. P values <0.05 were considered statistically significant.

Results

Baseline Clinical and Angiographic Data

From December 1998 to June 2001, 187 patients were included in this study; 104 were randomized to receive irradiation, and 83 were randomized to the control group. Baseline clinical data did not differ between the 2 groups. Lesion characteristics and procedural parameters were also not different, except for the proportion of patients with restenotic lesions, which was significantly higher in the radiation group (Table 1).

Irradiation Data

The mean diameter of the 188Re-filled balloon was 3.09±0.43 mm, and the mean length was 24.66±4.01 mm. The prescribed dose of 17.6 Gy was delivered to all the patients in the radiation group. The mean irradiation time was 577.86±329.19 s. All procedures were free of major adverse events except for 1 case of balloon leakage. Dosimetry was performed, and the radiation exposures were within the tolerated ranges.
Angiographic Follow-up Data

The angiographic analysis included 90 patients from the radiation group and 61 from the control group (angiographic follow-up rate: 73.5% in the control group, 86.5% in the radiation group, \( p = 0.03 \)). Table 2 lists the results of QCA measurements. The minimal luminal diameter (MLD) before and after angioplasty did not differ between the 2 groups. At 9 months, the radiation group showed a significantly lower late loss, a significantly higher MLD, and a significantly lower % diameter stenosis both of the target lesion and the total segment. The 9-month binary restenosis rates of the target lesion and of the total segment were significantly lower in the radiation group than in the control.

Clinical Follow-up Data

There were no deaths, subacute occlusion, or Q-wave myocardial infarctions during the hospital stay. In the control group, 1 patient died of lung cancer 31 months after the intervention, and another patient with a history of myocardial infarction and gastric cancer died 2 months after intervention. In the radiation group, there was 1 sudden death of a patient who underwent stenting 3 months after intervention.

Table 1 Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=83)</th>
<th>Radiation (n=104)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.93±9.32</td>
<td>61.94±8.79</td>
<td>0.99</td>
</tr>
<tr>
<td>M:F</td>
<td>52:31</td>
<td>71:33</td>
<td>0.42</td>
</tr>
<tr>
<td>HT</td>
<td>32 (38.6%)</td>
<td>47 (45.2%)</td>
<td>0.36</td>
</tr>
<tr>
<td>DM</td>
<td>22 (26.5%)</td>
<td>30 (28.8%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Smoking</td>
<td>35 (42.2%)</td>
<td>42 (40.4%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>CSA</td>
<td>26 (31.3%)</td>
<td>46 (44.2%)</td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>52 (62.7%)</td>
<td>55 (52.9%)</td>
<td></td>
</tr>
<tr>
<td>OMI</td>
<td>5 (6.0%)</td>
<td>3 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Involved vessel</td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>1VD</td>
<td>32 (37.5%)</td>
<td>46 (43.3%)</td>
<td></td>
</tr>
<tr>
<td>2VD</td>
<td>33 (39.8%)</td>
<td>41 (39.4%)</td>
<td></td>
</tr>
<tr>
<td>3VD</td>
<td>18 (21.7%)</td>
<td>17 (16.3%)</td>
<td></td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>LAD</td>
<td>48 (57.8%)</td>
<td>47 (44.2%)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>15 (18.1%)</td>
<td>30 (28.8%)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>20 (24.1%)</td>
<td>27 (26.0%)</td>
<td></td>
</tr>
<tr>
<td>Lesion type</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>A/B1</td>
<td>63 (75.9%)</td>
<td>67 (64.4%)</td>
<td></td>
</tr>
<tr>
<td>B2/C</td>
<td>20 (24.1%)</td>
<td>37 (35.6%)</td>
<td></td>
</tr>
<tr>
<td>Lesion nature</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>De novo</td>
<td>72 (86.7%)</td>
<td>76 (73.1%)</td>
<td></td>
</tr>
<tr>
<td>Restenotic</td>
<td>11 (13.3%)</td>
<td>28 (26.9%)</td>
<td></td>
</tr>
<tr>
<td>New stent implantation</td>
<td>52 (62.7%)</td>
<td>49 (47.1%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

HT, hypertension; DM, diabetes mellitus; CSA, chronic stable angina; UA, unstable angina; OMI, old myocardial infarction; VD, vessel disease; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

Table 2 Quantitative Angiographic Analysis

<table>
<thead>
<tr>
<th></th>
<th>Control (n=83)</th>
<th>Radiation (n=104)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length (mm)</td>
<td>13.06±4.12</td>
<td>12.93±3.92</td>
<td>0.83</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>0.73±0.37</td>
<td>0.78±0.35</td>
<td>0.37</td>
</tr>
<tr>
<td>RD (mm)</td>
<td>2.96±0.40</td>
<td>2.96±0.41</td>
<td>0.91</td>
</tr>
<tr>
<td>DS (%)</td>
<td>74.26±14.45</td>
<td>73.41±13.07</td>
<td>0.68</td>
</tr>
<tr>
<td>Post-procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.55±0.44</td>
<td>2.55±0.51</td>
<td>0.93</td>
</tr>
<tr>
<td>RD (mm)</td>
<td>3.06±0.42</td>
<td>3.09±0.58</td>
<td>0.63</td>
</tr>
<tr>
<td>DS (%)</td>
<td>16.68±10.23</td>
<td>17.39±10.79</td>
<td>0.65</td>
</tr>
<tr>
<td>9 month angiographic F/U</td>
<td>61/83 (73.5%)</td>
<td>90/104 (86.5%)</td>
<td>0.03</td>
</tr>
<tr>
<td>9 month F/U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD (mm), target lesion</td>
<td>1.44±0.84</td>
<td>2.20±0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLD (mm), total segment</td>
<td>1.44±0.85</td>
<td>1.98±0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RD (mm)</td>
<td>2.89±0.38</td>
<td>2.99±0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DS (%), target lesion</td>
<td>50.59±28.13</td>
<td>27.00±25.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DS (%), total segment</td>
<td>50.58±28.34</td>
<td>34.01±26.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late loss, target lesion</td>
<td>1.12±0.89</td>
<td>0.35±0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late loss, total segment</td>
<td>1.12±0.90</td>
<td>0.57±0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Restenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target lesion</td>
<td>28/61 (45.9%)</td>
<td>13/90 (14.4%)</td>
<td></td>
</tr>
<tr>
<td>Total segment</td>
<td>28/61 (45.9%)</td>
<td>19/90 (21.2%)</td>
<td></td>
</tr>
</tbody>
</table>

MLD, minimal luminal diameter; RD, reference diameter; DS, diameter stenosis; F/U, follow-up.
intervention. The clinical follow-up rate was 95.1% (79/83) in the control group and 94.2% (98/104) in the radiation group. The occurrence of MACE by the third year was observed in 27 (34.2%) patients of the control group and in 24 (24.5%) patients of the radiation group (p=0.16) (Table 3). We analyzed not only the target lesion but also the edge segment in order to investigate the reason for the lack of clinical benefit in the radiation group. GM was identified in 28 of 208 (13.5%) edges and in 25 of 104 (24.0%) vessels. The occurrence of GM was equally distributed between the proximal (13 of 104) and distal (12 of 104) edges. The incidence of restenosis was 35.0% for patients with GM versus 14.3% for patients without GM (p<0.05). The rate of restenosis at the edges of irradiation was also significantly higher in patients with GM than in patients without GM (20.0% vs 7.9%, p<0.05).

In addition, we identified 15 cases of residual dissection, and 6 of them developed at the edge of the 188Re-filled balloon after IRT. The follow-up angiogram showed delayed healing of the residual dissections. The rate of target-vessel revascularization (TVR) was also significantly higher in patients with a residual dissection (53.5% in patients with dissections vs 15.7% in patients without dissections, p<0.05). Excluding all the TVRs associated with GM (6/22, 28.6%) and unhealed dissections (3/22, 13.6%), which could be avoided, the MACE rate was significantly decreased with radiation therapy (Fig 1). Late total occlusion was identified in 6 patients (6.1%, 6/98), and new additional stents were deployed in 5 of them. The mean duration of antiplatelet agent (clopidogrel or ticlopidine) use was 59 days, and 4 patients were prescribed an antiplatelet agent for 30 days post procedure.

Subgroup Analysis
In the radiation group, 49 patients (47.1%) underwent additional new stent implantation and the outcomes of irradiated patients were compared according to the event of additional stenting. The angiographic and clinical outcomes showed no significant difference between the 2 groups. In the subgroup of patients with restenotic lesions (n=39, 28 patients for radiation, 11 patients for control), the 188Re irradiation resulted in significant reduction of late loss and % diameter stenosis (Table 4). There was no cardiac death or myocardial infarct in either group, but TVR occurred in

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**Table 3 Clinical Events During Follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=83)</th>
<th>Radiation (n=104)</th>
<th>p value</th>
<th>Control (n=79)</th>
<th>Radiation (n=98)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVR</td>
<td>18 (21.7%)</td>
<td>15 (14.4%)</td>
<td>0.20</td>
<td>24 (30.4%)</td>
<td>22 (22.4%)</td>
<td>0.23</td>
</tr>
<tr>
<td>AMI</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>1 (2.4%)</td>
<td>1 (2.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.8%)</td>
<td>1 (1.0%)</td>
<td>NS</td>
<td>2 (2.5%)</td>
<td>1 (1.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>MACE</td>
<td>19 (22.9%)</td>
<td>16 (15.4%)</td>
<td>0.19</td>
<td>27 (34.2%)</td>
<td>24 (24.5%)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

TVR, target-vessel revascularization; AMI, acute myocardial infarction; MACE, major adverse cardiac events; F/U, follow-up.

**Fig 1.** Comparison of major adverse cardiac events (MACE) rate in each group at 9 months and 3 years. Excluding all cases of target-vessel revascularization (TVR) associated with geographic miss and unhealed dissections, the MACE rate was significantly decreased with radiation therapy. The MACE rate because of edge injuries during the radiation procedure had not decreased after 9 months, which suggests that edge failures might lead not only to short-term events, but also late adverse outcomes.
significantly higher than for patients without GM (14.3%, 25 patients, and the restenosis rate was 35.0%, which was GM and residual dissection. GM edges were identified in
the lesion site, but also the edge segment. Lack of clinical
benefit was mainly derived by edge restenosis caused by
the lesion site, but also the edge segment. Lack of clinical
IRT. To examine this discrepancy, we analyzed not only
the 1-year follow-up failed to show significant clinical benefit of
angiographic outcome at 9 months, but results from the 3-
limited. In the present study, we observed a favorable
outcomes in treating de novo or restenotic lesions, but data
regarding outcomes beyond the 1-year follow-up are
limited. In the present study, we observed a favorable
angiographic outcome at 9 months, but results from the 3-
year follow-up failed to show significant clinical benefit of
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benefit was mainly derived by edge restenosis caused by
GM and residual dissection. GM edges were identified in
25 patients, and the restenosis rate was 35.0%, which was
significantly higher than for patients without GM (14.3%,
p<0.05). GM is the main cause of the edge effect and is
caused by the combination of injury and low-dose radia-
ion. The adverse clinical outcomes of GM have been
described. In contrast, in the uninjured segment that
received radiation, there was positive remodeling that
favored late luminal gain. Therefore, it is usually recom-
mended that sufficient coverage of the lesion with radiation
might reduce a delayed adverse outcome, but when using
the 188Re-filled balloon system to deliver the radiation
dose, the possibility of edge injury caused by the radioiso-
tope-filled balloon should be considered. Dissections
following angioplasty were occasionally observed, but
previous studies verified that the presence of non-obstruc-
tive residual dissections was not associated with a poor
outcome. However, because radiation impairs the healing
process, the injury caused by the 188Re-filled balloon may
be related to late adverse outcome. We identified 15 cases
of residual dissection after IRT, and the TVR rate was sig-
nificantly higher in these patients. Late adverse outcomes
caused by GM and the edge injury induced by the isotopo-
entated balloon might be the reasons for the lack of radiation
benefit. Interestingly, we observed that the MACE because
of GM and residual dissection did not decrease after 9
months, which suggests that edge injury during radiation
procedure might lead not only to short-term events, but
also late adverse outcomes.

There are several reports that show the short-term safety and
efficacy of β-radiation using the 188Re-filled balloon system is safe and shows
favorable outcomes in treating restenotic lesions. The mechanisms of IRT are a reduction of smooth muscle prolif-
eration, the prevention of late contraction, and a delayed
healing response following vascular injury. IRT using
liquid β-emitting isotopes has several benefits compared
with solid sources. Radiation treatment can be adminis-
tered using the standard percutaneous transluminal coronary
angioplasty equipment. Because centering occurs automati-
cally after balloon inflation, complete source contact with the
vessel wall is guaranteed, irrespective of cardiac motion
and lesion morphology. Therefore, radial dosimetry is less
critical with the liquid radioisotope-filled balloon system.
Beta-radiation therapy produces a significant dose-depen-
dent decrease in the rate of restenosis after angioplasty
of de novo lesion and we designed our system to deliver
17.6 Gy to 1.0-mm tissue depth, which was the most effec-
tive dose in a previous study.

There are several reports that show the short-term safety and
efficacy of β-radiation using the 188Re-filled balloon system in treating de novo or restenotic lesions, but data
regarding outcomes beyond the 1-year follow-up are
limited. In the present study, we observed a favorable
angiographic outcome at 9 months, but results from the 3-
year follow-up failed to show significant clinical benefit of
IRT. To examine this discrepancy, we analyzed not only
the lesion site, but also the edge segment. Lack of clinical
benefit was mainly derived by edge restenosis caused by
GM and residual dissection. GM edges were identified in
25 patients, and the restenosis rate was 35.0%, which was
significantly higher than for patients without GM (14.3%,
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ion. The adverse clinical outcomes of GM have been
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entated balloon might be the reasons for the lack of radiation
benefit. Interestingly, we observed that the MACE because
of GM and residual dissection did not decrease after 9
months, which suggests that edge injury during radiation
procedure might lead not only to short-term events, but
also late adverse outcomes.

Late total occlusion because of thrombosis is mainly the
results of impaired re-endothelialization and the current
recommendation is prolonged antiplatelet regimen for
more than 12 months in stented patients undergoing radia-
tion therapy. In the early stages of the present study, the
patients who underwent stenting received double antiplatelet
regimen for only 4 weeks, but after we became aware of
the reports of late thrombosis and late adverse outcome of
new additional stent deployment, we used the antiplatelet
regimen for more than 6 months.

Subgroup analysis of the restenotic lesions showed sig-
ificant differences in the restenosis rate between the control
and treatment groups (14.3% vs. 41.7%, p<0.05). The
restenosis rate was significantly higher in the treatment
group. Late adverse outcomes caused by GM and the edge
injury induced by the isotope-filled balloon might be the
reasons for the lack of radiation benefit. Interestingly, we
observed that the MACE because of GM and residual
dissection did not decrease after 9 months, which suggests
that edge injury during radiation procedure might lead not
only to short-term events, but also late adverse outcomes.

Discussion

This study demonstrates that intracoronary β-radiation
using the 188Re-filled balloon system is safe and shows
favorable outcomes in treating restenotic lesions. The mechanisms of IRT are a reduction of smooth muscle prolif-
eration, the prevention of late contraction, and a delayed
healing response following vascular injury. IRT using
liquid β-emitting isotopes has several benefits compared
with solid sources. Radiation treatment can be adminis-
tered using the standard percutaneous transluminal coronary
angioplasty equipment. Because centering occurs automati-
cally after balloon inflation, complete source contact with the
vessel wall is guaranteed, irrespective of cardiac motion
and lesion morphology. Therefore, radial dosimetry is less
critical with the liquid radioisotope-filled balloon system.
Beta-radiation therapy produces a significant dose-depen-
dent decrease in the rate of restenosis after angioplasty
of de novo lesion and we designed our system to deliver
17.6 Gy to 1.0-mm tissue depth, which was the most effec-
tive dose in a previous study.

Table 4 Angiographic Analysis in the Restenotic Subgroup

<table>
<thead>
<tr>
<th>Lesion nature</th>
<th>Control (n=11)</th>
<th>Radiation (n=28)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon restenosis</td>
<td>2 (18.2%)</td>
<td>4 (14.3%)</td>
<td>0.77</td>
</tr>
<tr>
<td>In-stent restenosis (ISR)</td>
<td>9 (81.8%)</td>
<td>24 (85.7%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Classification of ISR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>4 (44.5%)</td>
<td>10 (41.7%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>2 (22.2%)</td>
<td>5 (20.8%)</td>
<td></td>
</tr>
<tr>
<td>Proliferative</td>
<td>2 (22.2%)</td>
<td>7 (29.2%)</td>
<td></td>
</tr>
<tr>
<td>Total occlusion</td>
<td>1 (11.1%)</td>
<td>2 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Lesion characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length (mm)</td>
<td>15.88±4.27</td>
<td>14.41±3.54</td>
<td>0.24</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>0.64±0.29</td>
<td>0.65±0.34</td>
<td>0.89</td>
</tr>
<tr>
<td>RD (mm)</td>
<td>2.80±0.31</td>
<td>2.80±0.31</td>
<td>0.96</td>
</tr>
<tr>
<td>DS (%)</td>
<td>70.0±24.81</td>
<td>74.8±17.50</td>
<td>0.85</td>
</tr>
<tr>
<td>Post-procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.28±0.26</td>
<td>2.36±0.39</td>
<td>0.82</td>
</tr>
<tr>
<td>RD (mm)</td>
<td>2.79±0.29</td>
<td>2.87±0.35</td>
<td>0.34</td>
</tr>
<tr>
<td>DS (%)</td>
<td>17.79±11.46</td>
<td>18.31±9.50</td>
<td>0.61</td>
</tr>
<tr>
<td>9 m angiographic F/U</td>
<td>9/11 (81.8%)</td>
<td>26/28 (92.9%)</td>
<td>0.31</td>
</tr>
<tr>
<td>9 m F/U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>1.37±0.56</td>
<td>2.11±0.51</td>
<td>0.002</td>
</tr>
<tr>
<td>RD (mm)</td>
<td>2.77±0.22</td>
<td>2.77±0.31</td>
<td>0.95</td>
</tr>
<tr>
<td>DS (%)</td>
<td>54.69±27.57</td>
<td>22.90±17.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late loss</td>
<td>1.08±0.76</td>
<td>0.24±0.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Restenosis</td>
<td>5 (55.6%)</td>
<td>2 (7.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MLD, minimal luminal diameter; RD, reference diameter; DS, diameter stenosis; F/U, follow-up.
nificant benefit of IRT and although the number of patients with a restenotic lesion was too small to suggest any clinical implications, further study to verify the role of IRT in treating diffuse ISR is warranted.

The potential risk of late adverse effects of radiation, as previously reported with the use of external radiation, should be taken into consideration and a long-term follow-up is imperative for assessing coronary aneurysms, perforation, and accelerated atherosclerosis. Regarding aneurysmal dilatation, we observed 3 cases of aneurysmal change on follow-up angiography that were related to residual dissection, without restenosis or an adverse clinical outcome. Considering the delayed healing process after the radiation, long-term follow-up is necessary.

Study Limitations

Because eligible patients were randomly assigned to the 2 treatment groups without stratification regarding the nature of the lesion, the proportion of patients with restenotic lesions was significantly higher in the radiation group. The outcome of a restenotic lesion is known to be inferior to that of a de novo lesion and this difference might affect late clinical outcome.

Conclusion

IRT using the $^{188}$Re-filled balloon system is safe, technically feasible, and reduces the 9-month restenosis rate. The clinical benefits in restenotic lesions were maintained at 3 years without new adverse effects related to the radiation therapy. Furthermore, preventing GM and additional injury leading to dissection might improve long-term clinical outcomes.

Acknowledgments

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References


