Limitations and Long Term Outcome of Intracoronary Radiation Therapy With Catheter Based Systems and Radioactive Stents

Georgios Sianos
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Limitations and Long Term Outcome of Intracoronary Radiation Therapy With Catheter Based Systems and Radioactive Stents

Beperkingen en lange termijn resultaten van intracoronaire bestralingstherapie met catheterbronnen en radioactieve stents

Thesis

to obtain the degree of Doctor from the Erasmus University Rotterdam by command of the Rector Magnificus

Prof.dr.ir. J.H. van Bemmel

and according to the decision of the Doctorate Board The public defence shall be held on

Wednesday 24 September 2003 at 15.45 hrs

by

Georgios Sianos

born at Kastoria, Greece
Doctoral Committee

Promoters
Prof.dr. P.W. Serruys
Prof.dr. P.J. de Feyter

Other members
Prof.dr. J.R.T.C. Roelandt
Prof.dr. M.L. Simoons
Prof.dr. J.J. Piek

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For Eleni
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Chapter 9  Sianos G, Wijns W, de Feyter PJ, van Domburg R, Serruys PW. 

The black hole

The black hole: echolucent tissue observed following intracoronary radiation. International Journal of Cardiovascular Interventions, in press.

Long term outcome after brachytherapy

Long-term outcome following intracoronary beta-radiation therapy. Submitted for publication.

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Late-late occlusion after intracoronary brachytherapy. Circulation, in press

Predictors, Incidence and Prognosis of Coronary occlusion following intracoronary beta-radiation therapy Submitted for publication.
Treatment and long term outcome of radiation failures

Long term outcome of percutaneous interventions following failed beta-brachytherapy.
Submitted for publication.

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Part II  Radioactive stents

The pattern of restenosis and vascular remodelling after cold-end radioactive stent implantation.

Radioactive stents delay but do not prevent in-stent neointimal hyperplasia.

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Acknowledgements
CHAPTER 1

Introduction and Outline
Balloon angioplasty was the first non-surgical therapeutic modality for coronary artery disease introduced in 1977. It was related with high rates of acute complications and restenosis that limited its application to a minority of patients with coronary artery disease with relatively simple lesion morphology. Continuous developments during the next decade led to the introduction of stents in 1986. They were proven extremely efficient in reducing acute complications, dramatically expanding the indications for percutaneous interventions. In addition they were associated with favourable outcome in reducing restenosis compared to balloon angioplasty but they were also limited by the development of in-stent restenosis. In-stent restenosis remained a therapeutic challenge for almost a decade and many mechanistic and pharmacological attempts failed to solve it. Ionic forms of radiation (radioactive stents and localised catheter based intracoronary radiation therapy) were introduced. Radioactive stents showed no benefit compared to conventional stenting. However intracoronary brachytherapy, which was first applied in human coronaries in 1995, was proven effective for the treatment of in-stent restenosis (secondary prevention of restenosis). Its efficiency for treatment of de novo lesions (primary prevention of restenosis) especially in combination with the use of stents is limited. In 2001 drug eluting stents were introduced into clinical practice and they revolutionised the treatment of coronary artery disease. They are the first therapeutic modality in interventional cardiology expected to show equal or superior results in comparison to coronary artery by pass surgery.

In Europe were conducted the majority of the human trials with radioactive stents and pioneering and exploratory studies with intracoronary radiotherapy with catheter based systems mainly with beta emitters for de-novo lesions. This thesis addresses issues central to both of these therapeutic modalities.

It consists of two parts:

Chapter 1 Is the introduction and overview of the thesis.

In Part I (chapters 2-15) we present our experience with intracoronary radiation therapy with catheter based systems.

Chapter 2 Is an introduction to the principles of radiation and summarises our and the international experience with this therapeutic modality.

Chapter 3 Describes the developments in Quantitative Coronary Angiography necessary to describe the implications of edge restenosis and relocation of the minimal luminal diameter observed after intracoronary radiation therapy which occurs in a significantly higher incidence compared to standard techniques.

Chapter 4 Reports on our initial experience with intracoronary radiation therapy with the Beta Radiation In Europe registry. This was the registry that introduced brachytherapy in Europe. Both the problems of edge restenosis and late vessel occlusion became evident in this registry. The sponsoring company organised a randomised trial in USA without waiting for the results of this registry which resulted in the negative Beta-Cath trial.

Chapter 5 Is a case report describing the application of beta radiation under challenging anatomical conditions.
Chapter 6 Summarises our experience and the outcome of unselected patients treated with intracoronary radiation therapy in a routine fashion (RENO registry).

Chapter 7 Is a detailed angiographic analysis of patients enrolled in the BRIE registry with focus on the concept of geographical miss. We found a strong association with geographical miss and edge restenosis.

Chapter 8 The same angiographic analysis described in the previous chapter was performed in patients treated according to the protocol of the Dose Finding study. No association between geographical miss and edge restenosis was documented in this study.

Chapter 9 Summarises the differences between the BRIE and Dose Finding studies explaining the differential outcome in relation to geographical miss and gives a final answer for its strong association not only with edge restenosis but also with the overall angiographic outcome of patients treated with beta radiation therapy.

Chapter 10 Describes the intravascular ultrasound finding of the “black hole”, an echo lucent tissue, as a limitation of intracoronary brachytherapy.

Chapter 11 Describes the unfavourable long term outcome of patients treated with intracoronary beta radiation therapy in our institution.

Chapter 12 Is a case report describing a total occlusion 5 years after intracoronary brachytherapy in a patient treated according to the BERT protocol.

Chapter 13 Reports on the high incidence of late total occlusion observed after intracoronary beta radiation therapy and the unfavourable clinical outcome of these patients. Late silent or thrombotic occlusion remains the main and unfortunately unresolved limitation of brachytherapy.

Chapter 14 Describes the long term clinical outcome of patients treated with percutaneous interventions after brachytherapy failure.

Chapter 15 Reports on the modest efficiency of sirolimus eluting stents to treat brachytherapy failures in a small cohort of patients.

In Part II (chapters 16-18) we present our experience with radioactive stents.

Chapter 16 Is an intravascular ultrasound analysis that unravels the mechanism of restenosis after cold-end radioactive implantation, a modification that failed to eliminate the problem of edge restenosis observed after conventional radioactive stents.

Chapter 17 Reports on the mid term outcome of patients after radioactive stent implantation and the problem of delayed restenosis observed with this therapeutic modality.

Chapter 18 Presents the long term outcome of patients after radioactive stent implantation which despite the early failure of this treatment is not associated with long term irreversible sequelae.

Chapter 19 Summarises the thesis and quotes the conclusions
CHAPTER 2


Intracoronary Radiation Therapy

Intracoronary Radiation Therapy

Georgios Sianos*, Willem van der Giessen, Pim de Feyter, Peter Smits, Sjoerd Hofma, Eugene Mc Fadden, Patrick W Serruys

* Erasmus MC, Thoraxcenter, Rotterdam, The Netherlands
Introduction

Following coronary balloon angioplasty, restenosis of the dilated segment occurs in 30% to 50% of patients and results from elastic recoil, neointima formation, and negative remodelling\(^1\)\(^-\)\(^2\). The advent of coronary stenting reduced restenosis to 15% in certain type of lesions\(^3\)\(^-\)\(^4\), but introduced the even more difficult to treat in-stent restenosis\(^5\). Brachytherapy has been introduced as a promising technique for primary and secondary prevention of restenosis.

Most of the randomized clinical trials were conducted in the U.S.A. In Europe, experience has been gained with beta-radiation with pilot studies and registries, while gamma radiation has been used in a few centers and few patients. Important reasons are the strict regulatory requirements regarding shielding, storage and transportation of these sources.

A number of points have become evident in coronary application of radiation. First, radioactive stents do not show overall beneficial therapeutic effect. Second, beta-radiation therapy seems to be as effective as gamma in the mid-term follow-up. Third, vascular brachytherapy is effective for the treatment of in-stent restenosis, but its effectiveness in de novo lesions with new stent implantation is ambiguous. For the coming years, the questions regarding the duration of anti-thrombotic treatment, the long-term outcome and the benefit in de-novo lesions in patients at very high risk for restenosis have to be answered. This chapter summarizes the clinical experience and gives an overview of the current practice.

Definition

Brachytherapy is derived from the Greek “\(\beta\)ραχυ ἄρεν” (brachy) meaning short and “\(θέραπευτικός\)” (therapy) meaning treatment to describe the application of radioactivity by a sealed source at a very short distance to the target tissue, e.g. by intracavitary or interstitial source placement. Recently, the term vascular brachytherapy has been introduced to describe endovascular radiation therapy.

Rationale

Radiotherapy has been proven successful in the treatment of hypertrophic scars, keloids\(^6\), ophthalmic pterygia\(^7\), heterotopic bone formation\(^8\) and solid malignancies\(^8\). In non-malignant diseases, radiation inhibits efficiently fibroblastic activity, without influencing the normal healing process, and without causing significant morbidity during long term follow-up of up to 20 years. Brachytherapy has the physical benefit that very high doses of radiation can be delivered directly or almost directly to the target.

Basic radiation physics

Radioactivity

Radioactivity is the spontaneous process in which an unstable nucleus, which has either too many or too few neutrons, turns to a stable state (ground state) whereby superfluous energy is released. The release of energy is called radiation, which can be in the form of electromagnetic waves, like gamma radiation, or of particle rays, like alpha, beta and neutron rays. This process is often called the “disintegration” of an atom.

The activity (\(A\)) can be expressed by the quotient of the number of disintegrations (\(dN\)) within a time interval (\(dt\)).

\[
A = -\frac{dN}{dt}
\]

with the unit bequerel (Bq) according to the international system (SI) for units. This unit replaces the formerly used unit curie (Ci) whereby 1 Ci = 37 \(\times\) \(10^{10}\) Bq.

Decay

For most atoms the activity is proportional to the number of nuclei (\(A = \lambda N\)). The proportionality constant is called the decay constant. This leads to the decay law: \(A = A_0 \exp(-\lambda t)\), and \(\lambda = \ln 2 / T_{1/2}\) whereby \(T_{1/2}\) is called the "physical half-life time", being the time that the original activity of a nuclide has been reduced with a factor two. The physical half-life time is characteristic for nuclids (distinct nuclear species) and isotopes (various forms of an element).

Biological half-life

Biological half-life is used for the time needed by the body to eliminate one-half of an administered amount of any substance by regular process of elimination. This time is approximately the same for both, stable and unstable isotopes of the same element.

Effective half-life

In case radioactive material is ingested in the human body, both, physical and biological half-live, have to be considered. Combination of both half-lives gives the effective half-life, which can be expressed by \(1 / T_{1/2,\text{eff}} = 1 / T_{1/2,\text{phy}} + 1 / T_{1/2,\text{biol}}\). Half-lives can be replaced by the physical and biological decay constants: \(\lambda_{\text{eff}} = \lambda_{\text{phy}} + \lambda_{\text{biol}}\).

Absorption - radiation dose

The released energy during transformation of an unstable atom into a stable atom is absorbed in tissue. The quantity of absorbed energy in a tissue is called the “dose” with the SI unit Gray (\(\text{Gy} = 1 \text{ J/kg}\)). The dose is strongly dependent of the type of radiation (activity and decay) and the time span, also called “dwell time”.
**Radiation dose rate**

Dose rate is the dose of radiation per time (delivered or received). The dose rate delivered by a source depends on the activity of the source and the radionuclide that it contains. Currently, all vascular brachytherapy sources deliver energy at high dose rate.

**Dose**

Biological effects of the absorbed radiation are dependent on the type of radiation and the type of tissue, which is irradiated. The unit of the dose is joules per kilogram (Jkg⁻¹) and is called Sievert (Sv).

**Radiation weighting factor \( (WR) \)**

A correction factor that indicates the harmfulness of the type of radiation involved.

**Tissue weighting factor \( (WT) \)**

The tissue-weighting factor indicates the sensitivity of an organ/tissue to radiation.

**Equivalent dose \( (H_E) \)**

The equivalent dose is a quantity used for radiation protection purposes. It takes into account the probability of effects. It is defined as the product of the averaged absorbed dose in a specified organ or tissue \( (D_I) \) and the radiation-weighting factor \( (WR) \):

\[ H_E = WR \times D_I. \]

**Effective dose \( (HE) \)**

The sum of the products of the equivalent dose to the organ or tissue \( (H_E) \) and the tissue weighting factor \( (WT) \) applicable to each of the body organs or tissue that are irradiated:

\[ HE = \sum WRWTDI. \]

**Isodose**

Descriptive of a locus at every point of which the absorbed dose is the same.

**Isotopes**

The most important physical properties of currently used isotopes in vascular brachytherapy are listed below:

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Emission</th>
<th>Max. Energy</th>
<th>Av. Energy</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>192Ir</td>
<td>gamma</td>
<td>612 keV</td>
<td>375 keV</td>
<td>74 days</td>
</tr>
<tr>
<td>90Sr/90Y</td>
<td>beta</td>
<td>2270 keV</td>
<td>565 keV</td>
<td>28 years</td>
</tr>
<tr>
<td>32P</td>
<td>beta</td>
<td>1710 keV</td>
<td>690 keV</td>
<td>14 days</td>
</tr>
<tr>
<td>90Y</td>
<td>beta</td>
<td>2270 keV</td>
<td>970 keV</td>
<td>64 hours</td>
</tr>
<tr>
<td>188Re</td>
<td>beta</td>
<td>2130 keV</td>
<td>780 keV</td>
<td>69 days</td>
</tr>
</tbody>
</table>

Other potential candidates are the following:

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Emission</th>
<th>Max. Energy</th>
<th>Av. Energy</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>106Rh</td>
<td>beta</td>
<td>923 keV</td>
<td>307 keV</td>
<td>2.2 hours</td>
</tr>
<tr>
<td>48V</td>
<td>positron</td>
<td>696 keV</td>
<td>144 keV</td>
<td>16 days</td>
</tr>
<tr>
<td>125I</td>
<td>X-ray</td>
<td>35 keV</td>
<td>28 keV</td>
<td>60 days</td>
</tr>
<tr>
<td>103Pd</td>
<td>X-ray</td>
<td>21 keV</td>
<td>21 keV</td>
<td>19 days</td>
</tr>
</tbody>
</table>

These isotopes show important physical differences. Basically, gamma radiation consists of photons, beta radiation of electrons.

**Gamma radiation**

Gamma rays are photons originating from the nucleus of a radionuclide, which take the form of electromagnetic radiation. A heavy unstable nucleus will emit an alpha (heavyweight charged particle, which can travel only very short distances within tissues) or beta particle followed by gamma radiation. Gamma rays may have either 1 or 2 discrete energy values or a broad spectrum of many energy values. They penetrate deeply within tissues.

**X-ray radiation**

X-rays are comparable to gamma radiation. Their physical characteristics are similar, however, their origin is different. While the photons of gamma radiation originate from the nucleus, the photons of x-rays originate from the electron orbit. X-rays used in catheterization laboratories have an energy level of maximal 125 kVp.

**Beta radiation**

Beta particles are lightweight high-energy electrons, with either positive or negative charge. When beta particles, which can travel only finite distances within tissues, are slowed down by nuclei interactions, they give rise to high penetration X-rays, called Bremsstrahlung.

**Major differences between gamma and beta radiation**

The interaction of photons with other material is much lower than the interactions with electrons. That means, the energy transfer to other material is less intensive for gamma than for beta radiation. In the setting of brachytherapy, this has two major consequences.

1. **Dwell time**: to obtain a defined dose in a tissue at a certain distance from a source, gamma sources require much higher activities or much longer dwell times in comparison to beta sources.

2. **Radiation exposure**: the exposure to the staff inside and outside the catheteri-
zation laboratory is much higher during treatment with gamma radiation than beta radiation. In consequence, staff should leave the catheterization laboratory during radiation treatment and additional shielding facilities have to be implemented.

The clinically and practically most relevant advantages and disadvantages are as follows:

**Gamma radiation**

**Pro’s:**
- Deep tissue penetration (ideal for large vessel diameters)
- No attenuation of Ir-192 gamma radiation by stent struts (ideal for in-stent restenosis)

**Con’s:**
- Extensive shielding required (25mm lead)
- High radiation exposure for patient and staff
- Staff has to leave catheterization laboratory
- Long dwell times (8-20 min)

**Beta radiation**

**Pro’s:**
- Simple shielding by means of thick plastics
- Short dwell times (3-10 min)
- Radiation exposure to the patient only local
- Radiation exposure to staff is negligible
- Staff can remain in the catheterization laboratory

**Con’s:**
- Probable not able to treat vessels with diameters >4 mm (with existing devices)
- Inhomogeneity of the dose (potentially centering device required)
- Partially shielded by stents and calcified plaques
- Dose distribution calculations of beta emitters are more complicated.

**Mechanisms of action**

**Cell biological effects**

Absorbed radiation can cause damage in a tissue either directly by ionization or indirectly by interacting with other molecules to produce free radicals, which will subsequently damage the critical target. Approximately 80% of the radiation damage is caused by these free radicals. The most critical target is DNA. In consequence, early and late toxic effects in normal tissue are mainly caused by cell death.

These biological effects are independent of the radiation type (gamma, beta or X-rays) whereas total radiation dose and dose rate are of major importance, since damage caused by radiation can be repaired between fractionated doses or during low dose rate exposure. Furthermore, there seems also to be an inverse dose rate effect in human cells most probably by blocking cells in the mitosis (G2) phase of the cell cycle at low dose rate (approx. 6 mGy/min), which is known to be more radiosensitive, thereby causing more cell death.

Experiments with human cells addressed long-term effects of radiation. Human aortic cells show a significant decrease in their clonogenic potential after radiation. Modulation of the subsequent repopulation of the surviving cells under the assumption that the repopulation kinetics were similar to those in non-irradiated cells, revealed a delay by factors of approximately 6 to 8. This would shift the time to restenosis from a median of 6 months in non-irradiated cells to median values from 36 months (for 13 GY) to 43 month (for 15 Gy).

**Experimental data**

In injured vascular tissue, radiation doses of 12-20 GY appear to be efficacious in inhibiting neointimal formation in various animal restenosis models. The local mechanisms of action and time course are complex, dose dependent and poorly understood. Possible high dose radiation effects include an anti-angiogenic effect and decrease of smooth muscle cells on the adventitia, selective inactivation of smooth muscle cells and myofibroblasts, or complete elimination of their proliferative capacity at doses >20 Gy. Application of lower dose could mean that restenosis would only be delayed for the period of time necessary for the population of smooth muscle cells to regenerate.

Furthermore, low dose radiation even promotes cellular growth. Low dose radiation (±2 Gy) has been shown to potentiate cellular metabolic activities and hormesis (immunologic response) in various tissues (splenocytes, thymocytes, macrophages and hematopoietic cells). Furthermore, in experimental studies of endovascular brachytherapy it was shown that relatively low-doses (±10 Gy) caused a paradoxical increase in tissue response.

Long-term experiments in normal porcine coronary arteries after balloon injury and beta radiation showed that neointima formation is not inhibited at 6-month follow-up. Un-resorbed thrombus was an important contributor of augmented neointima formation. The adventitia showed thickening with substantial collagen accumulation. Fatal subacute and late thrombosis was seen at 5 days, 7 days, 3 months and 4 months after the index procedure. The animals had received the combination of aspirin and ticlopidin for 30 days after the index procedure and continued aspirin therapy until sacrifice.
In a balloon injury porcine restenosis model intracoronary radiation was related with increased thrombogenicity in a dose-dependent manner. This was more often a non-obstructive non luminal thrombus rather than an luminal thrombus and its morphology appeared to be less organized than the pattern of thrombosis observed in non irradiated injured arteries indicating that might not related with compromise the of the lumen volume.

In a porcine model, balloon injury and intracoronary radiation therapy altered the passive mechanical properties of the arterial wall. Furthermore, receptor operated release of endothelium-derived nitric oxide and endothelial hyperpolarising factor were reduced by brachytherapy and injury alone and completely prevented by their combination. In a rat model endothelial function was found to be impaired up to six months after irradiation without concomitant injury.

There is increased evidence in animal models that radiation is related with delayed and incomplete endothelialisation and that the new endothelium might be dysfunctional. An example is given in figure 1.

**Clinical trials**

Over the last years, radiation has been applied in various ways to human coronary arteries, using different sources and mode of applications. This includes catheter-based line sources, radioactive stents, radioactive wires, liquid filled balloons. The latter have been used in few patients only, whereas there is considerable clinical experience with catheter-based line sources and radioactive stents.

**Catheter-based line sources**

Clinical trials (Figure 2) have been completed for both, gamma (Table 1) and beta radiation (Table 2), and for different lesion types.
### Table 1. Results of gamma radiation trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No pts</th>
<th>Dose (Gy)</th>
<th>Lesion length</th>
<th>Source</th>
<th>Restenosis rate</th>
<th>MACE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCRIPPS</td>
<td>53</td>
<td>8-30*</td>
<td>&lt;30</td>
<td>Ir-192</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>WRIST-gamma</td>
<td>130</td>
<td>15**</td>
<td>&lt;47</td>
<td>Ir-192</td>
<td>22</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>Long WRIST</td>
<td>120</td>
<td>15**</td>
<td>36-80</td>
<td>Ir-192</td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>Long WRIST HD</td>
<td>120</td>
<td>18***</td>
<td>36-80</td>
<td>Ir-192</td>
<td>N/A</td>
<td>23 (1m plavix)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 (6m plavix)</td>
</tr>
<tr>
<td>SVG WRIST</td>
<td>120</td>
<td>14-15***</td>
<td>&lt;47</td>
<td>Ir-192</td>
<td>21</td>
<td>32</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>44</td>
<td>63</td>
</tr>
<tr>
<td>WRSST PLUS</td>
<td>120</td>
<td>14**</td>
<td>&lt;80</td>
<td>Ir-192</td>
<td>34</td>
<td>23 at 6m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.8 at 15m</td>
</tr>
<tr>
<td>WRSST 12</td>
<td>120</td>
<td>14</td>
<td>&lt;80</td>
<td>Ir-192</td>
<td>N/A</td>
<td>13.4 at 6m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.8 at 15m</td>
</tr>
<tr>
<td>GAMMA-1</td>
<td>252</td>
<td>8-30*</td>
<td>&lt;45</td>
<td>Ir-192</td>
<td>33</td>
<td>28</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>55</td>
<td>44</td>
</tr>
<tr>
<td>GAMMA-2</td>
<td>125</td>
<td>14**</td>
<td>&lt;45</td>
<td>Ir-192</td>
<td>34</td>
<td>30</td>
</tr>
</tbody>
</table>

MACE = major adverse cardiac events, N/A = not available, No pts = number of patients, *to the external elastic membrane, **at 2 mm from the source, ***at 2-2.4 mm from the source depending on the vessel size.

### Table 2. Results of beta radiation trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No pts</th>
<th>Dose (Gy)</th>
<th>Lesion length</th>
<th>Source</th>
<th>Restenosis rate %</th>
<th>MACE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geneva</td>
<td>15</td>
<td>18*</td>
<td>&lt;20</td>
<td>Y-90</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>BERT</td>
<td>20</td>
<td>12,14,16**</td>
<td>&lt;15</td>
<td>Sr/Y 90</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>BERT 1.5</td>
<td>35</td>
<td>12,14,16**</td>
<td>&lt;20</td>
<td>Sr/Y 90</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>BRIE</td>
<td>149</td>
<td>14**</td>
<td>&lt;22</td>
<td>Sr/Y 90</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Dose Finding</td>
<td>181</td>
<td>9,12,15,18†</td>
<td>&lt;15</td>
<td>Y-90-9Gy all</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td></td>
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<td>P-32</td>
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MACE = major adverse cardiac events, N/A = not available, No pts = number of patients, *at the inner arterial surface, **at 2 mm from the source, †at 1mm from the balloon, ‡at 1mm into the vessel wall, +control group from gamma-WRIST.
Safety and feasibility studies

Human coronary arteries were treated for the first time by Condado in 1995 in Venezuela. De novo lesions where treated by balloon angioplasty followed by gamma-radiation (Ir 192). No restenosis was observed after 6 months. The GRANITE registry is the only multicenter gamma radiation trial conducted in Europe. A low-dose iridium-192 source was used in patients undergoing percutaneous revascularization for in-stent restenosis. At six month, event-free survival was 70%, the angiographic restenosis rate 32%. Three-year follow-up is pending.

In 1997, Verin reported the feasibility of beta sources after balloon angioplasty. The BERT trial used beta-radiation (90Sr/90Y) in 23 patients after successful balloon angioplasty. Follow-up quantitative coronary angiography at 6 month showed a late loss of 0.05mm and a restenosis rate of 15%. BRIE was the registry that introduced beta radiation in Europe. In total 149 patients were enrolled and received 14 Gy at 2mm from the source with restenosis rate of 34% and MACE of 34%. It was one of the first trials who unravelled the problem of edge restenosis and correlated it with the geographical miss. BRITE was the safety and feasibility study with the beta emitting, P-32 balloon source for in-stent restenosis; 32 patients received 20 Gy with very low restenosis rate (9.7%) and MACE (3%)41.

Efficacy trials

Randomized, double blind, placebo-controlled trials or non randomised trials using for comparison the placebo arms of comparable randomised trials, have been completed for both gamma and beta radiation, and for different lesion types (Figure 3).

Gamma radiation trials

The SCRIPPS trial demonstrated first the effectiveness of 192-Ir gamma therapy for the treatment of de-novo and in-stent restenotic lesions in 55 randomized patients. The gamma-WRIST was the first randomised trial (130 patients) with gamma radiation for in-stent restenosis; the irradiated patients had improved angiographic and clinical outcome. The GAMMA-1 multi-center randomised trial (252 patients), with IVUS based dosimetry reconfirmed the beneficial effect of gamma radiation in the treatment of in stent restenosis, but it was limited by the high incidence of stent thrombosis, 5.3%. The GAMMA-2 trial with simpler no IVUS based dosimetry gave the same good results as the GAMMA-1 trial. The efficacy of gamma radiation for the treatment of long restenotic lesions (up to 80 mm) was confirmed in the LONG WRIST randomised trial, but a very high incidence of 15% late total occlusion was observed. The higher dose and the prolonged antiplatelet treatment prescribed in the LONG WRIST high dose registry, further improved the angiographic parameters and eliminated the problem of the late thrombosis and occlusion. The efficacy of gamma radiation for the treatment of in-stent restenosis in the vein-grafts was proved the SVG-WRIST randomised trial.

Beta radiation trials

- **De novo lesions**
  
  The PREVENT trial used a centered beta-emitting (32) P source wire. Patients with de novo or restenotic lesions received 0 (control), 16, 20, or 24 Gy. The clinical and angiographic outcome was better in the irradiated patients.

  In the Dose Finding study 181 patients randomly assigned to receive 9, 12, 15, 18 Gy at 1mm from the centering balloon
surface. Restenosis was reduced in a dose related manner with better angiographic outcome for the patients received the higher dose. An important observation was that patients treated with balloon angioplasty alone had the best outcome with a restenosis rate of 3.9% at 16 Gy. The Beta-cath trial was the largest randomised trial of beta-radiation for de-novo lesions (1455 patients). It failed to show any difference in the primary end point, the target vessel failure, in the combined radiation arms compared to the placebo arms. In the balloon group the reduction in binary restenosis observed with radiation in the lesion segment was not maintained in the vessel segment analysis. Even worse in the stent group the significant reduction in the stented segment inverted to a significant increment in the analysis segment with worse outcome in the radiation group. The late vessels thrombosis, the edge restenosis and the incompatibility of radiation with the use of stent for de novo lesions were the main lessons learned from this negative study.

In the multicenter BRIDGE randomized the concept of direct stenting followed by irradiation in combination with IIb-IIIa antagonists and prolonged antiplatelet up to 11 months was addressed, aiming to eliminate the two major problems of the combination of radiation with stenting; the edge restenosis and the late vessel occlusion/thrombosis. In total 112 patients randomised and 56 received 20Gy at 1mm in the vessel wall with a centred P-32 wire. The restenosis rate was 9% (15% in the control group) without edge restenosis but the problem of late thrombosis was not solved (10% in the radiation group).

- In stent restenosis
  
The beta-WRIST registry examined the beta-emitter 90-yttrium for the prevention of recurrent in-stent restenosis in 50 consecutive patients, which underwent PTCA, laser angioplasty, rotational atherectomy, and/or stent implantation followed by radiation with a 90-yttrium centered source. At 6 months, the binary angiographic restenosis rate was 34%, the target vessel revascularization rate and MACE were 34%. The START 30 trial was a multicenter randomized, placebo-controlled, trial, with the Beta-Cath System using Sr-90 in 476 patients with recurrent ISR following successful coronary intervention. The restenosis rate within the vessel segment was reduced by 36%, MACE was reduced by 31%; target vessel revascularization was reduced by 34%. The positive results observed in the START 30 were confirmed in the START 40 registry with the longer source.
  
The INHIBIT was the randomised trial used a centered P-32 beta emitting source for the treatment of in-stent restenosis; 332 patients received 20 Gy. Significant reduction in the restenosis rate and the MACE was observed.

Routine use registries

The RENO registry is a large post marketing surveillance registry. At 47 centers in Europe and Israel 1032 patients were prospectively included for treatment with standard angioplasty (balloon, stent, laser, rotational and/or directional atherectomy) followed by beta-radiation therapy (90-Sr/Y source). At 6-month follow-up, the MACE rate was 18.7% (with 1.9% death, 2.6% AMI (Q or non-Q), 16.3% target vessel revascularization) and the composite endpoint of late thrombosis 5.4%.

Clinical observations

Positive vessel remodelling

Balloon angioplasty followed by irradiation predominantly shows an increase in minimal lumen diameter at the treated segment at follow-up. This is in contrast to standard balloon angioplasty, where late lumen loss caused by neointimal growth and vessel shrinkage is the usual response. Irradiation inhibits neointimal growth, may prevent shrinkage after balloon angioplasty and even promote positive remodelling at the treated segments. Promotion of positive vessel remodelling is dose dependent and has been well documented with IVUS observations indicating increment of the total vessel volume and subsequently the lumen.

Late stent malapposition

The positive remodelling and tissue erosion around a previously well deployed stent combined with irradiation, will lead to late stent malapposition with blood flow behind the struts. An example is presented in figure 4.

Persistent dissections

Healing is the natural history of post-angioplasty dissections. Radiation appears to change the normal healing process resulting in unhealed dissection. An incidence of 40% persistent dissections has been reported at 6 months after irradiation.

Late occlusion

Early in the clinical phase, a new phenomenon became apparent, that of late occlusion. Possibly causes are increased thrombogenicity, delayed endothelialisation, persistent dissections, late stent malapposition. There are two forms depending on the clinical presentation:

a. Late total occlusion, usually asymptomatic, related with accelerated formation of restenotic tissue (figure 5).

b. Late thrombotic occlusion, always related with related with acute thrombosis leading to an acute coronary syndrome.
An overview of the incidence of late occlusion/thrombosis in various clinical trials is presented in figure 6. Initial clinical trials prescribed a combined antithrombotic treatment (aspirin and clopidogrel or ticlopidin) of 2 or 4 weeks after the index procedure. The first observation was that most of the acute events were presenting after discontinuation of the double antiplatelet treatment. In consequence, prolonged combined antithrombotic treatment was recommended. Two trials addressed the issue of prolonged antiplatelet treatment for the prevention of late occlusion/thrombosis. In the WRIST PLUS12 trial clopidogrel and aspirin were prescribed for 6 months and in the WRIST 12th for 12 months. Both showed
good results at 6 months follow up, but at 15 months the incidence of occlusion/thrombotic rates were unacceptably high; 15.9% in the WRIST PLUS and 13.5% in the WRIST 12. The second observation was that new stent implantation was related with late thrombosis both for de novo and restenotic lesions. Therefore at least for the treatment of in-stent restenosis it is recommended to be avoided.

The evolving clinical important question is the duration of platelet inhibition and whether or when to stop clopidogrel prescription. Current data suggest that combined anti-thrombotic medication for 12 months might be inadequate and probably should be prescribed indefinitely following intracoronary radiation treatment.

**Edge restenosis and geographical miss**

Restenosis at the edges of the irradiated segment is the second major limitation of brachytherapy. It was first described after radioactive stent implantation named as "candy wrapper" or "edge effect". An example after catheter based beta radiation is presented in Figure 7. In almost all the brachytherapy trials reported, there is a 10-15% increment in the restenosis rate observed between the segment that received radiation and the total analysed segment. This was a new phenomenon in interventional cardiology, the edge restenosis, and changed the way we interpret and report the results of brachytherapy trials in comparison with historical trials. By IVUS, edge restenosis, is
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a combination of increase in plaque volume without adaptive remodelling.

In concordance with known cell biological effects and animal data, low dose radiation at the extremities of the source and angioplasty induced vessel injury, referred as "geographical miss" seems to play a key role in edge restenosis and treatment failure for beta and gamma brachytherapy (figure 8). This is confirmed by experimental studies which could demonstrate that the edge effect is associated with the combination of periprocedural vessel injury and radioactive dose fall-off at the extremities of the source. The fall-off dose at the source edges is a inherent characteristic of all the sources, beta or gamma, and must be taken into account during application of radiation (figure 9).

Safety margins

The safety margins after brachytherapy for avoidance of geographical miss and subsequently edge restenosis have not yet been defined. Many factors such as the extent of the perivascular injury, which can extend up to 10 mm away from the microscopic injury, the barotrauma caused by the balloons which can be up to 2.5 mm away from the actual stent margins, the source displacement during the cardiac cycle (up to 5.4 mm) and the fall-off dose at the margins of each source must be taken into account.

It was proposed that for an 18 mm lesion treated with a 20 mm balloon, a 39 mm Iridium source should be used. In an animal model a safety margin of 14.5 mm was sufficient to eliminate edge restenosis. Recently a 10 mm safety margin per vessel found to have 95% specificity for avoidance of GM. As a general simple rule a ratio of one to two for the lesion to source length is advised. The availability of longer sources and stepping application of radiation will help for the elimination of geographical miss. In recently conducted trials such as the BRIDGE and BRITE in which the problem was known and prevented by protocol, edge restenosis was not an issue.

Beta versus gamma radiation: efficacy, impact of vessel size, lesion length and failure modes.

From meta-analysis of trials for in-stent restenosis the following have been observed:

a. Gamma and beta radiation have similar efficacy at dose tested in clinical trials. Beta radiation is more effective for inhibiting restenosis in the stent but it is associated with greater incidence of edge failures (figure 10).

b. When failing, both modalities change the pattern of restenosis at more focal lesions. The more diffuse the lesion is at baseline the greater the reduction of lesion length at follow up.

c. Gamma brachytherapy appears to have a consistent treatment effect at all vessel sizes and lesion lengths.

d. Beta brachytherapy appears to have greater treatment effect the larger the vessel size and the longer the baseline lesion length.
Long-term outcome

Progressively, long-term follow-up data of patients, which had received intracoronary brachytherapy, are becoming available. Major concerns are possible late catch-up with increased lumen loss at the treatment site, delayed restenosis and delayed major adverse clinical events.

The three-year follow-up of the SCRIPPS trial demonstrated a decrease in mean minimal luminal diameter between 6 months and 3 years from 2.49±0.81 mm to 2.12±0.73 mm in the irradiated patients, whereas the minimal lumen diameter was unchanged in placebo patients. This angiographic finding, however, was not associated with clinical events. The target-lesion revascularization was significantly lower in the 192Ir group (15.4% versus 48.3%) as was the restenosis rate (33% versus 64%)87. At five years follow up of the same study the target lesion revascularisation increased to 23.1% in the irradiated patients while remained unchanged in the placebo group and there was no more difference between the two groups in any revascularisation or the composite end point of death, myocardial infarction of target vessel revascularisation88.

A two-year follow-up is available of the 192Ir WRIST and BETA-WRIST patients. Irradiated patients had significantly lower rates of target vessel revascularizations than the placebo WRIST patients at 2 years. Beta and gamma radiation were independent predictors of event-free survival at 2 years. However, between 6 months to 2 years, significant rates of target vessel revascularization (14%) were noted in both radiation groups, yet no revascularization was required in placebo WRIST patients (p <0.05)89.

We followed 302 patients treated with brachytherapy in Thoraxcenter since 1997. The mean duration was 38.7 months. At six months the event free survival rate was 75%, but at 4 years only 42% (Figure 11). The same progression was also noticed in the target lesion revascularisation, 8.3% at six months, 19.9% at 12 months, 23.8% at 24 months and 28.5% at 4 years, indicating that brachytherapy delays rather than inhibits the restenosis process90.

Radioactive stents

The results of radioactive stents were disappointing and could not be favourably influenced by modification in design and activity90,92,93,94,95. The outcome at 6 months showed a high rate of clinical events and restenosis (up to 50%), preferably at the edges of the stent96, called the “candy wrapper”. Moreover delayed restenosis was also observed at longer follow up97 and their use never found a place in routine practice.
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Radiation protection and safety considerations

Radioactive material cannot be turned off. Therefore, secure control of the radioactive inventory and surveillance of staff and patients is of special concern.

Figure 9.

Fall-off the dose and its relation with geographical miss (GM). Right side: dosimetric characteristics of the 90Sr/90Y beta-cath source. At the last 2.5mm at the edge of the source the dose drops by 50% and at the end of the radiopaque gold marker (RGM) is almost negligible. Angiographic, the drawing corresponds to the insert in the left corner of the left image which is a magnification of the proximal part of the source in frame (d). It is important to realise that dose starts to drop 2.5mm within the length of the active source (red line) which is almost 7-8mm away from the delivery catheter marker (DCM), usually used for the positioning of the source. Left side: Angiographic example of GM. a) Tandem lesion in the proximal left anterior descending coronary artery. b,c) balloon dilatations. d) The radiation delivery catheter and radiation source 30mm in length. The source is short to cover the long injured segment by the sequential balloon inflations causing GM as indicated by the green vertical lines. The mismatch at the proximal edge is obvious (gross GM). At the distal edge it corresponds exactly at the fall-off of the dose zone, the last radioactive seed and distal radiopaque gold marker, as indicated by the arrowheads (subtle GM).

Figure 10.

Comparative efficacy of beta and gamma radiation therapy versus placebo for in-stent restenotic lesions.

Regulatory considerations

For transportation, storage and handling of nuclear sources, European countries require various licenses according to individual nuclear laws.

In general, the institute or hospital needs a license for using radioactive material. Within the institute or hospital a local permission has to be obtained which is mostly linked to specific room conditions and expertise of the personnel. Mandatory key personnel include a radiation oncologist, a medical physicist, a radiation safety officer and a cardiologist. Clinical responsibility lies with the radiation oncologist, though he may delegate practical aspects to others.

Practical safety considerations

In Europe, standards for the protection of patients, health workers and the public against exposure to radiation have been specified in two directives (96/29/EURATOM: 97/3/EURATOM) and are now being incorporated into national laws. Radiation protection is determined by two principles: exposure must be justified by showing that it confers more benefit than detriment and exposure should be as low as reasonable achievable (ALARA principle).
Monitoring

Individual personnel dosimeter badges allowing for effective dose equivalent reading are mandatory in controlled areas like catheterization laboratories. Radioactivity can be further assessed by two basic instruments, the portable Geiger-Müller counter and the ionization chamber survey meter.

Source

Every source must be inspected on receipt, which involves visual inspection in the shielding, calibration to verify the exact level of activity and, in line-sources, checking the number and activity of sources.

Storage

Sources must be stored securely and held under lock and key. Storing facilities must be provided with sufficient shielding, taking into account that 90Sr/90Y sources from the Beta-cath system produce Bremstrahlung. Pre-treatment checks and calibrations of the source are mostly performed in the storing facilities. 32P has a half-life of 14 days only. In consequence, 32P sources have to be exchanged every four weeks. 90Sr/90Y sources require a yearly check especially for the mechanical condition of the source. The time necessary to transfer the source in a special delivery device to the laboratory must be taken into account by treatment protocols.

Catheterization laboratory design and equipment

Actual shielding requirements are catheterization laboratory specific depending on size and configuration of the procedure room and the adjacent rooms. The radiation levels of the X-rays require approximately 4mm lead shielding in the walls. Beta radiation requires no additional specific shielding of the catheterization laboratory or adjacent rooms. Gamma radiation requires special shielding (minimum thickness 25mm lead) of the procedure room and the control room to block the gamma rays (e.g., mobile shields of approx. 200kg positioned close to the patient). Outside the laboratory, the level of exposure must be estimated and regularly monitored in adjacent rooms.

Patient safety

PRINCIPAL RISKS RELATED TO INTRACoronary RADIATION INCLUDE:
- Damage to the artery wall with consecutive perforation and/or aneurysm formation. This risk seems to be dose related (>30Gy) and low.35,38,89,90.
- Accelerated coronary artery disease as known side effect of high dose radiation (>35 Gy) for the treatment of neoplasms91,92. Intermediate doses (30-40 Gy) have shown a low risk of cardiac disease during long term follow-up93.
- Radiation-induced carcinogenesis. This risk appears to be low at least in beta radiation as the dose beyond the immediate target lesion is low and the exposed tissues (e.g., arteries, veins, cardiac muscle, and pericardium) have a low spontaneous carcinogenicity rate.

TECHNICAL RISK RELATED TO INTRACoronary RADIATION

The main technical risks related to intracoronary radiation is the failure to smoothly deploy and retrieve the source. Therefore, proper source passage into the target coronary artery should be routinely tested by deploying and retrieving a dummy source. A dummy source allows also for control of the treatment position within the coronary artery and repositioning of the delivery catheter if necessary.
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Staff safety
Every source is brought into the catheterization laboratory in a shielding device. The shielding device can be a source of radiation. The operator's hand dose can be reduced by not touching the shielding device. During delivery into the coronary artery and retrieval, the source is unshielded for a few seconds. Again, the operator's dose is reduced by not touching the treatment catheter and keeping distance. Direct finger contact with a high dose rate source is hazardous. During treatment with gamma radiation, all personnel with exception of the radiation oncologist must leave the catheterization laboratory in order to limit their exposure to radiation.

Procedure performance
Intracoronary radiation treatment requires a substantial commitment and collaboration between the interventional cardiologist and the radiation oncologist. Prior to every brachytherapy procedure, the radiation oncologist and the medical physicist have to be informed. The radiation oncologist must be able to review the patient's anamnesis and physical condition for proper treatment planning, the medical physicist guarantees secure source transportation.

Patient selection
Indications
Based on the outcome of the randomized clinical trials FDA approval is limited to the treatment of in-stent restenosis in the U.S. The findings of several clinical trials point to a possibly elevated risk for thrombotic events in patients receiving radiation therapy in newly implanted stents. Potential indications in all circumstances with elevated risk for restenosis after conventional catheter based intervention such as long lesions, saphenous vein grafts, small coronary arteries, diabetic patients and renal insufficiency patients still need to be established.

Contraindications
Contraindications are previous radiotherapy of the chest, previous intracoronary brachytherapy, pregnancy, genetic radiation sensitivity disorders (e.g. ataxia-telangiectasia).

Patient preparation - medication
Pre-procedural treatment requires no particular medication for brachytherapy other than antiplatelet regimen for routine angioplasty procedures: Aspirin (75mg-300mg) and ticlopidin or clopidogrel must be started at least 24h before the procedure, whereby we prescribe a loading dose of 750mg, followed by 250mg twice a day for ticlopidin and a loading dose of 300mg, followed by 75mg daily for clopidogrel. Beta-blockers, calcium antagonist and oral nitrates should be administered as usually prescribed.

At the begin of the procedure, we routinely administer neuroleptics and analgesics. Repeat bolus is given during the procedure, if needed. Furthermore, we administer 325mg aspirin intravenously and 10 000 IU heparin immediately after arterial sheath placement. Activated clotting time (ACT) is checked every 30 minutes after the first bolus injection in order to maintain ACT > 300 sec. Additional heparin is given if necessary.

During the procedure, GP IIb-IIIa receptor blockers are given deliberately in patients with unstable angina, periprocedural intracoronary thrombus formation or dissection.

Equipment set-up and special arrangements of the operating room
For the angioplasty procedure, a standard angioplasty set and eventually additional ablative devices (e.g. atherectomy catheter) is needed.

For brachytherapy, the catheterization laboratory must have appropriate shielding as described. The radiation oncologist prepares the brachytherapy device (e.g check for mechanical integrity, flushing of the system, dummy source, etc).

We recommend for this purpose an extra sterile table and light. A bail-out box must be in the procedure room, typically consisting of an assortment of long-handled instruments for grasping a source and of a shielded container (lead for gamma radiation, plastic for beta-radiation source) to safely place the source. Radiation detectors to survey the environment during the procedure and contamination monitors for source leakage are needed. At least two timers must be available to allow for correct dwell time and to minimize treatment errors.

Access method
We prefer the standard femoral approach using a 7F sheath and guiding catheter. Application through the radial approach is also feasible.

Angiography
Terminology
Brachytherapy as new treatment with complex mechanisms of action urges detailed angiographic assessment and necessitates the introduction of a new terminology (figure 12).

- Target segment. The target segment is defined by the proximal and distal margin of the obstructed segment.
- Injured segment. The macroscopic injured segment is defined as the segment encompassed by the most proximal
and most distal position of the angioplasty device (e.g. rotablator burr) or marker of the angioplasty balloon and all visible vessel injury as assessed by fluoroscopy.

• **Irradiated segment.** The irradiated segment is defined as the segment encompassed by the inner edge of the radiopaque markers of the source train.

• **Effective irradiated segment** is the segment receiving full prescribed therapeutic radiation dose (100% isodose) and it is shorter than the irradiated segment as a result of the dose fall-off caused by the limited size of the source train. The exact delineation of the effective irradiated segment is complicated, as it requires the knowledge of the individual dose-profiles for each isotope and source design.

• **Edge segments.** Edge segments are the vessel segments at the extremities of the radiation source, which do not receive full therapeutic radiation dose. The length of the edge segments is dependent on the isodose profile of the individual source.

• **Vessel segment.** The vessel segment is the coronary segment bordered by angiographically visible side-branches which encompass the original lesion, all angioplasty devices and the radiation source.

• **Geographic miss segment.** In coronary brachytherapy, it is defined as a mismatch between injured and irradiated segment: Geographical miss is present when the entire length of the injured segment is not completely covered by the irradiated segment (figure 13).
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GENERAL REQUIREMENTS

Angiography should be done in biplane views. At the start of the procedure, two projections are selected with more than 30 degrees difference in rotation and avoiding foreshortening and side branch overlapping. The entire procedure should be filmed in identical projections. The meticulous documentation of all angioplasty devices and the radiation source in place with contrast medium, using the same projections, is essential. Inadequate angiographic documentation, hampering the identification of the irradiated and the injured segment is seen in up to 50% of the cases enrolled in brachytherapy trials.

PRIMARY ANGIOGRAPHY

Primary angiography identifies the culprit lesion, the "target segment" and the "vessel segment". Basic considerations are:
- vessel size (dose prescription?)
- lesion accessibility for the source (dimensions, stiffness?)
- strategy of angioplasty prior to radiation
- lesion length (source long enough to cover complete injured segment?)
- side branches (in bifurcation lesions, only 1 side branch can receive radiation)

Primary angiography also serves for decision on the "best projection" to document the complete procedure.

Angioplasty

Prior angioplasty might consist in debulking (directional or rotational atherectomy, laser), stent implantation or "simple" balloon inflation and is performed in conventional technique. Any instrumentation has to be filmed at the site of treatment surrounded by contrast medium in identical projections! It is important, that angioplasty is not stopped before reaching a satisfactory result. Every instrumentation after radiation therapy carries inevitably the risk of geographic miss and subsequently edge restenosis. We strongly recommend that radiation should be the last intervention.

Dose prescription and source selection

The treated coronary artery is usually 2-5 cm of length, with a diameter of 3-5 mm and a vessel wall thickness of 0.5-3 mm. The radiation dose given to the vessel wall should target the media as well as the adventitia delivered at 0.5-5 mm from the source. Dose prescription and source selection are performed in close collaboration with the radiation oncologist. Dose is prescribed in relation to the long axis of the source (e.g. at 2 mm) and can be based on the angiography or intravascular ultrasound.

Given the radioactivity and dose rate of the selected source, dwell time is calculated in dependency of the vessel size. The length of the source should be selected in that way, that:
- the vessel segment, which has been "touched" by any angioplasty device and
- the vessel segment which shows macroscopic injury is completely covered
- there is sufficient safety margin at the proximal and distal end of the source to guarantee full dose radiation of the treated segment.

Radiation treatment

The radiation oncologist prepares the brachytherapy device. Meanwhile it might be helpful for the operator to review the angiograms. This allows for a precise image of the "injured segment" relative to landmarks such as side-branches. The guiding catheter should be correctly positioned at the coronary ostium: if it is too deep it will obstruct flow and may creep further into the coronary artery during the procedure, if it is too far away, it may slip during the procedure and move the source ribbon. Then the catheter accommodating the dummy source is carefully advanced into the vessel. Most radiation delivery catheters are fragile without inserted ribbon, it may easily kink during insertion. If stented lesions are treated, it has to be avoided, particularly in tortuous vessels, that the catheter becomes caught on the stent struts. An angiogram with the dummy source in place should be done. If angiography confirms correct positioning with complete coverage of the injured segment and safety margins, the radiation oncologist removes the dummy source, connects the afterloader device to the catheter and delivers the source. The radioactive source must be filmed in place with contrast medium repeating the projections used for angioplasty. Care should be taken to not over tighten the O-ring and Y-connector while attempting to obtain good quality contrast injections, as this may crimp the delivery catheter and obstruct movement. At the end of the dwell time, the radiation oncologist removes the source. The contrast medium should be withdrawn into the delivery syringe prior to injection down the coronary artery after withdrawal of the source to avoid thrombotic embolisation. While removing the delivery catheter, care should be taken not to push the guide to far distally into the vessel. A final angiogram should confirm good angioplasty result and the absence of dissections and/or thrombus.

How to avoid geographic miss

- Source length > lesion length!
- Select a projection without foreshortening and side branch overlap
• Film any instrumentation with contrast medium to allow for anatomical orientation
• Film any instrumentation in the same projection and respiratory position
• Film the dummy and active wire in the same projection and respiratory position
• Use proximal (or distal) side branches within the vessel segment as index anatomical landmarks to assess the distances to the markers of the angioplasty balloon and the radiopaque source markers
• Consider proximal and distal safety margins
• Do not perform brachytherapy before a satisfactory angioplasty result
• Avoid instrumentation (e.g. additional stents) after brachytherapy
• Listen to your radiation oncologist!

Complications

Procedural complications

Procedural complications include all complications typically linked to the angioplasty/debulking procedure. Most complications related to brachytherapy by removable sources are caused by the relatively high profile and stiffness of the delivery catheter:
• myocardial ischemia with angina and/or ECG changes, which might necessitate fractionation of the dose (approx. 4% of the patients) and
• dissection after manipulation of the delivery catheter (approx. 10% of lesions).

Furthermore, radiation increases local thrombogenicity, which promotes intracoronary thrombus formation during active treatment (approx. 4% of lesions). In these cases, GP IIb/IIIa inhibitors should be given deliberately.

Procedural emergencies

CATHETER BASED LINE SOURCES

Prolonged retrieval represents one of the most serious technical events which can produce unwanted dose to the patient and staff. In that case, the entire treatment catheter should be withdrawn and placed into the bail-out box. If that is not successful, an attempt should be made to move the source into a larger diameter artery whilst calling for emergency surgery.

BALLOON BASED FLUID OR GASEOUS SOURCES

Radioactive fluid filled balloons might leak or burst and spill their content’s into the patient’s blood stream. The radioactive material need to be physiologically cleared from the patient before an unacceptable dose is delivered to any tissue. Gaseous 133Xe is rapidly exhaled and presents minimum radiation hazard to the patient.

In all cases of emergency, the physicist’s responsibility is to remain focused on safely retrieving the sources and minimizing unnecessary exposure of patients and staff. To allow for rapid and well directed action, contingency plans must be made in advance, discussed and rehearsed for a variety of likely and unlikely occurrences.

Postprocedural care

The arterial sheath is withdrawn immediately after the procedure and the access site sealed with a closure device (Perclose or Angioseal). In case of a difficult arterial puncture with substantial fibrosis, the sheath is removed 6 hours after the procedure and the artery manually compressed. All patients must receive effective antiplatelet therapy for at least 12 months. In our institution, we prescribe aspirin indefinitely in combination with clopidogrel (75mg daily) for 12 months. This is essential to avoid late thrombotic occlusion.

Brachytherapy in the era of Drug Eluting Stents

Primary prevention of restenosis

The Drug Eluting Stents have been recently introduced in our clinical practice and proved to be very effective for the prevention of restenosis in de novo lesions. Most of the limitations of brachytherapy are strongly related with the use of stents. This incompatibility with the use of stents was the reason that it failed to find a place in the routine practice for de-novo lesions. Stents are the cornerstone therapeutic modality in interventional cardiology today and that doesn’t seem to change in the near future. Any technique incompatible with their use will not find wide application.

Secondary prevention of restenosis

The Drug Eluting Stents have been recently reported to be effective for the treatment of in-stent restenosis of non-eluting stents. The confirmation of these results in large randomised trials and the unique application of eluting stents, will limit brachytherapy as a specialised technique, for the limited number of patients with failure of eluting stents, in dedicated centers.

Limitations

Three appearing to be the main limitations of intracoronary radiation therapy:
1. **Edge restenosis.** The underline mechanism seems now well understood. Underdosing in combination with injury. Current data show that with appropriate application of the radiation, taking sufficient margins, it can be eliminated.

2. **Late occlusion and thrombosis.** Prolongation of the antiplatelet treatment just delayed its appearance. Life long aspirin and clopidogrel might be warranted, with questionable efficiency.

3. **Delayed restenosis.** Current data are still limited but seems that they support it. Furthermore, the treatment of these patients is another serious challenge in interventional cardiology.

**References**


Regar E, Kozuma K, Sianos G, Carlier SG, Serruys PW

Quantitative Coronary Angiography Methodology in Vascular Brachytherapy

Quantitative Coronary Angiography Methodology in Vascular Brachytherapy I

Evelyn Regar, MD, Ken Kozuma, MD, George Sianos, MD, Stephane G. Carlier, MD, and Patrick W. Serruys, MD, PhD

Introduction

The application of intracoronary radioactivity represents a relatively new therapeutic tool for the cardiologist. Radioactivity is administered by various techniques, e.g., intracoronary afterloading,1–5 radioactive stents,6–10 or radioactive balloons11–13 using gamma- or beta-emitting sources. The particular physics, application modalities, and mechanisms of action of this new treatment modality force us to adapt the procedural practice and the methodological approach of angiographic outcome assessment.14,15

Recently, a number of phenomena associated with intracoronary brachytherapy, such as positive remodeling,16 relocation of the minimal lumen diameter (MLD),17 geographic miss,18 and edge effect19 have been described. These entities have been recognized in the past; however, their incidence and their impact on clinical outcome has reached new and so far unknown dimensions. While, after standard balloon angioplasty, neointimal hyperplasia and vessel shrinkage at the site of injury is the usual response,20,21 in balloon angioplasty followed by irradiation, an increase in the MLD at the treated segment is predominantly seen16 as a result of positive remodeling and neointimal inhibition.22 This systematic change in vessel response after brachytherapy prompts us to adapt new angiographic approaches, taking into account the relocation of MLD at follow-up from its pre-interventional location. Similarly, the growing knowledge of the deleterious effects of geographic miss and the awareness of possible edge effects underline the need for standardized and detailed angiographic assessment.

This chapter will review standard quantitative coronary analysis and describe the current approach for vascular brachytherapy.

Classical Quantitative Coronary Angiography Analysis

Quantitative coronary angiography (QCA) is the well-established gold standard for the assessment of coronary angiograms.23 In classical QCA analysis, the

Figure 1. Classical quantitative coronary angiography (QCA) analysis. The analyst defines the vessel segment of interest bordered by major proximal and distal side branches. Minimal lumen diameter (MLD) and interpolated reference diameter (RD) at the site of MLD is calculated.

analyst defines the vessel segment of interest. Sophisticated edge detection algorithms define automatically the obstructed target segment. Within the target segment, MLD, interpolated reference diameter (RD), and diameter stenosis (DS) are calculated (Fig. 1). Pre-interventional, post-interventional, and follow-up measurements are compared to analyze treatment efficacy in such terms as residual DS, acute lumen gain, late lumen loss, or dichotomous restenosis rate.

Limitations of Classical Quantitative Coronary Angiography Analysis

Classical QCA analysis is comprehensive from a clinical perspective, as it detects reliably whether or not relevant lumen changes occurred in a previously treated vessel segment. From a scientific perspective, however, this method is of limited value: it fails to describe precisely the anatomic location of lumen changes, as it does not provide information on the topography of the MLD within the target vessel segment at the time of repetitive measurement. Recent studies after balloon angioplasty have demonstrated that changes in RD and in the anatomic position of the MLD occur during follow-up, invalidating direct comparison of quantitative parameters over time. This “relocation” makes the direct comparison of MLD questionable. The dynamic lumen changes have various causes such as plaque progression, unmasking of new lesions, or remodeling, and might be triggered intentionally by intervention or nonintentionally by periprocedural vessel injury. To overcome these problems, our group, over the last 15 years, has applied a strategy
of analyzing a treated “vessel segment,” rather than a focal spot representing the site of pre-interventional MLD. The treated “vessel segment” encompasses the culprit lesion and is defined in length by the most proximal and distal side branch. These side branches serve as reproducible landmarks for the follow-up analysis. Similarly, the TOSCA group introduced the concept of “target lesion work length,” defined as the length of contiguous target segment exposed to balloon inflation. Thus, not only is the segment of the original angiographic lesion analyzed, but also the vessel segment over the entire treated length.

New Concepts of Angiographic Assessment on Brachytherapy

Principle of Dose-Based Segmental Assessment

Intracoronary radiation has complex and dose-dependent effects on arterial tissue. It is usually used as an adjunctive therapeutic tool to other debulking and/or angioplasty devices. Thus, angiographic assessment must include radiation dose, proximal and distal vascular injury, and possible interactions of both (determinants of the edge effect), rather than the isolated target lesion. Based on these considerations, quantitative assessment of irradiated vessels should include different vessel segments, which are defined below (Fig. 2).

**Figure 2.** Schematic of dose-based segment definition within an irradiated coronary artery. TS = target segment; INS = injured segment; EIRS = effective irradiated segment; IRS = irradiated segment; VS = vessel segment.
**Target Segment**

The target segment is defined by the proximal and distal margin of the obstructed segment.

**Injured Segment**

The macroscopic injured segment is defined as the segment encompassed by the most proximal and most distal position of the angioplasty device (e.g., rotablator burr) or marker of the angioplasty balloon as assessed by fluoroscopy.

**Effective Irradiated Segment**

The effective irradiated segment is the vessel segment receiving the full prescribed therapeutic radiation dose (>90% isodose rate). In catheter-based line sources, the length of this full radiation dose segment is slightly shorter than the distance between the radiopaque markers as a result of the dose fall-off caused by the limited size of the source train (Fig. 3). The dose-fall characteristics vary in different isotopes.

**Figure 3.** Isodose rate contour map and radiation source train. **Left:** Isodose rate contour map measured at a depth of 1.89 mm (contour intervals: 10 mGy/s) as described by the National Institute of Standards and Technology. The depth (1.89 mm) illustrates an isodose model to resemble the radius of a coronary artery. Longitudinal dose fall-off may be extrapolated from this graphic. **Right:** Radiation source train (Beta-Cath, Novoste Corp.). The central part receives an approximately full radiation dose.
Similarly, the effective irradiated segment is slightly shorter than the stent length in radioactive stents, because of the dose fall-off at the extremities of the stent, involving the most proximal and the most distal stent struts. The length of the fall-off zone varies as it is dependent on isotope and stent design. Furthermore, the dose profile is not homogeneous, but peaks behind every individual strut. This effect varies depending on the distance and the angle of observation.

*Irradiated Segment*

In practice, the exact delineation of the effective irradiated segment is complicated, as it requires the knowledge of the individual dose profiles for each isotope and source design. Correction for the dose fall-off at the extremities of the irradiated segment is a matter of a few millimeters. Exact length measurement, however, is often hampered by the anatomy of the artery and foreshortening.

For these practical reasons, quantitative analysis is performed on an *irradiated segment*, which is defined as the segment encompassed by the inner edge of the radiopaque markers of the source train or the length of the radioactive stent.

*Edge Segments*

Edge segments are the vessel segments at the extremities of the radiation source (catheter-based source, radioactive stent, or balloon), which do not receive the full therapeutic radiation dose. The lengths of the edge segments are dependent on the isodose profile of the individual source.

*Geographic Miss Segment*

In coronary brachytherapy, this is defined as a mismatch between injured and irradiated segment: geographic miss is present when the entire length of the injured segment is not completely covered by the irradiated segment.

*Vessel Segment*

The vessel segment is the coronary segment bordered by angiographically visible side branches which encompass the original lesion, all angioplasty devices, and the radiation source.

*Image Acquisition and Procedural Implications*

In order to allow for such detailed analysis, image acquisition and angiographic documentation need to be performed in an accurate and standardized fashion. Angiography should be done in biplane views at a frame rate of 25 frames per second. The electrocardiogram (ECG) tracing must be visible on screen. Before each angiogram, nitrates should be administered by intracoronary infusion. Each angiogram should be performed at mid-inspiration. The empty (guiding) catheter
should be documented for calibration, preferably near the center of the screen. At the start of the procedure, two projections should be selected with more than 30 degrees celsius difference in rotation and avoiding foreshortening and side branch overlapping. The entire procedure should be filmed in identical projections. Any instrumentation (e.g., balloons or stents) should be filmed at the site of treatment surrounded by contrast medium in identical projections. The radioactive source should be filmed in place with contrast medium repeating the same projections. Follow-up angiography must performed using the same imaging projections, same contrast medium at 37°C, and documentation of the unfilled catheter. Again, intracoronary nitrates should be administered before each angiogram.

The meticulous documentation of all angioplasty devices and the radiation source using the same projections is essential. Inadequate angiographic documentation of the procedure, hampering proper angiographic assessment of geographic miss, is seen in up to 50% of the cases enrolled in brachytherapy trials.

**Angiographic Analysis of Brachytherapy**

**Qualitative Assessment**

The introduction the concept of “geographic miss,” originating from radiation oncology, into the scenario of intracoronary brachytherapy stressed the importance of assessment of the injured segment in relation to the radiation source.

To assess whether geographic miss is present or not, multiple angiographic loops and ECG-matched still frames should be displayed simultaneously, side by side, on the screen (e.g., Rubo Medical Imaging, Uithoorn, The Netherlands). This approach allows definition of the location of the various subsegments (irradiated segment, injured segment, edges) in relation to side branches, and the correct matching of the angiograms. By identifying the relationship between the irradiated segment and its edges relative to the injured segment, the occurrence of geographic miss can be determined (Fig. 4). Using this method, the agreement rate of two independent cardiologists is as high as 90%.

The procedure should be considered as not interpretable in the following cases: (a) lack of correct filming with the radiation source and the balloons deflated with contrast injection, so as to allow the location of the irradiated segment, injured segment, and the edges in relation to anatomic landmarks; (b) more than 10 degrees difference in the angiographic projections, not allowing for correct matching; (c) interventions reported in the technician’s worksheet, but not filmed.

**Quantitative Coronary Analysis**

Dedicated analysis software (CAAS II System; Pie Medical, Maastricht, The Netherlands) allows for simultaneous assessment of the different segments. By displaying an angiographic sequence showing the lesion pre-intervention, positions of angioplasty devices, and radiation source simultaneously on a screen, the analyst indicates the different analysis segments according to the location of the angioplasty devices and radiation source relative to the original lesion (Fig. 5). The proximal (or distal) side branch within the vessel segment can be used as an index anatomic landmark to assess additionally the distances (measured on the
**Figure 4.** Qualitative assessment of geographic miss. Pre-intervention lesion (A), balloon (B) and radiation source (C) (Radiance RDX radiation balloon, Radiance Corp.) have been filmed in the same imaging plane, allowing for accurate assessment of the injured and the irradiated segments. The injured segment is distally not completely covered by the irradiation source, resulting in distal geographic miss.

**Figure 5.** Dose-based definition of vessel segments within an irradiated coronary artery. **Lower panels:** The pre-intervention lesion, any instrumentation (balloon and source train), the post-interventional result, and follow-up have been filmed in identical projections and are displayed simultaneously on a screen. **Upper panels:** The vessel segment (VS) is defined by the analyst; the target segment (TS) is automatically defined by the quantitative coronary angiography system; the injured segment (IS) is defined as the segment encompassed by the most proximal and most distal radiopaque marker of the angioplasty balloon; the irradiated segment (IRS) has been defined between the radiopaque markers of the source.
center line) to: (1) the inner part of the proximal radiopaque marker of the radiation source; (2) the proximal marker of the angioplasty balloon; (3) the proximal margin of the obstruction segment; (4) the distal margin of the obstruction segment; (5) the distal marker of the angioplasty balloon; and, (6) the inner part of the distal radiopaque marker. All regions of interest are superimposed on the pre- and post-procedural angiograms. Thus, the occurrence of geographic miss can be directly assessed and quantified (Fig. 6). The accuracy of such quantification of geographic miss in the direction of the longitudinal vessel axis, however, is strongly dependent on an imaging projection without foreshortening. In all analysis segments, the MLD is determined by edge detection and the RD is automatically calculated. The percent DS is calculated from the MLD and the RD (Fig. 7).

**Analysis of Restenosis: Regional Restenosis**

As in classical QCA analysis, dichotomous restenosis is defined as greater than 50% DS. As long-term radiation effects on the coronary vessel wall have shown to be dependent on dose and injury, possibly resulting in the “candy wrapper” or “edge effect,” it is important to describe late outcome with respect to the dose-based subsegments.

![Quantitative assessment of geographic miss](image)

**Figure 6.** Quantitative assessment of geographic miss. Using the quantitative analysis software, the target segment (A), injured segment (B), and irradiated segment (C) have been defined. Ideally, the borders of the irradiated segment are most proximally and most distally situated, encompassing both, the target segment and the injured segment. Automated comparison of the position of the proximal and distal borders of each individual segment detects any deviation from this ideal pattern, indicating geographic miss. In the example, the proximal border of the irradiated segment is located more distal than the proximal border of the injured segment, indicating proximal geographic miss. The length of the geographic miss segment is 8.73 mm.
The pre-, post-intervention, and follow-up angiograms with the dose-based subsegments are superimposed and compared in two orthogonal projections. Thus, the location of the segment with restenosis can be assessed in relation to the dose-based segments. Regional restenosis is classified as restenosis in the irradiated segment, edge restenosis (proximal and/or distal), and restenosis outside the injured segment. The criterion for binary restenosis might be fulfilled in more than one subsegment in the same vessel segment.

**Subsegmental QCA Analysis: Relocation**

Using current analysis software, subsegmental analysis can be performed within the vessel segment. The vessel segment is automatically divided into subsegments of equidistant length (on average, 5 mm). In each subsegment MLD, RD, and percentage DS is automatically calculated.

**Relocation** For relocation analysis, the subsegment containing the MLD at baseline is taken as the index segment. Relocation is defined whenever the MLD in subsequent analysis is located in a subsegment other than the index segment. Sequential analysis may refer to pre-interventional to post-interventional MLD, or post-interventional (Fig. 8) to follow-up MLD (Fig. 9).
Figure 8. Subsegmental analysis. The vessel segment is automatically divided into subsegments of equidistant length (on average 5 mm). In each subsegment minimal lumen diameter (MLD), reference diameter (RD), and percentage diameter stenosis is automatically calculated.

Figure 9. Subsegmental analysis—relocation of minimal lumen diameter (MLD). This figure shows the same coronary artery as Figure 8 at 6-month follow-up. At post intervention (Fig. 8), the MLD is located in subsegment no. 6. At subsequent follow-up analysis (Fig. 9) the MLD is located in subsegment no. 7.
**Definition of Reference Diameter**

**Methods of Reference Diameter Calculation** In the early years of quantitative angiographic assessment, the RD was “user-defined.” The analyst set proximal and distal calipers at “normal” reference sites (Fig. 10). This method, however, was strongly user-dependent and showed high variability in measurements. To circumvent this limitation, the concept of the “interpolated reference diameter” was introduced in 1982. The interpolated RD is calculated at the site of the MLD and represents the diameter of the artery when the obstruction would not be present. This method is completely automated and user-independent, once the margins of the vessel segments are given (Fig. 11).

These concepts of RD definition are based on the assumption that a non-treated reference segment preserves its stable dimensions over time. Following intracoronary radiation, however, therapy-associated changes in vessel dimensions have been consistently observed due to edge effect, relocation of the MLD, and positive remodeling. Under these circumstances, the interpolated RD became less reliable. To overcome these problems, “computer-constructed reference diameter analysis” has been developed. The method is not influenced by development of a new (edge) stenosis close to the original treatment site as the RD is calculated apart from the treatment side. In the first step, proximal and distal boundaries for diameter construction are automatically set at 5% and 95% of the vessel length under study. This reference position is averaged over a width of 3 mm to suppress the influence of noise on the local diameter. In the second step, the computer-constructed RD is then reconstructed at the position of the MLD, based on a line fitted through the proximal and distal boundaries by linear interpolation. Thus, this approach gives more reliable reference dimensions over serial measurements;

![Diagram](image.png)

**Figure 10.** User-defined reference diameter. Diameter profile of a stenotic coronary artery segment. The analyst set proximal and distal markers at “normal” reference sites. MLD = minimal lumen diameter; RD = reference diameter.
however, it does not cure the principal problem of relocation of the MLD. In consequence, the RD might be calculated at different positions within a vessel segment at baseline and follow-up measurement (Fig. 12).

**Selection of Reference Diameter** Analysis of dose-based segments and subsegmental analysis gives an MLD and an RD for each individual segment. This might be helpful in the analysis of specific mechanistic questions. For the analysis of treatment efficacy and side effects, however, all measurements should be referred to one single “reference diameter.” The RD calculated for the vessel segment is considered to best represent the “true” vessel dimensions, and thus, should be used for standardized reporting.

**Clinical Implications**

Intracoronary radiation has shown an effective inhibition of neointimal proliferation. The local mechanisms of action are poorly understood. Recent intravascular ultrasound studies demonstrated that mechanic vessel injury in combination with radioactivity can cause both beneficial and deleterious effects. Irradiation may prevent shrinkage after balloon angioplasty\(^{53}\) and even promote positive remodeling at the irradiated site.\(^{54}\) In contrast, edge segments show an increase in plaque volume without adaptive remodeling.\(^{10,22,55}\) These findings have indicated a need to differentiate between the reporting of angiographic outcomes.

Dose-based segmental analysis allows for an accurate description of local lumen changes in different portions of the irradiated vessel. This is a prerequisite to study both the therapeutic and the side effects. Based on this methodology, angiographic analysis could demonstrate, that geographic miss plays a key role in
restenosis after (beta) brachytherapy, emphasizing the need for complete coverage of the injured segment.

It could also been shown that late lumen loss differs considerably according to the selected segment. In consequence, the dichotomous restenosis rate varied from 3.1% in the “target segment” to 13.8% when analysis was extended to the “vessel segment” (Table 1). Consistently, others found variation within a similar range (14.2% to 28.8%). This has important impact on the reporting, interpretation, and comparison of study results.

Detailed analysis of computer-defined subsegments is of great help to gain insights in pathophysiological effects, and might be highly recommended for in vitro and/or “mechanistic” studies. Such detailed angiographic analysis could demonstrate that within the target segment, positive remodeling is a major effect of irradiation therapy, whereas relocation of the MLD within the injured segment has a substantially higher incidence after brachytherapy compared to conventional angioplasty. Possible mechanisms of relocation include: tapering of the vessel; development of new coronary lesions in any of the dose-based subsegments; “unmasking” of pre-existing plaque (stenosis) outside the irradiated segment, which becomes angiographically apparent over follow-up time; progression of disease inside (treatment failure, edge effect?) or outside the irradiated area; and geographical miss. Further studies are needed to understand the complex interactions and mechanisms of action of radiation, dose, and normal and atherosclerotic arterial tissue. Analysis of the “target segment” may demonstrate the effect of brachytherapy in optimal conditions (maximum injury fully covered by radiation),
### Table 1

Quantitative Coronary Angioplasty Data for Dose-Based Coronary Vessel Segments*

<table>
<thead>
<tr>
<th></th>
<th>TS</th>
<th>INS</th>
<th>IRS</th>
<th>VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD pre-intervention (mm)</td>
<td>1.06±0.2</td>
<td>1.06±0.2</td>
<td>1.06±0.2</td>
<td>1.06±0.2</td>
</tr>
<tr>
<td>MLD post-intervention (mm)</td>
<td>2.17±0.5</td>
<td>1.99±0.4</td>
<td>2.00±0.4</td>
<td>1.91±0.4</td>
</tr>
<tr>
<td>MLD follow-up (mm)</td>
<td>2.36±0.5</td>
<td>1.97±0.5</td>
<td>1.97±0.5</td>
<td>1.84±0.5</td>
</tr>
<tr>
<td>DS follow-up (%)</td>
<td>20.3±11</td>
<td>33.2±11</td>
<td>33.4±11</td>
<td>37.9±10</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>1.12±0.4</td>
<td>0.93±0.4</td>
<td>0.94±0.4</td>
<td>0.85±0.4</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>-0.18±0.4</td>
<td>0.01±0.4</td>
<td>0.03±0.4</td>
<td>0.07±0.3</td>
</tr>
<tr>
<td>Restenosis rate (%)</td>
<td>2 (3.1)</td>
<td>5 (7.7)</td>
<td>6 (9.2)</td>
<td>9 (13.8)</td>
</tr>
<tr>
<td>Segment length (mm)</td>
<td>5.0±0.3</td>
<td>18.7±4.2</td>
<td>22.9±3.5</td>
<td>36.9±8.4</td>
</tr>
</tbody>
</table>

*From Reference 17.

MLD = minimal lumen diameter; DS = diameter stenosis; TS = target segment; INS = injured segment; IRS = irradiated segment; VS = vessel segment.

While analysis of the injured segment and the edge segments may be helpful to identify potential causes of failure (i.e., geographic miss, non-injury-related edge effect, etc.),

In clinical trials, however, treatment effectiveness is the major endpoint. Angiographic outcome measurements should therefore be referred to the clinically relevant “vessel segment.” This represents the targeted region used in most of the historical trials, under the assumption that the patients symptoms and need for re-intervention are driven by flow-limiting lesions within the treated vessel, irrespective of the precise anatomic position. A restrictive definition of the “target segment” with follow-up analysis of the site of the initial MLD pre-treatment would be misleading and would make any comparison to previous nonradiation studies inaccurate.

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CHAPTER 4


**Intracoronary β-Radiation to Reduce Restenosis After Balloon Angioplasty and Stenting. The Beta Radiation In Europe (BRIE) Study**

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Intracoronary β-radiation to reduce restenosis after balloon angioplasty and stenting

The Beta Radiation In Europe (BRIE) study

P. W. Serruys1, G. Sianos1, W. van der Giessen1, H. J. R. M. Bonnier2, P. Urban3, W. Wijns4, E. Benit5, M. Vandormael6, R. Dörr7, C. Disco8, N. Debbas9 and S. Silber10 on behalf of the BRIE study group

From the 1Thoraxcenter, Heartcenter, Rotterdam, Academisch Ziekenhuis Dijkzigt Rotterdam, The Netherlands; 2Catharina Ziekenhuis, Eindhoven, The Netherlands; 3Centre Hospitalier Vaudois, Lausanne, Switzerland; 4Onze Lieve Vrouw Ziekenhuis — Cardiovascular Center, Aalst, Belgium; 5UZ Virga Jesse Ziekenhuis, Hasselt, Belgium; 6Clinique St. Jean, Brussels, Belgium; 7Klinik Weisser Hirsch, Dresden, Germany; 8Cardialysis, Rotterdam, The Netherlands; 9Clinique Universitaire de Saint-Luc, Brussels, Belgium; 10Internistische Klinik, Munchen, Germany

Aims The BRIE trial is a registry evaluating the safety and performance of 90Sr delivered locally (Beta-Cath TM system of Novoste) to de-novo and restenotic lesions in patients with up to two discrete lesions in different vessels.

Methods and Results In total, 149 patients (175 lesions) were enrolled; 62 treated with balloons and 113 with stents. The restenosis rate, the minimal luminal diameter and the late loss were determined in three regions of interest: (a) in a subsegment of 5 mm containing the original minimal luminal diameter pre-intervention termed target segment; (b) the irradiated segment, 28 mm in length, and (c) the entire analysed segment, 42 mm in length, termed the vessel segment. Binary restenosis was 9.9% for the target segment, 28.9% for the irradiated segment, and 33.6% for the vessel segment. These angiographic results include 5.3% total occlusions. Excluding total occlusions binary restenosis was 4.9%, 25% and 29.9%, respectively. At 1 year the incidence of major adverse cardiac events placed in a hierarchical ranking were: death 2%, myocardial infarction 10.1%, CABG 2%, and target vessel revascularization 20.1%. The event-free survival rate was 65.8%. Non-appropriate coverage of the injured segment by the radioactive source termed geographical miss affected 67.9% of the vessels, and increased edge restenosis significantly (16.3% vs 4.3%, P=0.004). It accounted for 40% of the treatment failures.

Conclusion The results of this registry reflect the learning process of the practitioner. The full therapeutic potential of this new technology is reflected by the restenosis rate at the site of the target segment. It can only be unravelled once the incidence of late vessel occlusion and geographical miss has been eliminated by the prolonged use of thienopyridine, the appropriate training of the operator applying this new treatment for restenosis prevention, and the use of longer sources.


Key Words: Radiation therapy, balloon angioplasty, stents, restenosis.

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Introduction

Following coronary balloon angioplasty, restenosis of the dilated segment occurs in 30% to 50% of patients and results from elastic recoil, neointima formation, and negative remodelling[1–4]. The advent of coronary stenting reduced restenosis to 15% in certain type of lesions[5,6], but introduced the even more difficult to treat in-stent restenosis[7]. Radiation has been shown to be effective in the management of other benign proliferative conditions, such as keloids, heterotopic bone formation, pterygia, and Grave’s ophthalmopathy[8–11]. Endovascular radiation has been evaluated in animal balloon and stent restenosis models and was shown to reduce neointima formation in a dose-related manner both
with gamma and beta emitters\textsuperscript{[12–15]} Clinical feasibility studies and randomized trials with beta and gamma emitters have been proven to be effective in reducing restenosis after balloon angioplasty, and recurrent in-stent restenosis\textsuperscript{[16–21]}. Recent intravascular ultrasound studies have documented the favourable mechanisms of positive remodelling and inhibition of plaque formation\textsuperscript{[22,23]} resulting in lumen enlargement after radiotherapy of de-novo lesions. In contrast the development of re-narrowing at the edges of the irradiated segment — related to vascular injury non-effectively irradiated\textsuperscript{[24–26]} — the late total occlusions\textsuperscript{[27,28]}, the delayed healing\textsuperscript{[29]}, the increased thrombogenicity\textsuperscript{[30]}, and the persistent dissections\textsuperscript{[31,32]} are limiting the effectiveness of this treatment. The purpose of the BRIE study was to introduce in a registry mode this new technology in Europe while awaiting the results of a large randomized trial (Beta-Cath trial), using the same source, in the U.S.A.

**Methods**

**Objectives**

The primary clinical end-point was freedom from major adverse cardiac events including death, CABG, myocardial infarction (defined as increase in the level of creatine kinase or MB isoenzymes to more than twice the upper limit of normal), and target vessel revascularization assessed at 1 year. The major adverse cardiac events were adjudicated by an independent clinical event committee. The angiographic end-point was restenosis (diameter stenosis >50\%), by quantitative coronary angiography, at 6 months. Secondary angiographic endpoints were minimal luminal diameter and late loss.

**Patient selection**

Between July 1998 and June 1999, 149 patients were enrolled in the study. Major inclusion criteria were: (1) objective evidence of ischaemia on exercise testing, (2) lesions located in vessels >2.7 mm and <4.0 mm in diameter, (3) patients with up to two discrete de-novo or restenotic lesions in different native coronary arteries who were eligible to undergo elective balloon (<24 mm) angioplasty or provisional stent (<22 mm) placement. Major exclusion criteria were (1) patients with unstable angina or acute myocardial infarction, (2) patients with in-stent restenosis, (3) bifurcation lesions and total occlusions.

The Institutional Review Boards or Ethics Committees and the Radiation Safety Committees of the participating institutions approved the protocol of the study. Written informed consent was obtained from all patients. The study was conducted at nine clinical sites listed in the appendix.

**Table 1 Patients and procedural characteristics**

| Age (range) | 60 (35–85) years |
| Males | 111/149 (74.4\%) |
| Diabetes | 21/149 (14.1\%) |
| Hypertension | 54/149 (36.2\%) |
| Prior MI | 51/149 (34.3\%) |
| Prior CABG | 31/149 (21.1\%) |
| LAD | 65/175 (37.1\%) |
| CFX | 38/175 (21.7\%) |
| RCA | 72/175 (41.2\%) |
| Stenotic lesions | 10/175 (5.7\%) |
| Balloon angioplasty | 62/175 (35.6\%) |
| Rescue stenting | 13/175 (7.4\%) |
| Provisional stenting | 100/175 (57\%) |

MI=myocardial infarction; CABG=coronary artery bypass graft operation; LAD=left anterior descending; LCX=left circumflex; RCA=right coronary artery.

**Procedure**

Overall, 123 patients underwent single-vessel angioplasty and 26 patients double-vessel angioplasty. In total, 175 vessels were treated. In the single-vessel group, 48 vessels were treated with balloon angioplasty and 75 with stenting (64 provisional and 11 rescue). In the double-vessel group, 14 vessels were treated with balloon angioplasty and 38 with stenting (36 provisional and two rescue). Overall, 62 vessels were treated with balloon angioplasty alone. In 42 of these, radiation was the last intervention whereas additional balloon angioplasty was necessary after radiation in the remaining 20 (32.2\%). In 113 vessels, stents were implanted (100 provisional and 13 rescue). All the stents but four (109/113, 96.4\%) were placed after radiation. In these four cases, stenting was necessary before radiotherapy due to threatened vessel occlusion after the initial balloon angioplasty. Overall, post-radiation intervention was performed in 73.7\% (129/175) of the vessels treated. Baseline patients and procedural characteristics are presented in Table 1.

Balloon angioplasty and stent implantation was carried out according to investigator’s standard practice, with all patients receiving heparin and aspirin before the procedure. By-protocol stenting was not discouraged. The angiographic criteria for stent placement were residual stenosis >30\%, flow-limiting dissection or threatened vessel occlusion. After successful dilatation, the balloon catheter was removed, with the guidewire left in place. The radiation delivery catheter was then inserted over the guidewire and advanced so that the two marker bands encompassed the angioplasty site with a margin of 3 mm, as specified in the protocol. Once satisfactory positioning of the catheter was confirmed under fluoroscopy, the transfer device was connected to the delivery catheter, the gate of the transfer device was opened, and the source train was hydraulically delivered down the catheter. During the procedure, minimal pressure and fluid flow were required to maintain the source train at the distal end of the source lumen. After
radiation therapy, the source train was returned to the transfer device by reversal of the switching system, which enabled injected fluid to push the train back into the transfer device. Further intervention was carried out when necessary and after achievement of a satisfactory result the procedure was concluded with filming of the final result after administration of intracoronary nitrates.

Post-procedural antiplatelet treatment

By protocol, the recommendation of antiplatelet treatment was 2 to 4 weeks. Due to the high incidence of angiographic vessel occlusion observed in the initial period of recruitment before 1999, prolongation of antiplatelet treatment for at least 8 weeks and up to 6 months was recommended after 1999.

Radiation delivery system

The device has been described elsewhere\cite{20,33}. In summary, it consists of three components: (1) the transfer device which stores the radiation source train and allows its positioning within the catheter; (2) the delivery catheter, which is a 5 Fr multilumen non-centred catheter which uses saline to send and return the radiation source train; and (3) the radiation source train which consists of 12 independent cylindrical seeds which contain the radioisotope $^{90}\text{Sr}^{90}\text{Y}$ source bounded by two gold radiopaque markers (30 mm in length). The longitudinal distance of the ‘full’ prescribed dose (100% isodose) coverage, measured by radiochromic films, is about 26 mm\cite{34} constituting the effective irradiation length.

Dosimetry

The prescribed dose was 14–18 Gy, at 2 mm from the centreline of the source axis, based on the reference diameter, by on-line quantitative coronary angiography, which measured <3.35 mm or >3.35 mm, respectively. Overall, 57.5% of the patients received 14 Gy and 42.5% 18 Gy. The dwelling time was on average $3.12 \pm 0.43$ min (mean $\pm$ SD).

Angiographic analysis

Quantitative coronary angiography was performed off-line by an independent Core-lab (Cardialysis, Rotterdam, Netherlands). All angiograms were evaluated after intracoronary administration of nitrates. The analysis was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). Calibration of the system was based on the dimensions of the catheters empty of contrast medium\cite{15}. This method of analysis has been previously validated\cite{36,37}.

A new methodological approach, recently reported\cite{38}, was used in order to define accurately the effect of brachytherapy on the treated coronary arteries. In each analysed coronary artery the following segments were determined: The vessel segment was defined as the segment bordered by two side branches, which encompassed the original lesion, the angioplasty balloon and the radiation source. The irradiated segment was defined as the segment encompassed by the two gold markers of the radiation source train. The target segment was defined as the 5 mm subsegment containing the pre-procedural minimal luminal diameter. In each of the above subsegments minimal luminal diameter, reference diameter, late loss, and restenosis-defined as diameter stenosis >50% at follow-up was determined. The segment encompassed by the most proximal and distal markers of the angioplasty balloon-defined the injured segment. The effective irradiated segment was the segment that received the full-prescribed dose and corresponded to the vessel segment covered by the 26 mm long central part of the radioactive source train. These segments are illustrated in Fig. 1.

Geographical miss

Geographical miss was defined for those cases where the entire length of the injured segment was not fully covered by the radioactive source. To determine whether the edges of the effective irradiated segment were injured, we retrospectively analysed (blinded to the presence or absence of restenosis and its location at follow-up) all the baseline (intervention plus radiation) angiograms. The following steps were followed: during the procedure all the interventions (balloons or stents) deflated at the site of injury and the radioactive source in place were filmed during contrast medium injection in identical angiographic projections. This approach allowed us to define the location of the various subsegments (effective irradiated segment, injured segment, edges) in relation to side branches and the correct matching of the intervention and radiation angiograms in the off-line analysis. The ECG recording was also displayed on screen, allowing the selection of still frames in the same part of the cardiac cycle. Multiple angiographic loops and ECG matched still frames could be displayed simultaneously, side-by-side, on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). By identifying the relationship between the effective irradiated segment and its edges relative to the injured segment we determined the geometrical miss edges\cite{20}. Computer-defined subsegmental analysis (mean subsegment length was $5.0 \pm 0.3$ mm) was also performed. In each subsegment percentage diameter stenosis was also automatically calculated. This allowed the determination of restenosis location in relation to the edges of the effective irradiated segment.
Chapter 4

Statistical analysis

Patient survival curves were constructed according to the Kaplan–Meier method. Continuous parameters are presented as mean values and standard deviations, discontinuous parameters are presented as percentages. Continuous parameters are compared using Student’s t-test, where binary parameters are compared using Fisher’s Exact-test. The statistical significance of all tests was defined at the $P < 0.05$ level.

Results

Major adverse cardiac events

In-hospital major adverse cardiac events

Three patients developed Q myocardial infarction after the procedure. In two patients Q myocardial infarction was due to total occlusion of the treated vessel (one occlusive dissection and one thrombotic occlusion) related to radiotherapy. In the third case the Q myocardial infarction was due to the occlusion of a side branch.

There were three patients with non-Q myocardial infarction; one from occlusion of a side branch after additional balloon dilatation following radiation, another with distal embolization of the treated vessel, and the third related to transient vessel occlusion, due to type F dissection following radiation, that required three stents to restore flow.

Major adverse cardiac events up to 1 year

The major adverse cardiac events up to 1 year follow-up are presented in Tables 2 and 3. The event-free survival curve up to 1 year is presented in Fig. 2. The incidence of major adverse cardiac events in the balloon group was 40% and in the stent group 30-9%. There was no difference between the two groups ($P = 0.3$).

Angiographic results at 6 months

Twenty asymptomatic patients refused follow-up angiogram, leaving 129 patients with 152 lesions for angiographic analysis. The quantitative coronary analysis angiographic results are presented in Table 4.
Table 2 Major adverse cardiac events at 1 year — hierarchical ranking scale

<table>
<thead>
<tr>
<th>Event</th>
<th>Up to 31 days n</th>
<th>%</th>
<th>Up to 6 months n</th>
<th>%</th>
<th>Up to 365 days n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 0 0</td>
<td></td>
<td>3 2 0</td>
<td></td>
<td>3 2 0</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>7 4 7</td>
<td>14</td>
<td>9 4</td>
<td>15</td>
<td>10 1</td>
<td>10</td>
</tr>
<tr>
<td>Q MI</td>
<td>3 2 0</td>
<td>8</td>
<td>5 4</td>
<td>8</td>
<td>5 4</td>
<td></td>
</tr>
<tr>
<td>Non-Q MI</td>
<td>4 2 7</td>
<td>6</td>
<td>4 0</td>
<td>7</td>
<td>4 7</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>0 0 0</td>
<td>2</td>
<td>1 3</td>
<td>3</td>
<td>2 0</td>
<td></td>
</tr>
<tr>
<td>TVR</td>
<td>0 0 0</td>
<td>23</td>
<td>15 4</td>
<td>30</td>
<td>20 1</td>
<td></td>
</tr>
<tr>
<td>No MACE</td>
<td>142 95 3</td>
<td>107</td>
<td>71 8</td>
<td>98</td>
<td>65 8</td>
<td></td>
</tr>
</tbody>
</table>

Hierarchical ranking scale considers only the worst event; i.e. if a patient required repeat angioplasty and later coronary artery bypass graft operation the ranking scale would reflect only the worst event. MI=myocardial infarction; CABG=coronary artery bypass grafting the patient required repeat angioplasty and later coronary artery bypass grafting; TVR=target vessel revascularization; MACE=major adverse cardiac events.

Table 3 Major adverse cardiac events at 1 year — total count of events

<table>
<thead>
<tr>
<th>Event</th>
<th>Up to 31 days n</th>
<th>%</th>
<th>Up to 6 months n</th>
<th>%</th>
<th>Up to 365 days n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 0 0</td>
<td></td>
<td>3 2 0</td>
<td></td>
<td>3 2 0</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>7 4 7</td>
<td>14</td>
<td>9 4</td>
<td>15</td>
<td>10 1</td>
<td>10</td>
</tr>
<tr>
<td>Q MI</td>
<td>3 2 0</td>
<td>8</td>
<td>5 4</td>
<td>8</td>
<td>5 4</td>
<td></td>
</tr>
<tr>
<td>Non-Q MI</td>
<td>4 2 7</td>
<td>6</td>
<td>4 0</td>
<td>7</td>
<td>4 7</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>0 0 0</td>
<td>2</td>
<td>1 3</td>
<td>3</td>
<td>2 0</td>
<td></td>
</tr>
<tr>
<td>TVR</td>
<td>0 0 0</td>
<td>23</td>
<td>15 4</td>
<td>30</td>
<td>20 1</td>
<td></td>
</tr>
<tr>
<td>No MACE</td>
<td>142 95 3</td>
<td>107</td>
<td>71 8</td>
<td>98</td>
<td>65 8</td>
<td></td>
</tr>
</tbody>
</table>

All events reflects the total count of events i.e. if a patient required repeat angioplasty an later coronary artery bypass grafting the total count would reflect both events and not just the worst occurred. MI=myocardial infarction; CABG=coronary artery bypass graft operation; TVR=target vessel revascularization; MACE=major adverse cardiac events.

The average vessel size was 3.06 ± 0.5 mm, the minimal luminal diameter 1.01 ± 0.31 mm, the lesion length 11 ± 3.9 mm. The restenosis rate in the target segment was always significantly lower compared with the restenosis rate in the irradiated segment and the vessel segment in all groups of patients including or excluding the total occlusions (P<0.001). This association was less strong for the balloon group, including (7% vs 21.1%, P=0.06) or excluding (5.4% vs 19.6%, P=0.04) the total occlusions. There was no difference in the restenosis rate between the irradiated segment and the vessel segment in all groups of patients (P=ns). The late loss between target angiographic control as mandated by the protocol. From 6 months up to 1 year the curve remains reasonably stable.

Late vessel occlusions

In 5.3% (8/152) of the treated vessels a total occlusion was documented at the follow-up angiogram. In five of them (four stents and one balloon) the patients were asymptomatic (silent total occlusion). The other three (all stents) presented with an acute coronary syndrome (two with Q myocardial infarction and one with non-Q myocardial infarction) 94, 59 and 80 days after the index procedure and were revascularized successfully. The incidence of vessel occlusion was 10-5% (six out of 57, all stents) in the initial period of recruitment, before 1999, when the recommendation for the duration of the antiplatelet therapy was 2 to 4 weeks. It dropped to 2.1% (two out of 95, one balloon and one stent) (P=0.02) after 1999 with the prolongation of the antiplatelet treatment for at least 8 weeks and up to 6 months.

One patient in the balloon group with a patent vessel without restenosis at 6 months presented with unstable angina 279 days after radiation. A late thrombotic occlusion of the irradiated vessel was documented at the angiogram. The patient was revascularized successfully.

Geographical miss and treatment failure

Geographical miss could not be determined in 25.1% (44/175) of the treated vessels due to inadequate filming. The geographical miss was observed in 67.9% (89/131) of the interpretable vessels and in 41.2% (108/262) of the edges of the effective irradiated segment and resulted in
a 16.3% incidence of edge restenosis, while the restenosis at the edges without geographical miss was only 4.3% \((P=0.004)\)\(^{26}\). Out of the 44 vessels with restenosis at the irradiated segment, in 24 restenosis was located at the edges and in 18 it was related to geographical miss. This inadequate treatment was responsible for 40% (18/44) of the treatment failures. In 20 vessels the restenosis was located in the effective irradiated segment and they represent the true treatment failures.

**Table 4 Angiographic results**

<table>
<thead>
<tr>
<th></th>
<th>TS (5 mm)</th>
<th>IRS (28 mm)</th>
<th>VS (42 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post F/UP</td>
<td>Post F/UP</td>
<td>Post F/UP</td>
</tr>
<tr>
<td>All patients with total occlusions (n=152 lesions)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MLD mm</td>
<td>2.54</td>
<td>2.28</td>
<td>1.75</td>
</tr>
<tr>
<td>Reference diameter mm</td>
<td>2.86</td>
<td>2.68</td>
<td>2.84</td>
</tr>
<tr>
<td>Late loss mm</td>
<td>0.26</td>
<td>0.33</td>
<td>0.28</td>
</tr>
<tr>
<td>Restenosis rate %</td>
<td>9.9</td>
<td>28.9</td>
<td>33.6</td>
</tr>
<tr>
<td>All patients without total occlusions (n=144 lesions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD mm</td>
<td>2.58</td>
<td>2.41</td>
<td>2.08</td>
</tr>
<tr>
<td>Reference diameter mm</td>
<td>2.89</td>
<td>2.83</td>
<td>2.87</td>
</tr>
<tr>
<td>Late loss mm</td>
<td>0.17</td>
<td>0.24</td>
<td>0.20</td>
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<tr>
<td>Restenosis rate %</td>
<td>4.9</td>
<td>25.0</td>
<td>29.9</td>
</tr>
<tr>
<td>Balloon group with total occlusions (n=57 lesions)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MLD mm</td>
<td>2.20</td>
<td>2.23</td>
<td>1.97</td>
</tr>
<tr>
<td>Reference diameter mm</td>
<td>2.55</td>
<td>2.65</td>
<td>2.71</td>
</tr>
<tr>
<td>Late loss mm</td>
<td>-0.03</td>
<td>0.14</td>
<td>0.12</td>
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<tr>
<td>Restenosis rate %</td>
<td>7.0</td>
<td>21.1</td>
<td>24.6</td>
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<tr>
<td>Balloon group without total occlusions (n=56 lesions)</td>
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<td></td>
<td></td>
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<tr>
<td>MLD mm</td>
<td>2.20</td>
<td>2.27</td>
<td>1.97</td>
</tr>
<tr>
<td>Reference diameter mm</td>
<td>2.55</td>
<td>2.70</td>
<td>2.70</td>
</tr>
<tr>
<td>Late loss mm</td>
<td>-0.07</td>
<td>0.11</td>
<td>0.08</td>
</tr>
<tr>
<td>Restenosis rate %</td>
<td>5.4</td>
<td>19.6</td>
<td>23.2</td>
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<tr>
<td>Stent group with total occlusions (n=95 lesions)</td>
<td></td>
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<tr>
<td>MLD mm</td>
<td>2.77</td>
<td>2.33</td>
<td>2.13</td>
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<tr>
<td>Reference diameter mm</td>
<td>3.05</td>
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<td>2.93</td>
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<tr>
<td>Late loss mm</td>
<td>0.44</td>
<td>0.43</td>
<td>0.57</td>
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<tr>
<td>Restenosis rate %</td>
<td>11.7</td>
<td>33.7</td>
<td>38.9</td>
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<td>Stent group without total occlusions (n=88 lesions)</td>
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<tr>
<td>MLD mm</td>
<td>2.82</td>
<td>2.49</td>
<td>2.16</td>
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<tr>
<td>Reference diameter mm</td>
<td>3.10</td>
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<tr>
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<td>0.33</td>
<td>0.33</td>
<td>0.28</td>
</tr>
<tr>
<td>Restenosis rate %</td>
<td>4.6</td>
<td>28.4</td>
<td>34.1</td>
</tr>
</tbody>
</table>

MLD=minimal luminal diameter; TS=target segment; IRS=irradiated segment, VS=vessel segment.

**Discussion**

Endovascular radiotherapy has emerged as a promising treatment for reducing restenosis. Investigations using animal models of restenosis demonstrate a dramatic inhibition of neointima formation after balloon and stent injury both after intravascular gamma and beta-radiation\(^{15–19}\). Following these encouraging results, human feasibility studies both with beta\(^{39}\) and gamma\(^{16}\) emitters showed that intracoronary brachytherapy is feasible and safe. In two randomized trials intracoronary gamma radiation showed a significant reduction in angiographic and clinical assessment of restenosis in patients undergoing coronary intervention for restenotic lesions after balloon angioplasty treated with stent\(^{19}\) and in-stent restenosis\(^{17}\).

Beta sources with more limited penetration may have inherent safety advantages over gamma sources, but conversely less efficacy in preventing restenosis, particularly in stented arteries\(^{66}\). King et al\(^{26}\) in a non-controlled feasibility trial using \(^{90}\)Sr/\(^{90}\)Y demonstrated a
low late lumen loss and late loss index compared with historical controls in patients with de novo lesions treated with balloon angioplasty followed by radiation with a non-centred source. Using the $^{32}$P as a beta-emitter reduced the restenosis rate and improved clinical outcome, as reported in a small randomized trial\[24\]. Recently beta radiation was proved to be as effective as gamma in reducing in-stent restenosis in a non-randomized trial\[18\].

**Evidence of treatment efficiency**

The angiographic end-points in the current study suggest effective inhibition of restenosis (9-9%) within the target segment in patients receiving radiotherapy compared with historical cohorts\[5,6\] treated with balloon angioplasty or stents. Excluding the late total occlusions, which have a different pathophysiology from that of the restenotic process, binary restenosis in the same segment is as low as 4-9%. This result is comparable with the 3-9% restenosis observed in the balloon group that received 18 Gy in the Dose Finding study\[41\]. The target segment represents the subsegment in which inappropriate radiation is technically excluded since this corresponds to the treatment target and is always appropriately covered by the radiation source and thus receives the prescribed dose. The restenosis rate in this segment reflects the full therapeutic potential of this treatment. Late lumen loss in this segment was also substantially lower compared with historical trials with similar angiographic and demographic characteristics\[3,4\]. Most importantly, in patients treated with balloon angioplasty alone, a negative late loss is observed in the target segment with enlargement of the vessel lumen at follow-up. A similar result was reported in the balloon group that received 18Gy in the Dose Finding study. The vessel expansion in the target segment resulted in comparable minimal luminal diameters between the balloon and the stent group at the 6 months follow-up angiogram (2.23 mm and 2.31 mm, respectively) and no difference in the restenosis rate (7% and 11.7%, respectively, $P=0.41$). This confirms previous observations made with intravascular ultrasound\[22\] indicating positive remodelling with enlargement of the total lumen and vessel volume 6 months after intracoronary beta radiation in vessels treated with balloon angioplasty. Radiotherapy is the first therapeutic modality achieving such a beneficial effect.

**Edge restenosis and treatment failures**

Edges restenosis, the so-called ‘edge effect’, observed both after radioactive stent implantation\[20\] and catheter-based radiotherapy\[24\] limits considerably the positive results observed at the site of the target segment, increasing binary restenosis from 9.9% to 28.9% at the irradiated segment. Careful retrospective analysis of all the procedural films revealed the aetiology of this failure. The combination of low dose radiation with injury, the so-called geographical miss, was responsible for 75% (18/24) of the edge failures or 40% (18/44) of the restenosis observed in the irradiated segment. Our ignorance of the microscopic extent of the perivascular injury (up to 10 mm away from the macroscopic injury\[42\]) of the proliferative effect of low dose radiation on the injured tissue\[43,44\], and the actual length of the effective radiation source account for this phenomenon. Beta radiation due to low penetration in the tissue results in acute fall-off of the dose delivered at the edges of the sources in the axial direction. This in an inherent property of all beta sources. For the current source this fall-off area was 2 mm on each side of the source, as measured with radiochromic film\[40\] limiting the effective radiation length to 26 mm, as opposed to the 30 mm distance between the gold markers which were used as guides for proper positioning of the source. For achieving a sufficient margin of effectively irradiated vessel at the edges of the injured segment a balloon to source ratio of one to two is advised. The use of longer sources up to 60 mm in length, which are now available, will allow treatment of lesions up to 30 mm.

In 73-8% of the vessels treated post-radiation intervention was performed. This was responsible for 53% of the incidence of geographical miss\[26\]. To avoid this complication, radiation therapy should be planned as the last intervention.

All the edge restenotic lesions were new non pre-existing lesions. In seven vessels the minimal luminal diameter was located outside the irradiated segment but inside the analysed vessel segment increasing binary restenosis from 28-9% (irradiated segment) to 33-6% (vessel segment). These were pre-existing lesions (five vessels), unmasked after the treatment of the target segment, or progression of the disease (two vessels) non-related to brachytherapy, which has proved to be safe in non-injured vessels both with beta\[34\] and gamma\[45\] emitters.

The edge restenosis phenomenon and the positive vascular remodelling observed after brachytherapy increased the incidence of relocation of minimal luminal diameter compared to the standard treatments\[38\]. This, in conjunction with the increment in the mean length of the analysed vessel segment, 42 mm in our study compared to the 28 mm in the Benestent I trial\[5\], made the interpretation of the results in brachytherapy trials more complex and any direct comparison with historical trials unfair. New methodological approaches in the quantitative coronary analysis, such as the one used in the present study with reports of the angiographic parameters for the stenotic, the irradiated and the total analysed segment will improve our understanding of the results of brachytherapy.

In 20 patients the restenosis was located in the effective irradiated segment representing the true failures of the treatment. Dose inhomogeneity, since our system is not centred or inappropriate dose, are possible explanations for these failures.
Clinical thrombosis and late angiographic occlusion

Eight patients (5.3%) presented with late total occlusion. Seven of the patients had a stent implanted during the index procedure and one was treated with balloon angioplasty alone. The incidence of occlusion in the stent group was 7.3% and in the balloon group 1.7% (P=0.1). An incidence of 9.1%[28] for in-stent restenotic lesions and 6.6%[27] for non-restenotic lesions has been recently reported with higher prevalence in patients treated with stent implantation. Various causes such as delayed healing[28], persistent dissections[31,32], late stent malposition[49], and increased radiation induced thrombogenicity[48] have been hypothesized to be the reasons.

In our study, a significant decrement in the incidence of vessel occlusion was observed with the prolongation of the antiplatelet treatment up to 6 months (10.5% vs 2.1%, P=0.02). Reduction in the incidence of the total occlusion and the late thrombosis was recently reported with the use of clopidogrel for 6 months in combination with aspirin after intracoronary γ-radiation for the treatment of in-stent restenosis[41]. Further randomized trials are necessary to evaluate the efficacy and the duration of antiplatelet occlusion treatment for the prevention of late vessel occlusion after intracoronary radiation therapy.

Recently drug eluting stents have been introduced for the prevention of restenosis. Preliminary results indicate that restenosis may be completely abolished by the sirolimus drug-eluting stents[48], and if confirmed could have a drastic impact on the use of brachytherapy for de novo lesions.

Study limitations

This is not a placebo-controlled study and the number of patients included is limited. Further randomized placebo-controlled studies are warranted to validate the efficacy of 90Sr radiotherapy for prevention of restenosis.

Conclusions

The results of this registry reflect the learning process of the practitioner. The full therapeutic potential of the brachytherapy with strontium 90, potentially reflected by the restenosis rate in the target segment, can only be unravelled once the incidence of the late vessel occlusion and geographical miss has been eliminated. Probably this report will herald some of the results of the large randomized trial undertaken in the U.S.A. using the same source (Beta-Cath trial).

Appendix

The participating centres and investigators of the BRIE group are listed along with the number of included patients in parenthesis.

References


CHAPTER 5


Application of β-Irradiation Through the Struts of a Previously Deployed Stent

International Journal of Cardiovascular Interventions 2000;3:121-125
Application of β-irradiation through the struts of a previously deployed stent

Georgios Sianos1, I Patrick Kay1, Stephane G Carlier1, Jurgen MR Lighart1, Alexander J Wardeh1, Veronique LMA Coen2, Peter C Levendag3, Patrick W Serruys1

Introduction

In-stent restenosis affects 15–20% of patients undergoing balloon angioplasty (BA) and stenting for de novo lesions1,2 and can occur in up to 40–60% of stents implanted in long lesions in small vessels.3,4 Landmark studies have shown that γ-radiation is effective for the treatment of in-stent restenosis.5–7 Preliminary studies with β-radiation demonstrated feasibility for in-stent restenosis and results comparable with those of γ-radiation.8–10 However, most of the large-scale studies (START, START 40/20, INHIBIT) are still ongoing in order to determine the efficacy of β-radiation. The application of radiation in patients with complex anatomy such as the involvement of a major bifurcation or those whose native coronary anatomy has been greatly modified by previous interventions may be technically very challenging.

Case report

This is the first case in which the 5 F. delivery catheter of the Beta-Cath™ System (Novoste Corp., Norcross, GA) was advanced through the struts of a stent, previously deployed in an adjacent branch, so as to deliver radiation to the target vessel. (Int J Cardiovasc Intervent 2000, 3: 121-125)

Keywords: brachytherapy – restenosis
with 3 mm ST depression in leads II, III, AVF and V4-V6 at the electrocardiogram. For this reason, cardiac catheterization was undertaken. The coronary angiogram revealed a severe stenosis, 83%, by quantitative coronary angiography (QCA) (CAAS II analysis system; Pie Medical BV, Maastricht, The Netherlands) in the distal part of the saphenous vein graft (SVG) to the LAD, and severe in-stent restenosis in both stents implanted in the proximal (76%) and distal (87%) LCX (Figure 1(A)). The intermediate branch was occluded because of severe in-stent restenosis. This stent had been placed with significant encroachment into the proximal LCX artery (Figure 1(B)). Left ventricle (LV) function was preserved (ejection fraction 62%).

The patient was referred to the authors’ hospital for further treatment. After surgical consultation he was graded as a high-risk patient for repeat CABG and a decision to undertake further percutaneous intervention was taken. After detailed information and a written consent form had been obtained he was enrolled in the RENO registry. This is a prospective, multicenter, multinational surveillance registry for assessing the clinical event rate of 90Sr/90Y source (Beta-Cath system) combined with approved PTCA techniques in patients with coronary artery disease (native or bypass grafts).

Medication at the time of the intervention included beta-blockers, calcium antagonists, nitrates and aspirin. One hour before the intervention the patient received 300 mg clopidogrel. After intravenous administration of 7500 iu heparin and 250 mg acetylsalicylic acid the ostium of the SVG to the LAD was cannulated with an 8 F. JR4 guiding catheter (Vista Brite Tip; Cordis, Miami, FL) to accommodate the 5 F. radiation delivery catheter. After crossing the lesion with the guidewire (PT Graphix Intermediate, Boston Scientific, Galway, Republic of Ireland) direct stent implantation (Multi-Link Duet 3.5 × 13 mm; Guidant, ACS, Temecula, CA) was performed with a very good final angiographic result. Subsequently intracoronary radiation was performed (prescribed dose 16 Gy at 2 mm from the center of the source).

After engagement of the Left Main stem (LM) with an 8 F. AL2 guiding catheter (Vista Brite Tip; Cordis, Miami, FL) the procedure continued with the treatment of the LCX. A PT Graphix Intermediate 0.014″, 185 cm-long guidewire (Boston Scientific) was advanced with difficulty through the struts of the stent and placed at the ostium of the intermediate branch. The restenotic lesions in the proximal and distal LCX were crossed with the wire. The distal lesion was dilated with a 2.5 × 20 mm balloon (Worldpass; Cordis Europa, Roden, The Netherlands) with pressures up to 20 atm with an angiographic result. The proximal lesion, which included the proximal struts of the stent implanted in the intermediate branch, was dilated sequentially with 2.5, 3.0 × 20 mm and 3.5 × 10 mm Worldpass balloons with pressures up to 20 atm. Full expansion of the balloons was not achieved due to strut compression (Figure 2(A)), but with an acceptable angiographic result.

According to the RENO study protocol β-radiation was aimed to be delivered in both dilated segments. The 3 F. nontapering delivery catheter was advanced, with difficulty, through the dilated struts of the stent in the intermediate branch. This procedure was made more difficult by the acute angulation between the left main stem and the LCX. The catheter was carefully placed at the distal lesion so as to cover the whole length of the injured area (Figure 2(B)), and to avoid geographical miss. Subsequently, the delivery catheter was pulled back and placed in the proximal lesion without difficulty (Figure 3). In order to avoid overlapping and excessive radiation of a part of the vessel
the initial cine image of the radiation source in position in the distal lesion was projected over the real time roentgenographic image of the proximal lesion. By applying simultaneous roentgenographic overprojection and ensuring that the image was acquired in the same phase of the respiratory and cardiac cycle, excessive radiation to areas of the coronary artery was avoided. With a three-minute dwell time, 16 Gy, at 2 mm from the center of the radiation source, was also delivered to the proximal lesion. After completion of the irradiation, the source and the delivery catheter were withdrawn without difficulty, but a filling defect was noticed in the proximal irradiated segment with the angiographic appearance of thrombus (Figure 2(C)). An 8.5 ml bolus dose of intracoronary ReoPro (abciximab) was administered followed by a 2.2 ml per hour intravenous infusion. The activated clotting time at that moment was 343 seconds with a maximum value during the procedure of 362 seconds.
After a 15-minute wait it was apparent that there was no improvement in the angiographic appearance and the lesion was stented with a Multi-Link Tristar 3.5 × 13 mm stent with a good final angiographic result (Figure 2(D)). At the end of the procedure the patient was transferred back to the referring hospital. The same day he developed neurological symptoms and the diagnosis of intracerebral bleed at the left frontal lobe was made by means of a computerized tomography scan. Despite optimal medical treatment the patient died four days later.

Device description

The Novoste Beta-Cath device consists of three components: (1) the transfer device which stores the radiation source train and allows the positioning of these sources within the catheter; (2) the delivery catheter, which is a 5 F. multilumen over-the-wire noncentered catheter which uses saline solution to send and return the radiation source train; and (3), the radiation source train consisting of a series of 12 independent cylindrical seeds which contain the radioisotope 89Sr sources and which is boundaried by two gold radiopaque markers separated by 30 mm.12

Discussion

This paper reports the first case of intracoronary irradiation with the use of the Beta-Cath system, in which the delivery catheter crossed the struts of a stent previously deployed in another vessel, for the delivery of radiation in the target vessel. Although feasible, one must always keep in mind the risks of complications, such as thrombus formation, because of prolonged positioning of bulky devices in the coronary circulation. From animal studies there is evidence that radiation induces dose-dependent thrombosis.13 Also to be considered is the potential risk of kinking of the delivery catheter leading to entrapment of the radiation source and inability to retrieve the device, with subsequent potentially deleterious effects. Balloon entrapment during side-branch angioplasty through a stent has been described.14 New 3 F. delivery catheters are currently under development (Novoste, personal communication, 2000). This will make the application of beta-radiation with this system easier, safer and applicable in smaller vessels. Dose perturbations caused by stents, especially for the beta-radiation, which has a finite range in the tissue (typically a few millimeters) is an important issue for the management of in-stent restenosis. In a balloon liquid-filled model the average dose reduction varied from 4% to 14% in the presence of nine different types of stents, depending on stent mass, geometry, strut thickness and composition.15 For the NIR stent this attenuation was found to be in the area of 4%. If this shielding effect proves to be clinically important, dose adjustments may be required to use beta-sources effectively for treatment of restenotic lesions that have previously been stented, particularly when there are multiple or overlapping stents. Additionally, stents with low attenuation may be used for primary stenting before radiation whereas others should be reserved for postradiation stenting. The deformation of various types of stents with simulated side-branch dilation in phantom vessels has been recently reported.16 When the struts of an NIR stent were dilated with a 3.5 mm balloon at 6 atm the minimal lumen diameter at the side-branch ostium, which corresponds to the deformation of the struts, was 1.7 mm. This diameter is slightly bigger than the diameter of a 5 F. (1.65 mm) catheter. In the era of intracoronary brachytherapy, where bulky delivery catheters might need to cross stent struts, the selection of a stent with the bigger cell dimensions when fully deployed might be an important issue. Under these circumstances a seven-cell NIR stent, for example with a cell diameter of 1.1 mm when fully deployed, is more suitable than the nine-cell design of the same stent with a cell diameter of 0.6 mm.

Restenosis rate after balloon angioplasty is higher at a bifurcation site.17 Various techniques for stenting bifurcated lesions have been reported for better acute outcome and to reduce restenosis.18 True bifurcational stents have also been described with promising results,19 but restenosis remains a significant limitation. Brachytherapy usage is most compelling for the treatment of recurrent in-stent restenosis.20 Because of this, interventional cardiologists will face the challenge of crossing the struts of stents with radiation delivery catheters for irradiation of side-branches or bifurcation lesions.

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References


CHAPTER 6


Safety of Routine Intracoronary Beta-Irradiation: Acute and One Year Outcome in Patient at High Risk for Repeat Occurrence of Stenosis.

Eur Heart J 2002; 23: 1038-1044
Routine intracoronary beta-irradiation

Acute and one year outcome in patients at high risk for recurrence of stenosis

E. Regar1, K. Kozuma1, G. Sianos1, V. L. M. A. Coen2, W. J. van der Giessen1, D. Foley1, P. de Feyter1, B. Rensing1, P. Smits1, J. Vos1, A. H. M. Kno0k1, A. J. Wardeh1, P. C. Levendag2 and P. W. Serruys1

1Department for Cardiology, Thoraxcenter, University Hospital Rotterdam, Rotterdam, The Netherlands; 2Department for Radiotherapy, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

Aims Intracoronary radiation is a promising therapy potentially reducing restenosis following catheter-based interventions. Currently, only limited data on this treatment are available. The feasibility and outcome in daily routine practice, however, is unknown.

Methods and Results In 100 consecutive patients, intracoronary beta-radiation was performed with a 90Strontium system (Novoste Beta-Cath) following angioplasty. Predominantly complex (73% type B2 and C) and long lesions (length 24.3 ± 15.3 mm) were included (37% de novo, 19% restenotic and 44% in-stent restenotic lesions). Radiation success was 100%. Mean prescribed dose was 19.8 ± 2.5 Gy. A pullback procedure was performed in 19% lesions. Geographic miss occurred in 8% lesions. Periprocedural thrombus formation occurred in four lesions, dissection in nine lesions. During hospital stay, no death, acute myocardial infarction, or repeat revascularization was observed. Major adverse cardiac events occurred predominantly between 6 and 12 months after the index procedure with major adverse cardiac event-free survival of 66% at 12 months (one death, 10 Q-wave myocardial infarctions, 23 target vessel revascularizations; ranked for worst event).

Conclusion Routine catheter-based intracoronary beta-radiation therapy after angioplasty is safe and feasible with a high acute procedural success. The clinical 1-year follow-up showed delayed occurrence of major adverse cardiac events between 6 and 12 months after the index procedure. (Eur Heart J, 2002; 23: 1038–1044, doi:10.1053/euhj.2001.3045)

Key Words: Brachytherapy, angioplasty, safety, radio-isotopes.

See page 999, doi:10.1053/euhj.2001.3176 for the Editorial comment on this article

Introduction

Although balloon angioplasty and stent placement have become the predominant modes of coronary revascularization, restenosis remains the major limitation for catheter-based therapies. Restenosis rates in short type A and B lesions are reported to be 30–40% for conventional balloon angioplasty and 15–30% for stents[13]. Coronary radiation is a promising therapy potentially reducing restenosis. Current concepts for coronary irradiation include external radiation[1], radioactive balloons[4], radioactive stents[5–7] and afterloading. Currently, only limited data on this treatment are available[8–10]. The safety and feasibility in daily routine application, however, are unknown. We report on the acute procedural and long-term clinical success using routine 90Strontium/Yttrium radiation in a patient population at high risk for recurrence of stenosis.

Methods

Patients

The patient population consisted of consecutive patients within the multicentre RENO registry[11] with angina
and/or objective evidence of ischaemia, who had angiographically documented coronary artery disease and were scheduled to undergo beta-brachytherapy. Patients were included after successful treatment with conventional angioplasty and/or debulking procedures. Patients with impaired left ventricular function (<30%), undergoing or having prior chest radiotherapy, acute myocardial infarction or angiographic evidence of fresh thrombus (filling defect proximal to or involving the stenosis) prior to radiation therapy were excluded. All included patients had given written informed consent.

**Angioplasty and radiation procedure**

Angioplasty was performed via the femoral approach using routine procedures with commercially available systems and 8F guiding catheters. The position of all balloons, stents or debulking devices was documented angiographically. After the initial catheter-based procedure, the absence of dissection, thrombus or spasm prior to placement of the Beta-Rail delivery catheter was assured by contrast injection after a waiting period of 5–10 min.

Pre-interventional medication included non-enteric aspirin (325 mg) and intravenous heparin (10 000 to 15 000 IU), in order to keep the activated clotting time to >300 s during the procedure. Post-interventional medication consisted of long-term aspirin and antiplatelet therapy (clopidogrel 75 mg daily after a loading dose of 300 mg on the day of the procedure) for 3–7 months.

Intracoronary beta-irradiation was performed using a 90Strontium/Yttrium source with a non-centring catheter (Novoste Beta-Cath). Following successful angioplasty, the Beta-Rail delivery catheter was advanced over the guide wire into the vessel so that the radiopaque markers on the delivery catheter were equidistant from the centre of the injured segment, with a margin to the edge of the injured segment of 7 mm. After withdrawal of the guide wire, the source train was transported hydraulically to the distal end of the delivery catheter. The position of the source was documented angiographically. At the end of the calculated radiation time, the source was withdrawn and the Beta-Rail delivery catheter was removed over the guide wire. The dose was delivered at 2 mm from the source axis and adapted to the vessel diameter. Dosage calculation and delivery of the radioactive seeds was carried out by a radiation oncologist. The length of the source train was 30 mm, 40 mm or 60 mm. If the injured segment could not be covered completely with one source, a pullback procedure was performed. The source train was first positioned to cover the distal portion of the injured segment, then withdrawn to cover the proximal portion of the injured segment. Proximal positioning of the delivery catheter was performed using a dummy source train and overlay imaging technique. An ECG-gated videoloop, showing the distal source position projected on the fluoroscopic image, was performed in the same projection, table position and expiration position of the patient. The delivery catheter was placed in such a way that the radiopaque marker, indicating the proximal end of the distal source, overlapped with the distal marker of the proximal dummy source. After exact positioning, the dummy source was removed hydraulically and the active source train inserted.

**Success**

Procedural success was defined as ≤30% residual stenosis post procedure before removal of the guiding catheter and a successful radiation therapy procedure. Brachytherapy success was defined as complete (>90%) delivery of the prescribed radiation dose, including dose interruption and resumption. Clinical success was defined as procedural success without the occurrence of major adverse cardiac events (death, myocardial infarction, target vessel re-PTCA or coronary artery bypass grafting (CABG)) during the hospital stay.

**Angiography**

On-line quantitative coronary analysis was performed using the CAAS II system (Pie Medical, Maastricht, NL). All angiograms were evaluated after intracoronary administration of nitrates. The minimal lumen diameter was determined by edge detection; the reference diameter was automatically calculated by the interpolated method. The percent diameter stenosis was calculated from the minimal lumen diameter and the reference diameter. Lesions were classified as discrete (<10 mm length) or diffuse (>10 mm length).

**Follow-up**

Clinical follow-up for the occurrence of major adverse cardiac events, was performed within 12 months of the radiation procedure.

**Statistical analysis**

All statistical analysis was performed with commercially available software (SPSS 9.0, SPSS Inc. Chicago, Illinois, U.S.A.). Data are presented as mean ± standard deviation, median and [interquartile range] or proportions. Survival analysis was conducted using the Kaplan–Meier method.

**Results**

In the 100 patients who were included prospectively, 108 arteries were treated.

**Patient characteristics**

Patient baseline characteristics are given in Table 1. Coronary risk factor distribution was typical of the
Routine use of Brachytherapy

Lesion characteristics and angiographic data

Lesions were located in 102 native arteries (36 LAD, 28 LCx, 38 RCA) and in six venous bypass grafts. Forty were de-novo lesions and 68 were restenoses, of which 47 were in-stent restenotic lesions. Lesion type was A in four lesions, B1 in 17, B2 in 46 and C in 33 lesions, of which 12 showed total occlusion. Lesion length was 24.3 ± 15.3 mm, with 90% of lesions being longer than 10 mm. Reference diameter was 3.02 ± 0.58 mm and minimal lumen diameter 1.09 ± 0.18 mm, resulting in a mean diameter stenosis of 77.2 ± 13.4%. The final reference diameter was 3.13 ± 0.56 mm, the final minimal lumen diameter 2.47 ± 0.21 mm and the final diameter stenosis 21.2 ± 7.8%.

Angioplasty procedure

Angioplasty was performed in all lesions (n=108). In four lesions, debulking was used prior to balloon angioplasty and irradiation (three laser, one directional atherectomy). Angioplasty consisted of balloon inflation in 25 lesions and stent implantation in 79 lesions. Stenting was performed electively in 80%, due to an insufficient angioplasty result in 9% and to dissection after balloon dilatation in 11%. In 39 lesions direct stenting was performed. The procedural success rate was 92%.

Brachytherapy success

Intracoronary beta-irradiation was possible in all 108 lesions, resulting in a brachytherapy success rate of 100%. The mean prescribed dose was 19.8 ± 2.5 Gy at 2 mm from the centre of the source axis. To cover the injured vessel segment, a long source of 60 mm was used in three lesions and in 21 lesions a pullback procedure was performed (Table 2). Complete coverage with a safety margin of at least 7 mm proximal and distal to the injured segment could be achieved in 99/108 lesions; thus geographic miss occurred in only 8.3% of the lesions.

Irradiation had to be fractionated in four patients due to severe angina and ECG changes indicative of myocardial ischaemia. Non flow-limiting thrombus formation, successfully treated with GPIIb/IIIa inhibitors, occurred in four lesions. Dissections were observed after manipulation of the delivery catheter in nine lesions. Of these, three were type B and C dissections, necessitating stent implantation, six were non flow-limiting type A dissections not requiring further treatment.

Clinical success

After the procedure and during hospital stay, no death, acute myocardial infarction, or repeat revascularization was observed. One patient, who underwent the procedure for acute myocardial infarction showed a rise in creatinine kinase up to 723 IU. l⁻¹. Thus, the clinical success rate was 91%. Median time to hospital discharge after the procedure was 2 (1;2) days. One patient, treated for a type C lesion in the medial right coronary artery with direct stent implantation (slotted tube stent 3.0/20 mm) followed by irradiation with a 30 mm source, developed pericardial tamponade after the procedure caused by the exit of the PTCA guide wire prior to irradiation. It was successfully treated with pericardial drainage. The patient was discharged 4 days after the procedure. Two patients with insulin-dependent diabetes mellitus and pre-existing impairment of renal function (creatinine 137 mmol. l⁻¹ and 154 mmol. l⁻¹)
developed acute transient renal insufficiency after the procedure. This resolved after forced hydration in combination with furosemide. The subsequent hospital stay of these patients was uneventful, one left the hospital 4 days, the other 10 days after the procedure. Four patients developed isolated mild creatinine kinase elevation (mean 374 ± 123 IU l⁻¹) within 24 h of the procedure without chest pain or ECG changes (Table 3).

### One year follow-up

During 12 months clinical follow-up, 34 patients experienced major adverse cardiac events, which are given in Table 4. Mean follow-up time was 359 ± 34 days. Event-free survival is given in Fig. 1. Target vessel repeat PTCA was clinically driven by the recurrence of angina in all patients. In the patient group undergoing CABG, one patient showed severe progression of coronary artery disease, including the left main stem, but no restenosis at the target vessel. Three patients experienced myocardial infarction prior to CABG.

In the 29 patients with target vessel restenosis, restenosis was discrete (<10 mm length) in 17 patients and located at the proximal (n=6), the distal (n=5) or both extremities (n=6) of the index lesion. Seven patients showed diffuse restenosis (>10 mm length) and five patients total vessel occlusion. During the follow-up period, nine patients experienced acute myocardial infarction (while one patient underwent the index procedure for acute myocardial infarction as described above). Out of these nine patients, three received a new coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; CK=creatinine kinase.

*One patient underwent the angioplasty procedure for acute myocardial infarction.

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiac event (MACE)</td>
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</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
<td>1*</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
</tr>
<tr>
<td>Repeat PTCA</td>
<td>0</td>
</tr>
<tr>
<td>Clinical event</td>
<td></td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>1</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2</td>
</tr>
<tr>
<td>Isolated CK elevation</td>
<td>4</td>
</tr>
</tbody>
</table>

CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; CK=creatinine kinase.

Table 3. In-hospital major adverse cardiac and clinical events. Data are given as numbers (no.) of events, no patient experienced multiple events.

<table>
<thead>
<tr>
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<th>Ranking</th>
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<tbody>
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<td>1</td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
<td>10*</td>
<td>10</td>
</tr>
<tr>
<td>CABG</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Repeat PTCA</td>
<td>24</td>
<td>20</td>
</tr>
</tbody>
</table>

CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty.

*One patient underwent the angioplasty procedure for acute myocardial infarction.

Table 4. Major adverse cardiac events at 12 months follow-up. Data are given as numbers (no.) of events and ranked (ranking) as follows: death, Q-wave myocardial infarction, CABG, repeat PTCA.

Figure 1 Event-free survival at 12 months follow-up (Kaplan–Meier). TVR=target vessel revascularization, includes repeat PTCA and CABG. MACE=major adverse cardiac events. Events are given ranked as follows: death, Q-wave myocardial infarction, CABG, repeat PTCA.
patients who developed transient renal insufficiency. This increased the consumption of contrast agents, which was not without risk, as seen in our study. This was similar to that seen in 4/15 patients in the Geneva series\(^{18}\). In our study with a non-centred device, dose fractionation was necessary in only 4/108 lesions. The need for dose fractionation might be further reduced by the introduction of smaller 3·5 F brachytherapy catheters.

**Discussion**

**Study population**

This study describes the clinical outcome of routine intracoronary beta-irradiation in a large number of patients at high risk for recurrence of stenosis. This is indicated by the relatively high proportion of patients with multivessel disease, restenosis, type B2 and C lesions and the lesion length. Thus, our series is likely to reflect ‘real world’ lesions in a tertiary care centre. The generalizability of study results is important as the lesion length. This was similar to that seen in 4/15 patients in the Geneva series\(^{18}\). In our study with a non-centred device, dose fractionation was necessary in only 4/108 lesions. The need for dose fractionation might be further reduced by the introduction of smaller 3·5 F brachytherapy catheters.

**Feasibility in the ‘real world’**

Brachytherapy was applied routinely and with considerable success. The prescribed radiation dose could be delivered to all lesions. Special care was taken to completely cover the injured vessel segment in order to avoid ‘geographic miss’, the deleterious effect of balloon-induced injury and low dose radiation at the extremities of the source train\(^{14}\). To overcome this potential limitation of intracoronary irradiation, sequential pullback or a combination of source trains of different lengths was performed in a relatively high proportion of patients. The 60 mm long source became available only at the end of the study. The use of a long source, however, might in future spare the relatively complex pullback procedures. Every step of the procedure needed to be documented by contrast injection to avoid geographic miss. This increased the consumption of contrast agents, which was not without risk, as seen in our patients who developed transient renal insufficiency.

**Procedural complications**

No acute or subacute major adverse cardiac events or irradiation-induced major complications were seen. The procedural costs (assessed by the costs of the used material), however, were raised substantially from a mean of 3200 Euro for conventional coronary angioplasty procedures (1/2000–5/2000) to 4100 Euro. Thus, the cost-effectiveness of intracoronary brachytherapy still needs to be proven. Our findings are in accordance with previous published data\(^{16}\) on various afterloading techniques. In some of these series, however, irradiation-induced adverse events were reported. Using a 192 Iridium source, Condado et al. describe successful gamma-radiation delivery in all 21 patients following balloon angioplasty; however, one patient developed prolonged coronary spasm, and another suffered subacute thrombosis\(^{15}\). In contrast in another series of 26 patients with restenotic or in-stent restenotic lesions, no in-hospital adverse events were seen\(^{16}\). In a larger patient cohort (n=130) undergoing randomized gamma irradiation for in-stent restenosis, two patients in the placebo and two in the radiation group required fractionation of radiation due to angina and ischaemia, two patients required vascular access site repair and 8% of patients had creatine kinase MB elevation\(^{17}\). Similarly, dose fractionation due to ischaemia was required in 11/50 patients receiving beta-afterloading with a centred device for in-stent restenosis\(^{17}\), indicating insufficient distal perfusion with the centring balloon during irradiation. This was similar to that seen in 4/15 patients in the Geneva series\(^{18}\). In our study with a non-centred device, dose fractionation was necessary in only 4/108 lesions. The need for dose fractionation might be further reduced by the introduction of smaller 3·5 F brachytherapy catheters.

**Thrombus**

The most frequently seen events with a possible irradiation association were thrombus formation and dissections. In our series, in four lesions intracoronary thrombus formation during the procedure could be visualized by angiography as a contrast filling defect. In all four lesions, thrombus formation was not flow-limiting. All patients received GP IIb/IIIa inhibitors intravenously for 12 h, their in-hospital course was uneventful, without evidence for (sub-)acute thrombosis.

**Dissection**

In 9/108 lesions, dissections were documented angiographically at the end of the irradiation procedure. In 3/9 lesions, further preventive stent implantation was performed\(^{19}\). However, the prognostic impact of non flow-limiting dissections in patients undergoing brachytherapy is poorly understood. Previous case series (16 patients each) with acute dissection following balloon angioplasty and intracoronary beta-irradiation have shown that these dissections persist in approximately 50% of the patients\(^{20,21}\) at the 6 month follow-up. Persisting dissections were not associated with a change in angina status or any acute or subacute clinical
follow-up showed delayed major adverse cardiac events occurring between 6 and 12 months after the index procedure.

The authors appreciate the efforts of the catheterization laboratory staff and the radiation staff and would like to thank Mrs J. van Wijk-Edelman for the careful administration of patient data. The Weenckebach prize was awarded to Dr Serruys by the Dutch Heart Foundation for brachytherapy research. Dr Regar is supported by a grant of the ‘Deutsche Forschungsgemeinschaft’.

**References**


**Limitations**

This is a non-randomized, non-placebo controlled monocentre experience. We evaluated only one type of beta-radiation delivery catheter; thus, these results cannot be extrapolated to other radiation (e.g. centering) delivery systems or other (e.g. gamma) sources. These data are restricted to the 12 month outcome. Radiation-induced delayed restenosis needs to be further investigated. The small number of events in this study does not allow the identification of patient- or lesion-related factors predicting adverse procedural outcome.

**Conclusion**

Routine catheter-based intracoronary beta-radiation therapy after angioplasty is safe and feasible with a high acute procedural success. However, the clinical 1-year
Routine use of Brachytherapy


CHAPTER 7


Geographical Miss During Catheter-Based Intracoronary Beta-Radiation: Incidence and Implications in the BRIE Study. Beta-Radiation In Europe

J Am Coll Cardiol 2001;38:415-20
Geographical Miss During Catheter-Based Intracoronary Beta-Radiation: Incidence and Implications in the BRIE Study
Georgios Sianos, MD,* I. Patrick Kay, MBChB,* Marco A. Costa, MD, PhD,* Evelyn Regar, MD,* Ken Kozuma, MD,* Pim J. de Feyter, MD, PhD,* Eric Boersma, PhD,* Clemens Disco, MSc,† Patrick W. Serruys, MD, PhD, FESC, FACC* Rotterdam, Netherlands

OBJECTIVES We sought to determine the incidence and causes of geographical miss (GM) and to evaluate its impact on edge restenosis after intracoronary beta-radiation therapy.

BACKGROUND Edge restenosis is a limitation of intracoronary beta-radiation therapy. Geographical miss is the situation in which the radiation source does not fully cover the injured segment and may lead to edge restenosis.

METHODS We analyzed 175 vessels treated according to the Beta-Radiation In Europe (BRIE) study protocol. The effective irradiated segment (EIRS) and both edges were studied with quantitative coronary angiography. The edges of the EIRS that were injured constituted the GM edges. Restenosis was defined as diameter stenosis >50% at follow-up. Geographical miss was determined by simultaneous electrocardiographic-matched, side-by-side projection of the source and balloons deflated at the injury site, in identical angiographic projections surrounded by contrast.

RESULTS Geographical miss affected 41.2% of the edges and increased edge restenosis significantly compared with non-GM edges (16.3% vs. 4.3%, respectively, p < 0.004). Restenosis was increased both in the proximal (p = 0.05) and distal (p = 0.02) GM edges compared with noninjured edges. Geographical miss associated with stent injury significantly increased edge restenosis (p = 0.006), whereas GM related to balloon injury did not significantly increase edge restenosis (p = 0.35). The restenosis in the EIRS was similar between vessels with and without GM (24.3% and 21.6%, respectively, p = 0.8).

CONCLUSIONS Geographical miss is strongly associated with restenosis at the edges of the EIRS. This effect is more prominent when caused by stenting. Geographical miss does not increase restenosis in the EIRS. (J Am Coll Cardiol 2001;38:415–20) © 2001 by the American College of Cardiology

Intracoronary radiation therapy is a new technique for the prevention of restenosis after percutaneous coronary interventions (1–3). Catheter-based systems and radioactive stents are currently used to deliver radiation (4). The development of stenotic lesions at the edges of the segment receiving the full-prescribed dose is a potential limitation of this treatment. This phenomenon described both after radioactive stent implantation and catheter-based intracoronary radiation was termed the “edge effect” (5–7). The pathophysiology of the “edge effect” may be the result of vessel wall injury (8–10) concomitant with low-dose radiation at the edges of the irradiated segment (11,12). The term geographical miss (GM) was invented in radio-oncology to define a cause of treatment failure due to low dose radiation. In such cases, a small part of the treatment zone either escaped radiation or was inadequately irradiated because the total volume of the tumor was not appreciated and hence an insufficient margin was taken (13). This concept was translated in interventional cardiology to define those coronary segments that were injured but received low-dose radiation (14). Aims of the study were to determine the incidence and causes of GM and to evaluate the impact of this inadequate treatment on the angiographic outcome in vessels treated according to the protocol of a multicenter intracoronary beta-radiation study using a catheter-based system.

METHODS Patient selection. We retrospectively analyzed 149 patients treated with catheter-based beta-radiation using the Beta-Cath system (Novoste Corp., Norcross, Georgia) enrolled in the Beta-Radiation In Europe (BRIE) trial. Patients included in the radiation protocol were those with objective signs of ischemia and presence of significant de novo lesions. Out of the total population, 123 patients underwent single-vessel percutaneous transluminal coronary angioplasty and the remaining 26 patients underwent two-vessel angioplasty, giving 175 vessels in total. In 36 patients (44 vessels) GM was not interpretable, leaving 113 patients with 131 vessels for further analysis. Characteristics of patients with interpretable angiographic documentation are summarized in Table 1.
Device description. The device consists of three components: 1) the transfer device, which stores the radiation source train and allows its positioning within the catheter; 2) the delivery catheter, which is a 5 Fr multilumen noncentered catheter that uses saline to send and return the radiation source train; and 3) the radiation source train, consisting of 12 independent cylindrical seeds that contain the radioisotope $^{90}$Sr/$^{90}$Y source, encompassed by two radiopaque gold markers (30 mm in length) (4). The longitudinal distance of the “full” prescribed dose (100% isodose) coverage measured by radiochromic film is about 26 mm (15), constituting the effective irradiation length.

Dosimetry. Prescribed dose at 2 mm from the centerline of the source axis was 14 to 18 Gray (Gy), based on the reference diameter, by on-line quantitative coronary angiography (QCA), measured <3.35 mm or >3.35 mm, respectively. The radiation source remained at the treatment site for approximately 2 to 4 min to deliver the prescribed dose. Post-hoc QCA confirmed appropriate dosimetry in all treated vessels.

Definitions. Vessel segment (VS) defined the coronary segment bordered by two side branches that encompassed the original lesion, angioplasty balloon and radiation source. The injured segment (INS) was encompassed by the balloons used for dilation or stent implantation. The proximal and distal position of the radiopaque markers of the original lesion, angioplasty balloon and radiation source. The injured segment (INS) was encompassed by the most proximal and distal position of the radiopaque markers of the balloons used for dilation or stent implantation. The irradiated segment, 30-mm in length, was defined as the segment encompassed by the two gold markers of the radiation source train. The effective irradiated segment (EIRS) was the segment that received the full-prescribed dose and corresponded to the 26-mm central part of the radioactive source train. These segments are illustrated in Figure 1. The edges of the EIRS are the adjacent (proximal and distal) 5 mm coronary segments, consisting of the 2 mm inside and 3 mm outside the gold markers. These edges received low-dose radiation because of fall-off of dose in the beta-emitting $^{90}$Sr/$^{90}$Y source (16,17). The highest prescribed dose was 18 Gy at 2 mm from the centerline of the source axis and the calculated dose at each millimeter away from the 100% isodose in the axial direction was expected to be 15.5 Gy at 1 mm, 11 Gy at 2 mm, 5.5 Gy at 3 mm, 2.4 Gy at 4 mm and <1 Gy at 5 mm (Fig. 1). Those edges, which were traumatized by balloon inflation (minimum inflation pressure was 6 atmospheres) or received new stent implantation during the procedure, were defined as GM edges. Noninjured edges were those that were not traumatized during the procedure.

Determination of the GM edges. To determine whether the edges of the EIRS were injured, we retrospectively analyzed, blind to the presence or absence of restenosis and its location at follow-up, all the baseline (intervention plus radiation) angiograms. The following steps were followed: during the procedure all the interventions (balloons or stents) deflated at the site of injury and the radioactive source in place were filmed with contrast in identical angiographic projections. This approach allowed us to define the location of the various subsegments (EIRS, INS and edges) in relation to side branches and the correct matching of the angiograms in the offline analysis. A continuous electrocardiogram recording was also displayed, allowing the selection of still frames in the same part of the cardiac cycle. Multiple angiographic loops and electrocardiographic-matched still frames could be displayed simultaneously, side by side, on the screen with the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, Netherlands). By identifying the relationship between the EIRS and its edges relative to the INS, we determined the GM edges. Two independent cardiologists (G.S., M.C.) performed the above-mentioned analysis. There was only 10% disagreement on the presence or absence of GM and its location proximal or distal. These were borderline cases that were reanalyzed by a third reviewer (P.W.S.) with the use of transparencies before a final conclusion was determined.

In cases where one or more of the following criteria were present, the procedure was reported as noninterpretable: 1) incorrect filming of the radiation source or the balloons deflated with contrast injection; 2) more than 10° difference in the angiographic projections not allowing correct matching; and 3) interventions reported in the technician’s work sheet but not filmed.

Table 1. Patients and Procedural Characteristics

| Age (range) | 59 (35 to 85 yrs) |
| Males | 83/113 (73.4%) |
| Diabetes | 17/113 (15%) |
| Hypertension | 39/113 (34.5%) |
| Prior MI | 39/113 (34.5%) |
| Prior CABG | 5/113 (4.4%) |
| LAD | 51/131 (38.9%) |
| LCX | 28/131 (21.4%) |
| RCA | 21/131 (39.7%) |
| Balloon angioplasty | 48/131 (36.6%) |
| Rescue stenting | 12/131 (9.2%) |
| Provisional stenting | 71/131 (54.2%) |

CABG = coronary artery bypass graft operation; LAD = left anterior descending; LCX = left circumflex; MI = myocardial infarction; RCA = right coronary artery.

Chapter 7
Geographical Miss in BRIE study

orthogonal projections was performed with the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). Calibration of the system was based on dimensions of the catheters not filled with contrast. This method of analysis has been previously validated (18–20). The following QCA parameters were computed in the VS: computer-defined minimal luminal diameter, reference diameter obtained by an interpolated method and percentage diameter stenosis. Binary restenosis was defined in every segment as diameter stenosis >50% at follow-up. This allowed the determination of restenosis in the VS (overall restenosis). Computer-defined subsegmental analysis (mean subsegment length was 5 ± 0.3 mm, depending on the length of the analyzed VS) was also performed. In each subsegment, percentage diameter stenosis was also automatically calculated. This allowed the determination of restenosis in relation to the dose-based subsegments, which was termed regional restenosis.

**Determination of the restenosis location.** Three observers analyzed all the films that appeared to have restenosis at the follow-up angiogram. The printouts of the pre-, post- and follow-up angiograms, in two orthogonal projections, with the subsegmental analysis and the dose-based subsegments superimposed, were compared. The observers designated the location of the computer-defined QCA subsegments with restenosis in relation to the dose-based segments. Restenosis was classified as restenosis in the EIRS, edge restenosis (proximal or distal) and restenosis outside the irradiated segment. It is important to realize that the criterion for binary restenosis might be fulfilled in more than one subsegment in the same VS.

**Statistical analysis.** Continuous data are presented as mean values; discontinuous data are presented as percentages. Differences in restenosis rates between edges with and without GM were evaluated with chi-square or Fisher exact tests as appropriate. Because the behavior of different

![Diagram](image-url)
segments in the same vessel and the behavior of different vessels in the same patient may not be independent, the relation between GM and edge restenosis was further analyzed by logistic regression analysis, using generalized estimation equation modeling techniques to correct for possible within-patient effects. The presented odds ratios (OR) and 95% confidence intervals (CI) are based on these analyses. Statistical significance of all tests was defined at the p < 0.05 level.

RESULTS

Incidence and causes of GM. VESSELS. A total of 131 vessels were interpretable. The incidence of GM was 67.9% (Table 2).

EDGES. In each vessel, both proximal and distal edges of the EIRS were analyzed, giving in total 262 edges. Out of the 89 vessels with GM, 70 had one GM edge, proximal or distal, and in 19 vessels both edges were injured, giving in total 108 GM edges. The incidence of GM at the edges was 41.2%. The location proximal and distal was comparable (Table 3).

Procedural causes of GM. The following reasons were responsible for the GM: 1) development of procedural complications (additional stent implantation postradiation) that extended the treatment beyond the margins of the EIRS (52.8%, 57/108) (unexpected GM); 2) the INS from that extended the treatment beyond the margins of the EIRS (52.8%, 57/108) (unexpected GM); 3) treatment of long lesions requiring balloons or stents (34.2%, 37/108), termed as lack of accurate matching; and 4) prior inflations was not appropriately covered by the source (34.2%, 37/108), termed as stent edges (SE). The incidence of GM at the edges was 41.2%. The location proximal and distal was comparable (Table 3).

Table 2. Vessel Characteristics in Relation to GM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GM (%)</th>
<th>NonGM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninterpretable vessels</td>
<td>25.1%</td>
<td>74.9%</td>
</tr>
<tr>
<td>Intepretable vessels</td>
<td>74.9%</td>
<td>25.1%</td>
</tr>
<tr>
<td>Noninjured vessels</td>
<td>32.1%</td>
<td>67.9%</td>
</tr>
<tr>
<td>GM vessels</td>
<td>67.9%</td>
<td>32.1%</td>
</tr>
<tr>
<td>Vessels with GM proximal only</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>Vessels with GM distal only</td>
<td>41.5%</td>
<td>58.5%</td>
</tr>
<tr>
<td>Vessels with GM both proximal and distal</td>
<td>21.5%</td>
<td>78.5%</td>
</tr>
</tbody>
</table>

GM = geographical miss.

Regional restenosis rate is higher than the restenosis rate in the VS. There were three vessels with restenosis in both the EIRS and the proximal edge and four vessels with restenosis in both EIRS and the distal edge. There were no cases with restenosis in both edges.

Generalized estimation equation analysis, which was used to account for within-patient effects, showed that the probability for restenosis at the edges of the EIRS depended on the GM (p = 0.0039), but not on distal/proximal lesion location (p = 0.6) or the device (balloon/stent) used (p = 0.1).

Regional restenosis rate in relation to GM. In each of the 115 vessels (101 patients), the impact of GM on restenosis was analyzed in both proximal and distal edge (230 edges). Geographical miss significantly increased the incidence of restenosis at the edges of the EIRS compared with lesions without GM (4.35% vs. 16.3%, p = 0.004). This effect was observed both in the proximal (5.56% vs. 16.28%, p = 0.05) and distal (3.03% vs. 16.33%, p = 0.02) edges and seems to be more pronounced at the distal edge (OR = 5.3) compared with the proximal (OR = 3.2). The OR and the CI are presented in Figure 2.

Figure 2. Difference in the restenosis rate in the proximal distal and both edges of the effective irradiated segment between geographical miss (GM) and noninjured edges. White bars = no GM; black bars = GM. CI = confidence interval; OR = odds ratio.

Table 3. Edge Characteristics in Relation to GM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GM (%)</th>
<th>NonGM (%)</th>
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</thead>
<tbody>
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<tr>
<td>Intepretable edges</td>
<td>74.9%</td>
<td>25.1%</td>
</tr>
<tr>
<td>Noninjured edges</td>
<td>58.8%</td>
<td>41.2%</td>
</tr>
<tr>
<td>GM edges</td>
<td>41.2%</td>
<td>58.8%</td>
</tr>
<tr>
<td>Proximal GM edges</td>
<td>48.2%</td>
<td>51.8%</td>
</tr>
</tbody>
</table>

GM = geographical miss.

DISCUSSION

This study reports on the incidence and causes of GM and its implications on edge restenosis in vessels treated with intracoronary beta-radiation according to the BRIE proto-
col. By careful retrospective angiographic analysis of all vessels treated with the same radiation system, we defined the effect of the injury on those areas located at the margins of the source where the delivered dose was potentially rather low.

**Dosimetric zones.** In any given vessel undergoing an intervention followed by radiotherapy there are six possible combinations of injury and irradiation: 1) segments injured and fully irradiated (received the prescribed dose), representing the ideal treatment; 2) segments injured and receiving less than the prescribed dose defined as GM segments; 3) segments injured and receiving no dose (falling into the category of conventional interventions); 4) segments non-injured and receiving a full dose; 5) segments noninjured and receiving a low dose, which represents a well-applied treatment because there is no indication of any adverse impact from low-dose radiation without injury after either beta (15) or gamma radiation (21); and 6) segments non-injured and receiving no radiation, falling into the category of natural progression of atherosclerosis.

Geographical miss occurred in 67.9% of the vessels and 32.1% of edges analyzed. This concept requires the concurrence of two conditions: low-dose radiation and injury. It is a dose-related term rather than an anatomical one. Injury outside the field of radiation or low-dose irradiation of noninjured tissue cannot be termed GM.

**Stimulatory effect of low-dose radiation.** The stimulatory effect of low-dose radiation on smooth muscle cell proliferation has been previously reported in a swine coronary balloon overstitch injury model (11). In the low-dose radiation group (10 Gy), neointima was composed of smooth muscle cells with a marked increase in inflammatory cells and less medial and intimal fibrosis as compared with higher dose groups (15 and 20 Gy) and the control group. Similarly, after low-activity radioactive stent implantation (1.0 μCi) in a porcine model, neointimal hyperplasia was significantly greater than that after nonradioactive stenting (12). Our group reported a late loss in injured edges treated with the same system that was higher than that demonstrated in the noninjured edges (14) and in previous studies after balloon angioplasty or stent implantation (22,23). In a three-dimensional volumetric intravascular ultrasound (IVUS) investigation, our group again observed a decrease in lumen volume at the edges because of an increase in plaque volume not accommodated by vessel enlargement (7). In patients receiving 6 to 12 μCi 32P radioactive stents, where GM systematically occurs because of the current balloon technology (6), 50% edge restenosis was reported compared with 0% in-stent (5).

**Proximal versus distal.** Geographical miss increased restenosis in both edges of the EIRS. This effect seems to be more prominent at the distal edge compared with the proximal. The smaller lumen distally attributable to normal tapering of the vessels and the even less effectively irradiated proximal edge because of its larger diameter may also be the cause. Comparing the values of restenosis proximal and distal at the GM edges, we can see that they are identical in the range of 16.3%. What makes the OR higher for the distal edge is the increased incidence of restenosis in the noninjured proximal edges. Our group has reported this through analysis of the noninjured edges of irradiated segments by three-dimensional IVUS. Greater increase in the plaque volume in the proximal edges compared with the distal (27% vs. 9.2%, respectively) was reported (15). Nonmeasurable vessel injuries (guiding catheter guidewires) were hypothesized as the cause. Rheological factors may play an important role and careful shear stress analysis could elucidate the cause of restenosis at the proximal edge (24).

**Balloon versus stent injury in relation to GM.** Geographical miss related to stent injury is more prominently associated with edge restenosis than is GM related to balloon injury. The mechanisms involved in restenosis after balloon angioplasty are different compared with those of stenting. Negative remodeling and elastic recoil are the causes of restenosis after balloon angioplasty, as opposed to neointimal formation after stent implantation (25). Absence of negative remodeling has been reported at the edges of the irradiated segments after balloon angioplasty (14). This might partly compensate for the stimulatory effect of radiation on plaque growth at the balloon-injured GM edges, making the combination less harmful.

The acute injury after stenting differs from that of the coronary balloon angioplasty (8). The stent is a foreign body and produces a permanent strain on the vessel wall, resulting in a chronic injury and a prolonged stimulus for neointimal formation (26). It is logical to conclude that the greater and more prolonged the injury, the greater the impact on plaque growth, and subsequently on restenosis, in conjunction with low-dose radiation. In our study, significantly higher late loss was observed in the irradiated segment in patients treated with balloons compared with the stent-treated patients (0.14 mm vs. 0.44 mm respectively, p = 0.001).

This observation is in keeping with the other serious adverse effects of the combination of stenting and radiation, such as delayed stent thrombosis (27) and late stent malapposition (28).
Study limitations. This study is not placebo-controlled and the effect of a sham source on injured coronary segments has not been evaluated.

Only one type of radiation delivery catheter using the beta-source 90Sr/90Y has been evaluated. Thus, the effect of other systems using centering balloons and different sources or gamma-radiotherapy on the GM edges cannot be extrapolated from our results.

Balloon inflation or stent implantation was considered the only source of injury. Minor injuries from guiding catheters, guidewires or radiation delivery catheters cannot be completely ruled out.

Only binary restenosis data are quoted and the determination of GM is qualitative because there was no QCA methodology available at the time to measure the length of the GM.

Conclusions. Geographical miss is strongly correlated with the development of restenosis at the edges of the EIRS. This is a local phenomenon with a specific pathophysiology (combination of injury and low-dose radiation) and is different from the restenosis observed in the EIRS. This effect was observed in both edges of the EIRS and seems to be more pronounced at the distal edge compared with the proximal. Geographical miss related to stent injury is associated with higher edge restenosis compared with GM related to balloon injury. Geographical miss did not increase the incidence of restenosis in the EIRS. If GM can be eliminated, the results of intracoronary balloon angioplasty: new insights from the CERRIT study. J Am Coll Cardiol 1992;19:267–74.


CHAPTER 8

Sianos G, Wijns W, de Feyter PJ, Serruys PW

Geographical Miss During Centered Intracoronary Beta-Radiation With 90Yttrium: Incidence and Implications for Recurrence Rates After Vascular Brachytherapy for De-novo Lesions

*International Journal of Cardiovascular Interventions in press*
Geographical miss during centered intracoronary beta-radiation with \(^{90}\text{Yttrium}\): incidence and implications for recurrence rates after vascular brachytherapy for de novo lesions

Georgios Sianos\(^1\), William Wijns\(^2\), Pim J de Feyter\(^1\) and Patrick W Serruys\(^1\)

\(^1\)Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands
\(^2\)Onze Lieve Vrouwe Ziekenhuis—Cardiovascular Center, Aalst, Belgium

Correspondence:
Professor PW Serruys
Department of Interventional Cardiology
Erasmus MC Rotterdam
Thoraxcenter Bd 404
Dr Molewaterplein 40
3015 GD Rotterdam
The Netherlands
Tel: (+31) 10 463 5060
Fax: (+31) 10 436 9154
E-mail: p.w.j.c.serruys@erasmusmc.nl

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OBJECTIVES: The authors sought to determine the incidence and causes of geographical miss (GM) and evaluate its impact on edge restenosis after ‘primary’, centered, intracoronary \(\beta\)-radiation therapy.

BACKGROUND: Edge restenosis is a limitation of intracoronary \(\beta\)-radiation therapy. GM occurs when the radiation source does not fully cover the injured segment and may account for this phenomenon.

METHODS: One hundred and eighty-one patients enrolled in the Dose-Finding study were retrospectively analyzed. The patients were randomized to receive 9, 12, 15 or 18 Gy at 1 mm tissue depth. Using quantitative coronary angiography the effective irradiated segment (EIRS) and both edges were studied prior to and after intervention, and at six-month follow-up. GM was defined as a situation where the effective radiation source length (24 mm) did not fully cover the injured segment. The edges of the EIRS that were injured during the procedure constituted the GM edges. A greater than 50% diameter stenosis at follow-up was considered significant. GM was determined by the simultaneous, electrocardiographically matched, side-by-side projection of the source and balloons in place, in identical projections surrounded by contrast.

RESULTS: In 16% of patients GM was noninterpretable owing to inadequate filming. GM constituted 21.1% of the interpretable edges and 40.1% of the interpretable vessels analyzed. The occurrence of restenosis in the EIRS and the analyzed vessel segment (VS) was similar between procedures with and without GM. In vessels with GM, restenosis was significantly increased from the EIRS to the VS (from 8.77% to 51%, \(p = 0.05\)) as opposed to non-GM vessels (from 11.9% to 19%, \(p = 0.6\)). GM tended to be associated with a greater incidence of significant stenosis at the edges of the EIRS (8.3% versus 4.0%, \(p = 0.15\)) compared with individuals with >50% stenosis but no GM. This effect was more prominent at the distal edge. The relation of GM and edge restenosis was independent of dosage.

CONCLUSIONS: Since GM does not affect the incidence of restenosis in the EIRS, restenosis in this segment should be considered a treatment failure, probably due to inadequate dosage. GM is related to significant increase in restenosis from the EIRS to the VS. GM tends to be associated with restenosis at the edges of the EIRS. This is a local phenomenon, which is independent of dosage and which has a specific pathophysiology (combination of injury and low-dose radiation). If GM can be eliminated, the results of vascular brachytherapy will be improved. (Int J Cardiovasc Intervent 2003; 5:000-000)

Keywords: geographical miss — intracoronary radiation — restenosis
Introduction

Following coronary balloon angioplasty, restenosis of the dilated segment occurs in 30–50% of patients and results from elastic recoil, neointimal formation, and negative remodeling.1–4 The advent of coronary stenting reduced restenosis to 15% in certain types of lesions,5,8 but introduced the even more difficult-to-treat in-stent restenosis.7 After extensive evaluation in animal balloon and stent restenosis models,9–11 clinical feasibility studies with beta and gamma emitters proved that brachytherapy is safe, feasible and promising for prevention of restenosis.12–15 Following these encouraging results, large randomized studies confirmed the effectiveness of intracoronary radiation therapy for the treatment of in-stent restenosis, both with beta16–19 and gamma emitters.20–25

Soon after its application various limitations of this treatment, such as the development of re-narrowing at the edges of the irradiated segment (described as ‘edge effect’), late total occlusions,26–27 delayed healing,28 increased thrombogenicity,29 and persistent dissections30,31 were recognized, limiting its effectiveness.

The geographical miss (GM), a term invented in radio-oncology to define a cause of treatment failure due to low dose23 and translated to interventional cardiology to define those coronary segments which are injured but which received low-dose radiation,34 has been proven to be the cause of edge restenosis after both beta and gamma radiation therapy.33–35

The effect of this inadequate treatment after centered beta-radiation therapy for de novo lesions with 90Yttrium has not been studied. The present study is a retrospective quantitative coronary angiography (QCA) analysis of patients treated according to the protocol of the previously reported multicenter, dose-finding, intracoronary beta-radiation study using a catheter-based system,37 with focus on GM and its impact on the angiographic outcome of these patients.

Methods

Patient selection

The authors retrospectively analyzed 181 patients treated with catheter-based beta-radiation enrolled in the Dose-Finding study.36 The study was designed as a prospective, randomized, multicenter, dose-finding trial. One hundred and eighty-one patients were enrolled and randomly assigned to receive 9, 12, 15, or 18 Gy of radiation. Patients more than 50 years old who had a angina pectoris or silent ischemia were enrolled if they were suitable candidates for the dilation of a previously untreated native coronary stenosis. For the enrollment criteria to be met, the diameter of the vessel had to be between 2.5 and 4.0 mm, and the stenosis had to be shorter than 15 mm. Patients also had to be eligible for angiographic and clinical follow-up at six months. The baseline characteristics of the patients are summarized in Table 1. In 29 patients (16%) GM was noninterpretable owing to inadequate filming. The remaining 152 patients were analyzed for the incidence and causes of GM. For the correlation of GM with edge stenosis 40 patients were excluded (11 refused follow-up angiogram, GM was noninterpretable in 28 and one had both reasons), leaving 141 patients.

Device description

The system used for intra-arterial beta-radiation therapy has been previously described.37–40 It consists of the 90Yttrium beta-ray-emitting source (half-life 64 hours; maximal energy 2.284 MeV), a centering balloon, and an automated delivery device. The radioactive source consists of a 29 mm-long flexible coil, secured at the end of a 0.035 cm thrust wire between distal and proximal 6 mm-long, radiopaque tungsten markers, which allow precise localization of the source under fluoroscopy. The effective length of the vessel segment being irradiated (the 90% isodose line) is 24 mm. The centering balloon, consisting of four interconnected compartments, is designed to position the source wire centrally inside the coronary lumen, thereby contributing to a more homogeneous distribution of the dose of radiation along the vessel wall. Three radiopaque markers are located between the balloon compartments and allow the device to be positioned, with the use of fluoroscopy, at the exact

| Age | 64 ± 0.6 (mean ± SE) |
| Male sex | 133 (73%) |
| Medical history | |
| Previous infarction | 69 (38%) |
| Previous CABG | 6 (3%) |
| Previous PTCA | 24 (13%) |
| Current medical condition | |
| Stable angina | 120 (66%) |
| Unstable angina | 61 (34%) |
| Risk factors | |
| Diabetes mellitus | 22 (12%) |
| Hypertension | 84 (46%) |
| Hypercholesterolemia | 104 (57%) |
| Family history of CAD | 55 (30%) |
| History of smoking | 118 (65%) |
| Target vessel | |
| Left anterior descending artery | 75 (14%) |
| Right coronary artery | 64 (35%) |
| Left circumflex coronary artery | 92 (51%) |
| Lesion type* | |
| A | 25 (14%) |
| B1 | 64 (35%) |
| B2 | 92 (51%) |
| C | 0 |
| Single-vessel disease | 138 (76%) |

*The type of lesion was classified according to the American Heart Association–American College of Cardiology classification, with A denoting a short focal lesion, and C the most complex type of lesion. CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; CAD, coronary artery disease.

Table 1

Baseline characteristics of the patients studied (n = 181).
site of the previous angioplasty. The centering balloon is inflated with 5 ml of carbon dioxide up to a maximal pressure of 4 atm. In comparison with the use of contrast medium, the use of carbon dioxide permits faster inflation and deflation of the balloon and a shorter treatment time (because there is less attenuation of the radiation). The use of an automated delivery device ensures the safe storage of the source, its easy insertion and withdrawal, its accurate positioning, and the instantaneous calculation and delivery of the dose. At the end of each treatment, a printed report was automatically generated.

**Dosimetry**

The patients were randomly assigned by computer, over the telephone, to receive 9, 12, 15, or 18 Gy of radiation at a tissue depth of 1 mm. The mean duration of radiation treatment was 1.81 ± 0.10, 2.55 ± 0.20, 3.01 ± 0.16, and 3.17 ± 0.19 minutes, in the 9, 12, 15, and 18 Gy groups, respectively.

**Definitions**

Vessel segment (VS) was defined as the coronary segment bordered by two side-branches that encompassed the original lesion, angioplasty balloon and radiation source. The injured segment (INS) was the segment encompassed by the most proximal and distal position of the radiopaque markers of the balloons used for dilation or stent implantation. The irradiated segment (IRS) was defined as the segment encompassed by the two radiopaque tungsten markers of the radiation source train, 29 mm in length. The effective irradiated segment (EIRS) was the segment that received the full prescribed dose and corresponded to the 24 mm-long central part of the radioactive source train. These segments are illustrated in Figure 1. The edges of the EIRS are the adjacent (proximal and distal) 5 mm coronary segments, consisting of the 2.5 mm inside and outside the radiopaque tungsten markers. These edges received low-dose radiation owing to fall-off of dose in the beta-emitting \(^{103}\)Y source. Those edges which were traumatized by balloon inflation or received new stent implantation during the procedure were defined as GM edges. Non-injured edges were those which were not traumatized during the intervention.

**Determination of the GM edges**

To determine whether the edges of the EIRS were injured the authors retrospectively analyzed, blinded to the presence or absence of restenosis and its location at follow-up, all the baseline (intervention plus radiation) angiograms. The following steps were followed: during the procedure all the interventions (balloons or stents) deflated at the site of injury and the radioactive source in place were filmed with contrast in identical angiographic projections. This approach allowed the definition of the location of the various subsegments (EIRS, INS, edges) in relation to side-branches and the correct matching of the angiograms in the off-line analysis. A continuous electrocardiogram (ECG) recording was also displayed, allowing the selection of still frames in the same part of the cardiac cycle. Multiple angiographic loops and ECG-matched still frames could be displayed simultaneously, side-by-side, on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Lithoorn, The Netherlands). By identifying the relationship between the EIRS and its edges relative to the INS the GM edges were determined. Two independent cardiologists performed the above-mentioned analysis. There was only 10% disagreement on the presence or absence of GM and its location, proximal or distal. These were borderline cases that were reanalyzed by a third reviewer with the use of transparencies, and a final conclusion was drawn.

In cases where one or more of the following criteria were present, the procedure was reported as noninterpretable: (a) incorrect filming of the radiation source or the balloons deflated with contrast injection; (b) more than 10 degrees’ difference in the angiographic projections not allowing correct matching; (c) interventions reported in the technician’s worksheet but not filmed.

**QCA analysis**

The EIRS and both edges were analyzed by QCA prior to and after intervention, and at six-month follow-up. All angiograms were evaluated after intracoronary administration of nitrates. The off-line analysis of two orthogonal projections was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Nether-
lands. Calibration of the system was based on dimensions of the catheters not filled with contrast. This method of analysis has been previously validated.44-45 The following QCA parameters were computed in the VS: computer-defined minimal luminal diameter (MLD), reference diameter (obtained by an interpolated method), and percentage diameter stenosis. Binary restenosis was defined in every segment as diameter stenosis >50% at follow-up. This allowed the determination of restenosis in the VS (overall restenosis). Computer-defined subsegmental analysis (mean subsegment length was 5.0 ± 0.4 mm, depending on the length of the analyzed VS) was also performed. In each subsegment, percentage diameter stenosis was also automatically calculated. This allowed the determination of restenosis in relation to the dose-based subsegments, which was termed as regional restenosis.

**Determination of the restenosis location**

Three observers analyzed all the films that appeared to have restenosis at the follow-up angiogram. The printouts of the pre-, post- and follow-up angiograms, in two orthogonal projections, with the subsegmental analysis and the dose-based subsegments superimposed, were compared. The observers designated the location of the computer-defined QCA subsegments with restenosis in relation to the dose-based segments. Restenosis was classified as restenosis in the EIRS, edge restenosis (proximal or distal) and restenosis outside the IRS. It is important to realize that the criterion for binary restenosis might be fulfilled in more than one subsegment in the same VS.

**Statistical analysis**

Continuous data are presented as mean values; discontinuous data are presented as percentages. Differences in restenosis rates between edges with and without GM were evaluated with chi-square or Fisher’s exact tests as appropriate. Odds ratios (OR) and 95% confidence intervals (CI) are also presented. Statistical significance of all tests was defined at the \( p < 0.05 \) level.

**Results**

**Incidence of GM**

Vessels. Overall 152 vessels were interpretable. The incidence of GM was 40% (Table 2).

<table>
<thead>
<tr>
<th></th>
<th>Noninterpretable edges</th>
<th>Interpretable edges</th>
<th>Noninjured edges</th>
<th>GM edges</th>
<th>Proximal GM edges</th>
<th>Distal GM edges</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16.0% (58/362)</td>
<td>84.0% (304/362)</td>
<td>79.0% (240/304)</td>
<td>21.0% (64/304)</td>
<td>37.5% (24/64)</td>
<td>62.5% (40/64)</td>
</tr>
</tbody>
</table>

**Table 3**

Edge characteristics in relation to geographical miss (GM).

Edges. In each vessel, both proximal and distal edges of the EIRS were analyzed, giving in total 304 edges. Out of the 61 vessels with GM, 58 had one GM edge, proximal or distal and in three vessels both edges were injured, giving in total 64 GM edges. The incidence of GM at the edges was 21%. The location proximal was 37.5% and distal 62.5% (\( p = 0.03 \), Table 3).

**Procedural causes of GM**

The following reasons were responsible for this phenomenon: (a) development of procedural complications (additional intervention postradiation), which extended the treatment beyond the margins of the EIRS (56.3% (36/64)); (b) the INS from prior inflations was not appropriately covered by the source (32.8% (21/64)); and (c) treatment of long lesions requiring balloons or stents longer than 24 mm (EIRS) in length (10.9% (7/64)).

**Overall restenosis in relation to GM**

A follow-up angiogram was available in 141 out of 152 vessels. The occurrence of restenosis in the EIRS and the VS was similar between procedures with and without GM (Table 4). In the non-GM vessels there was no significant increment in restenosis between the EIRS and the VS (from 11.9 to 19%, \( p = 0.6 \). In the GM vessels restenosis was significantly increased from the EIRS segment to the VS (from 8.77% to 21%, \( p = 0.05 \)) resulting in significantly higher overall restenosis in the VS compared with the EIRS (from 10.63% to 19.85%, \( p = 0.03 \)).

**Edge restenosis rates in relation to the GM**

In each of the 141 vessels, the impact of GM on restenosis was analyzed in both proximal and distal edges (282 edges). The overall edge restenosis was 5% (Table 5). GM tends to be associated with a greater incidence of binary restenosis at the edges of the EIRS (8.3% versus 4%, \( p = 0.15 \), OR 2.2, CI 0.7–6.7) compared with individuals with >50% stenosis but no GM. This effect was mainly observed at the distal edge (1.96% versus 7.7%, \( p = 0.1 \), OR 4.2, CI 0.67–26). There was no association between GM and restenosis at the proximal edge (5.83% versus 9.5%, \( p = 0.5 \), OR 1.7, CI 0.32–8.5) (Table 5). This was due to a tendency toward significant increment in restenosis in the proximal non-GM edges in comparison with the distal (5.83% versus 1.96%, \( p = 0.1 \)) since the restenosis in the proximal and distal GM edges was comparable (Table 5). The relation
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<table>
<thead>
<tr>
<th></th>
<th>EIRS</th>
<th>VS</th>
<th>EIRS versus VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>15/141 (10.63%)</td>
<td>28/141 (19.85%)</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>GM</td>
<td>5/57 (8.77%)</td>
<td>12/57 (21.05%)</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>No GM</td>
<td>10/84 (11.90%)</td>
<td>16/84 (19.04%)</td>
<td>p = 0.6</td>
</tr>
<tr>
<td>GM versus no GM</td>
<td>p = 0.7</td>
<td>p = 0.8</td>
<td></td>
</tr>
</tbody>
</table>

EIRS, effective irradiated segment; VS, vessel segment.

Table 4
Overall restenosis and geographical miss (GM).

<table>
<thead>
<tr>
<th></th>
<th>All edges</th>
<th>Proximal edges</th>
<th>Distal edges</th>
<th>Proximal versus distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All edges</td>
<td>14/282 (5.00%)</td>
<td>9/141 (6.40%)</td>
<td>5/141 (3.55%)</td>
<td>p = 0.3</td>
</tr>
<tr>
<td>GM edges</td>
<td>5/60 (8.30%)</td>
<td>2/21 (9.50%)</td>
<td>3/39 (7.70%)</td>
<td>p = 0.8</td>
</tr>
<tr>
<td>No GM edges</td>
<td>9/222 (4.10%)</td>
<td>7/120 (5.83%)</td>
<td>2/102 (1.96%)</td>
<td>p = 0.1</td>
</tr>
<tr>
<td>GM versus no GM</td>
<td>p = 0.15</td>
<td>p = 0.5</td>
<td>p = 0.1</td>
<td></td>
</tr>
</tbody>
</table>

Table 5
Geographical miss (GM) and incidence of edge restenosis.

<table>
<thead>
<tr>
<th></th>
<th>9 Gy</th>
<th>12 Gy</th>
<th>15 Gy</th>
<th>18 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All edges</td>
<td>7/68 (10.3%)</td>
<td>3/70 (4.3%)</td>
<td>3/78 (3.8%)</td>
<td>1/66 (1.5%)</td>
</tr>
<tr>
<td>GM</td>
<td>2/17 (11.8%)</td>
<td>2/13 (15.4%)</td>
<td>1/16 (6.3%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>No GM</td>
<td>5/51 (9.8%)</td>
<td>1/57 (1.8%)</td>
<td>2/62 (3.2%)</td>
<td>1/52 (1.9%)</td>
</tr>
<tr>
<td>GM versus no GM</td>
<td>p = 0.9</td>
<td>p = 0.1</td>
<td>p = 0.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 6
Geographical miss (GM) and edge restenosis in relation to dosage.

<table>
<thead>
<tr>
<th></th>
<th>All edges</th>
<th>Balloon edges</th>
<th>Stent edges</th>
<th>Balloon versus stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>All edges</td>
<td>14/282 (5.00%)</td>
<td>9/202 (4.45%)</td>
<td>5/80 (6.25%)</td>
<td>p = 0.3</td>
</tr>
<tr>
<td>GM</td>
<td>5/60 (8.30%)</td>
<td>3/33 (9.09%)</td>
<td>2/27 (7.41%)</td>
<td>p = 0.6</td>
</tr>
<tr>
<td>No GM</td>
<td>9/222 (4.10%)</td>
<td>6/169 (3.55%)</td>
<td>3/53 (5.66%)</td>
<td>p = 0.4</td>
</tr>
<tr>
<td>GM versus no GM</td>
<td>p = 0.15</td>
<td>p = 0.15</td>
<td>p = 0.7</td>
<td></td>
</tr>
</tbody>
</table>

Table 7
Geographical miss (GM) and edge restenosis in relation to type of injury.

of GM and edge restenosis was independent of the dosage (Table 6).

Edge restenosis and GM in relation to the type of injury
Out of the 282 interpretable edges, 202 (71.7%) were related to balloon angioplasty, termed as balloon edges (BE), and 80 (28.3%) to stent implantation, termed as stent edges (SE). The incidence of GM at the BE was 16.3% (33/202) and at the SE 33.75% (28/80) (p < 0.001). At the BE, GM increased the incidence of restenosis (3.55% versus 9.09%, OR 2.7, CI 0.65–11.4) but this did not reach the level of statistical significance, p = 0.15. At the SE, GM did not increase the incidence of restenosis compared with edges without GM (5.66% versus 7.41%, p = 0.7, OR 1.3, CI 0.2–8.5) (Table 7).

Discussion
This study reports on the incidence and causes of GM and its implications for edge restenosis in vessels treated with intracoronary β-radiation according to the Dose-Finding study protocol. By careful retrospective angiographic analysis of all vessels treated with the same radiation system the authors defined the effect of the injury on those areas located at the margins of the source where the delivered dose was potentially rather low.

In all the brachytherapy trials for de novo or restenotic lesions,16–19,21–23 the restenosis between the lesion segment and the total analysis segment was increased in the range of 10–15% regardless of the
source and the type of radiation used, and irrespective of whether the edge effect was reported as a significant parameter for the outcome. This result attenuates or even reverses the favorable outcome observed in the stented segment (in-stent restenosis or de novo lesions with stent implantation) or the segment encompassing the initial MLD (de novo lesions treated with balloon angioplasty).

Stimulatory effect of low-dose radiation and mechanisms of edge restenosis

The stimulatory effect of low-dose radiation on smooth muscle cell proliferation has been previously reported in a swine coronary balloon overstretch injury model. In the low-dose radiation group (10 Gy), the neointima was composed of smooth muscle cells with a marked increase in inflammatory cells and less medial and intimal fibrosis as compared with higher-dose groups (15 and 20 Gy) and the control group. Similarly, after low-activity radioactive stent implantation (1.0 μCi) in a porcine model, neointimal hyperplasia was significantly greater than that after nonradioactive stenting. In catheter-based brachytherapy the authors’ group reported a higher late loss in injured edges than that demonstrated in the noninjured edges and in previous studies after balloon angioplasty or stent implantation. Three-dimensional volumetric intravascular ultrasound (IVUS) investigation revealed that the decrease in lumen volume at the edges was the result of an increase in plaque volume not accommodated by vessel enlargement. In patients receiving 6.0–12.0 μCi 32P radioactive stents, where GM systematically occurs because of current balloon technology, 50% edge restenosis was reported compared with 0% in-stent. This effect, known as the ‘candy-wrapper’ effect, is primarily a focal exaggeration of neointimal hyperplasia accumulation at the edge of the stent.

Incidence of edge restenosis

The incidence of edge restenosis after initial stent implantation without radiation has been reported to be between 5 and 10%. A clue to its incidence in the current area of new-generation stents can be obtained by the control group of the SIRIUS study. In the control group edge restenosis was around 8%, equal between the proximal and distal margins. It increased restenosis in the whole analyzed segment by only 1% as compared with the in-stent segment (35.4 versus 36.3%) owing to its concomitance with in-stent restenosis in the majority of cases. This was the reason that edge stent restenosis remained unattended during a decade of trials using bare stents.

GM and relation to edge restenosis in de novo lesions

In the first report by Sabate the incidence of GM was 32% and increased the edge restenosis from 2% in the noninjured edges to 41%, and the restenosis rate in the IRS was 10%. In the BRIE study the incidence of GM was 41% and was strongly associated with edge restenosis, especially after stent injury, but was not related to increased restenosis in the irradiated segment or the analyzed segment. With increased experience GM was reduced to 6.5% in the RENO registry and this was not associated with increased edge restenosis but with increased target vessel thrombosis and target-vessel-related death. The incidence of GM in this registry is probably underreported owing to the absence of a central core laboratory for the angiographic analysis.

The Beta-Cath trial, the largest randomized trial of beta-radiation for de novo lesions, failed to show any difference in the primary endpoint, the target vessel failure, in the combined radiation arms compared with the placebo arms. In the balloon group the reduction in binary restenosis observed with radiation in the lesion segment was not maintained in the vessel segment analysis. Even worse, in the stent group the significant reduction in the stented segment inverted to a significant increment in the analysis segment, with worse outcome in the radiation group. Clearly, in this study the dose fall-off zone appears to be the culprit for the higher restenosis, especially the proximal dose fall-off, likely due to a greater reduction in dose proximal relative to distal. Since GM was very frequent (>85%) the authors were unable to ascertain the contribution of GM to the higher restenosis in these zones.

In the present study, the incidence of edge restenosis was 5%. It was not strongly associated with GM, as opposed to the authors’ previous experience in the BRIE study. There are distinct differences between the two studies. The incidence of GM was significantly lower in the Dose-Finding study (67% versus 40%, p < 0.05 for the vessels, and 40% versus 20%, p < 0.05 for the edges analyzed). Additionally, by protocol, stenting was discouraged, resulting in significantly lower incidence of stent implantation compared with the BRIE study (33% versus 66%, respectively, p < 0.05). The differences between the two sources regarding the centering and the fall-off of the dose at the edges might also contribute to this differential outcome.

In the balloon edges restenosis was increased from 3.5% to 9.0% but this did not reach the level of statistical significance, thus confirming the findings of the BRIE study of no strong association between balloon injury and GM. The observation of no association between restenosis and GM at the stent edges is probably related to very small number of observations.

Although not statistically significant the association of restenosis and GM was higher for the distal edges as opposed to the proximal (OR 4.1 versus 1.7 respectively), despite comparative absolute values of edge restenosis (Table 5). This is due to a tendency for increased restenosis in the proximal non-GM edges in comparison with the distal (4.1% versus 1.96%, p = 0.1). This differential behavior between the proximal and distal edges was observed in the active arms of the RAVEL and SIRIUS studies and requires further attention. The equalization of restenosis in proximal and distal edges after brachytherapy for de novo lesions is also a constant observation.
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GM and edge restenosis in in-stent restenotic lesions

The incidence of edge restenosis after treatment of in-stent restenotic lesions without radiation is less clear. It varies between 14% in the placebo group of SCRIPPS32 to 3–4% in the control groups of WRIST31 and GAMMA 1,22 In a meta-analysis of patients enrolled in the placebo arms of randomized brachytherapy trials for in-stent restenosis with beta and gamma sources stent edge restenosis was 4.4%, significantly lower compared with irradiated patients. Interestingly, edge restenosis in the radiation group was reported to be higher with beta sources (17.1%) compared with gamma sources (9.3%).35

In the WRIST-gamma randomized trial the incidence of GM was 34% and was strongly associated with development of edge binary restenosis.34 Additionally, significantly higher late loss and significantly lower MLD was observed in the GM edges of the irradiated group compared with the GM edges of the control group and the non-GM edges of the control and the irradiated groups.

In the START 30 randomized trial there was no association of GM with edge restenosis but the authors speculate that this was related to the fact that the short source used in this study was insufficient to cover the injured zone in the majority of the cases.37 In the START 40 trial the incidence of GM was 46% and was associated with significant increase in edge restenosis and restenosis in the analysis segment (32% versus 18%). This was the first study to relate GM to restenosis in the total analyzed segment.38

In the INHIBIT trial, edge restenosis was rather high and comparable between the placebo and the irradiated groups (19.5% and 22% respectively).37 Although the incidence of GM was not reported there was no association between GM and edge restenosis. Despite that, there was an increase of 10% in the restenosis rate between the stented segment and the analysis segment in the irradiated group as opposed to 3% in the control group. The authors speculate that this might be due partly to insufficient radiation coverage of regions beyond the injured segments. In the SVG WRIST study the incidence of GM was 8% and there was no evidence of edge effect.31 Both of these studies were conducted in a period where the issue of GM and its implications were known and complete cover of the injured zone was mandated by the protocol. The avoidance of GM resulted in elimination of edge restenosis.

In a recently published study the incidence of GM was 37.5% and was significantly associated with significant increment of edge restenosis (16% versus 4%).35 More importantly, GM increased the restenosis rate in the target vessel and the irradiated segment but did not increase restenosis in the stent or the site of the initial lesion. A gradual and significant increment in restenosis and diameter stenosis was reported, with concomitant decrement in MLD from the fully irradiated segment to the dose fall-off segment and the segment of negligible irradiation. Interestingly, the highest restenosis rate was reported in injured segments which received negligible irradiation (<10% of the prescribed dose) indicating that the lower dose in combination with injury the worse the outcome. A 5 mm per edge safety margin was suggested which, theoretically, would have led to a 2.7% incidence of GM in this study.

Edge restenosis in the era of drug-eluting stents

In the RAVEL study34 binary restenosis at the edges was 0% in both arms but the late loss, a more sensitive index of restenosis, was significantly lower in the sirolimus-eluting stent group compared with the control group in both stent edges. IVUS analysis of patients enrolled in the FIM study revealed no significant changes in the lumen plaque or vessel volumes at the edges of sirolimus-eluting stents at up to two years’ follow-up.35 Edge restenosis was observed after sirolimus-eluting stent implantation in the randomized SIRIUS study, in which more complex patients were enrolled, with an incidence of 5%, predominantly in the proximal edge, and they increase restenosis in the analysis segment from 3.2 to 8.9.52 It is very clear that this effect is an unmasking of the edge restenosis due to very effective inhibition of restenosis within the stented segment, since its incidence is lower than the edge restenosis observed in the control group (8%).

The difference with brachytherapy for de novo lesions with stent implantation is that this effect, when in addition to a successful inhibition in the stented segment, significantly attenuates35 or inverses the favorable outcome34 observed, indicating that it is not an unmasking due to absence of neointima formation within the length of the stent, but an active phenomenon. The same happens after brachytherapy for de novo lesions treated with balloon angioplasty, although this association is less strong.36,44

Study limitations

This study was not placebo-controlled and the effect of a sham source on injured coronary segments has not been evaluated.

Only one type of radiation delivery catheter using the β-source 90Yttrium has been evaluated. Thus, the effect of other systems with different sources or γ-radiotherapy on the GM edges cannot be extrapolated from these results.

Balloon inflation or stent implantation was considered the only source of injury. Minor injuries from guiding catheters, guidewires or radiation delivery catheters cannot be completely ruled out.

Only binary restenosis data are quoted and the determination of GM is qualitative since there was no QCA methodology available at that time for the measurement of the length of the GM.

Conclusions

Since GM does not affect the incidence of restenosis in the EIRS, restenosis in this segment should be considered
a treatment failure, probably owing to inadequate dosage. GM is related to significant increment in the restenosis from the EIRs to the VS. GM tends to be associated with restenosis at the edges of the EIRs. This is a local phenomenon, which is independent of dosage and has a specific pathophysiology (combination of injury and low-dose radiation). If GM can be eliminated, the results of vascular brachytherapy will be improved.

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CHAPTER 9

Sianos G, Wijns W, de Feyter PJ, van Domburg R, Serruys PW

Geographical Miss and Restenosis During Catheter Based Intracoronary Beta Radiation For De-novo Lesions

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Geographical miss and restenosis during catheter-based intracoronary β-radiation for de novo lesions

Georgios Sianosa, William Wijnsb, Pim J. de Feytera, Ron van Domburga, Patrick W. Serruysa,*

a Department of Interventional Cardiology, Erasmus MC Rotterdam, Thoraxcenter Bd 404, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
b OLVG Cardiovascular Center, Aalst, Belgium

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Abstract

Objectives: We sought to determine the impact of geographical miss (GM) on restenosis rates after intracoronary β-radiation therapy for de novo lesions.

Background: GM is the situation in which injured vessel segments (VSs) are receiving low-dose radiation and is accounted for edge restenosis. Its impact on the overall restenosis rates remains to be determined.

Methods: We analyzed 330 patients (356 vessels) treated according to the Beta Radiation in Europe (BRIE) and the Dose Finding study protocols. Using quantitative coronary angiography (QCA), the effective irradiated segment (EIRS), its edges and the total VS were analysed. The edges of the EIRS that were injured constituted the GM edges. Restenosis was defined as diameter stenosis > 50% at follow-up. GM was determined by the simultaneous electrocardiographic-matched, side-by-side projection of the source and balloons deflated and surrounded by contrast, at the site of injury, in identical angiographic projections.

Results: In 20.5% of the vessels, GM was non-interpretable due to inadequate filming. GM occurred at 30.4% of the interpretable edges and 53% of the interpretable vessels that were analysed. Edge restenosis was significantly increased in the GM compared to non-GM edges (13.16% vs. 4.17%, respectively, \( P = .001 \)), both in the proximal (\( P = .03 \)) and the distal (\( P = .001 \)) edges. GM associated with stent injury significantly increased edge restenosis (\( P = .006 \)). GM related to balloon injury tended to be associated with increment in edge restenosis (\( P = .07 \)). The restenosis in the EIRS was similar between vessels with and without GM (17.8% vs. 14.85%, respectively, \( P = .6 \)). GM was associated with significant increment in the restenosis at the analyzed VS (17.85% vs. 21.48%, \( P = .05 \)).

Conclusions: GM is strongly associated with edges and restenosis in the analysed VS. GM does not increase restenosis in the EIRS.

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Keywords: Geographical miss; Intracoronary radiation; Restenosis; Edge restenosis

1. Introduction

Following coronary balloon angioplasty, restenosis of the dilated segment occurs in 30–50% of patients and results from elastic recoil, neointima formation and negative remodelling [1–4]. The advent of coronary stenting has reduced restenosis to 15% in certain types of lesions [5,6], but it also introduced the even more difficult to treat in-stent restenosis [7]. After extensive evaluation in animal balloon and stent restenosis models [8–11], clinical feasibility studies with beta and gamma emitters proved that brachytherapy is safe, feasible and promising for the prevention of restenosis [12–15]. Following these encouraging results, large randomised studies confirmed the effectiveness of intracoronary radiation therapy for the treatment of in-stent restenosis both with beta [16–19] and gamma emitters [20–23]. Its efficacy for the treatment of de novo lesions

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* Corresponding author. Tel.: +31-10-4635260; fax: +31-10-4369154.
E-mail address: serruys@card.azr.nl (P.W. Serruys).
especially in combination with the use of stents is questionable and remains to be determined [15,24,25].

Soon after its application, the limitations of this treatment such as the development of renarrowing at the edges of the irradiated segment, described as the “edge effect” [26,27], the late total and thrombotic occlusions [28,29], the delayed healing [30], the increased thrombogenicity [31] and the persistent dissections [32,33] were recognised, limiting its effectiveness.

The geographical miss (GM), a term invented in radio-oncology to define a cause of treatment failure due to low dose [34] and translated in interventional cardiology to define those coronary segments, which were injured but received low-dose radiation [26], has been related with the edge restenosis after beta and gamma radiation therapy for de novo and restenotic lesions [35–37]. Its implication on the overall angiographic outcome of patients is still unclear, mainly due to the limited number of observations.

The aim of the present study was to determine the incidence and causes of GM and to evaluate its impact in the angiographic outcome of a large cohort of patients treated according to the protocols of the Beta Radiation In Europe (BRIE) [15] and the Dose Finding [24] studies using catheter-based systems for de novo lesions.

2. Methods

2.1. Patient selection

We retrospectively analysed 330 patients treated with catheter-based γ-radiation enrolled in the BRIE (149 patients) [15] and Dose Finding studies (181 patients) [24]. Patients included in the radiation protocol were those with objective signs of ischaemia and presence of significant de novo lesions. Out of the total population, 304 patients underwent single vessel PTCA, and in the remaining 26 patients (all in the BRIE study), two vessels were treated, giving in total 356 vessels. In 55 patients (73 vessels), GM was not interpretable leaving 265 patients (283 vessels) for further analysis (Table 1). The baseline and angiographic characteristics of the patients have been previously reported [15,24].

2.2. Device description

Patients enrolled in the BRIE study were treated with the noncentered, 30-mm-long, 90Sr/90Y beta source (Beta-Cath System). The device has been previously described [38]. The longitudinal distance of “full” prescribed dose (100% isodose) coverage measured by radiochromic film is about 26 mm [39], constituting the effective irradiation length.

Patients enrolled in the Dose Finding study were treated with the centered, 29-mm-long, Yttrium-90 beta-emitting source. The device has been described previously [40–43]. It consists of the radioactive source (half-life, 64 h; maximal energy, 2.284 MeV), a centering balloon and an automated delivery device. The effective length of the vessel segment (VS) being irradiated (100% isodose) is 24 mm.

2.3. Dosimetry

According to the BRIE study protocol, the dose prescribed at 2 mm from the centerline of the source axis was 14–18 Gy, based on the reference diameter, by on-line quantitative coronary angiography (QCA), measured <3.35 or >3.35 mm, respectively. The dwelling time was on average 3.12 ± 0.43 min.

In the Dose Finding study, the patients were randomly assigned by computer, over the telephone, to receive 9, 12, 15 or 18 Gy of radiation at a tissue depth of 1 mm. The mean duration of radiation treatment was 1.81 ± 0.10, 2.55 ± 0.20, 3.01 ± 0.16 and 3.17 ± 0.19 min in the 9-, 12-, 15- and 18-Gy groups, respectively.

2.4. Definitions

VS defined as the coronary segment bordered by two side branches that encompassed the original lesion, angioplasty balloon and radiation source. The injured segment (INS) was the segment encompassed by the most proximal and distal position of the radiopaque markers of the balloons used for dilation or stent implantation. The irradiated segment was defined as the segment encompassed by the markers of the radiation source train, 30 mm in length for the 90Sr/90Y source and 29 mm for the Yttrium-90. The effective irradiated segment (EIRS) was the segment that received the full-prescribed dose (100% isodose) and corresponded to the central part of the radioactive source train, 26 mm in length for the 90Sr/90Y source and 24 mm for the Yttrium-90. These segments are illustrated in Fig. 1. The edges of the EIRS are the adjacent (proximal and distal) 5-mm coronary segments. These edges received low-dose radiation due to falloff of the dose in both sources. If these edges were traumatized by balloon inflation (minimum}

| Table 1 Vessel characteristics in relation to GM |
|-----------------|-----------------|
|                  | Total            | Noninterpretable vessels | Nonanalysable vessels |
| Interpretable vessels | Analysable vessels |
| All              | 79.5% (283/356)  | 72% (256/356)             |
| Non GM vessels   | 47% (133/283)   | 47.3% (121/256)           |
| GM proximal only | 53% (150/283)   | 52.7% (135/256)           |
| GM distal only   | 36% (54/150)    | 34.8% (47/135)            |
| GM both proximal | 49.3% (74/150)  | 52.6% (71/135)            |
| and distal       | 14.7% (22/150)  | 12.6% (17/135)            |
| Stent vessels    | 44.9% (127/283) | 44.1% (113/256)           |
| GM               | 68.5% (87/127)  | 68.1% (77/113)            |
| Non-GM           | 31.5% (40/127)  | 31.9% (36/113)            |
inflation pressure was 6 atm) or received new stent implantation during the procedure, they were defined as GM edges. Noninjured or non-GM edges were those that were not traumatized during the intervention.

2.5. Determination of the GM edges

To determine whether the edges of the EIRS were injured, we retrospectively analyzed, blinded to the presence or absence of restenosis and its location at follow-up, all the baseline (intervention plus radiation) angiograms. The following steps were followed: During the procedure, all the interventions (balloons or stents, deflated at the site of injury) and the radioactive source in place were filmed surrounded by contrast medium in identical angiographic projections. This approach allowed us to define the location of the various subsegments (EIRS, INS, edges) in relation to side branches and the correct matching of the angiograms in the off-line analysis. A continuous ECG recording was also displayed, allowing the selection of still frames in the same part of the cardiac cycle. Multiple angiographic loops and ECG matched still frames could be displayed simultaneously, side-by-side, on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoom, The Netherlands). By identifying the relationship between the EIRS and its edges relative to the INS, we determined the GM edges. Two independent cardiologists performed the above-mentioned analysis. There was only 10% disagreement on the presence or absence of GM and its location proximal or distal. These were borderline cases that were reanalyzed by a third reviewer with the use of transparencies, and a final conclusion was made.

In cases where one or more of the following criteria were present, the procedure was reported as noninterpretable: (1) absence of documentation of all interventions reported in the technicians work sheet or the radiation procedure, and (2) more than 10° difference in the angiographic projections not allowing correct matching.

2.6. QCA analysis

The EIRS and both edges were analyzed by QCA prior to, after intervention, and at 6-month follow-up. All angiograms were evaluated after intracoronary administration of nitrates. The off-line analysis of two orthogonal projections was performed by means of the CAAS II analysis system (Pie Medical, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters not filled with contrast [44–46]. The following QCA parameters were computed in the VS: computer-defined minimal luminal diameter (MLD), reference diameter, obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment as diameter stenosis > 50% at follow-up. This allowed the determination of restenosis in the VS (overall restenosis). Computer-defined subsegmental analysis (mean subsegment length was 5.0 ± 0.3 mm, depending on the length of the analyzed VS) was also performed. In each subsegment percentage diameter stenosis was also automatically calculated. This allowed the determination of restenosis location in relation to the defined subsegments, which was termed as regional restenosis.

2.7. Determination of the restenosis location

Three observers analyzed all the films that appeared to have restenosis at the follow-up angiogram. The printouts of the pre, post and the follow-up angiograms, in two orthogonal projections, with the subsegmental analysis and the

![Fig. 1. A diagram of the radiation sources and an irradiated coronary artery with the anatomical and dose-based subsegment definition. SB denotes side branch, RGM denotes radioopaque gold marker, RS denotes radioactive seeds, BRM denotes balloon radiopaque marker, RTM denotes radiopaque tungsten markers, CB denotes compartment balloons, EIRS denotes effective irradiated segment (24 mm for the 90Y source and 26 mm for the 90Sr/90Y source), INS denotes injured segment, IRS denotes irradiated segment (29 mm for the 90Y source and 30 mm for the 90Sr/90Y source), VS denotes vessel segment, IRL denotes irradiation length, EIRL denotes effective irradiation length.](image)

| Table 2: Edge characteristics in relation to GM |
|-----------------|------------------|------------------|
|                | Interpretable edges | Analysable edges |
| Total           | 712               | 20.5% (146/712)  |
| Noninterpretable edges | 28% (200/712)     |                  |
| All             | 79.5% (566/712)   | 72% (512/712)    |
| Noninjured edges | 69.6% (394/566)   | 70.3% (360/512)  |
| GM edges        | 30.4% (172/566)   | 29.7% (152/512)  |
| Proximal GM edges | 44.2% (76/172)   | 42.1% (64/152)   |
| Distal GM edges | 55.8% (96/172)   | 57.9% (88/152)   |
| Balloon edges   | 55.1% (312/566)   | 55.9% (286/512)  |
| GM              | 21.8% (68/312)    | 21.3% (61/286)   |
| Non-GM          | 78.2% (244/312)   | 78.7% (225/286)  |
| Stent edges     | 44.9% (254/566)   | 44.1% (226/512)  |
| GM              | 40.9% (104/254)   | 40.3% (91/226)   |
| Non-GM          | 59.1% (150/254)   | 59.7% (135/226)  |
dose-based subsegments superimposed, were compared. The observers designated the location of the computer-defined QCA subsegments with restenosis in relation to the dose-defined segments. Restenosis was classified as restenosis in the EIRS, edge restenosis (proximal or distal) and restenosis outside the irradiated segment. It is important to realize that the criterion for binary restenosis might be fulfilled in more than one subsegment in the same VS.

2.8. Statistical analysis

Continuous data are presented as mean values; discontinuous data are presented as percentages. Differences in restenosis rates between edges with and without GM were evaluated with chi-square or Fisher’s exact tests as appropriate. Because the behaviour of different segments in the same vessel and the behaviour of different vessels in the same patient may not be independent, the relation between GM and edge restenosis was further analyzed by logistic regression analysis, using generalized estimation equation modelling techniques to correct for possible within-patients effects. Statistical significance of all tests was defined at the \( P < .05 \) level.

3. Results

3.1. Incidence of GM

3.1.1. Vessels

Overall, 283 vessels (265 patients) were interpretable. The incidence of GM was 53%. There was a balance between GM 53% (CI: 47–59) and non-GM vessels 47% (CI: 41–53). The vessel characteristics in relation to GM are presented in Table 1.

3.1.2. Edges

In each vessel, both proximal and distal edges of the EIRS were analyzed giving in total 566 edges. Out of the 150 vessels with GM, 128 had one GM edge, proximal or distal and in 22 vessels both edges were injured giving in total 172 GM edges. The incidence of GM at the edges was 30.4% and comparable between the proximal and distal edges (44.2% [CI: 37–52] vs. 55.8% [CI: 48–63], respectively). The edge characteristics in relation to GM are presented in Table 2.

3.2. Procedural causes of GM

The following reasons were responsible for this phenomenon: (1) development of procedural complications (additional stent implantation post radiation), which extended the treatment beyond the margins of the EIRS, 54.1% (93/172); (2) noncomplete coverage of the INS by the radiation source, 33.7% (58/172); and (3) treatment of long lesions requiring balloons or stents longer than EIRL of the sources 12.2% (21/172).

3.3. Overall restenosis in relation to GM

Follow-up angiogram was available in 256 vessels (242 patients). The restenosis rate in the EIRS was 16.4% and in the VS 26.95%. Because binary restenosis can be encountered more than once per VS (either in the EIRS or at the edges), the summation of the regional restenosis rate is higher than the restenosis rate in the VS. The presence or absence of GM did not affect the incidence of restenosis in the EIRS (17.78% and 14.85%, respectively, \( P = .6 \)). GM significantly increased restenosis at the analyzed VS (31.85% vs. 21.48%, \( P = .05 \)), related to the significant increment in edge restenosis. The restenosis rate at the GM vessels was significantly increased from the EIRS to the VS (\( P = .007 \)) as opposed to the non-GM vessels (\( P = .2 \)), resulting in significant increment in the restenosis from the EIRS to the VS (\( P = .004 \)). The relation of GM with the overall restenosis is presented in Table 3.

3.4. Edge (regional) restenosis in relation to the GM

In each of the 256 vessels, the impact of GM on restenosis was analyzed in both proximal and distal edge (512 edges). Overall, edge restenosis was 6.83%, and there was no difference between the proximal and the distal edge. GM significantly increased the incidence of restenosis at the edges of the EIRS compared with the lesions without GM (4.17% vs. 13.16%, \( P = .001 \)). This effect was observed

<table>
<thead>
<tr>
<th>Table 3</th>
<th>GM and incidence of restenosis</th>
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<tr>
<td></td>
<td>EIRS</td>
</tr>
<tr>
<td>Total</td>
<td>42/256 (16.4%)</td>
</tr>
<tr>
<td>GM</td>
<td>24/135 (17.78%)</td>
</tr>
<tr>
<td>Non-GM</td>
<td>18/121 (14.85%)</td>
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<tr>
<td>GM vs. non-GM</td>
<td>( P = .6 )</td>
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<tr>
<th>Table 4</th>
<th>GM and incidence of edge restenosis</th>
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<tbody>
<tr>
<td></td>
<td>All edges</td>
</tr>
<tr>
<td>All edges</td>
<td>35/512 (6.83%)</td>
</tr>
<tr>
<td>GM edges</td>
<td>20/152 (13.16%)</td>
</tr>
<tr>
<td>Non-GM edges</td>
<td>15/360 (4.17%)</td>
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<tr>
<td>GM vs. non-GM</td>
<td>( P = .001 ), OR = 3.5 (1.7–7)</td>
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both in the proximal (5.73% vs. 14.06%, \( P = .03 \)) and distal (2.38% vs. 12.5%, \( P = .001 \)) edges. It seems to be more pronounced at the distal edge (OR = 5.9) compared to the proximal (OR = 2.7) mainly due to a tendency for increased restenosis at the proximal non-GM edges compared with the distal (\( P = .09 \)). The relation of GM with edge restenosis is presented in Table 4.

Generalized estimation equation analysis, which was used to account for within-patients effects, showed that the probability for restenosis at the edges of the EIRS depends on the GM (\( P = .001 \)), but not on distal/proximal lesion location (\( P = .4 \)), or the device (balloon/stent) used (\( P = 1 \)).

### 3.5. Edge restenosis and GM in relation to the type of injury

Out of the 512 interpretable edges, 286 (55.85%, CI: 41 – 49) were related with balloon angioplasty termed as balloon edges (BEs) and 226 (44.15%, CI: 41 – 49) with stent implantation termed as stent edges (SEs). Significantly higher incidence of GM was observed at the SE (40.2%, 91/226), compared to the BE (21.3%, 61/286) (\( P = .0001 \)). At the SE, GM significantly increased the incidence of restenosis compared to edges without GM (4.44% vs. 15.38%, \( P = .005 \)). There was a tendency for restenosis increment at the balloon GM edges compared with the non-GM BEs (4% vs. 9.84%, \( P = .07 \)). There was no difference in the restenosis between the balloon and SEs and in overall restenosis in vessels with and without GM. The vessel and edge characteristics in the balloon and stent vessels in relation to GM are presented in Tables 1 and 2. The effect of GM on restenosis rate in relation to the type of injury is presented in Table 5.

### 4. Discussion

The incidence of GM was significantly higher in the BRIE study resulting in significantly lower noninjured vessels compared with the Dose Finding study. Differences in the protocols led to imbalance of balloon and stent vessels in the two studies. These differences, in combination with the low number of observations, are limiting the conclusions made when analyzed separately. By combining the data, a balanced population between the GM and non-GM vessels (53% vs. 47%) and the balloon and stent vessels (55.1% vs. 44.9%) with overlapping confidence intervals is obtained. The differences between the two studies are summarised in Table 6.

#### 4.1. Stimulatory effect of low-dose radiation

The stimulatory effect of low-dose radiation on smooth muscle cell proliferation has been previously reported in a swine coronary balloon overstretch injury model [47]. There was a dose-dependent effect in the reduction of neointima formation with evidence of significant stimulatory effect at low dose (10 Gy), while the therapeutic dose begins at approximately 15 Gy. In patients treated with balloon angioplasty, a higher late loss in injured edges compared with the noninjured edges has been reported [26]. By IVUS, this was due to a significant increase on plaque volume not accommodated by vessel enlargement [48]. Similarly, after low-activity radioactive stent implantation (1.0 \( \mu \)Ci) in a porcine model, neointimal hyperplasia was significantly greater than that after nonradioactive stenting [49]. When half-radioactive stents were implanted in porcine coronary arteries, the highest late loss and neointimal thickening was observed at the midstenos dose falloff zone of the half-radioactive stents and not at the edges [50]. In patients receiving 6.0 – 12.0 \( \mu \)Ci \(^{32}\)P radioactive stents, where GM systematically occurs due to the current balloon technology, 50% edge restenosis was reported compared to 0% in-stent [27]. This effect, called “candy-wrapper,” is primarily a focal exaggeration of neointimal hyperplasia accumulation at the edge of the stent [51].

#### 4.2. Restenosis location and its relation to type of injury

The incidence of GM was comparable in the proximal and distal edges (44.2% [CI: 37 – 52] vs. 55.8% [CI: 48 – 63], respectively). GM significantly increased restenosis in both edges of the EIRS. This effect seems to be more prominent at the distal edge compared to the proximal edges.
(OR: 5.9 [CI: 1.8–18.9] and OR:2.7 [CI: 1.1–6.8], respectively). There was no difference in the restenosis rate between the proximal and distal GM edges (7.8% vs. 5.8%, respectively). What makes the OR higher for the distal edge is a tendency for increased restenosis in the noninjured edges proximal compared to the distal (5.7% vs. 2.3%, P=.09). This has been reported through analysis of the noninjured edges of irradiated segments by means of three-dimensional IVUS. Greater increase in the plaque volume in the proximal edges compared with the distal (27% vs. 9.2%, respectively) was reported [39]. The same was also observed after radioactive stent implantation [52].

There was a tendency for increased restenosis at the SEs compared to the BEs (8.84% vs. 5.24%, respectively, P=.1). GM related with stent injury is more prominently associated with edge restenosis compared with GM related with balloon injury (OR: 3.9 [CI: 1.5–10.6] vs. OR: 2.7 [CI: 1.1–6.8], respectively). The mechanisms involved in restenosis after balloon angioplasty are different compared with these of stenting. Negative remodelling and elastic recoil are the causes of restenosis after balloon angioplasty as opposed to neointimal formation after stent implantation [54]. Absence of negative remodelling has been reported at the edges of the irradiated segments after balloon angioplasty [26]. This might partly compensate for the stimulatory effect of radiation on plaque growth at the balloon injured GM edges making the combination less harmful. The significantly higher incidence of GM at the SEs compared to the BEs (68.5% vs. 40.4%, respectively, P<0.001), as a result of the studies design, might also account for this phenomenon.

4.3. GM and restenosis in de novo lesions

The incidence of edge restenosis after initial stent implantation without radiation has been reported to be between 5% and 10% [53–55]. A clue for its incidence in the current area of new generation stents can be obtained by the control group of the SIRIUS study [56]. Edge restenosis was around 8% equal between the proximal and distal margins. It increased restenosis in the whole analysed segment only by 1% as compared with the in-stent segment (35.4 vs. 36.3%) due to its concomitance with in-stent restenosis in the majority of cases. This was the reason that edge stent restenosis remained unattended during a decade of trials using bare stents.

In the first report by Sabate et al. [26], the incidence of GM was 32%, and it increased the edge restenosis from 2% in the noninjured edges to 41%, while the restenosis rate in the irradiated segment was 10%. The Beta-Cath trial, the largest randomised trial of β-radiation for de novo lesions, failed to show any difference in the primary end point, the target vessel failure, in the combined radiation arms compared to the placebo arms [25]. In the balloon group, the reduction in binary restenosis observed with radiation in the lesion segment was not maintained in the VS analysis. Even worse in the stent group, the significant reduction in the stented segment inverted to a significant increment in the analysis segment with worse outcome in the radiation group. Clearly, in this study, the dose falloff zone appears to be in the culprit for the higher restenosis, especially the proximally dose falloff, likely due to a greater reduction in dose proximal relative to distal. Because GM was very frequent (>85%), the authors were unable to ascertain the contribution of GM to the higher restenosis in these zones.

With increased experience, GM was reduced to 6.5% in the RENO registry, and this was not associated with increased edge restenosis but with increased target vessel thrombosis and target vessel related death [57].

4.4. GM restenosis in in-stent restenotic lesions

The incidence of edge restenosis after treatment of in-stent restenotic lesions without radiation is less clear. It was 3–4% in the control groups of WRIST [21] and GAMMA 1 [22]. In a meta-analysis of patients enrolled in the placebo arms of randomised brachytherapy trials for in-stent restenosis with beta and gamma sources, SE restenosis was 4.4%, significantly lower compared to radiated patients. Interestingly, edge restenosis in the radiation group was reported to be higher with beta sources (17.1%) as compared with gamma sources (9.3%) [58].

In the WRIST–GAMMA randomised trial, the incidence of GM was 34% and was strongly associated with development of edge binary restenosis [36]. A failure to demonstrate a relation of GM with the overall restenosis was probably related with the small number of observations.

In the START 30 randomised trial, there was no association of GM with edge restenosis, but the authors speculate that this was related to the fact that the short source used in this study was insufficient to cover the injured zone in the majority of the cases [17]. In the START 40 trial, the incidence of GM was 46% and was associated with significantly increased edge restenosis and restenosis in the analysis segment. This was the first study to relate GM with restenosis in the total analysed segment [18] and is in keeping with our observations.

In a recently published study, the incidence of GM was 37.5% and significantly increased edge and total vessel restenosis [37]. Interestingly, the highest restenosis rate was reported in INSs that received negligible irradiation (<10% of the prescribed dose). In the more recently conducted trials, INHIBIT [19] and WRIST-SVG [23], in which the issue of GM and its implications were known, its avoidance, as mandated by the protocol, resulted in the elimination of edge restenosis.

4.5. Restenosis in the era of drug-eluting stents

In the RAVEL study [59], binary restenosis at the edges was 0% in both arms, but the late loss, a more sensitive index of restenosis, was significantly lower in the sirolimus-eluting stent group compared with the control group in both
stent edges. IVUS analysis of patients enrolled in the FIM study revealed no significant changes in the lumen plaque or vessel volumes at the edges of sirolimus-eluting stents up to 2 years follow-up [60]. Edge restenosis was observed after sirolimus-eluting stent implantation in the randomised SIRIUS study, in which more complex patients were enrolled, with an incidence of 5% predominantly in the proximal edge, and they increase restenosis in the analysis segment from 3.2% to 8.9% [56]. It is very clear that this effect is an unmasking of the edge restenosis due to very effective inhibition of restenosis within the stented segment because its incidence is lower than the edge restenosis observed in the control group (8%).

The difference with brachytherapy for de novo lesions with stent implantation is that this effect, when added on the top of a successful inhibition in the stented segment, significantly attenuates [15] or inverses the favourable outcome [25] observed, indicating that it is not an unmasking due to absence of neointima formation within the length of the stent, but an active phenomenon.

4.6. Safety margins

The safety margins after brachytherapy for avoidance of GM and subsequently edge restenosis have not yet been defined. Many factors such as the extent of the perivascular injury, which can extend up to 10 mm away from the microscopic injury [61], the barotrauma caused by the balloons, which can be up to 2.5 mm away from the actual stent margins [62], the source displacement during the cardiac cycle (up to 5.4 mm) [63] and the falloff the dose at the margins of each source must be taken into account.

Taking into account these parameters, Tripuraneni et al. [64] proposed that for an 18-mm lesion treated with a 20-mm balloon, a 39-mm Iridium source should be used. In an animal model, a safety margin of 14.5 mm was sufficient to eliminate GM [37]. As a general simple rule, a ratio of 1–2 for the vessel was found to have 95% specificity for avoidance of edge restenosis [65]. Recently, a 10-mm safety margin per vessel was found to have 95% specificity for avoidance of GM [37]. As a general simple rule, a ratio of 1–2 for the lesion to source length is advised. The availability of longer sources and stepping application of radiation will help for the elimination of GM.

4.7. Study limitations

The studies were not placebo-controlled, and the effect of a sham source on injured coronary segments cannot be evaluated.

Balloon inflation or stent implantation was considered as the only source of injury. Minor injuries from guiding catheters, guidewires or radiation delivery catheters cannot be completely ruled out. Only binary restenosis data are quoted, and the determination of GM is qualitative because there was no QCA methodology available at that time for the measurement of the length of the GM.

5. Conclusions

GM is strongly related with the development of edge restenosis. This effect was observed in both edges of the EIRS and seems to be more pronounced at the distal edge compared to the proximal. GM related with stent injury seems to be associated with higher incidence of edge restenosis compared with GM related with balloon injury. GM significantly increase restenosis in the total analysed segment but was associated with increased restenosis in the EIRS. It is a local phenomenon with a specific pathophysiology (combination of injury and low-dose radiation). The elimination of GM will improve the outcome of patients treated with intracoronary β-radiation therapy.

References

Chapter 9


Geographical Miss for De-novo Lesions


CHAPTER 10


The Black Hole: Echolucent Tissue Observed Following Intracoronary Radiation

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The black hole: echolucent tissue observed following intracoronary radiation

I Patrick Kay1, Jurgen MR Ligthart1, Renu Virmani2, Heleen MM van Beusekom1, Ken Kozuma1, Andrew J Carter3, Georgios Sianos4, Willem J van der Giessen1, Alexander J Wardeh1, Pim J de Feyter1 and Patrick W Serruys3

1Thoraxcenter, Rotterdam, The Netherlands
2Department of Cardiovascular Pathology, Armed Forces Institute of Pathology, Washington, DC, USA
3Department of Interventional Cardiology, Stanford University Medical Center, Stanford, CA, USA

Correspondence:
Professor PW Serruys
Head of Interventional Cardiology
Thoraxcenter, Academisch Ziekenhuis Rotterdam
Dr. Molukwaterplein 40
3000 DR Rotterdam, The Netherlands
Tel.: (+31) 10 463 5860
Fax.: (+31) 10 436 91 54
E-mail: serruys@card.uaz.nl

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Introduction

Intracoronary radiation, a therapeutic modality aimed at decreasing restenosis, has been investigated in both animals and humans for several years. With the advent of human trials we have started to understand the consequences of this treatment. These include non-healing dissection,1 late occlusion2 and positive remodeling.3 The present authors describe a further new finding: an echolucent area within the lumen of the coronary artery, noted using intravascular ultrasound (IVUS). This phenomenon has been dubbed the ‘black hole’.4,5 The paper describes the finding in terms of IVUS characteristics and present data on its incidence in various subgroups treated conventionally and with radiation. Finally the pathological findings of this entity are described.

Methods

The authors analyzed 128 consecutive patients enrolled in brachytherapy protocols for the treatment of de novo lesions, who had completed six-month follow-up which included angiography with IVUS. These protocols included individuals who had undergone catheter-based radiation using the 192Ir/198Ir Retacath® (Novoste, Norcross, Ga) and 32P Guidant (Santa Clara, CA) systems. The radioactive stent group comprised those who received 0.75–1.5 μCi (n = 18), 6.0–12.0 μCi (n = 26) and ‘cold-end’ (n = 18) stents (Isostent Inc., San Carlos, CA).

The control group included individuals who underwent PTCA with (n = 48) and without stent implantation (n = 22). The stented patients were taken from a database (Cardalysis BV, Rotterdam, The Netherlands) and were
chosen so as to match the characteristics of the radioactive stent in particular (similar patient demographics, reference and stent diameter and length). The balloon angioplasty group comprised 18 patients who underwent balloon angioplasty followed by thorough IVUS assessment at the termination of the procedure. Demographics, lesion characteristics and treatment approaches were similar among those who underwent balloon angioplasty compared with those who underwent angioplasty plus catheter-based radiation.

**Catheter-based radiation**

The Novoste Betacath and the 32 P Guidant β-radiation systems have been described in detail elsewhere. The present authors followed certain steps to ensure the correct identification and analysis of the irradiated segment post-intervention and at six-month follow-up. First, an angiogram was performed after positioning the delivery catheter, and the relationship between anatomical landmarks and the two gold markers was noted. Typically, the aorto-ostial junction and the side-branches were used as landmarks. The landmark closest to either of the gold markers was used as a guide. During the motorized IVUS pullback, all side-branches were counted and the guiding landmark was identified. The correct selection of the marker was confirmed by visualizing the position of the IVUS probe during a contrast injection. At follow-up, the same region of interest was selected and compared with that after treatment.

**Radioactive stent**

The properties of low (0.75–1.5 μCi) and higher activity (6.0–12.0 μCi) radioactive stents and procedural characteristics specific to their implantation have been described elsewhere. All stents were implanted with a stent-to-artery ratio of 1.1 : 1.0. ‘Cold-end’ stents were 27.3 mm in length and available in diameters of 3.0 and 3.5 mm. The distal and proximal 5.7 mm of the stent was nonradioactive, whereas the central 15.9 mm had an activity of 3.0–24.0 μCi (see Figure 1).

**Figure 1.**

Cold-end stent with central radioactive segment and proximal and distal non-radioactive segments

**Figure 2.**

Left coronary angiogram performed at six-month follow-up. Proximal in-stent restenosis is seen in a 6–12 μCi stent implanted in the circumflex artery (left frame). Corresponding intravascular ultrasound performed at six-month follow-up demonstrating homogeneous black tissue from six to one o’clock (right frame).

**IVUS acquisition**

The authors used a mechanical 30 MHz IVUS system (ClearView, CVIS, Sunnyvale, CA). Motorized pullback was performed at 0.5 mm/second. The entire segment subjected to radiation was examined, plus the associated 10 mm proximal and distal edges. For radioactive stents this included 10 mm proximal and distal to the final stent strut. Images were stored on S-VHS tape for later analysis.

Findings were verified by three independent observers, who were blinded to whether images were from control or radiation cases. Where any one observer disagreed that

**Figure 3.**

(A) Baseline longitudinal intravascular ultrasound (IVUS) reconstruction of freshly implanted 6.0 μCi activity radioactive stent. (B) Longitudinal reconstruction of the same transverse IVUS image seen in Figure 2. This confirms the presence of a uniform, black, semicircular structure with a thin cap. Note the adjacent side-branch (SB). (C) The same image seen at one year, with echolucent tissue in a similar position as verified by the location of the side-branch. Note the greater reflectivity of the echolucent tissue and the thicker fibrous cap present. (D) Post-atherectomy image showing complete removal of tissue adjacent to the side branch.
The Black Hole

<table>
<thead>
<tr>
<th>Location</th>
<th>% BHA of NIH</th>
<th>Restenosis (QCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P edge</td>
<td>96</td>
<td>Yes</td>
</tr>
<tr>
<td>P edge</td>
<td>100</td>
<td>Yes</td>
</tr>
<tr>
<td>D edge</td>
<td>56</td>
<td>No</td>
</tr>
<tr>
<td>P edge</td>
<td>64</td>
<td>Yes</td>
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<tr>
<td>P edge</td>
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<td>Yes</td>
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<tr>
<td>D edge</td>
<td>71</td>
<td>Yes</td>
</tr>
<tr>
<td>P edge</td>
<td>52</td>
<td>No</td>
</tr>
<tr>
<td>D edge</td>
<td>68</td>
<td>No</td>
</tr>
</tbody>
</table>

**Cold-end (n = 18) (39%)**

- P within stent* 100 Yes
- D within stent 42 No
- P within stent* 90 No
- D within stent 26 Yes
- P within stent* 48 Yes
- D within stent 38 No
- P within stent* 51 Yes

**Guidant CBS (n = 16) (19%)**

- Within stent 26 Yes
- Within stent 34 No
- Out of stent 45 Yes

**Betacath CBS (n = 18) (22%)**

- Within stent 48 No
- Within stent 26 Yes
- Within stent 26 No
- Within stent 56 No

**Guidant: no stent (n = 11) (18%)**

- 24 – 34 Yes
- 25 – 90 No

**Betacath: no stent (n = 21) (14%)**

- 26 – 27 Yes
- 27 – 16 Yes
- 28 – 18 Yes

**Note:** % BHA of NIH—percentage of neointimal hyperplasia caused by echolucent tissue

*At junction of radio-opaque and nonradio-opaque segment of the stent.

BHA, black hole area; NIH, neointimal hyperplasia; QCA, quantitative coronary angiography; P, proximal; D, distal; CBS, catheter-based radiation plus stenting.

Table 1

the ultrasound image showed a black hole, then that case was not included in the analysis.

**IVUS definition of echolucent tissue**

Lesions with echolucent tissue had the following characteristics: a homogeneous black appearance without backscatter; lesions were discrete and readily distinguishable from conventional neointimal hyperplasia (NIH) (Figures 2, 3); commonly, a thin echodense cap was seen on the luminal aspect of the lesion.

After radioactive stenting all lesions were observed adjacent to stent struts. Images with ring-down or other artefacts were excluded, as were intraluminal echodense structures with associated attenuation. Other causes of relative echolucency such as contrast,^{8} thrombus^{9} or a lipid lake^{10} were excluded.

**Definitions**

The following dimensions were measured in each group: total vessel area (TVA), lumen area (LA), the area of echolucent tissue (black hole area = BHA) and the percentage of NIH caused by the echolucent tissue in the cross-section of greatest stenosis. Restenosis at six-month follow-up was defined using standard angiographic criteria after off-line quantitative coronary angiography (diameter stenosis > 50%)

**Medication**

All patients received clopidogrel for between one month (conventional stenting) and three to six months (stenting plus catheter-based radiation or radioactive stenting), plus life-long aspirin.

**Atherectomy and immunohistochemistry**

Atherectomy was performed using standard techniques with subsequent gross evaluation and subsequent microvascular staining and assessment.

For immunostaining, sections were preincubated with 0.3% hydrogen peroxide and Protein Block Serum-Free (X0909, Dako Corp., CA). A mouse monoclonal antibody against α-smooth muscle actin (1:5000 dilution, Dako Corp., CA) was used to identify smooth muscle cells. Polyclonal antibodies against biglycan (LF-51) and decorin (LF-122) were used for identification of proteoglycans (antibodies kindly provided as a gift by Larry Fisher, NIH, Bethesda, MD). Before incubating with proteoglycan antibodies, sections were first incubated with 1 U/l chondroitinase ABC (code 100332, Seikagaku Corp., Tokyo, Japan) for 15 minutes at 37 °C to detach glycosaminoglycan side-chains from the protein core; this procedure intensifies staining. All primary antibodies were incubated overnight in a humidified chamber at 4 °C. After rinsing in PBS, the primary antibody was labeled by a biotinylated link antibody directed against mouse using a peroxidase-based LSAB kit (Dako Corp., CA). Positive staining (brown reaction product) was visualized with a diaminobenzidine (Dako Corp., CA). After immunostaining, the sections were counterstained with Gill’s hematoxylin, dehydrated in a graded series of alcohols, rinsed in xylene and mounted in Permount (Fisher Scientific).

**Results**

At 6-month follow-up 28 discrete areas (22%) of echolucent tissue (‘black hole’) were identified. No echolucent tissue was seen in the control group or in the low-activity radioactive stent group. Angiographic restenosis was present in 63% of cases where echolucent tissue was present. Of those lesions with restenosis, echolucent tissue was on average responsible for 50% of
neointimal hyperplasia. More severe stenosis was more frequently observed in the 6.0–12.0 μCi and cold-end radioactive stent groups [mean stenosis = 63.1 ± 24.1%] compared with catheter-based techniques (mean stenosis = 37.2 ± 20.5%), p = 0.005. Mean length of the echoluent tissue was 4.0 mm ± 1.6 mm (range 2–8 mm).

**Radioactive stent**

Higher activity (35%) and cold-end radioactive stents (39%) were most commonly associated with echoluent tissue (Table 1). Both occurred at the proximal and distal margins of radiation within the stent or at the stent edges. By definition this fall-off in radiation occurred in the final 1–2 mm of 6.0–12.0 μCi stents and in-stent for cold-end stents. Bilateral echoluent tissue was seen in five out of seven cases that presented with restenosis six months after cold-end stent implantation. In four of these cases the proximal edge was more severely affected.

**Catheter-based radiation**

Echoluent tissue was seen in all groups treated with catheter-based radiation with (21%) and without (16%) stenting. These tended to be smaller lesions than those seen in the radioactive stent group (Table 1). After catheter-based radiation only one of the echoluent tissues described involved geographical miss (area of injury associated with a fall-off in radiation).12

**Pathology features**

Atherectomy was performed on four individuals (AtherCath-Bantam®, DVI, Guidant, Temecula, CA) at six-month follow-up after radioactive stent implantation (mean activity: 6.0 μCi). The corresponding IVUS images to these atherectomy specimens may be seen in Figures 2 and 3.

Macroscopic assessment of the tissue samples after atherectomy of in-stent restenosis in a radioactive stent showed two types of tissue: dark yellow, often containing pieces of stent strut, and white, more fibrotic-appearing tissue (Figure 4(A)). Note the presence of stent struts is in keeping with the IVUS image (Figure 3(D)) suggesting successful atherectomy of the lesion noted in Figure 3(C).

Microscopy revealed tissue containing smooth muscle cells in abundant extracellular matrix (myxoid change) with two distinct regions (Figures 4(B), (C)) and containing abundant proteoglycans (Figure 4(D)). Region 1 (Figure 4(E)) was more cellular in nature, contained collagen and elastin (Figure 4(C)), and was not distinguishable from normal restenotic tissue. Region 2 (Figure 4(F)) was more sparsely populated, showing pyknotic nuclei, with some of the extracellular matrix having a coagulated or dense appearance (fibri-
Echoluent tissue may be a dominant cause of restenosis as seen in four patients. Overall it appeared to contribute to approximately 50% of the restenotic burden associated with NIH seen at six-month follow-up. The lesion may be missed on IVUS examination because of its echolucency, caused by tissue rich in proteoglycans and poor in mature collagen and elastin.

What is unclear is the cause of such lesions. Certainly, irradiation is associated with proteoglycan accumulation in various tissues. Hehrlein has noted that the increase in neointimal volume in arteries treated with external beam radiation (EBR) was predominantly due to enhanced extracellular matrix production. This study suggested that the accumulation of extracellular matrix after stent deployment was augmented by external beam radiation and that excessive matrix formation was a determinant of failure of radiation therapy to prevent restenosis. The atherectomy specimens of the current paper reflect changes seen in Carter and co-workers’ porcine model with radioactive stents (Figure 4(G) and (H)). Carter et al. reported myxoid changes in low, intermediate and high-activity stents (30%, 60% and 37%, respectively) while no myxoid change was seen in control stents (personal communication, 2000). This would indicate that the echoluent tissue is a general response to irradiation of damaged vascular tissue. Finally, a recent brief report from Kim et al. corroborates the present findings.

The matrix seen is rich in biglycan proteoglycan; biglycan secretion by smooth muscle cells in culture has been shown to be controlled by TGF-β. Therefore it is likely that radiation may induce greater TGF-β production that results in excessive biglycan production and formation of echoluent tissue on IVUS.

O’Brien and colleagues suggest that biglycan may bind apoA and apoB in atherosclerotic intima. They also raise the possibility that apoA may act as a bridging molecule that traps apoA1-containing HDL in atherosclerotic intima. Taken together these findings are consistent with the hypothesis that biglycan may contribute to the pathogenesis of atherosclerosis by trapping lipoproteins in the artery wall.

Atherectomy samples taken at points where echoluent tissue is seen on IVUS show aberrant nuclear morphology, suggesting ongoing cell death. This process continues to take place long after stent radioactivity has decreased to background levels. This indicates that radiation indeed has long-term effects. The presence of fibrinoid change may also be indicative of delayed healing, as was also seen in the report by Carter et al.

With time an echodense cap forms over the area of the echoluent tissue; this cap is easily seen on IVUS evaluation (Figure 3). This cap is also seen on pathology, showing collagen and elastin-rich tissue. This may be in keeping with a phenotypic change in the SMCs, allowing for a more mature tissue response to the stent implantation.

**Figure 5.**
(A) Immunoperoxidase-stained section showing α-actin positive smooth muscle cells. (B) Immunoperoxidase-stained section showing strong matrix positivity for biglycan.

Discussion

Tissue may be hypodense owing to excess water content or a paucity of cellular tissue. In this study echoluent tissue (‘black hole’) noted at six-month follow-up was uniquely associated with intracoronary radiation. More common after radioactive stent implantation (>6.0 μCi), it was frequently located adjacent to the stent struts in areas of radiation fall-off, where it was associated with greater restenosis than the catheter-based techniques.

The latter was thought to be tissue constituting the echoluent tissue. The area of the myxoid, proteoglycan-rich matrix was thought to constitute the black hole. Three of the four biopsies were stained for α-actin (Figure 5(A)) to confirm presence of smooth muscle cells and for biglycan (Figure 5(B)), which is the dominant proteoglycan in restenotic lesions. All three biopsies were strongly positive for biglycan and one biopsy stained for decorin was weakly positive.
them to produce collagen and elastin-rich matrix typical of mature NIH with a lack of proteoglycan.

Conclusion
This paper describes a series of atherectomy samples extracted from humans after radioactive stent implantation. It also links the IVUS finding of echolucency noted after intracoronary radiation in various modalities with tissue rich in proteoglycans while poor in mature collagen and elastin. This tissue finding appears to be unique to intracoronary radiation and in particular radioactive stenting.

Limitations
Atherectomy was performed in only four patients and the findings described here will need to be substantiated with greater numbers. The issue of radiation dosimetry is complex and fundamental; however, this is beyond the scope of this report.

References

CHAPTER 11


Long-term Outcome Following Intracoronary Beta-radiation Therapy

Submitted for publication
Long-term outcome following intracoronary beta-radiation therapy

Georgios Sianos, MD, Angela Hoye, MB ChB, Francesco Saia, MD, Willem van der Giessen, MD, Pedro Lemos, MD, Pim J. de Feyter, MD, Peter C Levendag, MD, Ron van Domburg, PhD, Patrick W. Serruys, MD.

Department of Interventional Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands.

**Brief title:** Long-term outcome after brachytherapy

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**Correspondence address:**

Prof PW Serruys MD, PhD, FESC, FAAC

Department of Interventional Cardiology

Erasmus MC Rotterdam

Thoraxcentre Bd 404

Dr Molewaterplein 40

3015 GD Rotterdam

The Netherlands

Tel: (+31 10 4635260)

Fax: (+31 10 4369154)

e-mail: p.w.j.c.serruys@erasusmc.nl
Abstract

Objectives: We sought to determine the long term outcome after intracoronary beta-radiation therapy.

Background: Intracoronary beta-radiation therapy (IRT) is effective for the treatment of in-stent restenosis, though its efficacy for the treatment of de novo lesions especially in combination with the use of stents is questionable. The long-term outcome after IRT is not yet established.

Methods: The rate of major adverse cardiac events (MACE) was retrospectively determined in 301 consecutive patients who were treated with IRT. MACE was defined as death, myocardial infarction, or any re-intervention. Long-term clinical outcome was obtained from an electronic database of hospital records, and questionnaires to the patients and referring physicians. Long-term survival status was assessed by written inquires to the Municipal Civil Registries.

Results: The mean follow up was $3.55 \pm 1.17$ years. The cumulative incidence of MACE at six months was 19.1%, at one year 36.4%, and at 4 years 58.3%. The target lesion revascularization (TLR) rate at six months was 12.9%, at one year 28.3%, and at 4 years 50.4%. From multivariate analysis, dose <18 Gy was the most significant predictor of TLR. At 4 years the cumulative incidence of death was 3.8%, of myocardial infarction 13.4% and of coronary artery bypass surgery 11.3%. A total vessel occlusion was documented in 12.3% of the patients.

Conclusions: In the long-term follow-up of patients following IRT, there are increased adverse cardiac events beyond the first 6 months.
Introduction

Intracoronary radiation therapy has been evaluated as a therapeutic modality for restenosis prevention. Randomized studies have confirmed its effectiveness for the treatment of in-stent restenosis both with gamma (1-3), and beta emitters (4-6), but its efficacy for de novo lesions especially in combination with the use of stents is questionable (7-9).

The safety and efficacy of IRT in the long-term has yet to be determined. In a porcine model of restenosis of balloon and stent arterial injury followed by IRT, the inhibition of neointimal formation observed at 1 month was not sustained at six months. Furthermore this lack of effect on neointimal formation was also accompanied by subacute and late thrombosis that lead to cardiac death (10). Reports on the long-term outcome of small randomized studies and registries have raised issues regarding the long-term efficacy of IRT. The angiographic analysis from the SCRIPPS trial at 3 years showed a reduction of the MLD in irradiated patients but not the placebo group, (11) with a further increase in TLR between 3 to 5 years in the irradiated patients only (12). In addition, an increase in the revascularization rate between 6 months and 3 years was only observed in the irradiated group of the gamma-WRIST randomized trial (13).

In this study, we report the long-term outcome of patients treated with beta-radiation therapy for de-novo and in-stent restenotic lesions in our centre.

Methods

Patient population

Between April 1997 and December 2002, 331 patients received IRT in our institution. In 4 patients irradiation was not successful (total success rate 99%). Fifteen patients treated during 2002 with limited follow up were excluded from this analysis. Another 11 patients that were treated with gamma radiation (GRANITE study) were also excluded. In total 301 patients were
analysed for determination of the long-term follow-up after beta-radiation therapy. The baseline characteristics of the patients are presented in Table 1. Procedural characteristics and radiation details are presented in Table 2. The number of patients treated with IRT per year is presented in Figure 1.

Follow up

Baseline clinical and procedural data were entered prospectively into a dedicated database. Long-term clinical outcome was obtained from an electronic database of hospital records. The Thoraxcentre is a tertiary cardiology centre serving a group of 14 local hospitals, and is the only one with facilities for percutaneous interventions in the region of Rotterdam. As required by the local medical system organisation all baseline procedures were performed in this tertiary facility, as well as the vast majority of re-interventions.

Long-term survival status was assessed by written inquires to the Municipal Civil Registries. Questionnaires were sent to all living patients focusing on the occurrence of MACE such as, myocardial infarction, and repeat intervention (surgical and percutaneous). The referring physician and institutions as well as the general practitioners were directly approached whenever necessary. Complete follow-up was obtained in all patients.

Definitions

MACE was defined as: 1) death, 2) non-fatal myocardial infarction, 3) repeat revascularization. TLR was defined as any surgical or percutaneous re-intervention due to restenosis within the irradiated segment or the 5mm proximal or distal segments (edge restenosis). TVR was defined as any re-intervention driven by lesions located in the treated vessel beyond the target lesion limits. Non TLR-TVR was defined as any re-intervention in vessels other than the target vessel. CABG was considered not as a separate event but as a type of re-intervention (TLR,
TVR or non TLR-TVR). The diagnosis of acute myocardial infarction, indiscriminately Q or non-Q, required an elevation of creatine kinase to twice above the upper limit of normal together with a rise in creatine kinase-MB fraction, or if made following patient admission to another hospital, was confirmed through direct contact with the referring physician, using the same criteria.

Total occlusion was defined as occlusion of the irradiated segment documented by coronary angiography. Subacute thrombosis was defined as angiographically documented total occlusion ≤ 30 days. Late total occlusion was defined as angiographically documented total occlusion > 30 days post intervention. Thrombotic occlusion was defined as any occlusion that resulted in an acute coronary syndrome (myocardial infarction or unstable angina). (14).

For the determination of the length of follow up, the start day was that of the index procedure with IRT between April 1997 and December 2001. The last day for the follow up was the 31st March 2003.

Statistical Analysis

Event-free survival was estimated with Kaplan-Meier curves. Among patient subgroups the log rank test was used to compare survival curves. Data are expressed as mean value ± SD. Continuous variables were compared by Student’s t-test, categorical variables by chi-square-tests. Statistical significance of all tests was defined at the p<0.05 level. The independent association of clinical characteristics with long-term mortality, infarction, TLR and vessel occlusion (the first occurrence of death, myocardial infarction, TLR) was tested by using the Cox proportional hazard model. Pre-selected pre and peri-procedural variables were age, gender, diabetes, hypertension, hypercholesterolemia, smoking, unstable angina, prior myocardial infarction, prior CABG, extent of coronary artery disease, left ventricular ejection
fraction, indication for PTCA (de-novo or in-stent restenosis), device used (stent or balloon),
dose (<18 Gy or ≥18 Gy), and duration of dual antiplatelet medication (<6 months versus ≥6
months).

Results

MACE

The cumulative incidence of MACE at six months was 19.1%, at one year 36.4%, and at 4 years
58.3%. The MACE free survival curve is presented in Figure 2. The total count of MACE is
presented in Table 3. At four years, the cumulative incidence of MACE was neither dependent
on the indication (de-novo versus in-stent restenosis, p=0.8), nor the device used (balloon
versus stent, p=0.5). The independent predictors of MACE are presented in Table 6.

At 4 years the cumulative incidence of death was 3.8%, and of myocardial infarction 13.4%.
Half of the deaths were cardiac in origin and in the other half the aetiology is unknown. A
higher incidence of myocardial infarction was observed in patients treated for de novo lesions
compared to those treated for in-stent restenosis (13.7% vs 6.3%, p=0.04 respectively).

Re-intervention

The majority (85%) of re-interventions were TLRs, with low rates of TVR and non TLR-TVR
observed at 4 years (2.3% and 4.7% respectively). The cumulative incidence of TLR at 6
months was 12.9%, at one year 28.3%, and at 4 years 50.4%. The TLR free survival curve is
presented in Figure 2. The mean time to the first TLR was 1.15±1.0 years. The re-intervention
free survival rate at six months was 83.4% and at 4 years 46.2%. The total count of TLR and
re-intervention is presented in Table 3. At four years, the cumulative incidence of TLR was
neither dependent on the indication (de-novo versus in-stent restenosis p=0.8), nor the device
used (balloon versus stent, p=0.8), Figure 3. The cumulative incidence of TLR was higher in
patients who received <18 Gy compared with ≥18 Gy, \( p=0.01 \), Figure 4. The independent predictors of TLR are presented in Table 4.

**Total occlusions**

A total occlusion was documented in 37 patients (12.3%), Table 3. The incidence of sub-acute thrombosis was 0.3% (1/301) and of late total occlusion 12% (36/301). Almost half (6.0%) were related to an acute coronary syndrome (late thrombotic occlusion). Six patients underwent TLR before the vessel finally occluded. Patients treated for de-novo lesions had a higher incidence of total occlusions compared to those treated for in-stent restenosis (15.4% versus 7.9%, \( p=0.03 \)). The treatment of a de-novo lesion was an independent predictor for total vessel occlusion in the long-term HR=2, 95% CI: (1.1-5).

**CABG**

In total 30 patients underwent CABG, Table 3. In 15 patients surgery was the first TLR. In 11 patients it was the second TLR and in 1 the third TLR (recurrence after an initial percutaneous TLR). In two patients CABG was regarded as TVR and in one further patient as non-TLR-TV.

**Discussion**

**Evidence of reduced efficiency over time**

*Long-term outcome for de-novo lesions*

Very limited data are available for the long-term outcome of patients treated with intracoronary radiation for de-novo lesions. In the Canadian arm of the BERT trial the TLR rate at six months was 10% and increased to 23% at two years indicative of a late catch up phenomenon. The positive remodelling observed at six months was lost due to a decrease in
MLD between six months and two years. No death, myocardial infarction or late vessel occlusion were reported in this small cohort of thirty patients (15).

*Long-term outcome for in-stent restenosis for beta and gamma*

In the WRIST series of patients TLR increased by 14% between 6 months and 2 years both after beta and gamma radiotherapy, significantly higher than the 2% increment of the control group (16). Between 2 years and 3 years TLR further increased by 7% in patients treated with gamma radiotherapy compared with 2% in the control group (13) indicative that radiation therapy may merely delay the restenotic biological process.

The angiographic analysis from the SCRIPPS randomized study at 3 years showed a reduction of MLD by 0.37mm in the irradiation group while remaining unchanged in the placebo group (11). Between 6 months and 5 years TLR increased by 11.6% (from 11.5 to 23.1%) in the irradiated group compared with only 3.5% (44.8% vs 48.3%) in the placebo group; and at five years the composite end-point of death, myocardial infarction and TVR, no longer reached statistical significance between the two groups (12). In both studies, despite the apparent mitigation of efficacy of radiation over time there remained a significant overall benefit in the clinical outcome of irradiated patients compared to the non-irradiated in the long-term.

In our population between year 1 and 4, TLR increased from 28% to 50% and MACE from 36% to 58%. These results compare poorly with results after conventional stent implantation. In the Benestent I study TLR at five years was 17.2% (2% increment between years 1 and 5) and total MACE 34.4% (11% increment between years 1 and 5) (17). Even in more complex subsets of patients TLR was not higher than 20% up to 10 years follow up (18,19).
Indication, dosage administered, and antiplatelet treatment.

There was no difference in the long-term outcome based on the indication (de-novo versus in-stent restenosis) or the device used (balloon versus stent). Increased dose (≥18 Gy) was the strongest radiation-related independent predictor of TLR. In patients treated for de-novo lesions in a dose finding study the group who received 18 Gy had a better angiographic outcome compared with groups receiving lower doses (7). In the Long WRIST study of patients treated for diffuse in-stent restenosis, improved clinical and angiographic outcomes were observed in the group who received 18 Gy compared with placebo and those who received 15 Gy (20). Patients treated with gamma radiation in the Venezuela study had a better long-term outcome compared with patients from SCRIPPS and WRIST, and the authors speculate that this was related to the higher dose administered during this study (21).

In the current study the duration of double antiplatelet medication was not a predictor of MACE or TLR. In the WRIST 12 study at 15 months follow up, patients that received double antiplatelet medication for 12 months had improved clinical outcome compared to those received 6 months only (22,23). Since the majority of our patients received double antiplatelet medication for 6 months or less, the duration was probably not long enough.

Total occlusions

The incidence of late total occlusion and late thrombosis after brachytherapy varies between 6-14%. (14,24). In our study a 12.3% incidence of occlusion was documented with the majority of events occurring beyond 6 months. It probably underestimates the real incidence as it does not include silent occlusion in asymptomatic patients without angiographic follow up.
Patients treated for de-novo lesions had a significantly higher incidence of total occlusions and myocardial infarction suggesting that brachytherapy should not be used as treatment for primary prevention of restenosis.

**Brachytherapy in the era of DES**

Drug eluting stents have been proven to be very effective in preventing restenosis for relatively simple de-novo lesions (25). Preliminary reports are indicative that this beneficial effect is maintained in the long-term (up to two years) (26). These results, in combination with the disappointing outcome of brachytherapy for de-novo lesions (especially with the use of stents) have had a dramatic impact in the use of brachytherapy in our centre (Figure 1).

The broad application of eluting stents, may limit brachytherapy as a therapeutic technique, for the limited number of patients with failure of eluting stents.

**Limitations**

This is a single centre retrospective analysis with all the limitations originating from such an approach. The enrolment of the patients was done over a period of four and a half years. The dose administered and the duration of dual antiplatelet medication were variable, based on the protocol and the current evidence available at that time.

**Conclusions**

In the long-term follow-up of patients following IRT, there are increased adverse cardiac events beyond the first 6 months. Intracoronary beta-radiation therapy delays rather than abolishes cardiac events in the long-term. Patients treated with IRT require longer follow-up evaluation than those treated with standard techniques.
References


Table 1

Baseline and procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (years)</td>
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</tr>
<tr>
<td>Male sex</td>
<td>215</td>
<td>71.4</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
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</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>105</td>
<td>34.9</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>52</td>
<td>17.3</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>158</td>
<td>52.5</td>
</tr>
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<td>168</td>
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<tr>
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<td>30.9</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Smoking</td>
<td>57</td>
<td>18.9</td>
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<tr>
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<td>16.9</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal &gt;50%</td>
<td>280</td>
<td>93.0</td>
</tr>
<tr>
<td>Moderate 35-50%</td>
<td>16</td>
<td>5.3</td>
</tr>
<tr>
<td>Poor &lt;35%</td>
<td>5</td>
<td>1.7</td>
</tr>
</tbody>
</table>

CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty.
Table 2

Procedural characteristics and radiotherapy details

<table>
<thead>
<tr>
<th></th>
<th>n</th>
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<tr>
<td>Patients</td>
<td>301</td>
<td></td>
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<tr>
<td>Follow-up (range) in years</td>
<td>3.55 (1.2-5.92)</td>
<td></td>
</tr>
<tr>
<td>One vessel treated</td>
<td>273</td>
<td>90.7</td>
</tr>
<tr>
<td>two vessels treated</td>
<td>28</td>
<td>9.3</td>
</tr>
<tr>
<td>Total vessels</td>
<td>329</td>
<td></td>
</tr>
<tr>
<td>Failed radiation</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>Second radiation</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>Vessel treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>LAD</td>
<td>120</td>
<td>36.5</td>
</tr>
<tr>
<td>RCA</td>
<td>115</td>
<td>35.0</td>
</tr>
<tr>
<td>LCx</td>
<td>73</td>
<td>22.2</td>
</tr>
<tr>
<td>SVG</td>
<td>19</td>
<td>5.8</td>
</tr>
<tr>
<td>Dual antiplatelet treatment</td>
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<td></td>
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<tr>
<td>No</td>
<td>51</td>
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</tr>
<tr>
<td>1-3 months</td>
<td>71</td>
<td>23.6</td>
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<tr>
<td>6 months</td>
<td>142</td>
<td>47.2</td>
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<tr>
<td>&gt; 6 months</td>
<td>37</td>
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</tr>
<tr>
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<td>109</td>
<td>36.2</td>
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<td>Study</td>
<td></td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>BETA-CATH</td>
<td>13</td>
<td>4.3</td>
</tr>
<tr>
<td>BRIDGE</td>
<td>11</td>
<td>3.7</td>
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<tr>
<td>BRIE</td>
<td>14</td>
<td>4.7</td>
</tr>
<tr>
<td>COMPASSIONATE</td>
<td>23</td>
<td>7.6</td>
</tr>
<tr>
<td>EURO-START 40</td>
<td>12</td>
<td>4.0</td>
</tr>
<tr>
<td>PREVENT</td>
<td>29</td>
<td>9.6</td>
</tr>
</tbody>
</table>
| Routine use*                   | 169 | 56.1%

| Source                         |     |    |
| P32                            | 40  | 13.3 |
| Sr/Y                           | 261 | 86.7 |

| Source length (vessels)        |     |    |
| P32 27mm                       | 40  | 12.2 |
| 90Sr/90Y 30mm                  | 142 | 43.2 |
| 90Sr/90Y 40mm                  | 109 | 33.1 |
| 90Sr/90Y 60mm                  | 38  | 11.6 |
| Tandem radiation               | 48  | 14.6 |
| Delayed radiation              | 7   |  2.1 |

LM denotes left main coronary artery, LAD left anterior descending coronary artery, RCA right coronary artery, and LCX left circumflex coronary artery. Tandem radiation refers to administration in a stepwise fashion, and delayed radiation refers to patients who had delay between intervention and the administration of brachytherapy.

* 138 of these patients were enrolled in the RENO registry.
Table 3

All events

<table>
<thead>
<tr>
<th>Event</th>
<th>&lt;6m</th>
<th>&lt;1y</th>
<th>&lt;2y</th>
<th>&lt;3y</th>
<th>&lt;4y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4</td>
<td>4</td>
<td>9</td>
<td>10</td>
<td>12</td>
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<tr>
<td>MI</td>
<td>8</td>
<td>17</td>
<td>27</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>TLR</td>
<td>30</td>
<td>86</td>
<td>119</td>
<td>141</td>
<td>153</td>
</tr>
<tr>
<td>TVR</td>
<td>5</td>
<td>17</td>
<td>22</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>non TLR-TV R</td>
<td>15</td>
<td>36</td>
<td>50</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td>any re-intervention</td>
<td>50</td>
<td>139</td>
<td>191</td>
<td>222</td>
<td>245</td>
</tr>
<tr>
<td>CABG</td>
<td>4</td>
<td>12</td>
<td>22</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>total occlusions</td>
<td>6</td>
<td>17</td>
<td>29</td>
<td>34</td>
<td>37</td>
</tr>
</tbody>
</table>

All events reflects the total count of events i.e. if a patient required repeat intervention and later suffered a MI the total count would reflect both events and not just the worst occurred. For the CABG and the total occlusions the total count of events is the same as the hierarchical ranking since there were no patients with repeated such events. CABG was not considered as separate event but was regarded as a type of re-intervention.

MI denotes myocardial infarction, TLR denotes target lesion revascularization, TVR denotes target vessel revascularization, MACE denotes major adverse cardiac events and CABG denotes coronary artery bypass graft operation.

Table 4

Independent predictors of MACE and TLR during follow up

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
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<tbody>
<tr>
<td>MACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.6</td>
<td>1.1-2.1</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Previous intervention</td>
<td>1.7</td>
<td>1.2-2.4</td>
</tr>
<tr>
<td>TLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose &lt;18 Gy</td>
<td>1.6</td>
<td>1.1-2.3</td>
</tr>
<tr>
<td>Source length &lt;30mm</td>
<td>1.4</td>
<td>1.2-2.1</td>
</tr>
</tbody>
</table>

MACE denotes major adverse cardiac events, TLR denotes target lesion revascularization.
Figure 1

Number of patients treated with intracoronary radiation (IRT) per year. The recognition of the limitations of IRT and the advent of drug eluting stents in our institution had a dramatic impact in its use after 2000.

Figure 2

Death, myocardial infarction, re-intervention and MACE free survival curves up to four years (Kaplan-Meier). The TLR and MACE curves have three distinct segments. Up to six months a relapse is clearly visible followed by a sharp decrease related to the angiographic control undertaken in almost 65% of the patients. From one year and up to four years a constant and gradual decrease is clearly visible.

MACE denotes major adverse cardiac events, TLR denotes target lesion revascularization, MI denotes myocardial infarction.
Figure 3

TLR-free survival curves (Kaplan-Meier) based on the indication (de-novo/in-stent restenosis) and the device used (balloon/stent).

TLR denotes target lesion revascularization, ISR denotes in-stent restenosis.

Figure 4

TLR-free survival curves (Kaplan-Meier) between patients that received <18 Gy and ≥18 Gy

TLR denotes target lesion revascularization.
CHAPTER 12

Sianos G, Mollet N, Hofma S, de Feyter PJ, Serruys PW

Late-Late Occlusion After Intracoronary Brachytherapy

Circulation in press
Late-late occlusion after intracoronary brachytherapy

Georgios Sianos, MD, Nico Mollet, MD, Sjoerd Hofma, MD, Pim J de Feyter, MD,

Patrick W. Serruys, MD.

Department of Interventional Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands.

Correspondence address:
Prof PW Serruys MD, PhD, FESC, FAAC
Department of Interventional Cardiology
Erasmus MC Rotterdam
Thoraxcenter Bd 404
Dr Molewaterplein 40
3015 GD Rotterdam
The Netherlands
Tel: (+31 10 4635260)
Fax: (+31 10 4369154)
e-mail: serruys@card.azr.nl
A 57 year old male with a history of anterior myocardial infarction in April 1997, initially treated with successful thrombolysis, underwent cardiac catheterisation due to persistent post infarction angina. A single vessel disease, with a significant lesion in the left anterior descending coronary artery (LAD), was found. The patient was treated with balloon angioplasty followed by intracoronary beta radiation therapy according to the Beta Energy Restenosis Trial (BERT). He received 16 Gray at two millimetres from the centreline of the 90Sr/90Y source. He remained asymptomatic for four and a half years. During this period he underwent control angiography with the use of Intravascular Ultrasound (IVUS) at six months and three years, as mandated by protocol. After this period he developed again angina and an exercise test was positive for ischemia. Diagnostic coronary angiogram at almost five years revealed single vessel disease, with totally occluded LAD with collateral filling from the right coronary artery. The angiographic sequence is presented in figure 1. The IVUS images are presented in figure 2. Before the re-intervention a 16-row, electrocardiographic-gated, cardiac, multi-slice spiral computed tomography scan was also performed (figure 3). Attempt for percutaneous recanalisation was not successful and the patient underwent coronary artery bypass surgery with implantation of the left internal mammary artery in the LAD.
Figure 1

The left anterior descending coronary artery, filmed at the left anterior oblique and cranial projection. At baseline a severe focal lesion (arrow) just before the bifurcation of the second diagonal branch (D2) with a septal perforator branch (S) was observed. A big first diagonal branch (D1) can also been noticed. The patient was treated with balloon angioplasty (single dilatation with a 3 x 12 mm balloon at 12 atmospheres) followed by catheter based irradiation with the use of the 30mm long, 90Sr/90Y Beta-Cath source, with good final result. The balloon and the radiation source were filmed in the right anterior oblique and cranial projection. The irradiated segment (IRS) is indicated by the two black horizontal lines at the final result frame. Control angiogram at six months and 3 years revealed well preserved result without restenosis. At five years there is severe lumen compromise through out the length of the irradiated segment, with minimal contrast penetration up to the D2 and complete occlusion after its take off.
Figure 2

Left side: longitudinal Intravascular Ultrasound (IVUS) reconstruction of the left anterior descending coronary artery (LAD) at six months follow-up, corresponding to the angiographic projection in figure 1. The Left main coronary artery (LM) is on top of the image and the distal LAD at the bottom. (a) Slice depicting the bifurcations with the left circumflex coronary artery (LCx) and the first diagonal branch (D1). (b) Slice depicting the bifurcations with the second diagonal (D2) and the septal (S) branches. There is 60 degrees difference between the planes of slices (a) and (b). Right side: longitudinal IVUS reconstruction of the LAD at three years follow-up. (c) Corresponds to slice (a). (f) Corresponds to slice (b). Middle: cross-sectional images corresponding to the site of the initial stenosis at baseline, just before the bifurcations of the LAD with the D2 and the septal branches, as indicated by the yellow-red horizontal lines at the longitudinal reconstructions. (c) At six months. (d) At 3 years. The red line delineates the external elastic membrane and the green line the lumen surface. Between six months and three years a reduction in the total vessel area (TVA) can be observed (negative remodelling) with accompanying reduction in the plaque area (PA), (plaque regression). This results in unchanged lumen area (LA) between 6 months and three years.
Figure 3

(a) Electrocardiographic-gated multi-slice computed tomography three-dimensional volume rendered image of the heart and the great vessels. The aortic root (Ao) the pulmonary artery (PA) and the left ventricle (LV) are clearly visible. (b) Detailed picture of the left coronary artery corresponding to the angiographic frames in figure 1. The left main coronary artery (LM) is divided in the left anterior descending (LAD) and the left circumflex (LCx) coronary arteries. A severe stenosis at the ostium of the LAD (double arrowhead) can be seen. This lesion was not obvious at the angiographic images presented, due to overlap of the ostium of the LAD with LCx. More distally the LAD is occluded (arrowhead) after the take off of the first diagonal branch (D1), at the site of previous treatment with balloon dilatation and beta irradiation.
CHAPTER 13


Predictors, Incidence and Prognosis of Coronary Occlusion Following Intracoronary Beta-radiation Therapy

Submitted for publication
Predictors, Incidence and Prognosis of Coronary occlusion following intracoronary beta-radiation therapy

Angela Hoye, MB ChB, Georgios Sianos, MD, Francesco Saia, MD, Pedro Lemos, MD, Willem van der Giessen, MD, Pim J. de Feyter, MD, Veronique L.M.A. Coen, MD, Ron van Domburg, PhD, Peter C. Levendag, MD, Patrick W. Serruys, MD.

Department of Interventional Cardiology, Thoraxcentre, Erasmus MC, Rotterdam, The Netherlands.

Brief title: Vessel occlusion after intracoronary brachytherapy

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Correspondence address:
Prof PW Serruys MD, PhD, FESC, FAAC
Department of Interventional Cardiology
Erasmus MC Rotterdam
Thoraxcentre Bd 404
Dr Molewaterplein 40
3015 GD Rotterdam
The Netherlands
Tel: (+31 10 4635260)
Fax: (+31 10 4369154)
e-mail: p.w.j.c.serruys@erasmusmc.nl
Abstract

Aims: Intracoronary brachytherapy (IRT) has been associated with the development of late occlusion. We reviewed the presentation, incidence, and prognosis of coronary occlusion following beta-radiation therapy at our institution.

Methods and results: Between April 1997 and December 2001, 301 consecutive patients were treated with IRT, and 37 (12.3%) developed target vessel occlusion. Mean follow-up was 40.3 months, mean time between IRT and occlusion was 16.0 months (range 21 days-66.8 months). Presentation of occlusion was acute myocardial infarction in 27.0%, unstable angina in 21.6%, stable angina in 45.9%, asymptomatic in 5.4%. The timing of occlusion could be determined in 35 patients. Of these, 94.3% occurred once dual antiplatelet therapy had been stopped.

The only factor predictive for development of occlusion was treatment of a de novo lesion rather than in-stent restenosis (15.4% versus 7.9%, p=0.03), with a trend towards worse results when IRT was combined with new stent implantation compared with balloon-only therapy (14.6% versus 8.9%, p=0.07). Occlusion was not related to the dose, the source length, or the “learning curve” of brachytherapy use.

Those with occlusion had a significantly higher combined rate of death and myocardial infarction compared to both the population without target lesion revascularization (TLR), and the population who underwent TLR for non-occlusive restenosis (35.1% versus 8.8%, p<0.00001 and versus 15.7%, p<0.01 respectively).

Conclusion: A high incidence of late vessel occlusion is observed after IRT especially when used for de novo lesions, and is associated with significant morbidity. The majority occur after stopping dual antiplatelet medication. Further studies are warranted to evaluate whether longer/life-long dual anti-platelet therapy is advantageous in reducing vessel occlusion following IRT.
Introduction

In the mid-1990’s, intracoronary brachytherapy (IRT) was shown in the porcine animal model to inhibit smooth muscle cell proliferation and reduce the subsequent development of neointima hyperplasia (1-3). Following on from this, studies in clinical practice have subsequently proven its efficacy in the treatment of in-stent restenosis and it is currently the gold-standard therapy for these patients. It is the only therapy in this group proven in several randomised trials to be superior to placebo, with efficacy maintained up to 5 years (4-9).

The utilisation of stents in standard percutaneous coronary intervention (PCI) provides a scaffold, thus reducing the risk of abrupt vessel closure compared to balloon-only angioplasty. However, there still remains a risk of occlusion related to acute thrombosis. Acute and subacute thrombosis within the first month after stent implantation occurs in <1-2% cases (10). Although not common, studies have shown that it is associated with significant morbidity and mortality, with a combined rate of death and myocardial infarction of 64% (10). By definition, late thrombosis develops more than 30 days after treatment. Though it may occur following standard PCI in <1%, (11, 12) it has been a feature of brachytherapy occurring in up to 15% patients. (6, 13-15) It is thought to be related to delayed re-endothelialisation, and the strategy of prolonging dual antiplatelet therapy, with clopidogrel given in addition to aspirin in patients treated for in-stent restenosis, has proven to reduce the rate of late thrombosis to 3-4% (16).

A chronic total coronary occlusion may be associated with an adverse mortality in the long-term. A recent study of a 20 year period of treating chronic occlusions showed an increased rate of death at 10 years in those in whom angioplasty...
was unsuccessful compared to those with successful percutaneous revascularization.

The aim of this study therefore, was to evaluate the predictors of total occlusions of the target vessel following percutaneous coronary intervention (PCI) with intracoronary brachytherapy, together with the incidence, time course of presentation, and prognosis. In addition, we evaluated the impact of increased experience in the application of brachytherapy administration in conjunction with prolongation of antiplatelet therapy.

**Methods**

Between April 1997 and December 2001, 301 consecutive patients were successfully treated with intracoronary beta-radiation therapy at the Thoraxcenter, Rotterdam. Over a mean follow-up period of 40.3 months, 37 patients have subsequently been found to have an occlusion of the treated vessel and form the present study population. Patient and procedural data was retrospectively analysed from a dedicated database. Long-term survival status was assessed by written inquires to the Municipal Civil Registries. Follow-up clinical data were determined from electronic hospital archives and by questionnaires sent to all living patients focusing on the occurrence of adverse cardiac events such as myocardial infarction and repeat intervention (surgical and percutaneous). The referring physician and institutions as well as the general practitioners were directly approached whenever necessary. Complete clinical follow-up was obtained in all patients up until 31st March 2003.

**Definitions**

Target vessel occlusion was defined as 100% occlusion with TIMI 0 flow demonstrated on angiography at the site of previous brachytherapy. Timing of occlusion was defined as acute (<24 hours), subacute (≤30 days), or late (>30 days).
after therapy. Follow-up period was defined as that between the index procedure involving brachytherapy and 31st March 2003.

Brachytherapy treatment was classed as early if it was administered in the period April 1997 – 30th June 1999 inclusive, or late if given after 1st July 1999 up until 31st December 2001. This corresponds to a change in policy of dual antiplatelet therapy duration from 0-3 months to a minimum of 6 months, Table 1. The diagnosis of acute myocardial infarction, indiscriminately Q or non-Q wave, required an elevation of creatine kinase to twice above the upper limit of normal together with a rise in creatine kinase-MB fraction; if made following patient admission to another hospital, was confirmed through direct contact with the referring physician, using the same criteria. Dual antiplatelet therapy was defined as the use of either ticlopidine or clopidogrel given in addition to aspirin.

**Statistical Analysis**

Data are expressed as mean value ± SD. Continuous variables were compared by Student’s t-test with statistical significance defined at the p<0.05 level. The independent association of clinical characteristics with coronary occlusion was tested by using the Cox proportional hazard model. Pre-selected pre and peri-procedural variables were age, gender, diabetes, hypertension, hypercholesterolemia, smoking, unstable angina, prior myocardial infarction, prior CABG, extent of coronary artery disease, left ventricular ejection fraction, indication for PTCA (de-novo or in-stent restenosis), device used (stent or balloon), dose (<18 Gy or ≥Gy), and duration of dual antiplatelet medication (<6 months versus ≥6 months).

**Results**

Mean follow-up period for the total population treated with IRT was 40.3 months (range 15.1-70.1 months, median 40.1 months). The rate of coronary
occlusion in the overall population was 12.3% and presented a mean period of 16.0 months after brachytherapy (range 21 days-66.8 months, median 12.7 months). Baseline patient characteristics and site of vessel treated were not significantly different between those who did, or did not develop coronary occlusion, Table 2.

Brachytherapy was used in the treatment of de novo lesions in 175 patients (58.1%) and for in-stent restenosis in the remaining 126 (41.9%). Patients treated for a de novo lesion had a significantly higher incidence of occlusion compared to those treated for in-stent restenosis (15.4% versus 7.9% respectively, $p=0.03$). By multivariate analysis the treatment of a de-novo lesion was the only independent predictor for total vessel occlusion in the long-term (hazard ratio=2, 95%CI: 1.1-5). In addition, there was a trend towards worse results when brachytherapy was combined with new stent implantation (incidence 14.6%) compared with balloon-only therapy (incidence 8.9%), $p=0.07$. Target vessel occlusion rate was not related to the length of source used (13.0% for source length >30mm versus 11.6% for source length ≤30mm, $p=NS$); or the dosage administered (12.0% for >18 Gray versus 12.5% for ≤18 Gray, $p=NS$).

Over the course of brachytherapy administration, the duration of dual anti-platelet therapy increased (Table 1). During the early period of brachytherapy treatment, 108 patients were treated with a subsequent overall occlusion rate of 8.3%. During the later period, 193 patients were treated with a rate of subsequent occlusion of 14.5% ($p=NS$).

The presentation of target coronary occlusion was an acute myocardial infarction in 27.0%, with a further 21.6% presenting with unstable angina. The timing of occlusion was determined in 35 patients (2 asymptomatic patients were excluded) either due to the onset of an acute coronary syndrome or recurrence of anginal
symptoms. Of these, 94.3% occlusions occurred once dual antiplatelet therapy had been stopped.

Treatment was percutaneous intervention in 25 patients (67.6%) with a successful revascularization rate of 72% (18/25). In total 11 (29.7%) were treated medically (7 after failed intervention), and 8 (21.6%) underwent CABG, Table 3. There was just one subacute occlusion, with the majority of all occlusions (83.8%) presenting more than 6 months after brachytherapy treatment, including 8 myocardial infarctions (21.6%), Table 4.

There was no significant difference in the overall follow-up period duration between those patients with or without coronary occlusion. Compared to those who did not develop target vessel coronary occlusion, the cohort of 37 patients with coronary occlusion showed a trend towards an increased risk of death (8.1% versus 3.4%, p=0.09), with 2 patients (5.4%) dying as a direct result of AMI related to the occlusion event. Table 5 shows the clinical adverse events occurring in the population with target vessel occlusion compared with those with non-occlusive restenosis, and the population without any evidence of restenosis. Those who developed occlusion had a significantly higher combined rate of death and MI compared to both the population with non-occlusive restenosis and those without TLR (35.1% versus 15.7%, p<0.01 and versus 8.8%, p<0.00001 respectively).

**Discussion**

In current practice, acute and subacute thrombosis following standard PCI with stent implantation occurs in 1-2% patients, with nearly two-thirds suffering either a myocardial infarction or death (10). In the present population where successful PCI therapy was combined with the administration of beta-radiation therapy, there were no episodes of acute thrombosis and a single patient presented...
with acute myocardial infarction related to subacute thrombosis occurring 21 days after treatment (0.3%). However, a further 36 patients (12.0%) developed target vessel occlusion >30 days after treatment, the majority (83.8%) occurring more than 6 months after brachytherapy treatment, and more than half (54.1%) presenting more than 1 year after treatment. Approximately half of the patients (48.6%) presented acutely, suggestive of an underlying thrombotic occlusion.

The phenomenon of late thrombosis is a characteristic of brachytherapy and thought to relate to delayed healing and re-endothelialisation (18-22). In the porcine model, brachytherapy has previously been shown to induce apoptosis in the adventitia and media, and reduce re-endothelialisation at 14 days from 82% in a control group, to 36-38% in an irradiated group (18). More recently, in rabbit iliac arteries, stent endothelialisation was shown to be <50% complete at 6 months after IRT, compared to 98% complete in the control group (19). In humans, angioscopy carried out 3 months after stent implantation and brachytherapy has shown that the struts remain highly visible with only a very thin layer of intima; furthermore the presence of ulceration beneath the stent was also seen (20). In conjunction with this delayed re-endothelialisation there is evidence for impairment of endothelial function following IRT. Vasodilation to nitroglycerin has been shown to be impaired (21) and Thorin et al demonstrated in a porcine model that endothelium-derived nitric oxide and endothelium-derived hyperpolarizing factor release was reduced at 6 weeks following IRT, and actually prevented when IRT was combined with angioplasty (22). In addition to delayed re-endothelialisation, beta-radiation therapy used in patients with in-stent restenosis, has been found to be associated with sustained platelet activation more than 6 months after treatment, despite the use of clopidogrel in addition to aspirin throughout the period (23). Data from the WRIST-12 study have suggested
that in addition to aspirin, the use of 12 months of clopidogrel, as opposed to 6 months, leads to a reduction in the need for target lesion revascularization and rate of adverse cardiac events (16). In the current study, the majority (83.3%) of the 18 patients who presented acutely did so more than 6 months after brachytherapy; and all but one of these 18 (94.4%) presented following the termination of dual anti-platelet therapy. This is in concordance with results from both WRIST-PLUS and WRIST-12. In both studies the rate of total occlusion dramatically increased once the clopidogrel had been stopped. Between 6 months and 15 months follow-up, in WRIST-PLUS (6 months of dual antiplatelet therapy) the rate of occlusion increased from 5.8% to 11.7%, and in WRIST-12 (12 months dual antiplatelet therapy) it increased from 2.5% to 9.2% (16). This suggests that clopidogrel exerts a protective effect against occlusion, and there may therefore be a benefit in continuing dual antiplatelet therapy for much longer periods perhaps even life-long.

Brachytherapy was introduced into clinical practice in the Thoraxcenter in 1997 and like all new modalities has been associated with a learning curve. To try to overcome the problem of late thrombosis, the duration of dual anti-platelet therapy given to most patients was increased to a minimum of 6 months duration in the second half of 1999. In addition, early results of brachytherapy were hindered by the phenomenon of edge restenosis. This is thought to relate to geographical miss with mismatch between the segment of artery injured and the length of radiation source utilised (24). We hypothesised that with the evolution in IRT with increasing knowledge and understanding of the problems of late thrombosis and edge restenosis would come a reduction in the rate of events such as target vessel occlusion. However contrary to this, in our study, despite adopting a policy of increased duration of dual antiplatelet therapy, there was no such reduction between the early and late treatment
periods (8.3 versus 14.5% respectively, p=NS). In addition, neither the length of source used nor the dosage administered, were predictive for the development of target vessel occlusion.

Brachytherapy is the only treatment modality proven to be effective in the treatment of in-stent restenosis. However, its efficacy preventing restenosis in de novo lesions is more contentious. In the beta-cath study, restenosis following stent implantation for a de novo lesion in conjunction with the use of brachytherapy was actually higher than the controls (44.9% versus 35.3%) (25). Consistent with this, in our study, the factor most predictive for the development of coronary occlusion was the treatment of a de novo lesion, with a trend towards this being particularly associated with stent implantation.

The overall incidence of 12.3% target vessel occlusion in our study is likely to be an underestimate as patients did not undergo elective follow-up angiography beyond 6 months, and we cannot therefore assess the rate of silent occlusion. We have clearly demonstrated that the development of target vessel occlusion following brachytherapy is associated with a significant increase in morbidity, and a trend towards an increased rate of mortality. Almost a third of patients suffered an acute myocardial infarction, and 21.6% required CABG surgery.

It is perhaps not surprising that the rate of AMI and CABG was significantly higher in the population with target vessel occlusion compared to those without restenosis and TLR. However, survival free of death, AMI or CABG was also significantly worse in the population with occlusion compared to the population who underwent TLR for non-occlusive restenosis (51.4% versus 67.5%, p<0.05).
Study limitations

This is a single centre retrospective analysis and therefore carries all the inherent problems associated with this type of analysis. The cohort is somewhat heterogeneous, with the duration of dual antiplatelet therapy increasing over the treatment period based on the protocol and the current evidence at the time of therapy. However, this variability in treatment did not appear to influence the rate of target vessel occlusion.

Conclusions

The occurrence of target vessel occlusion following brachytherapy is high and is associated with significant morbidity. In order to reduce the risk of developing occlusion, the use of beta-radiation therapy should be limited to the treatment of in-stent restenosis where its efficacy is proven. Furthermore, studies are needed to evaluate whether there is a benefit in administering dual anti-platelet therapy for much longer periods - perhaps even life-long.

References


Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Source</th>
<th>Date of inclusion</th>
<th>Duration of dual antiplatelet therapy (months)</th>
<th>Lesion type</th>
</tr>
</thead>
<tbody>
<tr>
<td>BERT</td>
<td>30</td>
<td>90Sr/90Y</td>
<td>4/97-12/97</td>
<td>0-1*</td>
<td>De novo</td>
</tr>
<tr>
<td>Compassionate use</td>
<td>23</td>
<td>90Sr/90Y</td>
<td>5/97-6/99</td>
<td>0-1*</td>
<td>ISR</td>
</tr>
<tr>
<td>PREVENT</td>
<td>29</td>
<td>32P</td>
<td>4/98-5/99</td>
<td>0-1*</td>
<td>De novo</td>
</tr>
<tr>
<td>BETA-CATH</td>
<td>13</td>
<td>90Sr/90Y</td>
<td>4/98-5/99</td>
<td>1</td>
<td>De novo/ISR</td>
</tr>
<tr>
<td>BRIE</td>
<td>14</td>
<td>90Sr/90Y</td>
<td>10/98-6/99</td>
<td>1-3</td>
<td>De novo</td>
</tr>
<tr>
<td>Routine use**</td>
<td>169</td>
<td>90Sr/90Y</td>
<td>7/99-12/01</td>
<td>6-9</td>
<td>De novo/ISR</td>
</tr>
<tr>
<td>EURO-START 40</td>
<td>12</td>
<td>90Sr/90Y</td>
<td>5/01-12/01</td>
<td>6</td>
<td>ISR</td>
</tr>
<tr>
<td>BRIDGE</td>
<td>11</td>
<td>32P</td>
<td>2/01-12/01</td>
<td>12</td>
<td>De novo</td>
</tr>
</tbody>
</table>

The studies into which patients were enrolled, together with the time period of inclusion and the policy of dual anti-platelet therapy duration.

ISR denotes in-stent restenosis.

* In the absence of new stent implantation, some patients were not given additional anti-platelet therapy.

** 138 included as part of the RENO registry.
### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Target vessel occlusion population (n=37)</th>
<th>Total population without occlusion (n=264)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>59.3</td>
<td>59.1</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>24 (64.9)</td>
<td>190 (72.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>7 (18.9)</td>
<td>39 (14.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>7 (18.9)</td>
<td>49 (18.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>10 (27.0)</td>
<td>81 (30.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>19 (51.4)</td>
<td>149 (56.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous AMI (%)</td>
<td>12 (32.4)</td>
<td>93 (35.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous PCI (%)</td>
<td>15 (40.5)</td>
<td>143 (54.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous CABG (%)</td>
<td>8 (21.6)</td>
<td>44 (16.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMS (%)</td>
<td>0</td>
<td>1 (0.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>RCA (%)</td>
<td>15 (40.5)</td>
<td>94 (35.6)</td>
<td>NS</td>
</tr>
<tr>
<td>LCX (%)</td>
<td>8 (21.6)</td>
<td>52 (19.7)</td>
<td>NS</td>
</tr>
<tr>
<td>LAD (%)</td>
<td>11 (29.7)</td>
<td>101 (38.3)</td>
<td>NS</td>
</tr>
<tr>
<td>SVG (%)</td>
<td>3 (8.1)</td>
<td>16 (6.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor use (%)</td>
<td>14 (37.8)</td>
<td>95 (36.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Dual antiplatelet therapy ≥ 6 months (%)</td>
<td>24 (64.9)</td>
<td>155 (58.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Comparison of baseline patient characteristics, vessel treated, and usage of anti-platelet therapy between those treated with brachytherapy who did, or did not develop target vessel occlusion.

AMI denotes myocardial infarction, PCI denotes percutaneous coronary intervention, CABG denotes coronary artery bypass surgery, LMS denotes left main stem, RCA denotes right coronary artery, LCX denotes circumflex artery, LAD denotes left anterior descending artery, SVG denotes saphenous vein graft.
### Table 3

<table>
<thead>
<tr>
<th>Clinical presentation of occlusion</th>
<th>AMI (%)</th>
<th>10 (27.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstable (%)</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td></td>
<td>Stable (%)</td>
<td>17 (45.9)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic (%)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>&lt;24hours</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Time of presentation of occlusion</td>
<td>24hours to ≤30 days (%)</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td></td>
<td>&gt;30 days to ≤6months (%)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;6months to ≤12months (%)</td>
<td>10 (27.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;12months (%)</td>
<td>20 (54.1)</td>
</tr>
<tr>
<td></td>
<td>Medical (%)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td></td>
<td>Failed PCI – medical therapy (%)</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td></td>
<td>Balloon (%)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Total (%)</td>
<td>14 (37.8)</td>
</tr>
<tr>
<td></td>
<td>Stent Bare (%)</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td></td>
<td>Sirolimus (%)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td></td>
<td>CABG (%)</td>
<td>8 (21.6)</td>
</tr>
</tbody>
</table>

Clinical presentation of target vessel occlusion and its' treatment.
AMI denotes myocardial infarction, PCI denotes percutaneous coronary intervention, CABG denotes coronary artery bypass surgery.
Table 4

<table>
<thead>
<tr>
<th>Presentation of occlusion</th>
<th>≤30 days</th>
<th>&gt;30days - ≤6months</th>
<th>&gt;6months - ≤1year</th>
<th>&gt;1year - ≤2years</th>
<th>&gt;2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI (n=10)</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>UA (n=8)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>SA (n=17)</td>
<td>0</td>
<td>1*</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Timing of target vessel occlusion and its’ relationship to clinical presentation.
AMI denotes acute myocardial infarction, UA denotes unstable angina, SA denotes stable angina.
* An additional 2 patients were found to have asymptomatic target vessel occlusion at 6month control angiography.

Table 5

<table>
<thead>
<tr>
<th>Target vessel occlusion population (n=37)</th>
<th>Population with TLR for restenosis (n=83)</th>
<th>Population without TLR (n=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up period (months)</td>
<td>43.0 ± 12.7</td>
<td>39.6 ± 14.1</td>
</tr>
<tr>
<td>Death</td>
<td>3 (8.1%)</td>
<td>6 (3.3%)</td>
</tr>
<tr>
<td>AMI</td>
<td>12 (32.4%)</td>
<td>10 (5.5%)‡</td>
</tr>
<tr>
<td>Death or AMI</td>
<td>13 (35.1%)</td>
<td>16 (8.8%)‡</td>
</tr>
<tr>
<td>CABG</td>
<td>8 (21.6%)</td>
<td>3 (1.7%)‡</td>
</tr>
<tr>
<td>Death or AMI or CABG</td>
<td>18 (48.6%)</td>
<td>19 (10.5%)†</td>
</tr>
</tbody>
</table>

*p<0.05 †p<0.01 ‡p<0.00001 compared with the target vessel occlusion population.

Comparison of the rate of adverse events (death, myocardial infarction or coronary artery bypass surgery) between those treated with brachytherapy who developed target vessel occlusion, compared with the population who underwent target lesion revascularization for non-occlusive restenosis, and the remaining population without restenosis and target lesion revascularization.
AMI denotes acute myocardial infarction, CABG denotes coronary artery bypass surgery, TLR denotes target lesion revascularization.
CHAPTER 14


Long Term Outcome of Percutaneous Interventions Following Failed Beta-Brachytherapy

Submitted for publication
Long-term Outcome of Percutaneous Coronary Interventions Following Failed Beta-Brachytherapy

Francesco Saia, MD, George Sianos, MD, Angela Hoye, MB ChB, MRCP, Pedro A. Lemos, MD, Willem J. van der Giessen, MD, PhD, FACC, Pim de Feyter, MD, PhD, FACC, Ron T. van Domburg, PhD, Patrick W. Serruys, MD, PhD, FACC

Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

Address for reprints

Prof. P.W. Serruys, MD, PhD
Thoraxcenter, Bd 404
Dr. Molewaterplein 40
3015 GD Rotterdam
The Netherlands
Tel: +31-10-4635260
Fax: +31-10-4369154
E-mail: p.w.j.c.serruys@erasmusmc.nl
Abstract

Background: Recurrent restenosis following vascular brachytherapy has been reported in up to one third of the patients enrolled in clinical trials. The long-term outcome of repeat percutaneous intervention (PCI) after failed beta-brachytherapy is currently unknown.

Methods: We retrospectively analyzed 97 consecutive patients undergoing percutaneous coronary re-intervention after failed beta-brachytherapy at our institution (80.8% of all brachytherapy failures). Long-term incidence of major adverse cardiac events (MACE: death, myocardial infarction, target lesion revascularization) was assessed.

Results: The procedure was successful in 90 (92.8%) patients. A new stent was implanted in 72% of the procedures (sirolimus-eluting stent in 16.5%). After 3 years, survival was 94.3%, survival-free from myocardial infarction 86.7%, and MACE-free survival 66.1%. Overall, a second target lesion revascularization was performed in 27 (27.8%) patients after an average of 11.2±11.2 months; 21 (21.6%) patients had restenosis, and 6 (6.2%) developed late total vessel occlusion (related to acute myocardial infarction in 2 cases).

Conclusions: Repeat PCI is the most common choice after failed brachytherapy. This strategy appears as a reasonable therapeutic option for this complex iterative pathology.

Key words: restenosis, brachytherapy, coronary angioplasty
Introduction

Ionizing radiation has been shown to reduce neointimal formation after balloon angioplasty through the reduction of vascular smooth muscle cells proliferation and positive vessel remodeling (1). Whilst coronary vascular brachytherapy for prevention of restenosis in de novo lesions is controversial (2-4), it represents the gold standard treatment for diffuse in-stent restenosis (5-9). However, in clinical trials brachytherapy failure (angiographic restenosis and target lesion revascularization) has been reported in a consistent number of patients, with a slow but progressive increase over long-term follow-up (10). Although in this clinical setting bypass surgery may represent a more definitive choice of treatment, repeat percutaneous coronary intervention (PCI) remains an appealing strategy.

Recently, two studies reported the outcome of repeat PCI in patients after failure of gamma-brachytherapy in the GAMMA (11) and the WRIST trials (12). They showed that the pattern of recurrent restenosis was predominantly focal. In these studies, percutaneous re-intervention was accomplished safely, but in up to one third of the patients a repeat reintervention was necessary during follow up.

Beta radiation, in contrast with gamma, has limited penetration and does not require modifications to the standard shielding used in the catheterization laboratory. As a result, beta-sources became the most widely used type of vascular brachytherapy. Nevertheless, there is no specific information in the literature regarding the outcome of patients who failed beta-brachytherapy. The process of restenosis after coronary irradiation is still not entirely understood, and a possible different vascular response to percutaneous treatment following beta and gamma radiation cannot be ruled out a priori.
The aim of this study was therefore to assess the long-term clinical outcome of patients who underwent percutaneous revascularization for restenosis following intracoronary beta-brachytherapy with catheter-based techniques.

**Methods**

**Patient population**

We retrospectively analyzed the data from all patients treated with catheter-based beta-brachytherapy at our institution between the 29th of April 1997 and the 31st of December 2001 (n=301). The majority of the patients were enrolled in clinical studies whose design and principal results are published elsewhere (table 1) (4,6,13-17). A total of 120 patients with a diagnosis of brachytherapy failure were identified (39.9% of the entire brachytherapy-treated population in the pre-defined period): in 44 patients brachytherapy was originally administered for in-stent restenosis, and in 76 for de novo lesions. The subsequent management of these patients, including revascularization strategy (surgical or percutaneous), was decided conjointly by a team of interventional cardiologists and cardiac surgeons. Overall, 8 (5.8%) asymptomatic patients with angiographic restenosis were treated conservatively, 15 (12.5%) patients underwent bypass surgery, and the remaining 97 (80.8%) patients were treated with repeat percutaneous intervention and comprise the present analysis.

**Percutaneous re-intervention procedure**

All patients were pre-treated with aspirin (>75 mg/d). Clopidogrel (75 mg/d or 300 mg as a loading bolus dose) was given to those in which stent implantation was planned in advance. During the procedure weight-adjusted heparin was administrated to achieve an activated clotting time of >300 sec. Final treatment strategy and medications were left to the operator’s discretion.
Definitions

Restenosis was defined as >50% diameter stenosis by quantitative coronary analysis. At baseline, lesions were classified as: 1) restenosis in the irradiated segment; 2) edge-restenosis, defined as restenosis occurring in the 5 mm proximal or distal to the irradiated segment; 3) late total occlusion, defined as total vessel occlusion angiographically documented at the irradiated site more than 30 days after the brachytherapy procedure. The percutaneous re-intervention was considered successful when a good angiographic result was obtained in combination with TIMI flow 3. Major adverse cardiovascular events (MACE) were defined as death, nonfatal myocardial infarction, and target lesion revascularization, either percutaneous or surgical. The diagnosis of myocardial infarction was based on an increased level of creatine kinase to more than twice the upper limit of normal with an increased level of creatine kinase-MB isoform. For patients admitted to peripheral hospitals in the acute phase, the diagnosis of myocardial infarction was confirmed by the referring physician based on the same criteria. Target lesion revascularization was defined as any surgical or percutaneous re-intervention due to restenosis within the irradiated segment or the 5mm proximal or distal segments (edge restenosis). Target vessel revascularization was defined as any re-intervention driven by lesions located in the treated vessel beyond the target lesion limits. Non-target vessel revascularization was defined as any re-intervention in vessels other than the target vessel. Subacute thrombosis was defined as angiographically documented total occlusion ≤ 30 days after the percutaneous re-intervention. Late total occlusion was defined as an angiographically documented total occlusion at the treated site at >30 days after the percutaneous re-intervention.

Follow-up

Baseline clinical and procedural data were entered prospectively into a dedicated database. Information about re-interventions was obtained from an electronic database of hospital
records. The Thoraxcentre is a tertiary cardiology centre serving a group of 14 local hospitals, and is the only one with facilities for percutaneous interventions in the region of Rotterdam. As required by the local medical system organisation all baseline procedures were performed in this tertiary facility, as well as the vast majority of re-interventions. Long-term survival status was assessed by written inquiries to the Municipal Civil Registries. Questionnaires were sent to all living patients focusing on the occurrence of adverse cardiac events such as myocardial infarction and repeat intervention (surgical and percutaneous). The referring physician and institutions as well as the general practitioners were directly approached whenever necessary. Follow-up period was defined as that between the first re-intervention following failed brachytherapy and the 31st March 2003. Complete follow-up was obtained for all patients.

**Statistical methods**

Continuous variables are expressed as mean ± standard deviation, and categorical variables are reported as count and relative percentage. Event-free survival rates were estimated according to the Kaplan-Meier method.

**Results**

**Baseline clinical and angiographic characteristics**

Baseline characteristics of the 97 patients who failed brachytherapy and underwent a new PCI are described in table 2. The average time from the brachytherapy procedure to this first TLR was 13.4±13.4 months. In 11 patients (11.3%) irradiation had been performed with a ³²Phosphorus (³²P) source, and in 86 (88.7%) with a ⁹⁰Strontium/⁹⁰Yttrium (⁹⁰Sr/⁹⁰Y). The average dose administered was 18.7±5.5 Gy, and the average source length was 35±8 mm. Acute coronary syndrome was the presenting diagnosis in 36 (37.1%) patients; of these, 5 (4.2%) had acute myocardial infarction due to late thrombosis (all had been treated and had received
brachytherapy for *de novo* lesions, and 4 of them had received a new stent). Restenotic post-brachytherapy lesions were classified as restenosis within the irradiated segment in 55 (56.7%) patients, edge-restenosis in 21 (21.6%) patients, and late total occlusion in 21 (21.6%) patients.

During repeat PCI, procedural success was achieved in 90 (92.8%) patients. There were 7 procedural failures, all in patients with totally occluded vessel. A new stent was implanted in 65 (72.2%) cases. Sixteen patients (16.5%) received a sirolimus-eluting stent during the re-intervention.

*Follow-up*

Figure 1 shows a flowchart with the design and the principal results of the study. Total revascularization rate was 30.9% (30 patients). Repeat TLR was performed in 27 (27.8%) patients: 10 (10.3%) of these were treated with bypass surgery and in the remaining 17 (17.7%) a second percutaneous TLR was performed. The average time from the first to the second TLR procedure was 11.2±11.2 months. The clinical presentation at the time of the second TLR was stable angina in 17 patients (63.0%), unstable angina in 7 (25.9%), and acute myocardial infarction in 3 (11.1%). All the patients with acute myocardial infarction received a new stent during the first re-intervention following brachytherapy (in individual basis, the time elapsed from the brachytherapy procedure was 8.4, 11.5 and 28.1 months, whereas the time elapsed from the first re-intervention post-brachytherapy was 4.4, 5.9 and 12.0 months). Angiographically late total occlusion was documented in 6 patients. In two of these, the late total occlusion was associated with an acute myocardial infarction, (one of them was still on combined antiplatelet regimen). At three years the cumulative survival rate was 94.3%, the survival free of myocardial infarction 86.7%, and MACE free survival was 66.1%, Figure 2.
Sirolimus-eluting stent subgroup

Among the sixteen patients treated with sirolimus-eluting stents 3 patients (18.7%) underwent a second clinically-driven TLR, 1 (6.2%) patient died of progressive congestive heart failure (pre-existing) and in 2 more patients (12.5%) angiographic restenosis was found at elective angiographic control. No further re-intervention was done because they were asymptomatic. Overall, a failure of sirolimus eluting stents was clearly documented in 5 (31.2%) patients.

Discussion

In this study we report the outcome of a consecutive series of patients treated with PCI after recurrent restenosis following catheter-delivered coronary beta-irradiation. In this setting, a percutaneous strategy appeared feasible, with high rate of procedural success and low peri-procedural risk. Moreover, considering the complexity of these patients, the long-term outcome could be considered acceptable. Indeed, our results are similar to what previously described for re-interventions after failed gamma-brachytherapy, where a long-term incidence of MACE of 42.2%, and a revascularization rate of 33.3% were reported (11).

Defining the outcome after re-interventions following vascular brachytherapy failure is of great importance. In fact, although brachytherapy is considered the best therapeutic option for patients with complex in-stent restenosis (5-9), up to one third of these patients will subsequently develop restenosis and need for re-intervention (11,12). Geographical miss (18), late stent thrombosis (19), late total occlusion (20), delayed restenosis (21), persistent dissections (22), are well documented phenomena. Most of them are intrinsically related to the radiation’s effects and cannot be completely avoided, despite technical improvements and the increased experience of the operators using this therapeutic modality. Moreover, the risk of late thrombosis following
brachytherapy has been reduced, but not abolished, by prolonged antiplatelet therapy (23,24). In this scenario, a definitive intervention would be desirable, especially considering that these patients had already suffered a number of recurrent failures. Notably, repeat PCI was the most common choice at our institution, with 80.8% of the patients who failed brachytherapy treated with this modality. This is consistent with a previous report from the WRIST trial (12). As possible explanations for this choice we could indicate the high-risk baseline profile of many patients, therefore deemed unsuitable for coronary artery bypass graft surgery, coronary anatomy unfavorable for bypass surgery (for example, small vessel diameter), absence of disease in the left anterior descending coronary artery, patient’s preference. In our study, 24% of the patients had a previous coronary bypass operation. Coronary bypass re-interventions are associated with an operative mortality distinctly higher than the mortality of first-time operations, and carry a higher risk of peri-operative complications, including re-operation for bleeding, peri-operative myocardial infarction, and neurological and pulmonary problems (25).

Our study confirms that the risk of late vessel occlusion after re-intervention for failed brachytherapy remains in a sizable proportion (6.2%). In one third of these cases this led to an acute myocardial infarction. This was especially true for patients in which a new stent was implanted. Even if this phenomenon is well known when a new stent is implanted at the time of irradiation, it has not been described after a subsequent re-intervention. The most likely explanations are the long-term endothelial dysfunction and the delayed vascular healing, two established drawbacks of vessel irradiation (26).

Drug-eluting stents may have a role in the management of patients who have failed brachytherapy. However, preliminary results suggest that sirolimus-eluting stents, which have been proven to be very effective in other clinical settings (27-29), seem to have a reduced efficacy for recurrent restenosis after failed brachytherapy (30). Thus, although more extensive
evaluation is necessary, it seems unlikely that drug-eluting stents could further improve the results in this “biologically modified” environment.

**Conclusions**

The results of the present study, suggest that patients treated with coronary brachytherapy have a consistent risk for repeat interventions at the irradiated segment in the long-term. Percutaneous re-intervention is the most common choice. With this strategy, rates of MACE and further re-interventions are contained, although not negligible, with a residual risk of vessel occlusion, especially when a new stent is implanted. Percutaneous re-intervention appears as a reasonable therapeutic option for this complex iatrogenic pathology.

**References**


restenosis after balloon angioplasty and stenting; the Beta Radiation In Europe (BRIE) study. Eur Heart J 2002;23:1351-1359.


Repeat Percutaneous Intervention for Failed Beta-radiation Therapy


Table 1

Patient population and studies

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Radiation source</th>
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<td>De novo</td>
<td>$^{90}$Sr/Y</td>
</tr>
<tr>
<td>BETA-CATH\textsuperscript{13} *</td>
<td>De novo</td>
<td>$^{90}$Sr/Y</td>
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<tr>
<td>PREVENT\textsuperscript{6}</td>
<td>De novo / restenosis</td>
<td>$^{32}$P</td>
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<td>BRIE\textsuperscript{4}</td>
<td>De novo / restenosis</td>
<td>$^{90}$Sr/Y</td>
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<td>EURO-START 40\textsuperscript{*}</td>
<td>In-stent restenosis</td>
<td>$^{90}$Sr/Y</td>
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<tr>
<td>Compassionate use\textsuperscript{17}</td>
<td>In-stent restenosis</td>
<td>$^{90}$Sr/Y</td>
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<tr>
<td>RENO Registry\textsuperscript{14}</td>
<td>De novo / In-stent restenosis</td>
<td>$^{90}$Sr/Y</td>
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<tr>
<td>BRIDGE\textsuperscript{*}</td>
<td>De novo</td>
<td>$^{32}$P</td>
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*studies not published
Table 2
Baseline clinical and angiographic characteristics

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<tr>
<td>Age, y*</td>
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<td>Previous coronary bypass surgery, %</td>
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<td>Clinical presentation</td>
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<td>Lesion type</td>
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<td>Restenosis in the irradiated segment, %</td>
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<td>Edge-restenosis, %</td>
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<td>Total occlusion, %</td>
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<tr>
<td>Left circumflex, %</td>
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<td>Right, %</td>
<td>37.1</td>
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<td>Saphenous vein graft, %</td>
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<td>Time from brachytherapy procedure*, months</td>
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<td>Glycoprotein IIb/IIIa inhibitors, %</td>
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*values are expressed as mean ± standard deviation
Flowchart illustrating the design and the principal results of the study. Asterisk (*) denotes that all the percentages given between brackets refer to that number (97 patients). CABG denotes coronary artery bypass graft; PCI denotes percutaneous coronary intervention; non-TVR denotes other vessel revascularization; TLR denotes target lesion revascularization; TVR denotes target vessel revascularization; VBT denotes vascular brachytherapy.
Figure 2

Kaplan-Meier curves showing survival, survival free of myocardial infarction, and survival free of major adverse cardiac events (MACE) in patients treated with repeat percutaneous coronary interventions following failed beta-brachytherapy. Time “0” represents the first repeat target lesion revascularisation after failed vascular brachytherapy. MI denotes myocardial infarction, TLR denotes target lesion revascularization.
CHAPTER 15


Effectiveness of Sirolimus-Eluting Stent Implantation for Recurrent In-stent Restenosis After Brachytherapy

*American Journal of Cardiology 2003;92:200-3*
Effectiveness of Sirolimus-Eluting Stent Implantation for Recurrent In-Stent Restenosis After Brachytherapy

Francesco Saia, MD, Pedro A. Lemos, MD, Georgios Sianos, MD, Muzaffer Degertekin, MD, Chi-Hang Lee, MD, Chourmouzios A. Arampatzis, MD, Angela Hoye, MD, Kengo Tanabe, MD, Evelyn Regar, MD, PhD, Willem J. van der Giessen, MD, PhD, Pieter C. Smits, MD, PhD, Pim de Feyter, MD, PhD, Jurgen Ligthart, MSc, Ron T. van Domburg, MSc, PhD, and Patrick W. Serruys, MD, PhD

Coronary vascular brachytherapy is, to date, the only effective treatment available for complex in-stent restenosis (ISR). However, its efficacy is hampered by late restenosis, late thrombosis, edge effect, geographic miss, and delayed healing. Moreover, the fate of the patients after “failed” brachytherapy is uncertain, as well as the result of the various percutaneous treatments employed thereafter. Sirolimus is a macrolide antibiotic produced by Streptomyces hygroscopicus with immunosuppressive effects; it is approved for the prevention of renal transplant rejection. The main effect of sirolimus is the interruption of G1 to S cell cycle progression mediated by its binding to a cytosolic receptor (FK506 protein binding protein 12) and a cascade of subsequent actions. Importantly, sirolimus inhibits proliferation and migration of vascular smooth muscle cells, a key element in the development of restenosis after percutaneous coronary interventions (PCIs). Recently, stent-based local sirolimus delivery has been shown to strongly suppress neointimal hyperplasia and prevent restenosis in de novo lesions followed up for 2 years.

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The revolutionary results obtained with drug-eluting stents have encouraged the assessment of their efficacy in more complex clinical and morphologic subsets. The first human experience evaluating the sirolimus-eluting stent (SES) for the treatment of ISR has been recently reported; it showed this strategy to be highly effective.

We describe here the first series of patients treated with SESs for recurrent ISR after brachytherapy.

The patients described in this report consist of 2 cohorts treated during separate time periods. The first cohort was treated between March 2001 and June 2001, as part of a pilot study on SESs for treatment of ISR. Since April 2002, shortly after European Community market approval, SES implantation has been adopted as the default strategy in all patients treated with PCI at our institution, irrespective of clinical presentation and coronary morphology. These latter patients have been included in the RESEARCH Registry (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospitals) and will be followed up for 1 year. The only exclusion criteria were unavailability of an adequately sized SES at the time of the procedure and enrollment in another revascularization protocol (SESs were available in diameters from 2.25 to 3.0 mm and lengths of 8, 18, and 33 mm). All patients treated with SES after “failed” brachytherapy were scheduled for 6-month angiography.

ISR was defined as >50% diameter stenosis by quantitative coronary angiography within a previously stented vessel segment and classified as proposed by Mehran et al. Treatment strategy and device utilization other than stenting was left to the physician’s discretion. The procedure was considered successful when residual stenosis <30% by quantitative coronary angiography was achieved together with Thrombolysis In Myocardial Infarction (TIMI) flow grade 2 to 3. The study stent utilized was the sirolimus-eluting Cypher (Cordis Europa NV, Johnson & Johnson, Rotterdam, The Netherlands), which contains a 140 μg sirolimus/cm² metal surface area in a slow release formulation (>28 days). Pretreatment with clopidogrel for 48 hours or a 300-mg loading dose was required. During the procedure, intravenous heparin was given to maintain an activated clotting time >300 seconds. After the procedure, all patients received aspirin indefinitely (>75 mg/day) and clopidogrel (75 mg/day) for at least 2 months. Clinical status information was collected at follow-up visits or by telephone contact with the patient or referring physician. Data are presented as number and relative percentage or mean ± SD. Median and range have been reported when deemed necessary for a better description.

From the beginning of the study until August 15, 2002, 12 consecutive patients (both cohorts) underwent PCI with SES implantation for recurrent ISR after local radiation therapy. All of them presented with angina pectoris and/or myocardial ischemia as documented by stress test or thallium scan. Coronary brachytherapy had been previously performed in 11 patients with catheter-based local irradiation (10 beta, 1 gamma) and in 1 patient with phosphorus-32 radioactive stent implantation.

Baseline clinical and angiographic characteristics are listed in Tables 1 and 2, respectively.

Nine patients (75%) had had more than 1 previous episode of restenosis. Average time from the preceding percutaneous reintervention was 24 months (range 111 to 1,678 days, median 719).

Remarkably, 9 patients (75%) presented with a
proliferative pattern of restenosis, 5 of whom (42%) had a totally occluded target vessel. The occlusion dated more than 3 months in 4 patients.

Overall, we implanted 18 SESs (average 1.5/patient). Mean stent length was 33.9 \(\pm 30.1\) mm (range 8 to 92; median 18), and mean stent diameter was 2.88 \(\pm 0.33\) mm. Multivessel PCI was performed in 3 patients (25%).

Angiographic success was obtained in 11 of 12 patients (92%). The remaining patient showed a 34% residual stenosis during quantitative coronary angiography and stent underexpansion despite very high-pressure inflation (24 atm). Individual clinical outcomes are listed in Table 3. With the obvious exception of the single patient presenting with acute

<table>
<thead>
<tr>
<th>TABLE 1 Patients' Baseline Characteristics and Demographics</th>
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<td>Patients</td>
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<td>Current smoker</td>
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<td>Hypercholesterolemia*</td>
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<td>Systemic hypertension</td>
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<tr>
<td>Family history of coronary heart disease</td>
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<td>Stable angina pectoris</td>
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<td>Unstable angina pectoris</td>
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<td>Acute myocardial infarction</td>
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<td>Multivessel coronary disease</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td>Previous coronary bypass</td>
</tr>
<tr>
<td>Time from last target lesion</td>
</tr>
<tr>
<td>Time from brachytherapy (d)</td>
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<tr>
<td>Episodes of ISR</td>
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*Total cholesterol >200mg/dl and/or receiving lipid lowering treatment. Values expressed as mean ± SD; range [median], or as number of patients [%].

<table>
<thead>
<tr>
<th>TABLE 2 Angiographic and Procedural Characteristics</th>
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<td>Quantitative coronary analysis, before procedure</td>
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<tr>
<td>Quantitative coronary analysis, after procedure</td>
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<tr>
<td>Acute gain (mm)</td>
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<tr>
<td>Late loss (mm)</td>
</tr>
<tr>
<td>Multivessel coronary procedure</td>
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<td>Other devices utilized</td>
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*Intraluminal Therapeutics Inc., Carlsbad, California.

<table>
<thead>
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<th>TABLE 3 Individual Clinical and Angiographic Outcomes</th>
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</tr>
<tr>
<td>7</td>
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</table>

*Distal to the index lesion due to atherosclerotic disease progression.

BT = Brachytherapy; L = lifelong; MACE = major adverse cardiovascular event; 32P Rx Stent = phosphorus-32 radioactive stent; TLR = target lesion revascularization; TVR = target vessel revascularization; %DS = percent diameter stenosis.
myocardial infarction, no postprocedural cardiac enzyme elevation was observed, and all the patients were discharged home free from events.

Average follow-up was 8.5 ± 4.5 months. Ten patients (83%) underwent angiography between 4 and 7 months after the procedure. Two patients who refused angiographic follow-up were asymptomatic after 4 and 6 months. One patient died after 9.5 months because of congestive heart failure, shortly after hospital admission for acute pulmonary edema. He was 79 years old, with a history of 2 coronary artery bypass graft operations and 2 PCIs. Left ventricular dysfunction and end-stage congestive heart failure were diagnosed before the last coronary angioplasty. During the 4-month follow-up, no intravascular ultrasound evidence of neointimal hyperplasia was found.

Recurrent ISR after SES implantation was found in 4 out of 10 patients who underwent angiography during follow-up (40%). One of them, in whom complete stent expansion could not be achieved at index procedure, was found to have silent reocclusion after 4 months. No further treatment was performed, and at 19 months the patient remained asymptomatic. Two other patients, both diabetics, presented with stable angina (Canadian Cardiovascular Society class 3) and ISR that required target lesion revascularization. In 1 of them, intravascular ultrasound showed a clearly underexpanded stent with a very small minimal in-stent diameter (1.3 mm). In the fourth case, a very focal restenosis (<5 mm) was diagnosed by elective angiography 5 months after the procedure. Originally, the patient had been treated with 4 SESs (overall length 92 mm) for chronic total occlusion of the left anterior descending artery (ISR). Intravascular ultrasound examination confirmed the absence of neointimal hyperplasia in the remaining portion of the stents. The patient was asymptomatic, but percutaneous revascularization was performed based on intravascular ultrasound findings.

Another patient had recurrent angina 4 months after the procedure. Angiography showed minimal in-stent hyperplasia in the region of interest, whereas a severe lesion due to ISR requiring percutaneous treatment was found in a different vessel.

One of the lesions treated with an SES during the index procedure was composed of echolucent tissue (“black hole”). Interestingly enough, the intravascular ultrasound examination at follow-up showed a reappearance of this tissue, although it did not significantly affect the lumen area.

***

SESs have been recently shown to strongly prevent the development of neointimal hyperplasia after stenting. The first randomized clinical trial reported an exceptional 0% binary restenosis rate. Whether a similar result is obtainable in different clinical situations and for more complex coronary lesion subsets is the subject of extensive investigation. Preliminary results for their use in the treatment of ISR are positive, although less impressive than in de novo lesions.

In the present investigation, we sought to assess the safety and outcome of SES implantation in patients with recurrent ISR after brachytherapy. The strategy evaluated is safe and is believed to be clinically effective, considering the complex population under investigation. The 0% incidence of in-hospital events as well as the absence of subacute stent thrombosis is noteworthy because the average stent length was remarkably high, and these patients are likely to have endothelial dysfunction. The only death that occurred is highly unlikely to be related to either the procedure or to the stent, but rather to the severely compromised left ventricular function. Nevertheless, our report raises a series of unresolved issues. The antiproliferative effect of sirolimus after brachytherapy seems to be strongly reduced compared with other situations. The 40% incidence of restenosis in our population is noteworthy. Diabetes mellitus, a well-known risk factor for restenosis, may also represent a predisposing factor for failure in this setting. However, in 2 cases, technical causes of failure (stent underexpansion) could be implicated, and in a third patient, a very focal neointimal growth was observed compared with the very long baseline lesion and total stent length. The optimal duration of combined antiplatelet therapy is unclear. In this series, there was a striking variety in the duration of clopidogrel prescribed after the procedure due to decisions made on an individual patient basis. Currently, we prescribe combined antiplatelet therapy for 12 months or lifelong after very long stent implantation, but this approach deserves further evaluation.

Our investigation presents a few limitations. First, we do not have a control population. Whether a conventional approach would have provided comparable results cannot be inferred from our data. Second, the present series of patients is quite heterogeneous; this is not surprising given the “real world” setting. The time elapsed from the last target vessel revascularization was considerably different among patients. The underlying physiopathologic process of late (around 2 years) recurrent restenosis after brachytherapy and subsequent response to treatment is not known (whether it is neointimal tissue or late atherosclerotic progression is unclear). Moreover, the incidence of black hole may be higher than suspected, and the biologic properties of this tissue may be responsible for a blunted response to antiproliferative drugs. Last, but not least, the number of patients in our investigation was low, and larger studies with extended follow-up are warranted to draw definitive conclusions.

In this investigation, 12 patients were treated with sirolimus-stent implantation for recurrent ISR after failed brachytherapy. The strategy evaluated was safe and is believed to be clinically effective, although our data suggest a different attenuated efficacy of sirolimus in preventing neointimal growth in this setting compared with the treatment of de novo lesions.


CHAPTER 16


The Pattern of Restenosis and Vascular Remodelling After Cold-end Radioactive Stent Implantation

*Eur Heart J. 2001;22:1311-7*
The pattern of restenosis and vascular remodelling after cold-end radioactive stent implantation

I. P. Kay1, A. J. Wardeh1, K. Kozuma1, G. Sianos1, E. Regar1, M. Knooo1, W. J. van der Giessen1, A. Thury1, J. M. R. Ligthart1, V. M. A. Coen2, P. C. Levendag2 and P. W. Serruys1

From the 1Thoraxcenter and the 2Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

Background Edge restenosis is a major problem after radioactive stenting. The cold-end stent has a radioactive mid-segment (15.9 mm) and non-radioactive proximal and distal 5.7 mm segments. Conceptually this may negate the impact of negative vascular remodelling at the edge of the radiation.

Method and Results ECG-gated intravascular ultrasound with three-dimensional reconstruction was performed post-stent implantation and at the 6-month follow-up to assess restenosis within the margins of the stent and at the stent edges in 16 patients. Angiographic restenosis was witnessed in four patients, all in the proximal in-stent position. By intravascular ultrasound in-stent neointimal hyperplasia, with a >50% stented cross-sectional area, was seen in eight patients. This was witnessed proximally (n=2), distally (n=2) and in both segments (n=4). Echolucent tissue, dubbed the 'black hole' was seen as a significant component of neointimal hyperplasia in six out of the eight cases of restenosis. Neointimal hyperplasia was inhibited in the area of radiation: Δ neointimal hyperplasia = 3.72 mm³ (8.6%); in-stent at the edges of radiation proximally and distally Δ neointimal hyperplasia was 7.9 mm³ (19.0%) and 11.4 mm³ (25.6%), respectively (P=0.017). At the stent edges there was no significant change in lumen volume.


Key Words: Stents, remodelling, radioisotopes, angioplasty, ultrasonics.

See page 1245 for the Editorial comment on this article

Introduction

Conventional stenting has eliminated recoil and negative remodelling as components of the restenotic process. However, this has been at the cost of exacerbating neointimal proliferation secondary to chronic vessel wall irritation, leading to in-stent restenosis[1,2].

Intracoronary radiation has been developed in an attempt to decrease restenosis after balloon angioplasty and stent implantation. Studies recently performed in humans demonstrated a dose-dependent inhibition of neointimal hyperplasia at the 6-month follow-up in stents with activity levels >3 μCi[3-5]. However, a significant increase in neointimal hyperplasia was noted at the extremes of the stent and at the edges. Edge restenosis was mainly due to an increase in plaque and to a lesser extent, remodelling of the native vessel wall[4,5]. A fall-off in radiation in areas receiving vascular injury was proposed as a possible stimulatory mechanism. In order to minimize the effect of vascular remodelling on stent-edge restenosis, the stent design was modified. The 'cold-end' stent (Isostent® Inc., San Carlos, CA, U.S.A.) was rendered radioactive in its mid-portion (15.9 mm in length); the edges (5.7 mm each) were non-radioactive (Fig. 1).

We aimed to analyse tissue growth within the stent and at its edges and to define the segments that had the greatest propensity to restenosis after the implantation of a cold-end stent.
Chapter 16

Methods

Patient selection

We analysed neointimal hyperplasia and vascular remodelling in 16 patients who had completed a 6-month angiographic follow-up with intravascular ultrasound analysis. All patients had single native vessel coronary artery disease, normal left ventricular function and objective evidence of ischaemia.

Implantation technique

Pre-dilation of the lesion was performed where necessary followed by stent implantation. High-pressure balloon inflation to ensure good strut apposition to the vessel wall was then performed at the operator’s discretion. At this time we used a shorter balloon to ensure that the edges of the balloon did not extend beyond the limits of the stent. Intravascular ultrasound was used to ensure optimal stent deployment.

Medication

Patients received 250 mg aspirin and 10 000 international units of heparin at the initiation of the procedure and the activated clotting time was maintained at >300 s. All patients received aspirin 80 mg daily indefinitely and clopidogrel 75 mg daily for 6 months.

Radioactive stent

The stent was 27.3 mm in length and available in diameters of 3.0 and 3.5 mm. It was made radioactive in its central portion by phosphorus-32 ($^{32}$P$^3$). The 5.7 mm edges were shielded from radiation. The initial activity of the stents was measured and thereafter it was calculated at what date the activity had decreased to 3.0–12.0 μCi, suitable for implantation.

Intravascular ultrasound image acquisition analysis

After the final balloon inflation and administration of intracoronary nitrates, ECG-gated intravascular ultrasound pullback was performed. This was repeated at the 6 month follow-up. The segment was subjected to three-dimensional reconstruction and examined with a mechanical intravascular ultrasound system (Clearview, CardioVascular Imaging System, Sunnyvale, CA, U.S.A.) with a sheath-based intravascular ultrasound catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. The intravascular ultrasound transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor. Intravascular ultrasound images were acquired, coinciding with the peak of the R wave, which eliminates the artefacts caused by the movement of the heart during the cardiac cycle. After each image acquisition, the transducer was withdrawn 0.2 mm to acquire the next image coincident with the R-wave. By definition, this permits acquisition of five slices per mm, enabling the operator to easily define the stent margins. By increasing the frequency of sampling this approach may also decrease error due to regression to the mean created by the use of greater step sizes and non-ECG-gating.

ECG-gated image acquisition and digitization was performed using a workstation designed for three-dimensional reconstruction of echocardiographic images (EchoScan, Tomtec, Munich, Germany). A Microsoft Windows-based contour detection program, developed at the Thoraxcenter, was used for automated three-dimensional analysis of up to 200 intravascular ultrasound images. This program constructs two longitudinal sections and identifies the contours corresponding to the lumen-intima and media-adventitia boundaries, using a minimum-cost based software algorithm. The feasibility, reproducibility and the inter- and intra-observer variability of this system have been previously described in clinical protocols.

Quantitative intravascular ultrasound analysis

At the stent edges, the area encompassed by the lumen-intima and media-adventitia boundaries defined the luminal and the total vessel volumes, respectively. The difference between luminal and total vessel volumes defined the plaque volume. Within the boundaries of the stent total vessel volume, stent volume, neointimal hyperplasia, and lumen volumes were obtained. The

Figure 1 A cold-end stent with a central radioactive segment and proximal and distal non-radioactive segments. Analysis of each segment was performed individually to assess neointimal hyperplasia. This included neointimal hyperplasia over the length of the stent and edges.
Cold-end Radioactive Stents

neointimal hyperplasia presented was a value measured at follow-up (stent volume–lumen volume).

The assessment of total vessel volume in stented patients has previously been reported[5,10]. In our study the delineation of the total vessel volume boundary was possible in all stented patients. When the total vessel volume boundary was not visible in a single cross-sectional view, the computer extrapolated it from the contours of the immediately previous and following cross-sections. In addition, the use of three-dimensional reconstruction with multiple longitudinal views, facilitates the visualization of vessel structures outside the stent.

Definitions and segments of analysis

Stent edges were defined as those volumes axially 5 mm proximal and distal to the final stent strut. In addition, segments in-stent proximally and distally were analysed separately to assess neointimal hyperplasia in areas which were subject to injury and received stent implantation. Effectively, these were segments which received a fall-off in radiation. Finally the in-stent radioactive segment was analysed (see Fig. 1). To facilitate comparison between the non-radioactive in-stent segments (5–7 mm) and the central radioactive segment (15–9 mm), lengths were normalized to a standard length (5 mm) and appropriate comparisons made. Restenosis was defined as an angiographic restenosis >50% at 6-month follow-up, by off-line quantitative coronary angiography.

Statistical analysis

Quantitative data are presented as mean ± standard deviation. Volumetric data derived from the three-dimensional reconstruction of the intravascular ultrasound image were compared immediately after treatment and at follow-up using the two-tailed paired Student’s t-test. ANOVA was used to compare multiple variables. A value of P<0.05 was considered statistically significant.

The Medical Ethical Committee of the University Hospital Rotterdam approved the study and all patients provided written informed consent before the procedure.

Results

Baseline clinical and procedural characteristics are described in Tables 1 and 2. Table 3 describes quantitative coronary angiography data pre- and post-intervention and at the 6-month follow-up.

In-stent radioactive segment

Neointimal hyperplasia measured within the margins of the stent is presented in Fig. 2. Intra-stent neointimal

<table>
<thead>
<tr>
<th>Table 1 Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Prior MI (%)</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
</tr>
<tr>
<td>Smoking (%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
</tr>
<tr>
<td>Family history (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2 Procedural characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel</td>
</tr>
<tr>
<td>LAD</td>
</tr>
<tr>
<td>LCx</td>
</tr>
<tr>
<td>RCA</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
</tr>
<tr>
<td>Balloon length-post (mm)</td>
</tr>
<tr>
<td>Final balloon size (mm)</td>
</tr>
<tr>
<td>Max inflation pressure1 (atms)</td>
</tr>
<tr>
<td>Max inflation pressure2 (atms)</td>
</tr>
<tr>
<td>Balloon-to-artery ratio</td>
</tr>
</tbody>
</table>

Max inflation pressure1 = balloon at time of stent implantation. Max inflation pressure2 = balloon inflation within stent. LAD = left anterior descending coronary artery; LCx = left circumflex artery; RCA = right coronary artery.

<table>
<thead>
<tr>
<th>Table 3 Angiographic data</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Pre</td>
</tr>
<tr>
<td>MLD 0.98 ± 0.40</td>
</tr>
<tr>
<td>DS  67 ± 14</td>
</tr>
<tr>
<td>RD  2.97 ± 0.46</td>
</tr>
<tr>
<td>Acute gain 1.28 ± 0.46</td>
</tr>
<tr>
<td>Late loss 0.57 ± 0.56</td>
</tr>
<tr>
<td>Late loss index 0.57 ± 0.56</td>
</tr>
</tbody>
</table>

FU=6-month follow-up. MLD=minimum lumen diameter; DS=diameter stenosis; RD(reference diameter).

hyperplasia was significantly decreased in the radioactive mid-segment of the stent: 3.72 ± 3.3 mm³ (8.5%), compared with the proximal: 7.90 ± 7.2 mm³ (19.0%) and distal: 11.42 ± 10.5 mm³ (25.6%) in-stent segments. Over the entire stent length there was a 30.48 mm³ (14%) increase in neointimal hyperplasia. No evidence of remodelling was seen behind the stent with the total vessel volume remaining unchanged.

In-stent non-radioactive segment

Significant neointimal in-growth was noted distally and proximally from 2–3 mm within the radioactive segment and extended on average to the extremities (non-radioactive) of the stent (see Fig. 3). Four individuals experienced angiographic restenosis in the proximal
portion of the stent. However, the greatest mean volume of tissue growth as quantified by intravascular ultrasound was seen in the distal stent. Neointimal hyperplasia, with a >50% stented cross-sectional area, was seen in eight patients. This was witnessed proximally (n=2), distally (n=2) and in both segments (n=4). Tissue growth in-stent was due to a combination of conventional neointimal hyperplasia and echolucent, hypodense material, described by this group as the ‘black hole’ (P. W. Serruys, personal communication, Rotterdam, 1999). This was witnessed (Fig. 4) in the non-radioactive proximal and distal in-stent segments in six out of the eight patients.

**Total vessel volumes**

No significant change in total vessel volumes or plaque behind the stent was seen between post-procedure and follow-up. No echolucent tissue was seen behind the stent.

**Stent edge**

Late lumen loss was seen at the stent edge without evidence of restenosis. On average, there was evidence of a decrease in total vessel volume, with little change in plaque as a cause of late lumen loss.

**Stent activity**

Mean stent activity at implantation was 6.9 ± 1.9 μCi.

**Discussion**

Dose-finding studies in humans have shown that in-stent neointimal hyperplasia is decreased in a dose-dependent manner after the implantation of stents with activity levels >3.0 μCi\[^{[3,4]}\]. Unfortunately, stent edge restenosis was a side effect of this treatment modality at these activity levels. Because the stent edge is systematically
damaged by barotrauma at the time of balloon expansion, a situation of geographical miss\(^\text{11}\), in which the damaged edges receive low dose radiation, is germane to radioactive stenting in the absence of appropriately shaped balloons. Previously we have argued: ‘If the candy wrapper (bilateral edge restenosis) were purely the result of negative remodeling induced by low-dose radiation in an injured area, then the lengthening of the stent by a non-radioactive, cold-end would be a logical solution to prevent remodeling at the extremities. If plaque constitutes a large percentage of the healing process manifested by the candy wrapper then cold-end stent implantation is unlikely to work. Similarly neointimal proliferation may occur at the edges of the radiation within stent using this treatment modality\(^\text{12}\). This prediction appears to have materialized in the current study, with migration of the restenotic edge from outside the stent to within the stent at the edges of radiation."

### Echolucent tissue

In nearly 50% of subjects, echolucent tissue was present within the stent at the distal or proximal (in-stent) edge of radiation and constituted on average 50% of neointimal ingrowth in areas of restenosis. These echolucent lesions had the following characteristics: a homogeneous black appearance without backscatter. Images with ring-down or other artefacts were excluded and no attenuation behind intraluminal echodense structures was seen. Exclusion of other causes of relative echolucency such as contrast\(^\text{13}\), thrombus\(^\text{14}\) or a lipid lake\(^\text{15}\) was performed. Lesions were discrete and readily distinguishable from conventional neointimal hyperplasia. After radioactive stenting, all appeared to be juxtaposed to stent struts.

We have performed atherectomy on four such lesions detected at the 6-month follow-up after radioactive stenting and found that they contain a hypocellular matrix with areas of proteoglycan, similar to that seen in the animal model\(^\text{16,17}\). The mixture of neointimal hyperplasia and proteoglycan, which has a high water content, may explain the echolucent tissue adjacent to the stent struts noted in Fig. 5. Further pathological
assessment is required before definitive comment can be made on this interesting observation. Equally, the long-term incidence of restenosis from such lesions is yet to be determined.

**Edge remodelling**

This was similar to that seen after non-radioactive stenting, whereby non-restenotic late lumen loss was due to negative remodelling\(^5\).\(^{18}\)

*Figure 5* Photomicrographs (a) and (b) show neointima consisting of arboryzing smooth muscle cells in a proteoglycan matrix. H&E stain; bars=50 μm.

**Implications for the future: dealing with the edge effect**

If the edge effect is the result of balloon-induced trauma and low dose radiation then limiting the trauma to outside the stent and expanding the irradiated area beyond the injured area should be attempted. For radioactive stents, conceivably the most practical approach may be to extend the area of irradiation beyond the injured area using a ‘hot-end stent’. This involves literally concentrating the greatest activity of the stent at
Cold-end Radioactive Stents

the stent edges; such stents are already undergoing multicentre trials. A further therapeutic option is that of hybrid treatment with radioactive stent implantation followed by catheter-based therapy localized to the stent edges only.

**Conclusion**

Cold-end stent implantation, a strategy devised to prevent edge restenosis after radioactive stenting results in migration of the restenotic edge from outside the stent to within the stent at the edges of radiation. This adds credence to the hypothesis that injury and low-dose radiation stimulate neointimal hyperplasia [19].

The Wenckebach award was made to P. W. Serruys by the Dutch Heart Foundation and is utilized for brachytherapy research in the catheterization laboratory. I. P. Kay is supported by the National Heart Foundation of New Zealand, Auckland and the Ian Gordon Mackenzie Scholarship, University of Otago, Dunedin, New Zealand.

**References**

CHAPTER 17


Radioactive Stents Delay but do not Prevent In-stent Neointimal Hyperplasia

_Circulation._ 2001;103:14-7
Radioactive Stents Delay but Do Not Prevent In-Stent Neointimal Hyperplasia

I. Patrick Kay, MBChB; Alexander J. Wardeh, MD; Ken Kozuma, MD; David P. Foley, MBBCh, PhD; A.H. Marco Knook, MD; Attila Thury, MD; George Sianos, MD; Willem J. van der Giessen, MD, PhD; Peter C. Levendag, MD, PhD; Patrick W. Serruys, MD, PhD

**Background**—Restenosis after conventional stenting is almost exclusively caused by neointimal hyperplasia. β-Particle-emitting radioactive stents decrease in-stent neointimal hyperplasia at 6-month follow-up. The purpose of this study was to evaluate the 1-year outcome of 32P radioactive stents with an initial activity of 6 to 12 μCi using serial quantitative coronary angiography and volumetric ECG-gated 3D intravascular ultrasound (IVUS).

**Methods and Results**—Of 40 patients undergoing initial stent implantation, 26 were event-free after the 6-month follow-up period and 22 underwent repeat catheterization and IVUS at 1 year; they comprised half of the study population. Significant luminal deterioration was observed within the stents between 6 months and 1 year, as evidenced by a decrease in the angiographic minimum lumen diameter (−0.43±0.56 mm; P=0.028) and in the mean lumen diameter in the stent (−0.55±0.63 mm; P=0.001); a significant increase in in-stent neointimal hyperplasia by IVUS (18.16±12.59 mm³ at 6 months to 27.75±11.99 mm³ at 1 year; P=0.001) was also observed. Target vessel revascularization was performed in 5 patients (23%). No patient experienced late occlusion, myocardial infarction, or death. By 1 year, 21 of the initial 40 patients (65%) remained event-free.

**Conclusions**—Neointimal proliferation is delayed rather than prevented by radioactive stent implantation. Clinical outcome 1 year after the implantation of stents with an initial activity of 6 to 12 μCi is not favorable when compared with conventional stenting. *(Circulation. 2001;103:14-17.)*

**Key Words:** radioisotopes ■ restenosis ■ stents ■ angiography

Implantation of 32P radioactive stents with activities ranging from 3.0 to 12 μCi in coronary artery lesions has been reported to inhibit neointimal hyperplasia within the stent at 6-month follow-up.1,2 The major limitation of this therapy is significant renarrowing at the stent edges, which is called the “candy wrapper” or “edge effect.”3 Catheter-based radiation significantly reduces the recurrence of restenosis 6 months after percutaneous transluminal coronary angioplasty for in-stent restenosis, but 3-year follow-up reveals greater luminal deterioration in γ-radiation-treated patients.4,5 Such findings indicate the need for longer follow-up beyond the traditional 6 months in patients treated with intracoronary radiation. The purpose of this study was to assess late results after the implantation of radioactive stents using repeat catheterization with quantitative coronary angiography and 3D intravascular ultrasound (IVUS) at 1 year.

**Methods**

**Patient Population**

The European 32P Dose-Response Trial was a nonrandomized multicenter trial evaluating the safety and efficacy of implanting radioactive stents with activity levels of 3 to 12 μCi in single, native coronary artery lesions. All stents were implanted in de novo lesions, except for 1 case of in-stent restenosis. For the purposes of this analysis, this case was excluded. Other inclusion and exclusion criteria, as well as immediate and 6-month results, were previously reported.1,2 Only patients undergoing 6-month angiographic and IVUS follow-up who did not experience major adverse cardiac events during the first 6 months were included. The study was performed in accordance with the Declaration of Helsinki and the European Guidelines for Good Clinical Practice. Ethical approval was provided by the Medical Ethical Committee of the University Hospital Rotterdam. All patients gave written, informed consent.

**Radioactive Stent**

The BX Isotest (32P) (Isostent Inc), which is 15 mm in length and 3.0 or 3.5 mm in diameter, was used. The initial activity of the stents was measured and, thereafter, the date at which the radioactivity would have decreased to 6 to 12 μCi was calculated.

**Procedure and Clinical Follow-Up**

Procedural details have been published previously.5 All patients received either 250 mg of ticlopidine BID or 75 mg of clopidogrel per day for 3 months after stent implantation and 80 mg of aspirin per day indefinitely. Revascularization was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing. Clinical end points were death, Q-wave myocardial infarction, non-Q-wave myocardial infarction (creatine kinase-MB rise >2
Contour detection program was used for the volumetric 3D analysis. A Microsoft Windows-based and digitization was performed by a workstation designed for 3D angiography (CAAS II analysis system, Pie Medical BV) and stented vessel segments were examined with quantitative coronary procedure, after stenting, and at 6-month and 1-year follow-up. The Angiographic and IVUS Procedures

Angiography in multiple projections was performed before the target vessel. Angiographic and IVUS Procedures

Angiography in multiple projections was performed before the target vessel. Angiographic and IVUS Procedures

TABLE 1. Baseline Characteristics of the 22 Patients Studied

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Male sex (%)</th>
<th>Age, y (range)</th>
<th>Male sex (%)</th>
<th>Age, y (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>20 (91)</td>
<td>57 (38–73)</td>
<td>12 (55)</td>
<td>41 (30–55)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (14)</td>
<td>57 (38–73)</td>
<td>3 (14)</td>
<td>41 (30–55)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (82)</td>
<td>57 (38–73)</td>
<td>12 (55)</td>
<td>41 (30–55)</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (36)</td>
<td>57 (38–73)</td>
<td>4 (18)</td>
<td>36 (21–50)</td>
</tr>
<tr>
<td>Family history</td>
<td>7 (32)</td>
<td>57 (38–73)</td>
<td>4 (18)</td>
<td>36 (21–50)</td>
</tr>
</tbody>
</table>

TABLE 2. Subsegmental Quantitative Coronary Angiography Analysis

<table>
<thead>
<tr>
<th>Lesion length, mm</th>
<th>Baseline 6 Months 1 Year</th>
<th>Baseline 6 Months 1 Year</th>
<th>Baseline 6 Months 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2 (9)</td>
<td>2.92±0.53* 2.23±0.73*</td>
<td>0.69±0.80† 0.15±0.51†</td>
</tr>
<tr>
<td>B1</td>
<td>10 (45.5)</td>
<td>2.50±0.47* 2.36±0.47*</td>
<td>0.14±0.52‡ 0.43±0.56‡</td>
</tr>
<tr>
<td>B2</td>
<td>8 (36.5)</td>
<td>2.29±0.61 2.17±0.58*</td>
<td>0.36±0.49‡ 0.09±0.49‡</td>
</tr>
<tr>
<td>C</td>
<td>2 (9)</td>
<td>3.19±0.56 2.73±0.57*</td>
<td>0.39±0.62§ 0.22±0.51‡</td>
</tr>
<tr>
<td>Proximal edge</td>
<td>3.12±0.42 3.09±0.58</td>
<td>2.54±0.41* 2.36±0.50</td>
<td>0.03±0.62‡ 0.09±0.63‡</td>
</tr>
</tbody>
</table>

Core Laboratory Analysis Procedures

Quantitative coronary angiography using at least 2 orthogonal projections was performed. For analytical purposes, the following 3 regions of interest were defined: (1) stent, (2) target lesion, and (3) target vessel. The stent included only the radioactive stent. The target lesion was defined as the stent and 5 mm proximal and 5 mm distal to the edge. The target vessel was defined as the target lesion and the remaining segments of the treated vessel. Target lesion restenosis was defined as >50% diameter stenosis, located within the target lesion, at follow-up. Edge restenosis was defined as >50% diameter stenosis, located at the proximal and/or distal edge, at follow-up.

Quantitative IVUS analysis of the stent and 5 mm proximal and distal to the stent was performed. Lumen and stent boundaries were detected using a minimum cost algorithm. Total stent and lumen volumes were calculated as previously described. Neointimal volume was calculated as stent volume minus luminal volume. Feasibility, reproducibility, and interobserver and intraobserver variability of this system have been validated in vitro and in vivo.

Statistical Analysis

Data are presented as mean±SD. Continuous data were compared using repeated measures ANOVA or a 2-tailed Student t test as appropriate.

Results

Baseline demographics and lesion characteristics are shown in Table 1. Between 6 months and 1 year, target lesion revascularization and target vessel revascularization were performed in 4 patients (18%) and 5 patients (23%), respectively. No late closure was seen. No patient died or experienced myocardial infarction. In total, 21 of 40 patients (53%) were event-free through the 1-year follow-up.

Quantitative Coronary Angiography and IVUS Measurements

Quantitative coronary angiography data, presented as a subsegmental analysis of the stent area and the edges, are shown in Table 2. A significant decrease in the minimum and mean lumen diameters was noted between 6 months and 1 year (P=0.028 and P=0.001, respectively) compared with both edges. The late loss of mean lumen diameter was significantly larger after 6 months than before 6 months. Furthermore, in 11 patients (50%), the minimum lumen diameter at the edge at 6 months was detected within the stent at 1 year ("migration" from the stent edge to within the stent). Lesion progres-
Intermediate Outcome After Radioactive Stents

Sion to >50% diameter stenosis was observed in 5 patients. This was due to a progression of in-stent restenosis in 4 patients and a progression of a proximal stent-edge lesion in the other.

IVUS was completed in 19 patients; omissions were due to equipment failure or patient clinical instability. IVUS analysis demonstrated a significant increase in neointimal hyperplasia between 6 months and 1 year (18.16 ± 12.59 mm³ to 27.75 ± 11.99 mm³; increase of 52.8%; P = 0.001), mainly in the mid and distal portions of the stent (Figure 1). An increase in neointimal hyperplasia >25% (range, 25% to 360%) occurred in 12 cases (63%), as shown in Figure 2. No change in lumen volume was noted at the stent edges between 6 months and 1 year.

Radiation Doses

The radioactive stents had a mean activity of 8.6 ± 1.6 μCi at implantation and delivered 58 ± 10 Gy to a depth of 1 mm from the stent at 100 days, with a dose rate of >15cGy/h. There was no correlation between stent activity or delivered dose and changes in minimum or mean lumen diameter at 6-month or 1-year follow-up.

Discussion

A worrying late progression of in-stent neointimal hyperplasia was observed between 6 months and 1 year after the implantation of radioactive stents, leading to target vessel or lesion reintervention in 5 of 26 patients (19%) who had been event-free at 6 months. The event-free rate at 1 year after the implantation of 6 to 12 μCi radioactive stents was 21 of 40 patients (53%), which compares poorly to the expected outcome after the implantation of a nonradioactive stent. In contrast to the tissue growth seen in malignancy, the DNA synthesis that occurs after nonradioactive stenting in experimental models terminates after 6 weeks. At this time point, the activity of the radioactive stent used in this study would have been sufficient to inhibit cellular proliferation. Thereafter, the majority of lumen deterioration occurs in the first 3 months after conventional stent implantation, with minimal change between 6 months and 1 year, and actual regression of neointimal hyperplasia between 1 and 3 years after stenting. This latter phenomenon has been attributed to a reduction in the proteoglycan content of hyperplastic tissue. Accordingly, the findings reported here of “breakthrough” or “rebound” hyperplasia causing further lumen deterioration between 6 months and 1 year must be interpreted as being specific to the effects of radioactivity, presumably due to a fall-off in radiation levels. The observation that the radioactive stent may provide a substrate for atherosclerosis may well have been predicted by Carter et al’s porcine model.

Because no significant stenosis progression was observed at the stent edges among our patients, the candy wrapper effect may be considered a short-term healing response to vessel wall injury beyond the stented vessel segment combined with the effects of low-dose radiation. Unexpected late luminal deterioration has also been reported between 6 months and 3 years among patients treated by catheter-based γ-radiation after repeat intervention for in-stent restenosis (mean loss of 0.37 mm with 4 of 17 patients [26%] progressing to restenosis [diameter stenosis >50%]), compared with no major changes in the placebo group. The difference in the time frame of this virtual “rebound hyperplasia” between radioactive stenting and catheter-based γ-radiation therapy may be a function of the biological effects of and response to the type and dosage of radiation administered. Alternatively, late loss may also have
occurred between 6 months and 1 year and remained subclinical in the catheter-based study.

Conclusions
Neointimal hyperplasia is delayed rather than prevented by radioactive stent implantation. The combination of this phenomenon of rebound hyperplasia with the established phenomenon of edge restenosis calls into question the clinical applicability of radioactive stenting using current approaches.

Acknowledgments
The Wenckebach prize was awarded to P.W. Serruys by the Dutch Heart Foundation and was used for brachytherapy research in the catheterization laboratory.

References
CHAPTER 18


Long Term Outcome After Radioactive Stent Implantation; an Example of Treatment Failure Without Irreversible Clinical Sequaellae

Submitted for publication
Long term outcome after radioactive stent implantation: a treatment failure without irreversible long term clinical sequelae

Georgios Sianos, MD, Ron van Domburg, PhD, Francesco Saia, MD, Angela Hoye, MD, Willem J van der Giessen, MD, Eugene Mc Fadden, MD, Marco van Duuren, MSc, Pim J de Feyter, MD, Patrick W Serruys, MD.

Department of Interventional Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands.

Correspondence address:
Prof PW Serruys MD, PhD, FESC, FACC
Department of Interventional Cardiology
Erasmus MC Rotterdam
Thoraxcenter Bd 404
Dr Molewaterplein 40
3015 GD Rotterdam
The Netherlands
Tel: (+31 10 4635260)
Fax: (+31 10 4369154)
e-mail: p.w.j.c.serruys@erasusmc.nl
Abstract

Purpose: To determine the long term outcome of patients after radioactive stent implantation.

Background: Radioactive stent implantation has been proposed as a modality to prevent restenosis. Its unfavourable short term outcome, due to edge restenosis prohibited its therapeutic use and the long term outcome of patients who underwent radioactive stent implantation is evidently a cause of concern.

Methods and Results: The rate of major adverse cardiac events (MACE) was retrospectively determined in 133 patients who underwent successful radioactive stent implantation. MACE were defined as death, myocardial infarction, and any re-intervention. Long term clinical outcome was obtained from an electronic database of hospital records and questionnaires to the patients and the referring physicians. Long term survival status was assessed by written inquiries to the Municipal Civil Registrries. The mean follow up was 3.85±0.75 years. The target lesion revascularisation (TLR) at six months was 30%, mainly due to edge restenosis, and at one year 36.8%. It did not significantly changed up to 4 years; 41.3%, p=0.45. The incidence of a second TLR was 9%. The incidence of MACE at six months was 30.8% and at one year 39.1%. There was no significant increment up to 4 years; 48.9%, p=0.1. At 4 years the cumulative incidence of death was 3%, of myocardial infarction was 6.8%, of CABG was 10.5%, and of total occlusions was 7.5%, with the majority of events observed during the first year.

Conclusion: A high incidence of MACE and re-intervention was observed during the first year following radioactive stent implantation, mainly related to TLR for edge restenosis. After the first year the clinical outcome of these patients remained stable indicating that there are no late adverse effects related to low dose-rate intracoronary radiation therapy.
Introduction

Radioactive stents were evaluated as a treatment for restenosis prevention. Preclinical evaluation in two animal models showed discordant results with reduction of neointimal formation in a dose related manner in the rabbit iliac artery but more complex dose relationship in the pig coronary artery (1-3). Initial human studies with low activity (0.75-1.5 μCi) radioactive stents, showed that their use was feasible and safe but ineffective for the prevention of in-stent restenosis (4). Dose finding studies with intermediate activity (3-12 μCi) radioactive stents, proved their efficacy in preventing intra-stent restenosis but simultaneously revealed their major limitation related to the development of stent edge restenosis, the so-called “edge effect” or “candy wrapper” (5,6). Efforts to eliminate edge restenosis with high activity radioactive stents (12-21 μCi) (7), stent edge activity modification (cold-end, hot-end radioactive stents) (8-10) or the use of dedicated, edge non-traumatic square shouldered balloons (11), failed.

The aim of the present study was to describe the long term clinical outcome after radioactive stent implantation. Although no longer in clinical use, these results might improve our understanding on the, potentially long lasting, interaction between localised radiation therapy and vascular response in humans.

Methods

Patient population

Between November 1997 and July 2000, 133 patients received one or two radioactive stents, in our institution. The baseline characteristics of the patients are presented in Table 1. The patients were parts of five different studies. The design and short term outcome of the studies has been previously reported. An overview of the studies is presented in Table 2. Briefly the
IRIS 1 (4) study was a safety and feasibility study and IRIS 2 (5) was a European dose finding study. The cold end (8,9), the hot end (10) and the square shouldered balloons (11) were studies with dedicated radioactive stents and balloons to overcome the problem of edge stent restenosis observed with this therapeutic modality. In all studies follow up angiography was performed at six months and one year as mandated by protocol.

Follow up

Baseline clinical and procedural data were entered prospectively in a dedicated database. Long term clinical outcome was obtained from an electronic database of hospital records. The Thoraxcenter is a tertiary cardiology center, serving a group of 14 local hospitals for percutaneous coronary interventions in the region of Rotterdam. As required by the local medical system organisation all baseline procedures were performed in this tertiary facility, as well as the vast majority of re-interventions.

Long term survival status was assessed by written inquiries to the Municipal Civil Registries. Questionnaires were sent to all living patients focusing on the occurrence of MACE such as, myocardial infarction, and repeat intervention (surgical and percutaneous). The referring physician and institutions as well as the general practitioners were directly approached whenever necessary. Complete follow-up was obtained in all patients.

Definitions

MACE were defined as: 1) death, 2) non-fatal myocardial infarction, 3) repeat revascularisation. This order was used for the hierarchical ranking. TLR was defined as any surgical or percutaneous re-intervention due to restenosis within the radioactive stent or in the 5mm proximal or distal peri-stent segments (edge restenosis). TVR was defined as any re-
intervention driven by lesions located in the treated vessel beyond the target lesion limits. Non TLR-TVR was defined as any re-intervention in vessels other than the target vessel. By protocol, in all studies, radioactive stent implantation in more than one vessel was prohibited. For the hierarchical ranking presentation of re-intervention TLR was regarded as the more serious and non TLR-TVR as the less serious one. CABG was not considered as separate event but was regarded as a type of re-intervention (TLR, TVR or non TLR-TVR).

Total occlusion was defined as radioactive stent occlusion documented by coronary angiography. Subacute thrombosis was defined as angiographically documented total occlusion ≤ 30 days. Late total occlusion was defined as angiographically documented total occlusion > 30 days post intervention. Late-late total occlusion was applied for patients who had a patent artery at six months follow-up and subsequently presented with total occlusion at the same site. Thrombotic occlusion was defined as any late or late-late occlusion that resulted in an acute coronary syndrome (myocardial infarction or unstable angina). (12).

For the determination of the length of the follow up, the start day was the day of the index procedure with radioactive stent implantation between November 1997 and June 2000. The last day for the follow up was the 31st March 2003.

**Statistical analysis**

Data are expressed as mean value ± SD. Survival and event-free survival were estimated by Kaplan-Meier curves. Continuous variables were compared by Student’s t-test, categorical variables by chi-square-tests. Statistical significance of all tests was defined at the p<0.05 level.
Chapter 18

Results

MACE

In hierarchical ranking the incidence of MACE at six months was 30.8%, and at one year 39.1%, p=0.15. A non-significant increment was observed up to 4 years. 48.9%, p=0.1, Table 3. The total count of events is presented in Table 4. The MACE free survival rate at 4 years was 51.1%. The MACE free survival curve is presented in Figure 1. At 4 years the cumulative incidence of death was 3%, and of myocardial infarction 6.8%. One death was cardiac in origin and in the other 3 cases the aetiology is unknown. Nine patients suffered a myocardial infarction. Four were referred for primary PTCA. Angiographic total occlusion of the radioactive stent was documented in two (in one 1276 days after the index procedure) and severe in-stent restenosis in the third. In the fourth patient the infarction was due to occlusion of a vessel other than that in which the radioactive stent was implanted. The remaining five patients were initially treated with thrombolysis; elective angiography showed edge restenosis of the radioactive stent in four and in-stent restenosis in the fifth. All patients were treated successfully (one referred for CABG).

Re-intervention

The majority (90%) of re-interventions were TLRs. Low rates of TVR and non TLR-TV were observed at 4 years (3% and 1.5% respectively). In hierarchical ranking the TLR at six months was 32.3% directly related to the first angiographic follow-up. A second wave occurred at one year related to the second angiographic follow up (36.8%, p=0.25). A non-significant increment was observed up to 4 years (41.3%, p=0.45), Table 5. The total count of re-interventions is presented in Table 4. The re-intervention free survival curve is presented in Figure 1.
CABG

In total 10.5% patients underwent CABG, Table 4. In eight patients surgery was the first TLR. In four patients it was the second TLR (recurrence after an initial percutaneous TLR). In one patient CABG was a TVR and another one non-TLR-TVR.

Total occlusions

The incidence of total occlusions up to 4 years was 7.5%, Table 6. No sub-acute thrombosis was observed. The incidence of late total occlusion was 3.8% and that of late-late total occlusion was also 3.8%. In three patients (2.2%) the occlusion was resulted in an acute coronary syndrome (late thrombotic occlusion). Two patients underwent TLR for edge restenosis, with bare stent implantation, before the vessel finally occluded.

Outcome after first TLR

In total 61 patients underwent a repeat intervention; 55 (90%) of them were TLRs, mainly due to edge restenosis (69%). The average time to the first TLR was 279±235 days. Clinical and angiographic characteristics related to the first TLR are presented in Table 7. Among patients who had a first TLR, a second TLR was performed in 21.9% (12 patients). The average time between implantation of the radioactive stent and the second TLR was 413±234 days. Clinical and angiographic characteristics related to a second TLR are presented in table 8. The MACE and re-intervention free survival rate was 76.3%. The event free survival curve of patients after a first TLR is presented in Figure 2. There was only one patient who underwent TLR for a third time.
Discussion

Edge effect

Radioactive stents were proposed as a therapy for restenosis prevention. During safety-feasibility and dose finding studies they proved to be efficient for preventing in-stent restenosis but the edge restenosis, called the edge effect, became clearly apparent as their limitation (13). Intravascular ultrasound studies demonstrated that this effect is a combination of negative remodelling and plaque progression at the stent edges (6). The fall of the dose at the stent edges in combination with balloon injury which systematically occurs was regarded to be the cause. This is a well established phenomenon in catheter based brachytherapy, called geographical miss, responsible for development of edge restenosis (14,15). Animal studies with half radioactive stents confirmed this hypothesis (16).

Attempts to resolve the problem, by making the edges of the stents non-radioactive (cold-end radioactive stents), for prevention of negative remodelling, or by increasing the activity at the edges (hot-end radioactive stents) to avoid under-dosage, failed (8-10). A last attempt with the use of square shouldered balloons aiming to minimize injury outside the stent edges was also not successful (11) and radioactive stents never found a place in routine clinical use (17,18).

Effect of the angiographic control

The event-free rate at 4 years after the implantation was 51% which compares poorly to the expected outcome after the implantation of a non-radioactive stent (19). The angiographic control at six months and one year affected the re-intervention rate since 20% of the TLRs were performed in asymptomatic patients. This probably influenced the time distribution of the re-interventions and the relative composition of the MACE rather than the event free survival
Long Term Outcome After Radioactive Stents

rate. All these patients had severe angiographic restenosis, and it is highly likely that they would have developed symptoms if they remained untreated.

Comparison with non-radioactive stents and catheter based brachytherapy

The main of lumen deterioration after conventional stent implantation occurs in the first 3 months, with minimal change between 6 months and 1 year (20) and actual regression of neointimal hyperplasia between 1 and 3 years after stenting (21). A non-significant increase in the incidence of MACE and re-intervention was observed in our population between six months and one year. This might well be attributed to the second angiographic control, although there is evidence that radioactive stents, in contrast with the promising results observed at 28 days, promote the formation of “atheromatous” neointima in a porcine atherosclerotic coronary model at six months (22). Our group reported a significant increment in the in-stent neointimal hyperplasia between six months and one year (13-26 half-lifes of the P32 isotope) in radioactive stents with activity 6 to 12 µCi, by means of intravascular ultrasound (23). These results may indicate that the TLRs between 6 and 12 months were a result of late neointimal formation (delayed healing response). After the first year the clinical outcome following radioactive stent implantation is stable and comparable to non-radioactive stents indicative that there are no long term adverse effects after low dose rate irradiation (17,24).

The long term outcome after brachytherapy for de-novo lesions has not yet been reported. Angiographic analysis from the SCRIPPS trial (gamma radiation for in-stent restenosis) at 3 years showed a reduction of the MLD in irradiated patients but not in the placebo group (25) with further increase in the TLR rate in the irradiated patients only, between 3 to 5 years (26). Increase in the revascularization rate between 6 months and 3 years in the irradiated group only
of the WRIST trial (gamma radiation for in-stent restenosis) was also observed (27). The difference in the time frame of the restenosis process between radioactive stenting and catheter-based gamma-radiation therapy may be a function of the biological response to the type and dosage of radiation administered.

**Type of failure in clinical trials with or without irreversible sequelae**

Radioactive stents represent an example of a technology whose premature application in humans was based only on preliminary and short term results in animal models. Results of long-term animal experiments, published when clinical trials in humans were already at an advanced stage, revealed the problem of late restenosis (22) and proved that the edge effect was unavoidable and without solution (16). Fortunately it resulted only in an increased rate of re-intervention without further consequences such as death and myocardial infarction. In the era of drug eluting stents, actinomycin (ACTION trial) is another example of failed treatment that did not result in irreversible clinical events (28). The latest example of 7-hexanoytaxol polymer sleeve eluting stents, that reached human application (SCORE trial) without proper animal documentation, unfortunately led to an unacceptable 21% incidence of myocardial infarction during the first year (29). Concern was raised recently that the safety-feasibility and the potential efficacy of new technologies should be based on firm animal data of at least six months before human trials (30).

**Conclusions**

A high incidence of MACE and re-intervention was observed during the first year after radioactive stent implantation that led to this technique being abandoned. After that period the
long term clinical outcome is stable and comparable to non radioactive stents, indicating that there are no late adverse cardiac effects related to low dose-rate intracoronary radiation therapy.

References


**Table 1**

**Baseline and procedural characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>58.75±10.8</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>95 (71.4%)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>60 (45.1%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>18 (13.5%)</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><strong>Current medical condition</strong></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>83 (62.4%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>50 (37.6%)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>71 (53.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (36.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (9.8%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>33 (24.8%)</td>
</tr>
<tr>
<td>Family history</td>
<td>31 (23.3%)</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
<td></td>
</tr>
<tr>
<td>Normal &gt;50%</td>
<td>112 (84.2%)</td>
</tr>
<tr>
<td>Moderate 35-50%</td>
<td>14 (15.5%)</td>
</tr>
<tr>
<td>Poor &lt;35%</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td><strong>Lesion type †</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>23 (17.2%)</td>
</tr>
<tr>
<td>B1</td>
<td>41 (30.9%)</td>
</tr>
<tr>
<td>B2</td>
<td>65 (48.9%)</td>
</tr>
<tr>
<td>C</td>
<td>4 (3%)</td>
</tr>
<tr>
<td><strong>Vessel treated</strong></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>59 (44.4%)</td>
</tr>
<tr>
<td>RCA</td>
<td>28 (21.1%)</td>
</tr>
<tr>
<td>LCx</td>
<td>46 (34.5%)</td>
</tr>
<tr>
<td><strong>IIb-IIIa inhibitors</strong></td>
<td>37 (27.8%)</td>
</tr>
<tr>
<td><strong>Two radioactive stents</strong></td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td><strong>Bare stent</strong></td>
<td></td>
</tr>
<tr>
<td>Other vessel</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>Same vessel</td>
<td>16 (12%)</td>
</tr>
<tr>
<td><strong>Follow-up (range) in days</strong></td>
<td>1384 (985-1917)</td>
</tr>
</tbody>
</table>

CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, LAD left anterior descending artery, RCA right coronary artery, and LCX left circumflex coronary artery.  
† The type of lesion was classified according to the American Heart Association–American College of Cardiology classification, with A denoting a short focal lesion, and C the most complex type of lesion.
Table 2

Study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>patients</th>
<th>stent</th>
<th>length (mm)</th>
<th>dose (Gy)</th>
<th>activity (µCi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS 1</td>
<td>26</td>
<td>$^{32}$P Palmaz-Schatz $^{32}$P BX Isostent</td>
<td>15</td>
<td>7.5±1.6</td>
<td>0.75-1.5</td>
</tr>
<tr>
<td>IRIS 2</td>
<td>40</td>
<td>$^{32}$P BX Isostent</td>
<td>15</td>
<td>58.1±10.4</td>
<td>6-12</td>
</tr>
<tr>
<td>Cold ends</td>
<td>21</td>
<td>$^{32}$P BX cold-ends</td>
<td>25</td>
<td>47.2±13.5</td>
<td>6-24</td>
</tr>
<tr>
<td>Hot ends</td>
<td>17</td>
<td>$^{32}$P BX hot-ends</td>
<td>18</td>
<td>89.8±20.8</td>
<td>18.5</td>
</tr>
<tr>
<td>Square shouldered balloons</td>
<td>29</td>
<td>$^{32}$P Multi-Link DUET</td>
<td>23</td>
<td>64.8±22.1</td>
<td>15-23</td>
</tr>
</tbody>
</table>

IRIS denotes Isostents for Restenosis Intervention Study.

Table 3

MACE hierarchical ranking

<table>
<thead>
<tr>
<th></th>
<th>&lt;6m</th>
<th>&lt;1y</th>
<th>&lt;2y</th>
<th>&lt;3y</th>
<th>&lt;4y</th>
<th>6m vs 1y</th>
<th>1y vs 4y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.75%)</td>
<td>1 (0.75%)</td>
<td>2 (1.5%)</td>
<td>4 (3%)</td>
<td>p=0.3</td>
<td>p=0.2</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5 (3.8%)</td>
<td>5 (3.8%)</td>
<td>7 (5.3%)</td>
<td>8 (6%)</td>
<td>9 (6.8%)</td>
<td>p=1</td>
<td>p=0.3</td>
</tr>
<tr>
<td>Re-intervention</td>
<td>36 (27.1%)</td>
<td>46 (34.6%)</td>
<td>48 (36.1%)</td>
<td>49 (36.8%)</td>
<td>52 (39.1%)</td>
<td>p=0.2</td>
<td>p=0.45</td>
</tr>
<tr>
<td>Total MACE</td>
<td>41 (30.8%)</td>
<td>52 (39.1%)</td>
<td>56 (42.1%)</td>
<td>59 (44.3%)</td>
<td>65 (48.9%)</td>
<td>p=0.15</td>
<td>p=0.1</td>
</tr>
</tbody>
</table>

Hierarchical ranking scale considers only the worst event; i.e. if a patient required repeat intervention and later suffered a MI the ranking scale would reflect only the worst event. The MACE were ranked as follows: death, non-fatal MI, and re-intervention.

MI denotes myocardial infarction, and MACE denotes major adverse cardiac events.
Table 4

Total count of events

<table>
<thead>
<tr>
<th></th>
<th>&lt;6m</th>
<th>&lt;1y</th>
<th>&lt;2y</th>
<th>&lt;3y</th>
<th>&lt;4y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.75%)</td>
<td>1 (0.75%)</td>
<td>2 (1.5%)</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5 (3.8%)</td>
<td>5 (3.8%)</td>
<td>7 (5.3%)</td>
<td>8 (6%)</td>
<td>9 (6.8%)</td>
</tr>
<tr>
<td>TLR</td>
<td>43 (32.3%)</td>
<td>56 (42.1%)</td>
<td>63 (47.3%)</td>
<td>66 (49.6%)</td>
<td>68 (51.1%)</td>
</tr>
<tr>
<td>TVR</td>
<td>4 (3%)</td>
<td>6 (4.5%)</td>
<td>7 (5.3%)</td>
<td>7 (5.3%)</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td>Non TLR-TVR</td>
<td>13 (9.8%)</td>
<td>14 (10.5%)</td>
<td>16 (12%)</td>
<td>16 (12%)</td>
<td>18 (13.5%)</td>
</tr>
<tr>
<td>Any re-intervention</td>
<td>59 (44.4%)</td>
<td>76 (57.1%)</td>
<td>86 (64.6%)</td>
<td>89 (66.9%)</td>
<td>93 (69.9%)</td>
</tr>
<tr>
<td>Any MACE</td>
<td>64 (48.2%)</td>
<td>82 (61.6%)</td>
<td>93 (69.9%)</td>
<td>99 (74.4%)</td>
<td>106 (79.7%)</td>
</tr>
<tr>
<td>CABG</td>
<td>8 (6%)</td>
<td>10 (7.5%)</td>
<td>13 (9.8%)</td>
<td>13 (9.8%)</td>
<td>14 (10.5%)</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>5 (3.8%)</td>
<td>6 (4.5%)</td>
<td>6 (4.5%)</td>
<td>8 (6%)</td>
<td>10 (7.5%)</td>
</tr>
</tbody>
</table>

All events reflects the total count of events i.e. if a patient required repeat intervention and later suffered a MI the total count would reflect both events and not just the worst occurred. For the MI, CABG and the total occlusions the total count of events is the same as the hierarchical ranking since there were no patients with repeated such events. CABG was not considered as separate event but was regarded as a type of re-intervention.

MI denotes myocardial infarction, TLR denotes target lesion revascularisation, TVR denotes target vessel revascularisation, MACE denotes major adverse cardiac events and CABG denotes coronary artery bypass graft operation.
Table 5
Re-intervention hierarchical ranking

<table>
<thead>
<tr>
<th></th>
<th>&lt;6m</th>
<th>&lt;1y</th>
<th>&lt;2y</th>
<th>&lt;3y</th>
<th>&lt;4y</th>
<th>6m vs 1y</th>
<th>1y vs 4y</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR</td>
<td>40 (30%)</td>
<td>49 (36.8%)</td>
<td>52 (39.1%)</td>
<td>53 (39.8%)</td>
<td>55 (41.3%)</td>
<td>p=0.25</td>
<td>p=0.45</td>
</tr>
<tr>
<td>TVR</td>
<td>3 (2.3%)</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
<td>p=0.7</td>
<td>p=1</td>
</tr>
<tr>
<td>Non TLR-TVR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (1.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any re-intervention</td>
<td>43 (32.3%)</td>
<td>53 (39.8%)</td>
<td>56 (42.1%)</td>
<td>57 (42.8%)</td>
<td>61 (45.8%)</td>
<td>p=0.2</td>
<td>p=0.3</td>
</tr>
</tbody>
</table>

Hierarchical ranking scale considers only the worst event; i.e. if a patient required repeat TLR and later TVR, ranking scale would reflect only the worst event. Events are given ranked as following: TLR, TVR, non TLR-TVR.

TLR denotes target lesion revascularisation, TVR denotes target vessel revascularisation.

Table 6
Total occlusions

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>incidence</td>
<td>10 (7.5%)</td>
</tr>
<tr>
<td>timing</td>
<td></td>
</tr>
<tr>
<td>&lt;30 days</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>6m-1 years</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>1y-2 years</td>
<td>0</td>
</tr>
<tr>
<td>2y-3 years</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>3y-4 years</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>clinical presentation</td>
<td></td>
</tr>
<tr>
<td>asymptomatic</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>angina</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>unstable angina</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>MI</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Stent implantation</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>medical (failed re-intervention)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>TLR before the occlusion</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>average time (range) in days</td>
<td>524 (144-1276)</td>
</tr>
<tr>
<td>average dose</td>
<td>59.5 Gy</td>
</tr>
</tbody>
</table>

CABG denotes coronary artery bypass surgery and TLR denotes target lesion revascularisation.
Table 7

**First TLR**

<table>
<thead>
<tr>
<th>Category</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any re-intervention</td>
<td>61 (45.8%)</td>
</tr>
<tr>
<td>First TLR</td>
<td>55 (41.3%)</td>
</tr>
<tr>
<td><strong>Additional intervention during first TLR</strong></td>
<td></td>
</tr>
<tr>
<td>TVR</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Non TLR-TVR</td>
<td>8 (14.5%)</td>
</tr>
<tr>
<td><strong>Other re-intervention before first TLR</strong></td>
<td></td>
</tr>
<tr>
<td>2 (3.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Angiographic appearance</strong></td>
<td></td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>9 (16.4%)</td>
</tr>
<tr>
<td>Bilateral edge restenosis</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Proximal edge restenosis</td>
<td>26 (47.3%)</td>
</tr>
<tr>
<td>Distal edge restenosis</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>8 (14.5%)</td>
</tr>
<tr>
<td><strong>Device used †</strong></td>
<td></td>
</tr>
<tr>
<td>Balloon</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Cutting balloon</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Stent</td>
<td>34 (61.8%)</td>
</tr>
<tr>
<td>Atherectomy</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>CABG</td>
<td>8 (14.5%)</td>
</tr>
<tr>
<td>Sonotherapy</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>35 (63.6%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>6 (10.9%)</td>
</tr>
<tr>
<td>MI</td>
<td>3 (5.4%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>11 (20%)</td>
</tr>
<tr>
<td><strong>Average time (range) in days</strong></td>
<td>279 (70-1276)</td>
</tr>
</tbody>
</table>

TLR denotes target lesion revascularisation, TVR denoted target vessel revascularisation and CABG denotes coronary artery bypass surgery.

†Not mutually exclusive
### Table 8

**Second TLR**

<table>
<thead>
<tr>
<th>Category</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-intervention after first TLR</td>
<td>13 (9.8%)</td>
</tr>
<tr>
<td>Second TLR</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Third TLR</td>
<td>1 (0.75%)</td>
</tr>
<tr>
<td><strong>Additional intervention during second TLR</strong></td>
<td></td>
</tr>
<tr>
<td>non TLR-TVR</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td><strong>Other re-intervention between first and second TLR</strong></td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td><strong>Angiographic appearance</strong></td>
<td></td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>5 (41.7%)</td>
</tr>
<tr>
<td>Bilateral edge restenosis</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Proximal edge restenosis</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td>Distal edge restenosis</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td><strong>Device use †</strong></td>
<td></td>
</tr>
<tr>
<td>Balloon</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td>Stent</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>CABG</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>PMR</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Conservative (failed intervention)</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td><strong>Average time (range) in days</strong></td>
<td>413 (148-835)</td>
</tr>
</tbody>
</table>

TLR denotes target lesion revascularisation, TVR denotes target vessel revascularisation, CABG denotes coronary artery bypass surgery, PMR denotes percutaneous myocardial revascularisation.

† Not mutually exclusive.
MACE and re-intervention free survival curves up to four years (Kaplan-Meier). Since the majority of events were re-interventions the two curves are almost identical. These curves have four distinct segments. Up to six months a relapse is clearly visible followed by a sharp decrease related to the first angiographic control. From six months up to one year the curve remains stable. Around one year a second sharp decrease occurs related to the second angiographic control. From one year and up to four years the curve remains reasonably stable. MACE denotes major adverse cardiac events.

MACE and re-intervention free survival curves (Kaplan-Meier) after first TLR. MACE denotes major adverse cardiac events, TLR denotes target lesion revascularisation.
CHAPTER 19

Summary and Conclusions
SUMMARY

Balloon angioplasty was the first non surgical treatment of coronary artery disease but it was limited by a high incidence of complications and restenosis. Stents almost eliminated the problem of acute complications but they also created the most challenging problem of in-stent restenosis. After a decade of failures to solve the problem of in-stent restenosis with mechanistic and pharmacological approaches intracoronary radiation therapy was introduced both with catheter based systems and radioactive stents. This thesis addresses issues central to both of these therapeutic modalities.

Catheter based Intracoronary Radiation Therapy

New observations such as positive remodelling, relocation of the minimal luminal diameter, edge restenosis and geographical miss have been associated with intracoronary brachytherapy. They created confusion in the interpretation of the results of the first brachytherapy trials with a discrepancy between a “good” angiographic outcome in the irradiated segment and a “bad” clinical outcome related to restenosis that developed in the adjacent segments. This systematic change in vessel response after vascular radiation therapy prompted us to adopt new quantitative angiographic approaches aimed at optimal interpretation of the results of brachytherapy trials. The incidence of restenosis was determined in sequentially longer segments termed as injured segments, effectively irradiated segments, irradiated segments and total analysed vessel segments. The quantitative assessment of geographical miss became also possible (chapter 3). This type of analysis became the gold standard for all the new therapeutic modalities that followed brachytherapy including drug eluting stents.

The Beta Radiation In Europe (BRIE) registry introduced beta radiation therapy in Europe in a multicenter fashion for the treatment of de-novo lesions using the non-centred 90Sr/90Y source. Despite the fact that it was a safety and feasibility study with a limited number of patients significant observations were made. First the problem of edge restenosis became obvious by the significant increment in binary restenosis observed between the target segment and the total analysed vessel segment. The second significant observation was the high incidence of late vessel, silent or thrombotic, occlusion. It was the first study to prove that prolonged use of antiplatelet medication can eliminate this problem at least in the short term. Finally the incompatibility of brachytherapy with the use of stents was also documented as expressed by the increased late loss observed in patients in whom stents were implanted compared to those that were treated with balloon angioplasty and brachytherapy (chapter 4).

By careful and detailed retrospective angiographic analysis in the same cohort of patients we proved that edge restenosis was related to geographical miss. This was a term invented in radio-oncology to define a cause of treatment failure due to low-dose, and translated in interventional cardiology to define those coronary segments which were injured but received low-dose radiation. It was the first study indicating that the elimination of geographical miss can improve the results of beta radiation therapy for de-novo lesions (chapter 7). Interestingly the randomised trial (Beta-Cath trial), conducted in USA, was launched prematurely without awaiting the results of our registry. The lessons learned were not awaited and taken into account and the trial had a negative outcome, mainly because the same mistakes in the
application of beta-radiation were repeated. This had a drastic negative impact in the use of beta radiation for primary prevention of restenosis globally.

This initial experience was followed by the implementation of brachytherapy in routine use as part of the multicenter surveillance RENO registry. Although the application of brachytherapy is more complex compared to standard angioplasty procedures a high success rate was achieved proving that its application is feasible in routine practice. However the mid term outcome was hampered by the delayed occurrence of major adverse cardiac events between 6 and 12 months after the index procedure (chapter 6).

The Dose Finding study was a European multicenter dose finding study with the use of the centered 90Yttrium source for de-novo lesions, published in the New England Journal of Medicine. Using the same angiographic analysis performed in the BRIE trial, no association between geographical miss and edge restenosis was documented in this study (chapter 8). The differences in the sources, the delivery devices (centering vs non-centering), and in the design of the studies, in addition to the small number of patients enrolled were possible causes for this differential outcome. For this reason the two studies were analysed together aiming to increase the statistical power. From this analysis it became obvious that geographical miss is strongly related to the development of edge restenosis particularly at the proximal edge and when caused by stent injury. For the first time a correlation of geographical miss with restenosis in the total vessel segment was documented (chapter 9).

Hypoechoic tissue, dubbed the ‘black hole’ was first described at 6-month follow-up after radioactive stenting and catheter based brachytherapy. Such tissue was difficult to diagnose initially due to its echolucency. Atherectomy specimens demonstrated that the echolucent tissue was predominantly proteoglycan with a paucity of collagenous tissue. Concern was raised that such a tissue may be the precursor of atherogenic tissue, explaining the late lumen loss (> 6 months) in patients that have undergone radioactive stenting (chapter 10).

In the long-term follow-up of our patients following catheter based intracoronary beta radiation an incremental adverse cardiac event rate was documented beyond the first 6 months and up to 4 years. A low dose (<18 Gy) was the most significant predictor of target lesion revascularisation in the long term indicating that higher doses are required. We concluded that brachytherapy delays rather than abolishes cardiac events in the long-term and that patients treated with this therapeutic modality require longer follow-up evaluation than those treated with standard techniques (chapter 11). Further to that, high incidence (12.3%) of late vessel silent and thrombotic occlusions was observed, mainly in patients treated for de-novo lesions with new stent implantation and more importantly, after the cessation of double antiplatelet medication. This was another indication of the incompatibility of intracoronary radiotherapy with stents for the treatment of de-novo lesions and indicative that life long treatment with aspirin and clopidogrel may be required in these patients to avoid this complication (chapter 13).

The treatment of brachytherapy failures with conventional percutaneous techniques is safe and feasible, with a reasonable outcome, up to three years follow up, but a residual risk of development of late vessel occlusion (chapter 14). The sirolimus eluting stents were proven
less effective in treating brachytherapy failures compared to other clinical situations (chapter 15).

**Radioactive stents**

Conventional radioactive stents are limited by a high incidence of edge restenosis at 6 months follow up. The implementation of cold-end radioactive stents did not prevent the edge-effect. Instead of restenosis occurring outside the stent, it appeared in-stent, always at the edges of radiation (chapter 16).

Further to that although inhibition of neointimal hyperplasia was successful within the body of the radioactive stent at six months at the activity levels 6-12 \( \mu \text{Ci} \) this was not the case at 1 year. Here there was evidence of late restenosis, which was unprecedented after conventional stenting. Consequently there was an excessive amount of patients who underwent late revascularisation. (chapter 17). These observations led to the early abandonment of this therapeutic modality.

Longer term follow-up, up to 4 years, after radioactive stent implantation revealed that beyond the first year where high incidence of MACE and re-intervention was observed, the long term clinical outcome of these patients is stable, indicating that there are no irreversible late adverse cardiac effects related to low dose-rate intracoronary radiation therapy (chapter 18).

**CONCLUSIONS**

1. Intracoronary radiation therapy is safe and feasible in de-novo lesions, but not effective for the primary prevention of restenosis especially when combined with the use of stents.
2. Edge restenosis is a major limitation of intracoronary beta radiation therapy. Geographical miss, defined as low dose irradiation administered in treated segments, accounts for this phenomenon.
3. Intracoronary beta radiation therapy is limited by the development of delayed restenosis which results in an unfavourable long term clinical outcome of patients treated with this therapeutic modality both for the treatment of de-novo as well as restenotic lesions.
4. Repeat percutaneous intervention is a reasonable therapeutic option for patients after failed intracoronary beta radiation therapy.
5. Late vessel occlusion (silent or symptomatic) is a major limitation of intracoronary beta radiation therapy. Increasing the duration of double antiplatelet medication simply delays its appearance but it cannot prevent it. Presently there is no solution to this limitation.
6. Radioactive stents are limited by the development of edge restenosis in the short term and delayed restenosis in the mid term follow up. The long term clinical outcome after radioactive stent implantation is not associated with further irreversible clinical sequelae.
Samenvatting en Conclusies
**SAMENVATTING**

Ballonangioplastiek was de eerste niet-chirurgische behandeling van kransslagaderziekte. Het werd echter beperkt door het hoge percentage complicaties en hervernaaiingen (restenose). Door de introductie van stents verdwenen de acute complicaties, echter een nieuw hardnekkig probleem was het optreden van hervernaaiingen in de stent. Na een decade van mislukte pogingen om dit probleem op te lossen met mechanische middelen of medicijnen, werd de intracoronaire bestralingstherapie (brachytherapie) geïntroduceerd. Dit is mogelijk door middel van het inbrengen van catheterbronnen of door middel van radioactieve stents.

**Bestralingstherapie met catheterbronnen**

Nieuwe observaties zoals positieve remodelering, het zich verplaatsen van de kleinste vaatdiameter, hervernaaiing aan de rand van het behandelde gebied (edge restenose) en geografisch incorrecte positionering (geographical miss) zijn in verband gebracht met intracoronaire bestralingstherapie. Zij hebben gezorgd voor verwarring in de interpretatie van de resultaten van de eerste brachytherapie trials met een discrepantie tussen de goede angiografische resultaten in de bestraalde coronairsegmenten en de slechte klinische uitkomsten door het ontstaan van restenose in de aangrenzende segmenten. Deze systematische veranderingen in vaatreactie na bestralingstherapie, hebben ons gedwongen om nieuwe kwalitatieve angiografische benaderingen te kiezen om de resultaten van brachytherapie trials goed te kunnen interpreteren. De incidentie van restenose werd bepaald in steeds langere segmenten, n.l. de beschadigde segmenten, de effectief bestraalde segmenten, de bestraalde segmenten en de totale geanalyseerde segmenten. Hierdoor was het mogelijk een kwalitatieve analyse te verrichten van de geographical miss (hoofdstuk 3). Dit type analyse is de gouden standaard geworden voor alle nieuwe behandelmogelijkheden die geïntroduceerd werden na de brachytherapie, inclusief de met medicijnen bedekte stents (drug-eluting stents).

De Beta Radiation In Europe (BRIE) studie was een multi-center registry die de beta-bestralingstherapie in Europa introduceerde voor de behandeling van de-novo vernauwingen. Er werd gebruik gemaakt van een niet-gecentreerde 90Sr/90Y bron. Ondanks het feit dat het een veiligheids- en haalbaarheids-studie was met slechts een beperkt aantal patienten, werden toch belangrijke observaties gedaan. Door het grote verschil in restenosepercentage van het behandelde segment en het totaal geanalyseerde vaatsegment werd het probleem van de edge stenose (aan de randen van het behandelde gebied) duidelijk. Daarnaast was het hoge percentage late vaatocclusie (trombotisch of asymptomatisch) opvallend. Het was de eerste studie die aantoonde dat langdurig gebruik van plaatjesaggregatieremmers dit probleem tenminste op de korte termijn kon voorkomen.

Tot slot bleek dat de combinatie van stenting met het gebruik van brachytherapie resulteerde in meer “late loss” (afname van vaatlumen diameter) dan ballonangioplastiek en brachytherapie (hoofdstuk 4).

Door middel van gedetailleerde retrospectieve angiografische analyse in hetzelfde cohort patiënten hebben we aangetoond dat “edge restenosis” gerelateerd was aan “geographical miss”. Deze term werd voor het eerst gebruikt in de radio-oncologie om het falen van therapie door te lage dosering te beschrijven. In de interventiecardiologie werd deze term geïntroduceerd om die coronaire segmenten te beschrijven, die beschadigd werden door de ballon maar slechts een lage doses bestraling ontvingen. Het was de eerste studie die aanwijzingen opleverde dat eliminatie van “geographical miss” de resultaten van beta-
radiatie therapie kan verbeteren voor de-novo stenosen (hoofdstuk 7). Het is opvallend dat de gerandomiseerde trial (Beta-Cath trial), uitgevoerd in de USA, gestart werd voordat de resultaten van onze registry bekend waren. De geleerde lessen werden niet afgewacht en geïmplementeerd met als gevolg een negatieve uitkomst van de trial. Dit had een dramatisch negatief effect op het gebruik van beta-straling voor primaire preventie van restenose wereldwijd.

Deze eerste ervaring werd gevolgd door het routinegebruik van brachytherapie in het kader van de multicenter observationele RENO registry. Hoewel het gebruik van brachytherapie ingewikkelder is dan standaard behandelingen werd een hoog succespercentage gehaald, hiermee bewijzend dat gebruik van brachytherapie in de praktijk haalbaar is. Helaas bleken de middellange termijnresultaten minder gunstig door het verlate optreden van “major adverse cardiac events (MACE)” tussen 6 en 12 maanden na de interventie (hoofdstuk 6).

De Dose Finding studie was een Europees multicenter studie waarin gebruik gemaakt werd van een gecentreerde 90 Yttrium bron voor de-novo lesies, gepubliceerd in de NEJM. Gebruik makend van dezelfde angiografische analyse als in de BRIE trial, werd geen verband gevonden tussen “geographical miss” en “edge restenosis” in deze studie (hoofdstuk 8). De verschillen in de bronnen, de transportcatheters (gecentreerd vs. niet-gecentreerd), het studiedesign tezamen met het geringe aantal geïncludeerde patienten waren de mogelijke oorzaken voor deze andere uitkomst. Wegens deze discrepantie werd een analyse uitgevoerd van de twee studies samen om de statistieke power te vergroten. In deze analyse bleek een sterke correlatie tussen “geographical miss” en “edge restenosis”, met name ter hoogte van de proximale edge en wanneer gerelateerd aan beschadiging door een stent. Voor het eerst werd een correlatie gedocumenteerd tussen “geographical miss” en restenose in het totale vaatsegment (hoofdstuk 9).

Echolucent weefsel, waaraan de naam “black hole” gegeven werd, werd voor het eerst beschreven tijdens analyse van de 6 maanden follow-up intravasculaire echo van patienten die behandeld waren met radioactieve stents of brachytherapie met catheterbronnen. Wegens de echolucentie was dit weefsel in het begin moeilijk te karakteriseren. Uit onderzoek van weefsel verkregen met atherectomie bleek dat dit weefsel vooral bestond uit proteoglycanen met een geringe hoeveelheid collageen weefsel. Er ontstond de vrees dat dergelijk weefsel de voorloper zou kunnen zijn van atherogeen weefsel. Dit zou een verklaring kunnen zijn voor het onstaan van de late hervernauwing (late lumen loss) meer dan 6 maanden na radioactieve stenting (hoofdstuk 10).

De lange-termijn follow-up van onze patienten na behandeling met intracoronair beta-stralingsbronnen liet een toename zien van de MACE tussen de eerste 6 maanden en 4 jaar follow-up. Lage stralingsdosis (< 18 Gy) was de belangrijkste voorspeller voor target lesie revascularisatie op lange termijn, implicerend dat hogere doses noodzakelijk zijn. We concludeerden dat brachytherapie “cardiac events” niet voorkomt echter slechts uitstelt. Dit impliceert dat deze patienten langer vervolgd dienen te worden dan patienten die met standaardtechnieken behandeld worden (hoofdstuk 11). Bovendien werd een hoog percentage (12,3%) late stille en trombotische occlusies gezien, m.n. in patienten die behandeld werden wegens de-novo lesies met een stent en vooral na het stoppen van dubbele plateletaggregatieremende medicatie. Dit was weer een aanwijzing dat de combinatie van brachytherapie met implantatie van stents niet verstandig is voor de behandeling van de-novo lesies en mogelijk zouden deze patienten levenslang behandeld dienen te worden met aspirine en clopidogrel om deze complicatie te voorkomen (hoofdstuk 13).
De behandeling van gefaalde brachytherapie met conventionele interventietechnieken is veilig en mogelijk, met een redelijke uitkomst tot 3 jaar follow-up, echter met een persisterend risico op een late vaatafsluiting (hoofdstuk 14). De sirolimus-eluting stents (SES) bleken minder effectief bij deze patienten met gefaalde brachytherapie dan in andere patientengroepen om restenose te voorkomen (hoofdstuk 15).

**Radioactieve stents**

Gebruik van conventionele radioactieve stents resulteerde in een hoog percentage edge restenose na 6 maanden follow-up. Het gebruik van "cold-end"radioactieve stents voorkwam dit edge-effect niet. In plaats van net buiten de stent ontstond de restenose nu in de stent, altijd op de rand van het bestraalde gebied.(hoofdstuk 16).

Hoewel er in stents met een stralingsactiviteit van 6-12 mcCi een reductie van neointima hyperplasie aanwezig was na 6 maanden, bleek dit effect niet meer aanwezig na 1 jaar. Deze late restenose werd nooit gezien na implantatie van conventionele niet-radioactieve stents. Het gevolg hiervan was dat een groot aantal patienten een late revascularisatie onderging. (hoofdstuk 17). Dit leidde al vroeg tot het stoppen van het gebruik van deze stents.

Langere follow-up tot 4 jaar liet zien dat na het eerste jaar met een hoge incidentie van MACE en reinterventie, de klinische uitkomst stabiel is. Hieruit kan geconcludeerd worden dat er geen irreversibele late negatieve effecten zijn, gerelateerd aan lage doses intracoronaire bestralingstherapie (hoofdstuk 18).

**CONCLUSIES**

1. Intracoronaire bestralingstherapie is veilig en mogelijk voor de-novo lesies, maar niet effectief in de primaire preventie van restenose, met name wanneer gecombineerd met stents.
2. Edge restenose is de meest belangrijke beperking van intracoronaire beta-bestralingstherapie. Geographical miss, gedefinieerd als lage dosis straling op behandeld segmenten, is verantwoordelijk voor dit fenomeen.
3. Het gebruik van intracoronaire beta-bestralingstherapie wordt beperkt door het optreden van late restenose. Dit resulteert in een ongunstige lange-termijn uitkomst zowel voor de-novo als voor restenose lesies.
4. Herhaalde percutane interventie is een redelijke therapeutische optie voor patienten met gefaalde bestralingstherapie.
5. Late vaatocclusie (stil of symptomatisch) is de belangrijkste beperking van intracoronaire beta bestralingstherapie. De lange termijn toediening van dubbele plaatsesaggregatieremmende medicatie vertraagt, maar kan deze occlusie niet voorkomen. Op dit moment is er geen oplossing voor dit probleem.
6. Het gebruik van radioactieve stents wordt beperkt door edge restenose op korte termijn en verlate restenose op de middellange termijn. De lange termijn klinische uitkomst wordt niet verder negatief beïnvloed door irreversibele klinische events.
Name: Georgios Sianos

Date of birth: 18 February 1967

Nationality: Greek

Marital status: married to Eleni Vourvouri

Education and Professional Experience

April 02-today: Senior Interventional Cardiologist, Department of Interventional Cardiology, Thoraxcenter, Erasmus MC, Erasmus University Rotterdam, The Netherlands.

March 2002: KNMG Cardiologist recognition diploma, Utrecht, the Netherlands.

Sept 01-Feb 02: Training in Transradial Coronary Angioplasty in Onze Lieve Vrouwe Gasthuis (OLVG) Hospital, Amsterdam, The Netherlands (director Dr G.J. Laarman).

Aug 00-March 02: Interventional Cardiologist, at the Department of Interventional Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (director Prof. J.J. Piek).

Aug 99-Aug 2000: Clinical and research fellow, at the Department of Interventional Cardiology, Thoraxcenter, Dijkzigt Hospital, Erasmus University Rotterdam, The Netherlands (director Prof. P.W. Serruys).

Sept 98-Aug 99: Locum Specialist Registrar at the Department of Cardiology, University Hospital of Wales, Cardiff, UK.

October 1998: Diploma in Cardiology, Department of Cardiology, AHEPA University Hospital, Aristotle University, Thessaloniki, Greece.

Mar 98-Sept 98: Research Fellow of the European Society of Cardiology and Honorary Clinical Registrar at the Department of Cardiology, University Hospital of Wales, Cardiff, UK (supervisor Dr A.G. Fraser).

Sept 95-Mar 98: Resident Trainee in Cardiology, Department of Cardiology, AHEPA University Hospital, Thessaloniki, Greece (director Prof. G. Louridas).

Nov 93-Mar 95: Military Doctor at the Special Forces Training Center, Redina, Greece, appointed by the Ministry of Defense (national military service).

Nov 92-Nov 93: Resident Trainee in General Medicine at the Department of Medicine, Agios Dimitrios General Hospital, Thessaloniki, Greece.

Sept 91-Nov 92: General Practitioner appointment for the Ministry of Health and Welfare at the Hatzicosta General Hospital, Ioannina, Greece.

1985-1991: MD diploma (Psychico Iatrikis), Faculty of Medicine, Aristotle University of Thessaloniki, Greece with magna cum laude.

1984: High School Diploma from the second Lyceum Harilau Thessaloniki, Greece with distinction.
AWARDS AND DISTINCTIONS

1998 Research Fellow of the European Society of Cardiology.

2001 European Cardiologist, granted by the European Board for the Specialty in Cardiology.

2003 Fellow of the European Society of Cardiology (FESC).

MEMBERSHIP

European Society of Cardiology (FESC)

Hellenic Cardiological Society.

North Hellenic Cardiological Society.

Medical Association of Thessaloniki.

General Medical Council, full registration

Big Register full registration
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Manuscripts


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11. EC Vourvouri, D Poldermans, JJ Bax, G Sianos, FB Sozzi, AF Schinkel, J de Sutter, GP Parcharidis, R Valkema, JRTC Roelandt. Evaluation of left ventricular function and volumes in patients with ischaemic cardiomyopathy: gated single-photon emission


40. F Saia, PA Lemos, A Hoye, **G Sianos**, CA Arampatzis, P de Feyter, W J van der Giessen, PC Smits, RT van Domburg, PW Serruys. Similar clinical outcome with
sirolimus-eluting stent implantation and vascular brachytherapy for the treatment of in-stent restenosis. *Submitted for publication.*

**Book chapters and review articles**


**Abstracts**


27. **G Sianos**, PW Serruys, WJ van der Giessen, J Bonnier, P Urban, W Wijns, M Vandormael, R Door, C Disco, S Silber. Intracoronary β-radiation to reduce restenosis


ACKNOWLEDGEMENTS

Six years! It took me some time to realise. Trying to write something for this part of the thesis I had to look back and what a surprise! I counted again; six years since I left Greece, it is correct. It was supposed to be a six months trip just to take a look “what’s going on around”.

It was June of 1996 while in the first year of my residency in cardiology in Thessaloniki. After a busy overnight on call and few hours before my flight to Cardiff, visiting a friend, and for the first time abroad, I asked my colleague Dimitris Tsikaderis if he knew anybody there related to Cardiology. He had recently returned from UK having completed his training in Sheffield. “Alan Fraser is there” he told me.

Three days later I knocked the door of his secretary asking to see him. Of course I didn’t have an appointment. She stated that I was very lucky since he was going to be in the hospital next morning coming from a congress before his departure again and that she was going to arrange for a brief meeting for me. At that point I didn’t realise how lucky I was. Dear Alan, I will never forget the surprise in your eyes when I asked you, with my very poor English, what a CV is upon your request. This was the beginning of my international career. Two weeks later I returned to Greece with the address of the European Society of Cardiology written on a napkin of the hospital cantina from my dearest friend Dragos Vinereanu, already a Research Fellow of the ESC.

February 1998, I arrived in Cardiff as a Research Fellow of the ESC. This trip wouldn’t be possible without the support and the encouragement of Professor Louridas, the head of the Department of Cardiology in Thessaloniki. Dear Prof Louridas, in a period of shortage in trainees you didn’t only allow me to leave the department but in contrary you encouraged me to pursue a career abroad. During all this period you stayed close to me with your valuable advice and support. For all of these I am deeply indebted. Your participation in my committee is a very great honour.

Dear Alan, I was not a good researcher, always looking the door of the cath-lab. You never pressed me, you didn’t control my enthusiasm for the cath-lab. And when the fellowship period finished you arranged for me to work as a locum registrar to support myself. What an exciting period. But we did manage to organise and publish a nice study together. The echo was not meant to be my destiny and you saw it. And for one more time you were there for me, suggesting the best: “You will apply to Thoraxcenter and I will support you. I know Serruys and Roelandt from my time there”. Dear Alan I don’t know what about to thank you first for but words are not enough to express my gratitude. I will always recognise you as my mentor and treasure your friendship.

After the necessary paperwork and the traditional visit to Thoraxcenter to meet THE professor everything was arranged; I thought, until 15 days before my departure from Cardiff to Rotterdam I received a letter from Mrs Schoonmaker, the manager of Thoraxcenter explaining to me that due to overfilling with international fellows unfortunately there was no place for me. With the suitcases packed and after a couple of meaningless phone contacts with her, complete desperation. A few days later, Saturday evening, I decided to call Stephane Carlier, a good friend and my guide to the fame of the 23rd floor during my first visit to Thoraxcenter, to ask for help. “I am sitting close to him working on a manuscript” he explained after my introduction. Saturday evening I thought! This was the first feeling that something was not “the same” there. At that point I could not imagine how many Saturday evenings I was
going to spend at Serruys’s “place”. After a short conversation the “misunderstanding” was solved and the trip to the dream took place and I crossed the channel again.

“Whether the seashore is crooked or we are sailing in the wrong direction”. This was the first feeling when I arrived in Thoraxcenter. People from all around the world talking with passion about strange things “stent malapposition”, “relocation of the MLD”, “geographical miss” and working overnight to submit a manuscript before the “others” across the Atlantic. Manel Sabate, Partrick Kay, Marco Costa, Ken Kozuma, Mariano Albertal, Alex Wardeh, Glenn van Langenhove all good friends that came, “finish the job” and went back home in prestigious positions. I arrived late to be part of the team but you all represented the best example of dedication and efficiency and thank you for that.

“Thoraxcenter is not the place just to learn how to push wires, everybody can place a stent in a coronary artery”, Patrick was explaining to me every time that with great disappointment I was looking at the white board without my name on it, and trying to persuade me for the value of scientific research. But the stubborn Greek didn’t want to hear. There was such a great will to learn the “job”. For me it was clear. I couldn’t be an expert on something that I have never practiced, on something that I never felt. No meaning on that.

And when the letter, from Professor Jan Piek from Amsterdam arrived, in July of 1999, asking for a “fellow met ervaring” I didn’t hesitate. Part time at the beginning, full time later I found the place to practice interventional cardiology in the Academic Medical Center. From five in the morning to ten at night including the life experience of travelling with the Dutch trains from Rotterdam to Amsterdam return every day. This was the place I was looking for.

Beste Jan, I am very proud to say that I became an interventional cardiologist under your direction. Thank you for unravelling to me to the secrets of the coronary circulation. The “Griek van Piek” will be always grateful to you.

Karel Koch, the 5F active support lover, the low dose heparin/early mobilisation pioneer, the “ultimate” interventionalist, my mentor in clinical Interventional Cardiology. Dear Karel your passion for practicing interventional cardiology will always be a guide for me. Thank you for encouraging me to go ahead by justifying all my complications as it was the most natural thing to happen. Thank you for these stimulating discussions regarding every detail of the guide wires and the behaviour of guiding catheters, for all the tips and tricks, for the challenging cases at the end of these long cath-lab days. Take care of the corners with the bike.

Robert de Winter, the master of balloon angioplasty, the voice of sense. Dear Rob thank you for teaching me the art of balloon angioplasty, thank you for keeping me always on the ground wisely advising not to stent the left mains in acute myocardial infarctions, (I still do, its impossible to go against your nature). There is no pleasure without discipline, there is no freedom without control. I greatly appreciated all your suggestions.

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In September of 2000 and while the “groin” experience already in an advanced stage, the Amsterdam adventure was enriched in OLVG hospital by mastering the radial approach in a center of excellence. Every Tuesday and Thursday for six months while continuing the other three days in AMC. Geritt Jan Laarman and Ferdinand Kiemenij, the pioneers in transradial approach. Dear Ferdinand, thank you for revealing to me the secrets for a successful radial artery puncture, (filling the database was the most challenging part of the procedures, apologies for messing up). Dear Gerrit Jan, a real gentleman, it was a great pleasure working with you. I have to assure you both that you created another supporter of the transradial approach.

At the time that I stopped dreaming every night the mistakes of the previous day and the cases of the next one I knew that I was there. After one and a half years and more than 1000 angioplasties in three different centers all around The Netherlands, the “restless wire” found its peace, the war was over. A Sunday evening in November 2001, after 12 primary angioplasties during the weekend, for the first time, I felt the need for a more intellectual approach in interventional cardiology. What a surprise you felt Eleni when I told you that same day “I want to become again a research fellow”, wasn’t it? And the question appeared again “and now what?” And one of these Saturday evenings working with Patrick in his house on a manuscript, with his classical diplomatic style of keeping a door open without promise, he said to me “we might need you back in Rotterdam”. It was the answer to the question.

Four months later, in April 2002, the departure of Jeroen Vos, Stefan Carlier and David Foley and the retirement of Marcel van den Brand brought me back to Rotterdam as a senior Interventional Cardiologist. This time I was mature, I was ready for the greatness of the place. As always, things had proceeded fast. Nothing was the same compared to one and a half years ago. My first day in the cath-lab coincided with the premiere of sirolimus eluting stents in routine use. In a place where there are no indications and limits for the interventions, I found the ground to extend my initial clinical experience to another level and be a senior not only in hands but also in mind.

Dear Patrick I read the acknowledgements of all the thesis of your numerous promoventi trying to avoid repeatability and find something novel to say but it was impossible. Then I looked myself over time and the answer was there. Inspiring someone, so deeply devoted to clinical practice, to appreciate the greatness of academic life that led to this thesis is indicative of your passion and your devotion to it. The repeatedly stated “without your encouragement this thesis would have never been accomplished” was never closer to its truth meaning. I don’t know who should be credited for creating this legendary center but I do know your tremendous efforts keeping it where it stands for that long. Definitely “your” Thoraxcenter “it’s not a place just to learn how to push wires” is something so much more, and you have all the credits for that. What a privilege to practice and live interventional cardiology in a place just like this. Under your guidance my staying in Thoraxcenter was not only a scientific and professional
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In Bd 408

Eugene Mc Fadden, the Irishman from France. This room didn’t miss an Irish for years; this was the main criterion for your selection; grapje. Mastering the Dutch language certainly caused you some throat discomfort. Let’s try again “de schhhhhhhhhhhhhooomhoeder”; water please. Don’t give up Eugene after a couple of years it is getting easier. The food, forget it, no hope.

Sjoerd Hofma, my second room mate and soon a senior. It took me some time to persuade you to stop reading manuals of interventional cardiology. I hope during the time we share the room you learned something from me: the notaris is simply a delay. The final result is known: you loose. Good luck and groetjes Sjoerd.

Edith de Getrouwe, our secretaresse, the fighter. Whatever we do she will always be the winner. Thank you for everything Edith and … eet smakelijk.

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