Medical Radiology

Radiation Oncology

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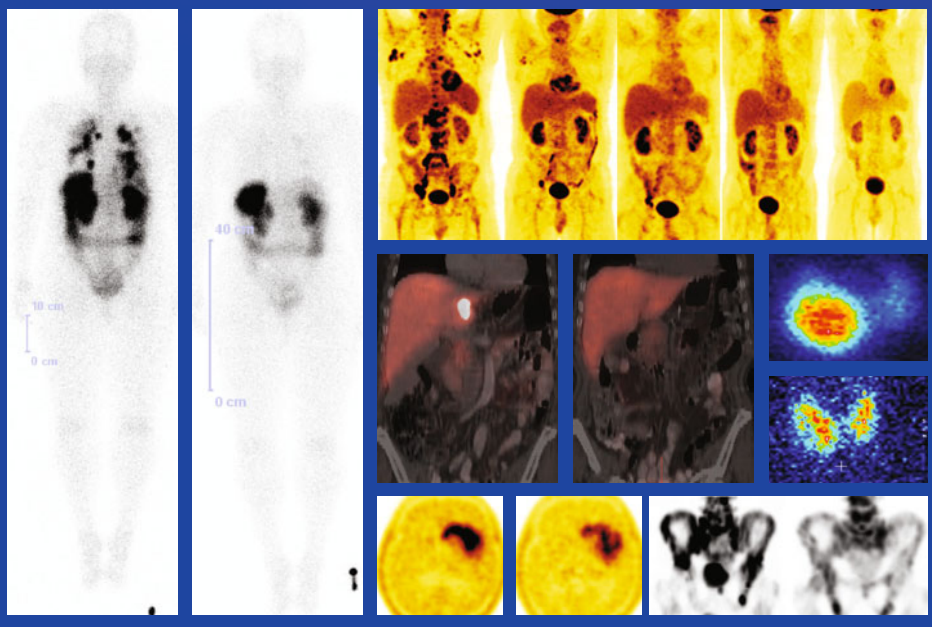

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Endovascular Brachytherapy to Prevent Restenosis After Percutaneous Coronary Intervention

Jörg Kotzerke and Sigmund Silber

Contents

Abstract

Radiation can prevent not only keloid scar formation at the skin but also an excess of intraluminal neointimal proliferation following injury of balloon angioplasty. This was demonstrated in animal models of restenosis and was validated in multiple clinical trials. Beta irradiation was as effective as gamma irradiation, however, low dose radioactive stents caused edge stenosis. Filling a balloon catheter with a radioactive solution (e.g. rhenium-188-perrhenate) restenosis could be prevented or at least delayed which was demonstrated in in-stent restenosis as well as in de novo stenosis. Late thrombosis of irradiated bare metal stents has been overcome by dual antiplatelet treatment for 12 months. Recommendations and standardizations for vascular brachytherapy were developed to secure this highly interdisciplinary approach. However, the interest in this technique vanished when drug-eluting stents were available which can be delivered by the interventionalist alone without the limitations and expenditure from application of irradiation. Nevertheless, intracoronary brachytherapy with isotope-filled balloons or beta radiation is still applied in some specialized centers.

1 Rationale and History of Intracoronary Brachytherapy

Intracoronary brachytherapy was developed and clinically applied to prevent restenosis after percutaneous coronary intervention since the early and mid-1990s (Sabate 2009). The rationale behind it was the fact that radiotherapy had proven to be effective in treating the exuberant fibroblastic activity of keloid scar formation and other non-malignant tumor-like process such as ocular pterygia. As in-stent restenosis (ISR) is mainly induced by an excess of neointimal proliferation, it was assumed that this therapy would also inhibit this proliferative process (Fig. 1). The first

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R. P. Baum (ed.), *Therapeutic Nuclear Medicine*, Medical Radiology. Radiation Oncology,
DOI: 10.1007/174_2012_682, © Springer-Verlag Berlin Heidelberg 2012
Published Online: 21 August 2012

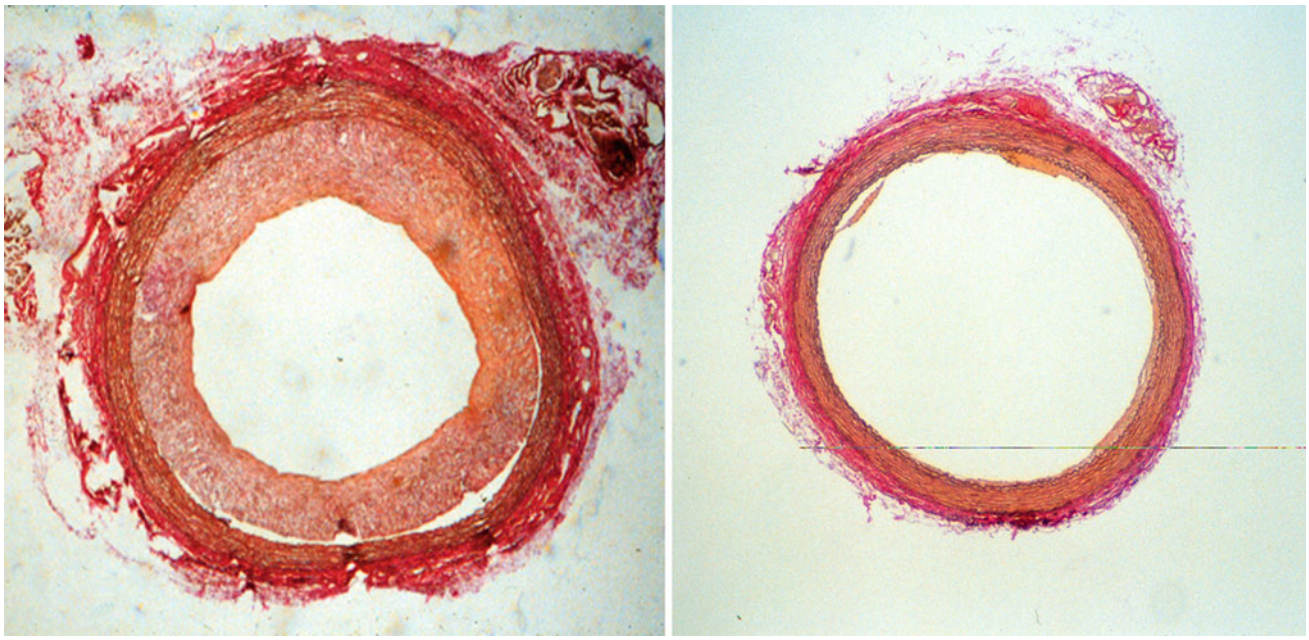

Fig. 1 Reduction of neointima formation due to irradiation: Cross-sections of rabbit carotid arteries at 4 weeks after denudation trauma (magnification × 10). Control artery (*left*) demonstrates intense neointimal proliferation. Following endovascular irradiation from a Re-188-filled balloon catheter (30 Gy at the balloon surface) the proliferation is almost completely inhibited (reprinted with permission from (Kotzerke et al. 2000)

experimental study in this field was carried out in 1964 by Friedman et al. through the use of iridium-192 in the cholesterol-fed rabbit (Friedman et al. 1964). In 1992, in Frankfurt/Main, Liermann et al. performed the first four cases of brachytherapy in patients who had undergone a femoral percutaneous angioplasty (Liermann et al. 1994). A second wave of experimental work was carried out in the United States by Wiedermann and Weinberger in New York (Wiedermann et al. 1995), Waksman and Crocker in Atlanta (Waksman et al. 1995), and Mazur and Raizner in Houston (Mazur et al. 1996). In parallel, Verin and Popowski in Geneva conducted experimental studies with the pure beta emitter yttrium-90 in carotid and iliac arteries of rabbits (Verin et al. 1995). The first clinical experience in coronary arteries in humans was performed by Condado et al. using a hand-delivered Ir-192 wire into a non-centred, closed-end lumen catheter (Condado et al. 1997) and by Verin et al. using a beta-source and a centred device (Verin et al. 1997). Both studies demonstrated that the delivery of radiation in the coronary artery is feasible and safe, although the restenosis rate remained relatively high (Sabate 2009).

Restenosis is the major drawback of percutaneous coronary intervention (PCI) and occurs even after stenting within 6 months in approximately 30 % of all cases (Califf et al. 1991). Various mechanisms for restenosis have been proposed: migration of myocytes from the media to the intima, forming the neointima (Austin et al. 1985); damage of the adventitia resulting in proliferation of adventitial fibroblasts and migration of these mesenchymal cells to the media and neointima (Wilcox et al. 1996); organization of mural thrombus, resulting in a local hypertrophic scar (Schwartz et al. 1992); and release of cytokines and growth factors, e.g., by monocytes/macrophages which mediate the cellular migration and proliferation (Libby et al. 1992; Rubin et al. 1998). Clinical research aimed at overcoming restenosis has included the administration of mechanical and pharmacological approaches such as atherectomy, rotablation, laser ablation, and drugs, including heparin and irradiation as well as drug-eluting stents.

Restenosis is an important economic issue and the potential cost benefit of restenosis reducing techniques can be estimated in a similar approach performed when comparing coronary stenting and balloon angioplasty as well as PCI and bypass surgery (Cohen et al. 1994; Fischman et al. 1994; Kupersmith et al. 1994, 1995; Reeder et al. 1984). Assuming the restenosis rates of 33 % followed by bypass surgery for the first, second, and third restenosis in 10, 50, and 100 %, respectively, repeated PCI procedure and bypass surgery would be necessary in 35.2 and 12.8 per 100 initial stenoses, respectively (Kotzerke et al. 2000). Assuming the costs of PCI and of bypass surgery to be 3.250€ and 16.000€, respectively, the current cost of treatment of restenosis is 3.200€ per initial stenosis (Kotzerke et al. 2000). The assumption that any approach can reduce restenosis rate by 50 %, repeated PCI procedures, and bypass surgery would be necessary only in 16.2 and 3.5 per 100 initial stenosis, respectively. This would reduce the cost of restenosis treatment from 3.200€ to 1.100€ per initial

Table 1 Radionuclides used for vascular brachytherapy

Isotope	Emission	Half-life	Energy maximum	Energy average	Activity required
–	–	–	[MeV]	[MeV]	[GBq]
–	–	–	–	–	–
Ir-192	Gamma	74 days	0.67	0.18	18.5
Sr/Y-90	Beta	29 years	2.28	0.93	3.7
Y-90	Beta	64 h	2.28	0.93	3.7
P-32	Beta	14 days	1.71	0.69	3.7
Re-186	Beta	90 h	1.08	0.38	11.1
Re-188	Beta	17 h	2.12	0.77	3.7
Xe-133	Beta	5.2 days	0.35	0.10	11.1
Sm-153	Beta	47 h	0.81	0.22	3.7
Ga-68	Beta+	68 min	1.89	0.83	3.7
Cu-62	Beta+	9.7 min	2.93	1.30	1.5
Ho-166	Beta	27 h	1.85	0.67	7.5

stenosis. The magnitude of this health problem becomes apparent when one recognizes that stents are reportedly used in as many as three-quarters of the approximately 1 million PCI procedures performed annually in the United States with increasing frequency (Sapirstein et al. 2001).

2 Radiation Sources

Gamma-emitters are characterized by deep tissue penetration and delivery of almost the same dose to all vessel layers. However, radiation protection of the personal and the environment needs considerable care. With the available γ-sources intracoronary dwelling times of approximately 30 min are required (Table 1). Beta-emitters are characterized by high energy delivery but a low tissue penetration which simplifies radiation protection but complicates to achieve a homogeneous dose distribution without centering of the irradiation source. A balloon catheter filled with liquid β-emitter has the advantage of homogeneous dose delivery due to the self-centering irradiation source; however, its application occludes temporarily the coronary blood flow (Table 1) (Amols et al. 1996a, b; Weinberger 1999).

2.1 Beta-Versus Gamma-Emitters

If radiation energy is delivered to a dividing cell, its effects are independent of the source used (Teirstein 1998). That is, cell division should be equally inhibited by gamma and beta

Table 2 Variation in radial radiation dose depending on balloon dimension, calculated using the point kernel function. Reference dimension is 3.0 × 20 mm (reprinted with permission from (Kotzerke et al. 2000)

Length [mm]	10	20	30	40	50
Diameter	–	–	–	–	–
2.0	0.67	0.67	0.67	0.67	0.67
2.5	0.84	0.85	0.85	0.85	0.85
3.0	0.99	1.00	1.00	1.00	1.00
3.5	1.12	1.12	1.13	1.12	1.12
4.0	1.22	1.23	1.23	1.23	1.23
5.0	1.37	1.39	1.39	1.39	1.39
6.0	1.48	1.49	1.49	1.49	1.49

Table 3 Dose gradients with beta (Y-90) versus gamma (Ir-192) sources delivering a dose of 8 Gy at 2 mm depth (adopted from (Waksman 1998))

–	Yttrium-90 [Gy]	Iridium-192 [Gy]
–	–	–
Dose at Lumen	53.0	23.0
Dose at 1 mm	16.0	12.0
Dose at 2 mm	8.0	8.0
Dose at 3 mm	2.7	6.3

energy as long as the energy is brought to the intended target. Gamma rays penetrate human tissues deeply and are not shielded by stents. This makes gamma energy ideal for treating large vessels by a line source and for the treatment of in-stent restenoses. However, there are disadvantages in terms of radiation protection of the patient and personal. A heavy lead shield several centimeters thick is required for effective attenuation of the photons. Furthermore, in the catheterization laboratory, all "non-essential" personal have to leave during the irradiation procedure. The use of lower activity circumvents some of these problems, but irradiation times then have to be extended to achieve prescribed doses. In contrast, beta sources emit electrons with low penetration and high local energy deposition which can easily be shielded even with plastic. Prescribed dose can be achieved within 5–8 min depending on specific volume (Table 2). Tissue penetration is restricted to a few millimeters and use of metallic stents or thick plaque material might restrict effective energy deposition (Amols et al. 1998). Delivery of beta energy using a line source will probably not provide adequate treatment of large-diameter vessels (>4 mm) and will require centring devices (Table 3). However, a meta-analysis of randomized controlled trials of intracoronary gamma- and beta-irradiation therapy for in-stent restenosis demonstrated effectiveness for both radiation sources (Uchida et al. 2006).

2.2 Balloon Versus Wire

A gamma source for endovascular irradiation will always be a line source because the deep penetration of the energy obviates the need for an exact geometry. However, when using beta sources the limited penetration makes careful centring essential for homogeneous dose delivery to the vessel wall. A number of systems have been devised to deliver intravascular brachytherapy from removable beta sources including yttrium-90 wire sources (Schneider, Bükach, Switzerland), encapsulated Sr-90/Y-90 seeds (Novoste, Norcross, Ga., USA), and phosphorus-32 seeds (Guidant, Santa Clara, Calif., USA). However, only some of these catheter-based systems had centering capabilities, such as segmented or helical balloons (Popowski et al. 1995). A comparison of a centred P-32 source wire system with a noncentered Sr-90/Y-90 brachytherapy system for intracoronary β-radiation following PCI of diffuse in-stent restenosis yielded a significant superiority of the centered source (Haase et al. 2005). In contrast to a radioactive wire, a beta-emitting radioisotope-filled balloon provides a radiation field that conforms to the vessel geometry in an optimal fashion regarding the vessel lumen (Amols et al. 1996a; Weinberger 1998). Centering of the radiation delivery balloon occurs during inflation even in vessels bend. The radiation dose to the vessel wall is uniform and can be prescribed easily based on the specific volume of the beta-emitter and the balloon's dimensions (Table 2). Larger vessels can be irradiated using a more voluminous balloon catheter, resulting in a shorter dwell time in comparison with radioactive beta emitting wires, which necessitate much longer irradiation times. A disadvantage of the balloon technique is the occlusion of the vessel, which will be tolerated only for a limited time in the case of the coronary arteries. However, the balloon can be easily deflated and irradiation can be fractionated according to the clinical symptoms (Hoher et al. 2000, 2003). After re-opening of an occluded vessel, the collateralization will prevent pain even during time-consuming irradiation procedures. The main disadvantage is the risk of balloon rupture or leakage with resultant patient contamination (Hausleiter et al. 2000). The prime potential candidates for the liquid-filled balloon are high-energy beta-emitters such as Y-90, P-32, Re-186, Re-188, Ga-68, Ho-166, or Sm-153. However, bone- and bone marrow-seeking isotopes such as Y-90 and P-32 cannot be used because of the high radiation absorbed dose that would occur in the event of balloon rupture. Compared with Re-186, Re-188 has the advantages of higher beta energy and availability from a generator and it is therefore the most promising candidate. The "hot balloon" filled with Xe-133 might be an alternative and carries only a low risk of incorporation in the event of balloon leakage because it would be exhaled. However, it is much more expensive than Re-188. Ga-68, a positron emitter, has also been proposed (Stoll et al. 2001). However, the advantage of the short half-life of 68 min in the unlikely event of leakage is an important disadvantage for routine use: generator cannot be eluted in advance but on demand to obtain the highest specific volume and the shortest irradiation time. Moreover, radiation protection of the stuff is much more difficult to realize because of the 511 keV gamma emission. In clinical routine, Re-188 was and is used most.

2.3 Radioactive Stents

Hehrlein et al. introduced activated Palmaz-Schatz stents which were placed in a cyclotron and bombarded with deuterons (Hehrlein et al. 1995). Later, proton bombardment was used to reduce the portion of high-energy gamma radiation emitted by the stents. A mixture of radioactive isotopes was created (e.g. cobalt-55, -56, and -57, nickel-57 and iron-57) with different energies and half-lives. This stent delivered most of the energy within 5 days and 15–20 % within 20 and 260 days.

Another method was based on the selective implantation of a single radioisotope into stents (Hehrlein et al. 1996). The activity of the emitting stents used in clinical trials ranged from 19 to 222 kBq. The dosimetry of a P-32 stent has been previously described in detail by Janicki et al. (Janicki et al. 1997): for a 37 kBq 15-mm-long P-32 stent at a distance of 0.1 mm dose values of 25 Gy are delivered at the strut wires (peaks) and 8 Gy between the wires (valleys) voer on half-life. The nonuniformity of dosing, which reflects the stent geometry, decreases at distances of 1–2 mm from the surface (Carter and Laird 1996). The actual dose distribution will also be affected by variations in atherosclerotic plaque morphology and the symmetry of stent expansion. Another development was the coating of a stent with Re-188 or Re-188 directly before implantation (Hafeli et al. 1998). This method allows any used stainless steel or tantalum stent to be coated with radioactive electroplating solutions, one of which contains radioactive rhenium. The overall processing time is only 15 min.

Unfortunately, initial clinical trials using the P-32 stent demonstrated restenosis rates of approximately 50 %, largely due to intimal proliferation at the stent edges, so-called "candy wrapper stenosis" (Albiero et al. 2000; Serruys and Kay 2000). These clinical failures have terminated further studies and closed the use of radioactive stents (Teirstein and Kuntz 2001).

3 Rhenium-188: Production, Properties, Dosimetry, and Safety

Carrier-free Re-188 can be obtained from the W-188/Re-188-generator by elution with saline (Knapp et al. 1997). Coupling the parent radioisotope to alumina, and loading on a column, allows production of a W-188/Re-188-generator (Callahan et al. 1989). The parent W-188 has a half-life of 69 days, while the daughter isotope Re-188 possesses a half-life of 17 h. Depending on starting activity, the generator system can be used for up to 6 months. The specific volume of the radiotracer can be increased by anion exchange columns to as high as 20 GBq/ml and a semi-automated system for elution and concentration has been developped (Oh et al. 2003; Wunderlich et al. 2008). Re-188 is an ideal candidate regarding the long half-life of 69 days of the parent W-188 and the properties of the daughter Re-188: short half-life of 17 h, high-energy beta particles ($E_{\beta max} = 2.12$ MeV, average energy 764 keV) for therapeutic use and gamma emission of 155 keV (15 % intensity) for imaging purposes. The latter one also permits simple contamination control of the patient and his surroundings.

Radiation absorbed dose from a balloon catheter has been measured by means of thermoluminescent dosimetry (TLD) and compared to calculations using point kernel function of Re-188 (Kotzerke et al. 1998b). A very good correlation between these methods was demonstrated for the absolute radiation absorbed dose which showed a rapid reduction of 50 % within 0.5 mm. Assuming a specific volume of 3.7 GBq/ml at the surface of a typical balloon catheter (3.0 x 20 mm, 135 µl volume) and at 0.5 mm distance (i.e., 2 mm distance from the centre of the balloon), doses of 7.8 and 3.9 Gy/min could be achieved, respectively (Fig. 2) (Kotzerke et al. 1998b). It was calculated that the filling pressure of the balloon catheter is not critical for variation of the balloon volume and varies by only 1 % per atmosphere filling pressure (Kotzerke et al. 1998b). Using the point kernel function, the radial radiation dose of other balloon dimensions was calculated (Table 2). Similar Tables were calculated for various radionuclides including P-32, Y-90, and Re-188 (Fox 1997; Fox and Henson 1999; Fox et al. 1999).

The radiation exposure due to intravascular application of a radionuclide depends on physical properties and its biological pharmacokinetics. Perrhenate will behave in the human body like pertechnetate with accumulation in the thyroid and the gastric mucosa as well as urinary excretion. To minimize the radiation exposure in the hazardous event of balloon rupture, chelation of Re-188 for increased renal elimination was proposed (Cho et al. 2004; Lee et al. 2000; Lin et al. 2000). The total body absorbed dose would be reduced to 10 % by the chelation. Another proposal has been the use of perchlorate following an unexpected release of Re-188 into the blood. Kotzerke et al. demonstrated that perchlorate will discharge perrhenate from the thyroid and stomach and will reduce the effective dose to 0.16 mSv/MBq (i.e., 38 % compared to the unblocked state) (Kotzerke et al. 1998a). Assuming a balloon catheter of 3.0 x 20 mm filled with 135 µl Re-188 in a specific volume of 1.85 GBq/ml, 259 MBq Re-188 would be released in the event of rupture. This acitivity would result in an effective dose equivalent of 109 mSv, which could be reduced to 41 mSv by oral administration of perchlorate. Forced diuresis might decrease the radiation absorbed dose even further.

A single balloon rupture has been reported ever (Hausleiter et al. 2000). In the largest trial of intracoronary irradiation using Re-188 filled balloon catheter no patient contamination has been observed nor acute or chronic injuries of the hands of the applicating physicians (Hoher et al. 2003). The very low probability of balloon rupture combined with the acceptable radiation absorbed dose from Re-188 and the effective discharge from the critical organs achieved by subsequent administration of perchlorate should render the chelating procedure unnecessary. This would save time, money, reduce radiation exposure to the technician and guarantee a maximum specific volume of perrhenate, thereby minimizing the irradiation time.

4 Recommendations and Standardization for Vascular Brachytherapy

Neither the exact absolute dose needed for successful vascular radiotherapy nor the optimal spatial and temporal distribution of dose inside the vessel lumen or wall is known (Quast et al. 2002). Many different irradiation techniques have been employed in experimental and clinical studies with good success. However, in most studies the doses delivered were prescribed, described, and reported poorly or inconsistently (Quast et al. 2002), complicating a meta-analysis. The American Association of Medical Physicist (AAMP) has provided a set of recommendations in their report on intravascular brachytherapy physics, but these recommendations are applicable only for radioactive wires and cannot completely transferred to liquid-filled balloon catheters (Nath et al. 1999). For example, one of the recommendations was specification of dose to a reference point 2 mm distant from the axis and the centre of a catheter-based system. However, in the case of a radioisotope-filled balloon the vessel surface, which is independent of the vessel diameter, represents a better reference point. Another important paper has dealt with the measurement of the beta energy. The National Institute of Standards and Technology

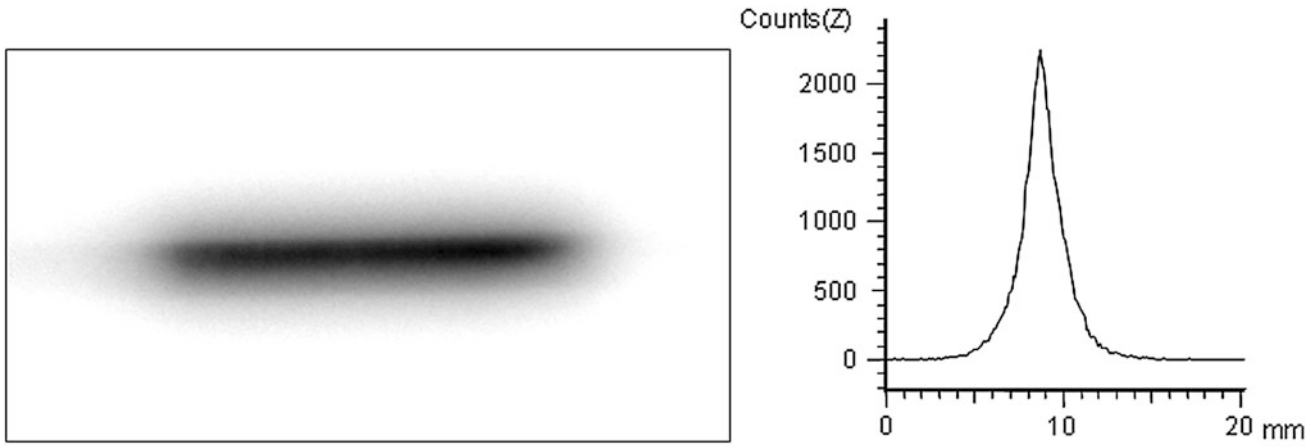

Fig. 2 Re-188 filled balloon catheter: Energy distribution from a Re-188-filled balloon catheter as visualized by a Phosphor imager (PosphorImager SI, Molecular Dynamics GmbH, Krefeld, Germany). The transaxial activity histogram demonstrates the low penetration of the beta particles and the steep dose drop off (reprinted with permission from (Kotzerke et al. 2000))

(NIST) published radioactivity standards for beta-emitting radionuclides used in intravascular brachytherapy concerning standard reference material, calibration for source manufactures and calibration factors for commercial instruments (Coursey et al. 1998). Uncertainties in the activity calibration for P-32, Sr–90/Y–90, and Re-188 are in the order ±0.5 %.

However, taken into consideration the real conditions of the irradiation procedure these recommendations seem too rigide. Irradiation is performed during heart beating which might cause also a movement of the irradiation source. Coronary vessels have curvatures which may cause huge differences in regional absorbed irradiation dose (Yue et al. 2004). The metal of the stents may attenuate the absorbed irradiation dose (about 10 %)—should we adjust for that or not? What about overlap in long irradiation fields and re-irradiation? Even in the application of a liquid radioisotope filled balloon catheter which blocks the vessel and provides optimal contact of the irradiation source with the target arterial segment—the vessel tapers off which may cause an inhomogeneous irradiation absorbed dose along the balloon.

5 Regulations

Besides the recommendations of the AAMP (Nath et al. 1999) several national and international (european) recommendations have been launched. The German Society of Cardiology published a position paper on intracoronary brachytherapy (Dietz et al. 2001). The Endovascular Groupe Européen de Curiethérapie/European Society for Therapeutic Radiology and Oncology Working Group published recommendations on prescribing, recording in endovascular brachytherapy including quality assurance, equipment, personnel, and education (Potter et al. 2001). The recommendations of the AAMP were adopted in national legal force (Quast et al. 2002). The German Radiation Protection Commission developed recommendations to perform intracoronary irradiation for implementation in the german "Richtlinie Strahlenschutz in der Medizin" (Herrmann 2001). A further recommendation from the Vienna group adressed the determination of planning target length to avoid geographic miss (Schmid et al. 2004). The task force for percutaneous coronary interventions of the European Society of Cardiology recommended brachytherapy to treat in-stent restenosis in native coronary arteries: IA; for brachytherapy to treat in-stent restenosis in saphenous venous bypass grafts: IB. The Food and Drug Administration (FDA) approved two devices for coronary artery brachytherapy because local intracoronary irradiation showed evidence to be an effective intervention for reducing the recurrence of obstruction after successful treatment of in-stent restenosis (Sapirstein et al. 2001). However, meanwhile both devices were withdrawn from the market.

6 Initial Experience of Radiotherapy in Animal Models of Restenosis

Wiedermann et al. and Waksman et al. were the first to demonstrate significant reduction in intimal proliferation using radiotherapy in the swine model of restenosis (Waksman et al. 1995; Wiedermann et al. 1994). Wiedermann et al. used a swine balloon overstrech injury model of coronary injury to test iridium-192 (Ir-192, a gamma-emitter), delivered 20 Gy over a 30–45 min dwell time. Morphometric analysis at 30 days demonstrated a maximal

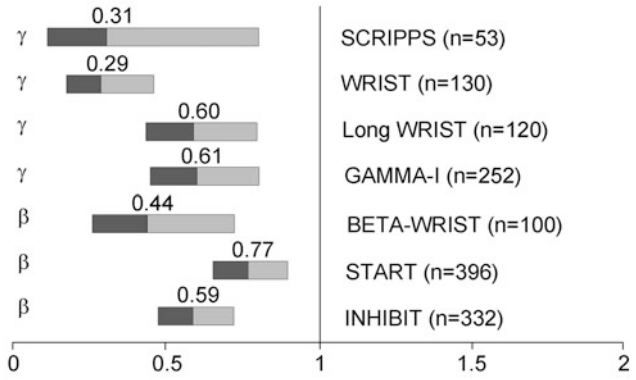

Fig. 3 Summary of benfit of intracoronary brachytherapy versus conventional treatment for restenosis prevention in main randomized controlled trials (adopted from (Sabate 2009))

neointimal area of 0.84 ± 0.60 mm^2 in control animals compared with only 0.24 ± 0.13 mm^2 in treated animal ($P = 0.001$). At 6 months follow-up, these differences were 1.59 ± 0.78 versus 0.46 ± 0.35 mm^2 ($P \leq 0.001$) (Wiedermann et al. 1995). Later, Waksman et al. provided insight into the target of vascular radiotherapy and its mechanism of action (Waksman et al. 1997). Balloon injury was performed on swine coronary arteries, followed immediately by either Sr-90/Y-90 or Ir-192 sources designed to deliver 14 or 28 Gy at a depth of 2 mm from the source. Animals were sacrificed at 3, 7, or 14 days. Bromodeoxyurdine was administered 24 h before scarifying to label proliferating cells. On day 3, cellular proliferation was significantly reduced in both the adventitia and the media of treated vessels compared with controls. At 2 weeks postinjury, there were fewer α-actin-positive myofibroblasts in the adventitia of treated compared with control animals, and morphometric analysis indicated the vessel perimeter of treated vessels was significantly larger than controls. Apoptosis was estimated by terminal transferase dUTP-biotin nick-end labeling (TUNEL) at 3 and 7 days after injury. No differences in TUNEL-labeled cells were found between treated and control vessels. These studies suggest that intracoronary radiation primarily inhibits cellular proliferation in both the media and adventitia and suggests a mechanism other than apoptosis. They also suggest a favorable effect on late remodeling probably by preventing adventitial fibrosis at the injury site. Numerous other investigators have demonstrated the efficacy of both, gamma- and beta-radiation in various animal models of restenosis including Re-188 filled balloon (Wohlfrom et al. 2001). All studies were performed as balloon injury which is a model of de novo stenosis. In-stent restenosis were not addressed in animal studies (Teirstein and Kuntz 2001).

7 Clinical Trials

7.1 In-Stent Restenosis

Seven double-blind, randomized clinical trials have investigated the efficacy of intracoronary brachytherapy in patients with in-stent restenosis (Fig. 3) (Grise et al. 2002; Leon et al. 2001; Popma et al. 2002; Raizner et al. 2000; Teirstein et al. 1997, 2000; Waksman et al. 2000, 2002b, 2002a). The Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS) study was the first double-blind, randomized study that investigated the effect of intracoronary brachytherapy on in-stent restenosis (Teirstein et al. 1997). 55 patients were randomized to intracoronary brachytherapy with iridium-192 or placebo. At 3 year follow up, the incidence of death, myocardial infarction, and target vessel revascularization was 23 % in the brachytherapy group versus 58 % in the placebo group ($P = 0.01$) (Teirstein et al. 2000). At 5-year follow-up, the incidence of death, myocardial infarction, and target vessel revascularization was 38 % in the brachytherapy group versus 65 % in the placebo group ($P = 0.02$) (Grise et al. 2002).

The Washington Radiation for In-Stent Restenosis Trial (WRIST) was a double-blind, randomized study that investigated the use of catheter-based low-dose gamma radiation (iridium-192) in 130 patients with in-stent restenosis (Waksman et al. 2000). At 6-month follow-up, the incidence of angiographic restenosis was 19 % in the brachytherapy group versus 58 % in the placebo group ($P = 0.001$). At 6-month follow-up, the incidence of death, myocardial infarction, and target vessel revascularization was 29 % in the brachytherapy group and 68 % in the placebo group ($P = 0.001$).

The Proliferation Reduction with Vascular Energy Trial (PREVENT) was a double-blind, randomized, sham-controlled study of intracoronary brachytherapy using a beta source of brachytherapy (phosphorus-32) in 105 patients with either de novo lesions or restenotic lesions (Raizner et al. 2000). At 6-month follow-up, the incidence of restenosis was 8 % in the brachytherapy group versus 39 % in the control group ($P = 0.0012$). At 6-month follow-up, the incidence of death, myocardial infarction, and target vessel revascularization was 26 % in the brachytherapy group versus 32 % in the control group (P not significant).

The GAMMA-1 trial was a multicenter double-blind, randomized, placebo-controlled study that investigated the effect of intracoronary gamma radiation using iridium-192 on in-stent restenosis in 252 patients (Leon et al. 2001). At 6-month follow-up, the incidence of in-stent restenosis was

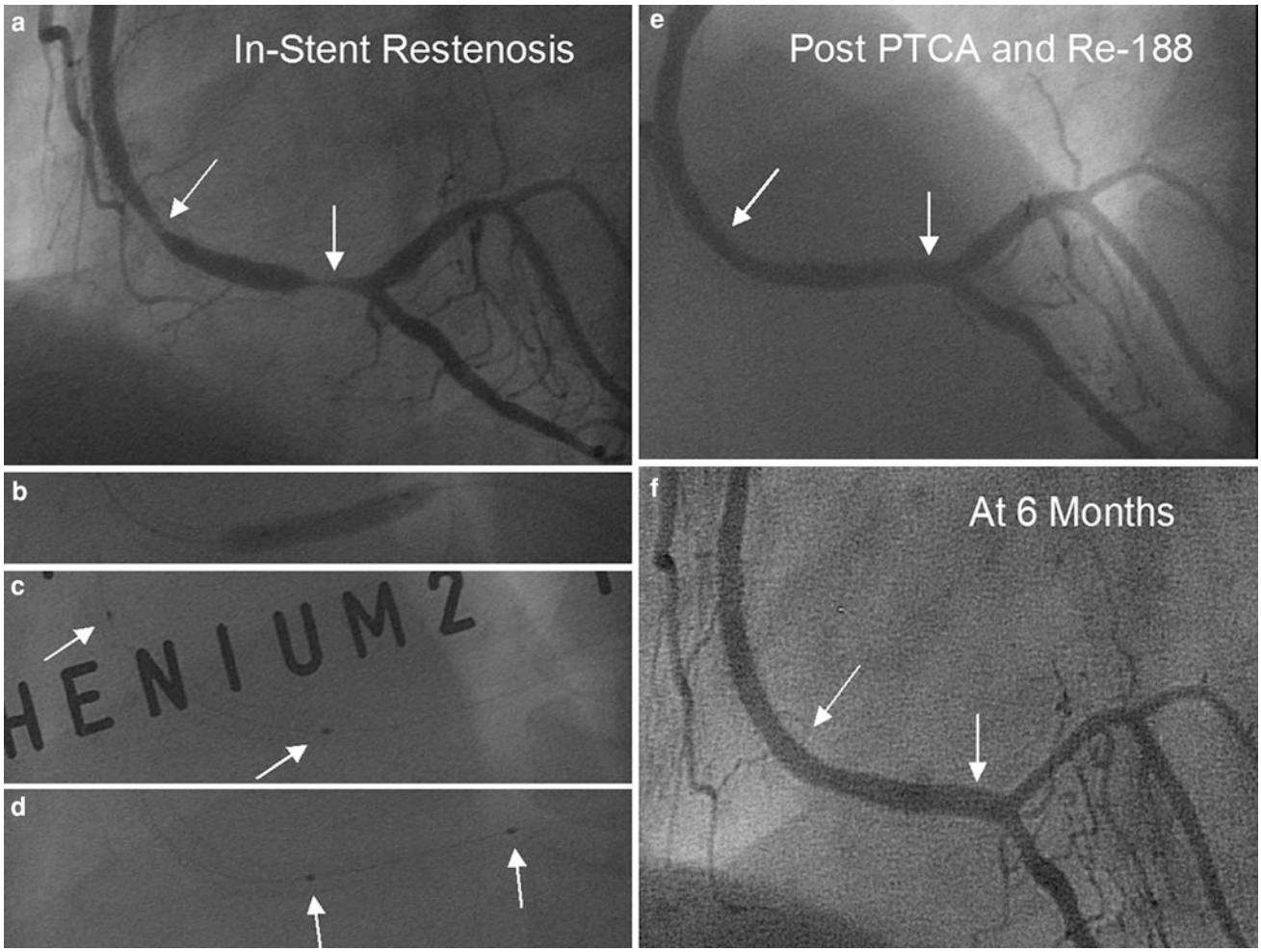

Fig. 4 Re-188 irradiation in a patient suffering from in-stent restenosis **a** Initial angiogram of the right coronary artery with a medium restenosis within the proximal part of a previously implanted stent without brachytherapy and a severe restenosis distally of the stent. The example demonstrates that edge stenosis also occurs following conventional PCI or stenting. **b** Initial balloon inflation of the distal stenosis. There are two metallic *markers* within the balloon indicating the nominal length of the balloon (20 mm). The real length of the balloon is somewhat longer, which has to be noted for correct selection of the irradiation balloon. **c**, **d** Fractionated irradiation with a 30 mm (nominal length) balloon at two positions with a minimal overlap. The irradiated segment clearly starts proximally of the stent **c** and continues behind the posterior descending artery **d**, fully covering the traumatized area plus at least 5 mm at each side. **e** Final result at the end of the intervention without residual stenosis. **f** Optimal clinical and angiographic result after 6 months follow-up

22 % in the brachytherapy group versus 51 % in the placebo group ($P \leq 0.001$). At 9-month follow-up, the incidence of death, myocardial infarction, and target vessel revascularization was 28 % in the brachytherapy group versus 44 % in the placebo group ($P = 0.02$).

The Stents and Radiation Therapy (START) study investigated the effect of the beta-catheter system, which uses $^{90}Sr/^{90}Y$ to prevent in-stent restenosis, in 476 patients with in-stent restenosis randomized to placebo or brachytherapy (Popma et al. 2002). At 8-month follow-up, target vessel revascularization occurred in 27 % of the placebo group versus 17 % of the brachytherapy group ($P = 0.015$). At 8-month follow-up, the incidence of death, myocardial infarction, and target vessel revascularization was 29 %, in the placebo group versus 15 % in the brachytherapy group ($P = 0{,}024$). At 2-year follow-up, target vessel revascularization occurred in 37 % of the placebo group versus 28 % of the brachytherapy group (Silber et al. 2005a). The Kaplan-Meyer analysis for target vessel revascularization (TVR) and MACE showed improvement beginning approximately 90 days after radiation and remained almost constant for the 2 following years. Freedom from TVR was significantly increased from 62.4 ± 3.8 to 71.6 ± 3.3 % ($P = 0.027$) and freedom from MACE from 58.9 ± 3.7 to 68.0 ± 3.4 % ($P = 0.035$).

The intimal Hyperplasia Inhibition with Beta In-Stent Trial (INHIBIT) was a double-blind, randomized, placebo-controlled trial that investigated treatment of in-stent restenosis with phosphorus-32 beta radiation in 162 patients and

placebo in 162 patients (Waksman et al. 2002b). At 9-month follow-up, angiographic binary restenosis was reduced 25 % by brachytherapy ($P \leq 0.0001$). At 9-month follow-up, the incidence of death, myocardial infarction, and target vessel revascularization was 31 % in the placebo group versus 15 % in the brachytherapy group ($P = 0.0006$).

The Saphenous Vein Graft-Washington Radiation fo In-Stent Restenosis Trial (SVG-WRIST) was a double-blind study that randomized 120 patients with in-stent restenosis in saphenous vein grafts to intracoronary gamma radiation or placebo (Waksman et al. 2002a). At 12-month follow-up, the incidence of target vessel revacularization was 17 % in the iridium-192 group versus 57 % in the placebo group ($P < 0.001$). At 12-month follow-up, the incidence of death, myocardial infarction, and target vessel revascularization was 32 % in the brachytherapy group versus 63 % in the placebo group ($P \leq 0.001$).

7.2 De Novo Stenosis

BETACATH, a randomized, placebo-controlled trial in de novo coronary stenosis and in restenosis without stent enrolled 1455 patients (placebo and Sr-90, 711 and 744, respectively) (Silber and fdB 2001; Silber 2002). The study observed late stent thrombosis; however, prolonged platelet therapy reduced this complication. Development of coronary aneurysms was not observed. Radiation therapy after PCI demonstrated an reduction of restenosis of 37.6 % compared to placebo and a reduction of 28.9 % after stent application and radiation therapy compared to placebo. The study addressed "geographic miss" as cause of edge stenosis in areas injuried but not sufficiently radiated. Fixed lengths of radioactive trains hindered extension of the radiation area to both sides of the injured vessel. This detail of the study design compromised the good effect on the primary lesion by induction of edge stenosis. In general the study confirmed the results of the BRIE study. Moreover, the study stresses the importance of placebo control.

BRIE, a multicenter European registry of intracoronary beta brachytherapy of 1098 patients, showed at 6-month follow-up that the incidence of death was 2 %, myocardial infarction was 3 %, and target vessel revascularization was 17 % (Urban et al. 2003). Nonrandomized studies have also demonstrated that intracoronary brachytherapy is efficacious in the treatment of totally occluded in-stent restenotic lesions (Sharma et al. 2003), in the treatment of de novo and in-stent restenotic lesions in saphenous vein grafts (Stone et al. 2003), in patients with diffuse in-stent restenosis (Waksman et al. 2001), in patients with native coronary ostial in-stent restenotic lesions (Costantini et al. 2003), in patients at high risk for recurrence of restenosis (Gruberg et al. 2002), in patients with diabetes with in-stent restenosis (Regar et al. 2002), in elderly patients with in-stent restenosis (Ajani et al. 2002), and in patients who failed intracoronary radiaton (Waksman et al. 2003). Angiographic outcomes after the use of beta versus gamma intracoronary brachytherapy for the treatment of in-stent restenosis are similar (Shirai et al. 2003).

8 Clinical Application of Re-188-Filled Balloon Catheter

Amols and Weinberger introduced the approach of beta-emitting radioisotope-filled balloon which is a technically simple, safe, and inexpensive means to deliver a radiation field that conforms to the vessel geometry in an optimal fashion (Amols et al. 1996a; Weinberger 1998). Six-months results from a clinical safety and feasibility study of intracoronary β-irradiation with a liquid Re-188-filled balloon were presented by Höher et al. from Ulm, Germany (Hoher et al. 2000). They observed low target lesion restenosis rate of 12 %; however, they found a high incidence (35 %) of new stenoses at the proximal or distal end of the irradiation zone ("edge" stenoses). They observed lower restenosis rate when the irradiation field was more than twice the lesion length and concluded "the observed edge stenoses appear to be avoidable by increasing the length of the irradiated segment". A randomized trial in patients with de novo and restenotic lesions enrolled 225 patients and applied 22.5 Gy in 0.5 mm depth (Hoher et al. 2003). After 6 months follow-up, late loss was significantly lower in the irradiated group compared with the control group, both of the target lesion (0.11 ± 0.54 vs 0.69 ± 0.81 mm, $P \leq 0.0001$) and of the total segment (0.22 ± 0.67 vs 0.70 ± 0.82 mm, $P \leq 0.0001$). This was also evident in the subgroup of patients with de novo lesions and independent from stenting (Fig. 4). Target vessel revascularization rate was significantly lower in the Re-188 compared with the control group (6.3 vs 19.8 %, $P = 0.006$). Another study from this group compared the intracoronary brachytherapy in restenotic lesions of native coronary arteries and venous bypass grafts (CABG) (Wohrle et al. 2006b). They observed no vessel thrombosis during antiplatelet therapy. Incidence of major adverse cardiac events (MACE) was 17.6 % in the native coronary artery group and 38.1 % in the CABG group ($P \leq 0.03$). Binary restenois rate was 22.5 and 55.6 % ($P \leq 0.01$), and late los was 0.38 ± 0.72 mm and 1.33 ± 1.11 mm ($P \leq 0.001$), respectively. They concluded that the procedure is effective in native coronary arteries but not in sapehnous vein grafts. A last paper from this group addressed repeated intracoronary brachytherapy using Re-188 filled balloon catheter for recurrent restenosis in patients who failed intracoronary radiation therapy (Wohrle et al. 2006a). A total of 14 patients with restenosis

after brachytherapy failure received brachytherapy (22.5 Gy at 0.5 mm depth) again after PCI. Angiographic follow-up was done in 13/14 patients and revealed neither edge stenoses nor formation of aneurysm.

The group at Dresden, Germany, prescribed 30 Gy at 0.5 mm depth. In an initial safety study including a total of 41 patients, 21 stents in 16 patients were newly implanted (Reynen et al. 2004). Despite acetylsalecylic acid and clopidogrel for 6 months, four episodes of stent thrombosis occurred with subsequent myocardial infarction in three patients (day 8, 37, 5, and 6 months after the irradiation procedure, respectively). This complication was seen exclusively in patients with newly implanted stents. Another prospective, randomized, placebo-controlled, double-blind evaluation included 165 patients. Angiographic control were performed 6 months later. Restenosis or reocclusion was observed in only 19/79 patients (24 %) of the radiation but in 31/78 patients (40 %) of the sham procedure ($P = 0.04$). Event-free survival (free of death, myocardial infarction, target vessel revascularization) at 1 year was 87 % for patients being radiated and 74 % for patients having undergone sham procedure ($P = 0.05$). Schühlen et al. from Munich published a small feasibility study of 21 patients, 11/21 with irradiation of 28 Gy at 0.5 mm depth (Schuhlen et al. 2001).

Most publications on Re-188 intracoronary brachytherapy originates from Seoul, South Korea (Cho et al. 2004; Hong et al. 2002, 2003a, b, 2004; Koo et al. 2004; Lee et al. 2005a, b, c, 2006; Park et al. 2001, 2008). Park et al. reported on treatment of diffuse in-stent restenosis with rotational atherectomy followed by radiation therapy (with a rhenium-188-mercaptoracetyltriglycine-filled balloon in 50 patients (Park et al. 2001). The prescribed dose was 15 Gy at 1.0 mm depth which is identical with 22.5 Gy at 0.5 mm depths (Ulm group). No adverse event, including myocardial infarction, death or stent thrombosis, occurred during the follow-up period of 10.3 ± 3.7 months, and nontarget vessel revascularization was needed in one patient. The 6 months binary angiographic restenosis rate was 10.4 %, and the loss index was 0.17 ± 0.31 which demonstrates the effectiveness of the irradiation procedure. Another publications refers to the problem of geographic miss or the misalignment of dilated and irradiated segment (Hong et al. 2002). The long-term outcome (2 years) was death-free survival and major adverse cardiac events in 98.0 ± 2.0 and 86.9 ± 5.0 %, respectively (Lee et al. 2005b). In a little bit different cohort, late recurrence between 6 months and 2 years was observed in 10/52 patients (19.2 %) (Lee et al. 2006). In comparison between rotational atherectomy versus balloon angioplasty followed by radiation therapy with a Re-188-filled balloon in the treatment of diffuse in-stent restensosis, the 6 months angiographic restenosis rate was 10 % (5/50) after rotational atherectomy and irradiation and 33 % (17/51) after PCI and irradiation ($P = 0.007$) (Lee et al. 2005a). From the same group another publication presents different technical details and results (Lee et al. 2005a): 18 Gy at 1.0 mm depths instead of 15 Gy and 6 months angiographic restenosis rates of 14.9 and 14.0 %, respectively.

They also investigated the vascular remodeling of nonstented adjacent segments after intracoronary irradiation by means of intravascular ultrasound (IVUS) (Hong et al. 2003a, b; Koo et al. 2004). The findings of the IVUS study were that positive remodeling (increased external elastic membrane area) occurred equally in both, control and irradiated patients with in-stent restenosis. The extent of remodeling was directly in proportion of intimal hyperplasia in the control group, but no such relationship existed in the irradiated patient group. They concluded that irradiation by means of Re-188-filled balloon appears to have no significant deleterious effect on angiographically normal reference segments over a 6 months follow-up after brachytherapy (Koo et al. 2004). Late intravascular ultrasound of patients treated with brachytherapy for diffuse in-stent restenosis 24 months before were performed in 30 patients (Hong et al. 2004). There was a significant decrease of mean external elastic membrane (from 10.1 ± 3.9 to 9.7 ± 3.9 mm^2; $P = 0.015$) and lumen area (from 5.6 ± 2.3 to 5.1 ± 2.3 mm^2; $P = 0.021$) within distal reference segments between 6 and 24 months. Target lesion revascularization (TLR) was performed in 6 patients (20 %) between 6 and 24 months, after irradiation therapy. There were no significant differences between TLR and non-TLR groups except for a smaller minimum lumen at 24 months in the TLR group. Because of a small amount of late loss between 6 and 24 months, most irradiated in-stent restenosis vessel segments remained stable for up to 2 years. Another study included a significant ratio of de novo stenoses (83 %) and a dose of 17.6 Gy at 1.0 mm depths was prescribed (comparable to 26.4 Gy at 0.5 mm depths) (Cho et al. 2004). At 6-month follow-up, binary restenosis developed with significantly lower frequency in the radiation group than in the control group (24.3 vs 46.3 %; $P = 0.009$), although target lesion revascularization rate did not show significant benefit. At 2-year clinical follow-up, cumulative target lesion revascularization rate was not significantly different between radiation group ($n = 86$) and control group ($n = 75$); 20.0 vs. 26.0 %; $P = 0.368$). The rate of major adverse cardiac events did not show significant difference between two groups either (22.3 vs. 30.1 %; $P = 0.266$). This observation supports the hypothesis that irradiation will not prevent but only delay restenosis.

There are two comparisons available by now between drug-eluting stents and Re-188-filled balloon irradiation therapy in diffuse in-stent restenosis (Park et al. 2008). Group 1 (sirolimus-eluting stents) included 65 patients, group 2 (20 Gy at 1.0 mm, which is comparable to 30 Gy at

0.5 mm) included 64 patients, randomly assigned. Baseline characteristics were similar between two groups including lesion lengths. Late loss in analysis segment at 6 months was smaller in group 1 than in group 2 (0.15 ± 0.62 vs. 0.55 ± 0.69 mm, $P = 0.003$). Angiographic restenosis for analysis segment at 6 months was 8.0 % (4/50) in group 1 and 30.2 % (16/53) in group 2 ($P = 0.006$). An update of the study included 120 patients in group 1 (sirolimus-eluting stents) and 240 patients treated with Re-188-filled balloon catheter (Lee et al. 2007). The two groups were similar in baseline clinical and angiographic characteristics. In-stent acute gain was greater in group 1 (2.23 ± 0.62 vs. 1.91 ± 0.54 mm, $P < 0.001$). Six-month angiography was available in 287 patients. In-segment angiographic restenoses were 7.4 % (7/94) in group 1 and 26.4 % (51/193) in group 2 ($p \leq 0.05$). At 3 years, survival rates without target lesion revascularization (94.1 ± 2.2 % vs. 84.6 ± 2.3 %, $P = 0.011$) and major adverse cardiac events (92.5 ± 2.4 % vs 84.2 ± 2.4 %, respectively, $P = 0.03$) were higher in group 1 than in group 2. It was concluded that drug-eluting stent implantation for diffuse in-stent restenosis is more effective in decreasing recurrent restenosis and improving long-term outcome than intracoronary brachytherapy using Re-188-filled balloon catheter.

8.1 Intracoronary Radiation Versus Drug-Eluting Stents

The introduction of drug-eluting stents drastically changed the utilization of intracoronary brachytherapy. First, the overall number of patients with restenosis decreased as the penetration of drug-eluting stents increased. Second, large companies decided not to invest in brachytherapy technology in light of the outstanding results offered by the drug-eluting stents. Finally, randomized controlled trials that compared intracoronary brachytherapy and drug-eluting stents for the treatment of in-stent restenosis demonstrated a superiority of drug-eluting stents (sirolimus-eluting stents and paclitaxel-eluting stents) in this setting (Holmes et al. 2006; Stone et al. 2006). In the TAXUS V-ISR trial, 396 patients with bare metal stent in-stent restenosis referred for percutaneous coronary intervention were prospectively randomized to either paclitaxel-eluting stent or a beta source intracoronary brachytherapy. At 24-month follow-up, ischemia-driven target vessel revascularization was significantly reduced with drug-eluting stents compared to brachytherapy (10.1 vs. 21.6 %, $P \leq 0.003$), as was ischemia-driven target vessel revascularization (18.1 vs. 27.5 %, $P = 0.03$). There were no significant differences between the two groups with regard to death, myocardial infarction, or target vessel thrombosis cumulative to 24 months (Ellis et al. 2008; Stone et al. 2006). The SISR trial randomized 384 patients to sirolimus-eluting stent (SES) or intracoronary brachytherapy (Holmes et al. 2006). At 9 months, the rate of target vessel failure was 21.6 % (27/125) with brachytherapy and 12.4 % (32/259) with the sirolimus-eluting stent (relative risk 1.7; 95 % confidence interval 1.1–2.8; $P = 0.02$). A 3-year follow-up was recently published and demonstrated that survival free from target lesion revascularization (TLR) and target vessel revascularization (TVR) continues to be significantly improved with SES: freedom from TLR 81.0 versus 71.6 % ($P = 0.018$) and TVR 78.2 vs. 68.8 % ($P = 0.022$), SES Vs. brachytherapy (Holmes et al. 2008). At 3 years, target vessel failure and major adverse cardiac events (death, myocardial infarction, emergency coronary artery bypass grafting, or repeat TLR) remained improved with SES, but did not reach statistical significance. There was also no statistically significant difference in definite or probable stent thrombosis (3.5 % for SES, 2.4 % for brachytherapy, $P = 0.758$). Another competition comes from the drug-eluting balloon which demonstrated high cure rate in in-stent restenosis of bare metal stents (Scheller et al. 2006). The inhibition of restenosis by local drug delivery may not require stent implantation and sustained drug release at the site of injury. Recommendations on application of drug-eluting stents and balloons are available (Silber et al. 2008).

The best remaining niche for intracoronary brachytherapy in the drug-eluting stent (DES) era might be the treatment of DES restenosis. In this setting, the only report exploring the usefulness of intracoronary brachytherapy was the Radiation for Eluting Stents in Coronary FAILURE (RESCUE) Registry (Torguson et al. 2006). It was an international, Internet-based registry of 61 patients who presented with in-stent restenosis of a DES and were assigned to intracoronary brachytherapy with commercially available systems after PCI. Outcomes of these patients were compared with those of a consecutive series of 50 patients who presented with in-stent restenosis of a DES and were assigned to repeat DES (r-DES) treatment. Baseline clinical and angiographic characteristics were similar between groups, except for more Cypher stents as the initial DES that restenosed in the r-DES group than in the intravascular irradiation group (88.5 vs. 69 %, $P < 0.01$). At 8 months, there were fewer overall major adverse cardiac events in the brachytherapy group compared with the r-DES group (9.8 vs. 24 %, $P \leq 0.044$). The need for target vessel and target lesion revascularization was similar in the two groups at 8 months. There has been no report of subacute thrombosis in either group.

Another report is from Price et al. regarding intracoronary radiation therapy for multidrug-resistant in-stent restenosis (Price et al. 2007). They irradiated five patients with in-stent restenosis after implantation of a sirolimus-eluting stent and a paclitaxel-eluting stent. Over a median

follow-up of 256 days (range 75–489 days), only one patient had a target lesion revascularization at 182 days and subsequently died at 483 days following the procedure due to congestive heart failure.

9 Conclusion

Intracoronary brachytherapy is backed by an impressive literature demonstrating its efficacy in the treatment of diffuse in-stent restenosis following the placement of a bare metal stent (Silber 2002). By the year 2000, brachytherapy had become an established technique, the devices had CE marks, and this technique was generally viewed as the gold standard treatment for in-stent restenosis. Therefore, in the first guidelines for percutaneous intervention (PCI) of the European Society of Cardiology (ESC), intracoronary brachytherapy was recommended as the first evidence-based treatment of in-stent restenosis at the highest level of I A (Silber 2005b). The Registry Novoste (RENO) prospectively collected data in over 1,000 patients receiving brachytherapy in routine clinical practice throughout Europe and Middle East. The problems "geographic miss" and "late thrombosis" had been overcome by enlargement of the irradiation field compared to the dilated segment and by dual antiplatelet treatment for 12 months. The combination of restrictive regulations and reluctance of the physicians to undertake the time-consuming licensing procedures limited the access of this treatment to patients. Then drug-eluting stents appeared on the horizon and many clinicians started to assume there was no longer need to provide a brachytherapy service. It was obvious that the demand for brachytherapy procedures does not make economic sense to the industry (Thomas 2005). However, Re-188-solution is further available and can be used in the isotope-filled balloon. In-stent restenosis in bare metal stents or following drug-eluting balloons might be a reasonable indication as well as in-stent restenosis in a drug-eluting stent. Therefore, as long as restenosis remains a clinical problem and bypass surgery is not an alternative, it is likely that intracoronary brachytherapy will contribute to its solution Waksman (2011).

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