Am J Cardiol (2004);94:1061-3
Two-year outcomes of repeated brachytherapy in patients with restenosis after intracoronary radiation therapy
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This study compared the 2-year outcomes of repeat brachytherapy (n = 10) and conventional percutaneous intervention (n = 14) in patients with restenosis after intracoronary brachytherapy with a rhenium-188-filled balloon system. The short-term target lesion revascularization rate was significantly lower in the repeat brachytherapy group (0% vs 36%, p = 0.038), and additional target lesion revascularization was required in 2 patients with repeat brachytherapy during 2-year follow-up. There were no vascular complications related to repeat brachytherapy.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15476627

Catheter Cardiovasc Interv (2004);62:318-22
Impact of radiation dose on late clinical outcome after intracoronary radiation therapy: three-year follow-up of Long WRIST
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To determine the safety and efficacy, including the impact, on the late recurrence rate of an incremental gamma-radiation dose from 15 to 18 Gy, we report the 3-year clinical outcome of Washington Radiation for In-Stent Restenosis Trial for Long Lesions (Long WRIST). One hundred eighty patients with recurrent in-stent restenosis (ISR) were enrolled in the Long WRIST series and treated with (192)Ir with 1 month of antiplatelet therapy. Between 6 months and 3 years, the need for repeat revascularization was low and similar among the three groups. At 3 years, target lesion revascularization (TLR) and major adverse cardiac events (MACE) were less frequent in the 18 Gy group than in the 15 Gy group (P = 0.12 for TLR, P < 0.05 for MACE) and less frequent in the 15 Gy group as compared to the placebo group (P < 0.05 for TLR and MACE). At 3 years, a higher dose of 18 Gy with (192)Ir continues to improve the outcome of patients treated for ISR when compared to patients treated with 15 Gy or placebo.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15224297

Catheter Cardiovasc Interv (2004);63:274-81
Two-year clinical follow-up results of intracoronary radiation therapy with rhenium-188-diethylene triamine penta-acetic acid-filled balloon
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We investigated the 2-year clinical follow-up results as well as 6-month angiographic and clinical follow-up results of intracoronary radiation therapy using a rhenium-188-diethylene triamine penta-acetic acid ((188)Re-DTPA)-filled balloon system. The study comprised of 161 patients with significant de novo (83%) or in-stent restenosis (17%) lesions. Irradiation to deliver 17.6 Gy at a depth of 1.0 mm into the

vessel wall was carried out after successful intervention. 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 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 including death, myocardial infarction, and target lesion revascularization did not show significant difference between two groups either (22.3% vs. 30.1%; P = 0.266). In conclusion, although significant reduction in restenosis rate was noted at 6-month angiographic follow-up, intracoronary radiation therapy mostly in patients with de novo lesion did not show significant clinical benefit in 6-month and 2-year follow-up results. The benefit was noted only in a small subgroup of patients with in-stent restenosis.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15505867

Catheter Cardiovasc Interv (2004);63:208-14
Late intravascular ultrasound findings of patients treated with brachytherapy for diffuse in-stent restenosis
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This study aimed at evaluating long-term (24-month) effects of beta-irradiation (188Re-MAG3-filled balloon) using intravascular ultrasound (IVUS) in patients with in-stent restenosis (ISR). Long-term effects of beta-irradiation on intimal hyperplasia (IH) within the stented segment and vessel and lumen dimensions of nonstented adjacent segments in patients with ISR have not been sufficiently evaluated. Two-year follow-up IVUS was performed in 30 patients with patent ISR segments at 6-month follow-up angiography. Serial IVUS images were acquired at five equidistant intrastent sites and at three different reference segment sites. IH burden (%) was defined as 100 x (IH/stent area). Mean intrastent IH area and IH burden significantly increased between 6 and 24 months, from 2.1 +/- 1.1 to 2.6 +/- 1.4 mm2 (P < 0.001) and from 26% +/- 10% to 33% +/- 14% (P < 0.001), respectively. There was a significant decrease of mean external elastic membrane (from 10.1 +/- 3.9 to 9.7 +/- 3.9 mm2; P = 0.015) and lumen area (from 5.6 +/- 2.3 to 5.1 +/- 2.3 mm2; P = 0.021) within distal reference segments between 6 and 24 months. Target lesion revascularization (TLR) was performed in six patients (20%) between 6 and 24 months after beta-irradiation therapy. There were no significant differences between TLR and non-TLR groups except for a smaller minimum lumen area at 24 months in the TLR group. Because of a small amount of late loss between 6 and 24 months, most irradiated ISR vessel segments remained stable for up to 2 years. However, quantitative evidence of late catch-up was evident in most patients and was significantly associated with 24-month TLR in some patients.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15390251

Catheter Cardiovasc Interv (2004);62:303-7
Favorable effect of gamma-radiation for in-stent restenosis: effect of diabetes on

angiographic and clinical outcomes
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The purpose of this study was to examine the effect of vascular brachytherapy with gamma-radiation (gamma-RT) in patients with diabetes mellitus (DM) with coronary in-stent restenosis (ISR). In the Washington Radiation for In-Stent Restenosis (WRIST) trial, 130 patients with ISR were treated with (192)Ir or placebo. Of the patients enrolled, 44 (34%) had DM (18 of them treated with gamma-RT and 26 with placebo). Gamma-radiation therapy of ISR in diabetics resulted in similar procedural success and in-hospital outcome compared to nondiabetics. At 6-month follow-up, both DM and non-DM patients treated with gamma-RT had significantly lower target lesion revascularization (TLR), target vessel revascularization, and major adverse cardiac event rates compared to placebo. DM remains a powerful predictor of TLR and major adverse cardiac events even after treatment of ISR with gamma-RT.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15224295

Am J Cardiol (2004);94:351-4
Effectiveness of sirolimus-eluting stent implantation for treatment of in-stent restenosis after brachytherapy failure
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The impact of the use of sirolimus-eluting stents (SESs) in the treatment of in-stent restenosis in previously irradiated sites has not been adequately evaluated. Fifteen consecutive patients who underwent percutaneous coronary interventions using SESs in lesion sites previously intervened with intracoronary radiation therapy were identified. All stents were implanted successfully, and there were no major in-hospital complications. At 30-day follow-up, there was 1 case of subacute thrombosis that led to target lesion revascularization (TLR). At 6 months, 2 patients underwent TLR because of recurrent angina with angiographic restenosis, and 1 patient underwent target vessel revascularization distally to the SES site; no other major adverse cardiac events occurred at long-term follow-up (mean 17 +/- 8 months).
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15276103

Catheter Cardiovasc Interv (2004);61:354-9
Gamma radiation for in-stent restenosis: effect of lesion length on angiographic and clinical outcomes
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The relation between lesion length and effectiveness of gamma radiation treatment (gamma-RT) has not been well described. We evaluated the acute and long-term outcome according to baseline lesion length in 130 patients treated with (192)Ir in the Washington Radiation for In-Stent Restenosis Trial; 44 (35.5%) had baseline short in-stent restenosis (ISR) lesions (length < 15 mm) and 80 (64.5%) long ISR lesions

(length > or = 15 mm). At 6-month follow-up after gamma-RT, the short ISR group had larger lumen dimensions and lower late loss than the long ISR group. Restenosis rate was significantly higher in patients with long ISR for both the placebo (74% vs. 39%; P = 0.01) and the gamma-RT arm (31% vs. 5.3%; P = 0.04). gamma-RT significantly improved the angiographic outcome in the short-lesion groups but had the more pronounced effect on the reduction of clinical events after treatment of long ISR group. Lesion length remains a powerful predictor of recurrent ISR and clinical events after treatment of ISR even with gamma-RT.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14988895

Catheter Cardiovasc Interv (2004);61:173-8
Intracoronary brachytherapy, a promising treatment option for diabetic patients: Results from a European multicenter registry (RENO)
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Despite advances in the interventional treatment of coronary disease, diabetics still have double the case fatality rate as nondiabetics. The purpose of this analysis from the Radiation in Europe With Novoste (RENO) registry was to assess the clinical and angiographic 6-month outcome of diabetic patients in comparison to nondiabetic patients after localized beta-radiation. A total of 1,098 patients (83.8% with in-stent restenosis) treated with the Novoste Beta-Cath system in Europe were enrolled in the RENO registry. Diabetes was, irrespective of the type of lesion treated, no significant risk factor for major adverse cardiac events or target vessel revascularization. Individuals with diabetes (n = 256) and without diabetes (n = 833) displayed no significant differences concerning clinical or angiographic endpoints. Vascular brachytherapy appears to be the first technique to even out the increased risk of diabetic patients undergoing percutaneous coronary interventions in the routine clinical setting. Thus, intracoronary brachytherapy represents a promising treatment option for diabetic patients.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14755807

Catheter Cardiovasc Interv (2005);64:61-6
Real-world clinical practice of intracoronary radiation therapy as compared to investigational trials
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Intracoronary radiation therapy (IRT) is well established in clinical practice as an effective treatment for in-stent restenosis. We aimed to determine if the 6-month clinical outcome of patients treated postapproval for marketing [commercial radiation (CR)] is equivalent to those patients enrolled in the Washington Radiation for In-Stent Restenosis Trials [Gamma WRIST and Beta WRIST; investigational radiation (IR)]. The 6-month clinical outcome of 110 consecutive patients with 125 lesions who received IRT (gamma, (192)Ir, 15-18 Gy, n = 6; or beta, (32)P, 20 Gy, n = 20; or (90)Sr/Y, 18.4-23.0

Gy, n = 99) in CR was compared with the 6-month clinical outcome of 117 patients with 117 lesions who received IRT ((192)Ir, 15 Gy, n = 65, in Gamma WRIST; and (90)Y, 20.6 Gy, n = 52, in Beta WRIST) in IR. Patients in CR were treated with wider radiation margins. The CR received antiplatelet therapy for at least 6 months and the IR for 1 month. The baseline characteristics of both groups were similar. Use of atheroablation devices was less in CR than IR (15.2% vs. 32.8%, respectively; P = 0.001). The overall major adverse cardiac events (death, Q-wave myocardial infarction, and target vessel revascularization; 18.2% vs. 29.1% in IR; P = 0.05) were significantly lower in the CR when compared with patients in the IR. The real-world clinical practice of IRT demonstrates lower events and better clinical outcomes. This is most likely a result of implementation of the lessons learned from the clinical trials such as optimizing the dosimetry by using a higher dose, treating wider margins to minimize edge effect, and administering prolonged antiplatelet therapy to abolish late thrombosis. Catheter Cardiovasc Interv 2005;64:61-66. (c) 2004 Wiley-Liss, Inc.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15619284

J Am Coll Cardiol (2004);44:520-7
Intracoronary brachytherapy after stenting de novo lesions in diabetic patients: results of a randomized intravascular ultrasound study
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OBJECTIVES: We studied the efficacy of intracoronary brachytherapy (ICB) after successful coronary stenting in diabetic patients with de novo lesions. BACKGROUND: Intracoronary brachytherapy has proven effective in preventing recurrences in patients with in-stent restenosis. However, the role of ICB for the treatment of de novo coronary stenoses remains controversial. METHODS: Ninety-two patients were randomized to either ICB or no radiation after stenting. Primary end points were in-stent mean neointimal area (primary end point of efficacy) and minimal luminal area of the entire vessel segment (primary end point of effectiveness), as assessed by intravascular ultrasound at six-month follow-up. Quantitative coronary angiography analysis was performed at the target, injured, irradiated, and entire vessel segments. RESULTS: At follow-up, the in-stent mean neointimal area was 52% smaller in the ICB group (p < 0.0001). However, there was no difference in the minimal luminal area of the vessel segment (4.5 +/- 2.4 mm2 vs. 4.4 +/- 2.1 mm2). Restenosis rates increased progressively by the analyzed segment in the ICB group: target (7.1% vs. 20.9%, p = 0.07), injured (9.5% vs. 20.9%, p = NS), irradiated (14.3% vs. 20.9%, p = NS), and vessel segment (23.8% vs. 25.6%, p = NS). At one year, 1 cardiac death, 6 myocardial infarctions (MIs) (3 due to late stent thrombosis), and 10 target vessel revascularizations (TVRs) (6 due to the edge effect) occurred in the ICB group, whereas in the nonradiation group, there were 11 TVRs and no deaths or MIs. CONCLUSIONS: Intracoronary brachytherapy significantly inhifn(ou)5 Tw[Tw[(fn(ou).6( )-5.1(the)-z.6( )-5w85(Tw[Twa

Catheter Cardiovasc Interv (2004);62:283-8
Clinical outcomes for sirolimus-eluting stent implantation and vascular brachytherapy for the treatment of in-stent restenosis
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The purpose of this study was to compare the mid-term clinical outcome of sirolimus-eluting stent (SES) implantation and vascular brachytherapy (VBT) for in-stent restenosis (ISR). We assessed the 9-month occurrence of major adverse cardiac events (MACE) in 44 consecutive patients with ISR treated with SES implantation and 43 consecutive patients treated with VBT in the period immediately prior. Baseline clinical and angiographic characteristics of the two groups were similar. During follow-up, three patients (7%) died in the VBT group and none in the SES group. The incidence of myocardial infarction was 2.3% in both groups. Target lesion revascularization was performed in 11.6% of the VBT patients and 16.3% of the SES patients (P = NS). The 9-month MACE-free survival was similar in both groups (79.1% VBT vs. 81.5% SES; P = 0.8 by log rank). The result of this nonrandomized study suggests that sirolimus-eluting stent implantation is at least as effective as vascular brachytherapy in the treatment of in-stent restenosis.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15224289

J Am Coll Cardiol (2004);44:528-37
Direct stenting versus direct stenting followed by centered beta-radiation with intravascular ultrasound-guided dosimetry and long-term anti-platelet treatment: results of a randomized trial: Beta-Radiation Investigation with Direct Stenting and Galileo in Europe (BRIDGE)
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OBJECTIVES: We sought to assess the efficacy of vascular brachytherapy (VBT) combined with stenting for the primary prevention of restenosis. BACKGROUND: Intravascular brachytherapy after stent implantation for de novo lesions has been abandoned for the present. We revisited this procedure by optimizing all procedural steps-the use of glycoprotein IIb/IIa blockers, direct stenting, adequate radiation coverage, avoidance of edge damage, source centering, intravascular ultrasound-guided dosimetry, and continuation of a dual anti-platelet regimen for one year. METHODS: The Beta-Radiation Investigation with Direct stenting and Galileo in Europe (BRIDGE) study is a multicenter, randomized controlled trial evaluating the long-term efficacy of VBT with P-32 (20 Gy at 1 mm in the coronary wall) after direct stenting. The primary end point was angiographic intra-stent late loss; secondary end points were six months binary restenosis and neo-intimal hyperplasia. Patients (n = 112) with de novo lesions (2.5 to 4.0 mm in diameter up to 15 mm long) were randomized to either VBT or no-VBT. RESULTS: At six months, intra-stent loss was 0.43 and 0.84 mm ($p < 0.001$) in the irradiated and control groups, respectively. Intra-stent neo-intimal volume was reduced from 36 mm3 to 10 mm3. However, in the irradiated group there were six late occlusions as well as eight restenoses outside the stented and peri-stented area at the fall-off dose edges of the irradiated area. Accordingly, the target vessel revascularization and major adverse cardiac and cerebrovascular events rates at

one year in the VBT group (20.4% and 25.9%, respectively) were higher than in the control group (12.1% and 17.2%, respectively). CONCLUSIONS: Despite the optimization of pre-, peri-, and post-procedural factors and despite the relative efficacy of the brachytherapy for the prevention of the intra-stent neo-intimal hyperplasia, the clinical outcome of the irradiated group was less favorable than that of the control group.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15358015

Circulation (2004);110:135-40
Deleterious effect of coronary brachytherapy on vasomotor response to exercise
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BACKGROUND: Intracoronary radiotherapy (brachytherapy) has been proposed as treatment option for in-stent restenosis. Long-term results of brachytherapy with regard to vascular integrity and vasomotor responsiveness are unknown. The purpose of the present study was to determine the vasomotor response after brachytherapy and to assess its influence on vasomotion during exercise. METHODS AND RESULTS: Biplane quantitative coronary angiography was performed at rest and during bicycle exercise in 27 patients with coronary artery disease. Fourteen patients underwent coronary stenting and were studied 10+/-3 months after intervention (control group). Thirteen patients were treated with brachytherapy (Guidant Galileo System) for in-stent restenosis with a mean dosis of 20 Gy at 1 mm into the vessel wall and were studied 9+/-1 months after radiation (brachytherapy group). Minimal luminal area, stent area, and proximal, distal, and a reference vessel area were determined. The reference vessel showed exercise-induced vasodilation (26+/-4%, P<0.001) in both groups. Vasomotion within the stented vessel segments was abolished. In control subjects, the proximal and distal segments showed exercise-induced vasodilation (17+/-2% and 22+/-7%, respectively; P<0.005). In contrast, there was exercise-induced vasoconstriction in the proximal and distal vessel segments of the brachytherapy group (-14+/-3% and -16+/-4%, respectively; P<0.01). Sublingual nitroglycerin was associated with maximal vasodilation of the proximal and distal vessel segments in both groups. CONCLUSIONS: Normal vessel segments elicit flow-mediated vasodilation during exercise. Stent implantation does not affect physiological response to exercise proximal and distal to the stent. Brachytherapy eliminates exercise-induced vasodilation, although dilatory response to nitroglycerin is maintained, suggesting endothelial dysfunction as the underlying mechanism.
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therapy (IRT) in patients with in-stent restenosis (ISR). METHODS AND RESULTS: One hundred thirty patients with ISR (100 native coronary and 30 vein grafts) underwent percutaneous transluminal coronary angioplasty, laser ablation, rotational atherectomy, or additional stenting (36% of lesions). Patients were randomized to either 192-Iridium IRT or placebo, with a prescribed dose of 15 Gy to a 2-mm radial distance from the center of the source. Angiographic restenosis (27% versus 56%, P=0.002) and target vessel revascularization (26% versus 68%, P<0.001) were reduced at 6 months in patients treated with IRT. Between 6 and 60 months, patients treated with IRT compared with placebo had more target lesion revascularization (IRT, 21.6% versus placebo, 4.7%; P=0.04) and target vessel revascularization (IRT, 21.5% versus placebo, 6.1%; P=0.03). At 5 years, the major adverse cardiac event rate was significantly reduced with IRT (46.2% versus 69.2%, P=0.008). CONCLUSIONS: In the Washington Radiation for In-Stent Restenosis Trial, patients with ISR treated with IRT using 192-Iridium had a reduction in the need for repeat target lesion and vessel revascularization at 6 months and 5 years.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14732756