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Intracoronary Brachytherapy

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Executive Summary

Percutaneous transluminal coronary angioplasty (PTCA) is used in approximately 700,000 Americans annually to treat coronary artery disease.¹ However, six months post-PTCA, restenosis occurs in 30 to 40 percent of patients after balloon angioplasty and in 20 to 30% of patients after balloon angioplasty followed by stenting, referred to as in-stent restenosis. Repeat in-stent restenosis has proven very difficult to treat^{2,3} and occurs in 54 to 66% of cases even after further treatment for in-stent restenosis.¹

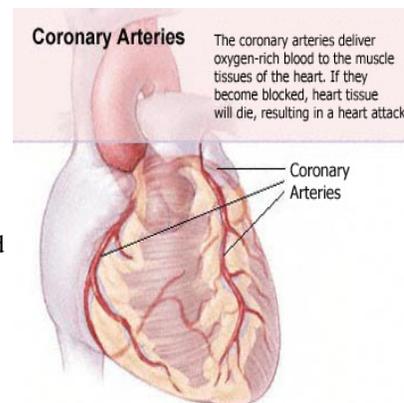
In an attempt to reduce the rate of restenosis, researchers have pursued a variety of novel therapeutic techniques aimed at preventing restenosis.⁴ One such technique, local ionizing radiation, has significantly reduced neointimal proliferation in animal models. Presumably, the theoretical benefit of radiation resides in its lethal effect on rapidly dividing smooth muscle cells and the inhibition of the recruitment and proliferation of adventitial myofibroblasts. Intracoronary radiation therapy (referred to as "brachytherapy") involves treating coronary stenoses with a radioactive source from within the artery lumen. Brachytherapy means 'short' therapy. Radiation, either gamma (g) or beta (b), is delivered to the affected vessel via a radioactive stent or catheter-based system.

This report is intended to assist physicians in finding answers to the following questions pertaining to intracoronary radiation therapy:

- How safe (short-term, long-term) is intracoronary radiation therapy?
- Do catheter-based g- or b-radiation effectively reduce restenosis rates following angioplasty and stenting? Do radioactive stents reduce in-stent restenosis rates?

Findings

- The currently available peer-reviewed, published medical literature on intracoronary brachytherapy for the prevention of in-stent restenosis consists of five randomized controlled trials (RCT) and several small case series reports. At present, randomized evidence for a beneficial effect of intracoronary radiation therapy is limited to three studies of catheter-based g-radiation therapy. Although more than one RCT evaluating catheter-based b-radiation therapy is published, outcome data are weakened by several study design flaws including variable patient selection criteria and pre-randomization treatment protocols.
- Catheter-based intracoronary g-radiation devices for the treatment of in-stent restenosis are evaluated in three RCT. At six month follow-up, two studies reported that restenosis rates were significantly lower in the irradiated group (19% and 17%, respectively) compared with the placebo group (58% and 54%, respectively). Both RCT report significantly lower six-month restenosis rates in irradiated patients compared with those assigned to placebo groups. The three-year binary restenosis rate remained significantly lower in the radiation group (33%) versus the placebo group (64%).
- Catheter-based intracoronary b-radiation therapy for restenosis is reported in one RCT and four case series. In the RCT, 105 patients with de novo lesions, restenotic lesions, or restenotic in-stent lesions were enrolled. Following balloon angioplasty with or without stenting, patients were randomized to placebo treatment (n=25) or one of three different b-radiation doses (n=80 for total brachytherapy groups). At 6 months, target site restenosis rates were significantly lower in



- brachytherapy patients compared with placebo patients (6% versus 24%, respectively).
- A study published by Leon et al. reports the results of the Gamma-One Trial, a multi-center study in which 252 patients were randomly assigned to receive either placebo or iridium-192 for the treatment of in-stent restenosis.⁵ As in previous trials, intracoronary brachytherapy caused an impressive reduction in recurrent in-stent restenosis at six months as compared with the incidence in the placebo group.
- In a randomized, uncontrolled, dose-finding study of 181 patients with previously untreated coronary stenosis,¹ patients were randomly assigned to receive various doses of yttrium-90 (beta radiation). Higher doses of radiation were associated with lower rates of restenosis at six months.

Catheter-based brachytherapy for the treatment of native coronary arteries to prevent restenosis in de novo lesions is an evolving technology that shows promise. However, data is lacking from well-designed, longitudinal, randomized, catheter-based g-brachytherapy clinical studies, in patients with de novo or non-stented restenotic lesions. More scientific and clinical evidence needs to be published to support the long-term safety and efficiency of this technology. Due to high incidence of late luminal losses, both proximal and distal to the edges of radioactive stents, their use for the treatment of de novo or restenotic lesions must be considered an investigational treatment. Further technological adaptations of current radioactive stent platforms and more scientific and clinical evidence from well-designed, randomized controlled trials are needed. Current evidence does not support the recommendation of either catheter or stent-delivered intracoronary brachytherapy for the prevention of restenosis of primary (de novo or non-stented) coronary artery stenosis. However, physicians are strongly encouraged to discuss potential short-term benefits of brachytherapy with patients having secondary or repeated restenosis.

Medical Background

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the United States. Percutaneous transluminal coronary angioplasty (PTCA) is used in approximately 700,000 Americans annually to treat coronary artery disease.¹ However, six month post-PTCA, restenosis occurs in 30 to 40 percent of patients after balloon angioplasty and in 20 to 30 percent of patients after balloon angioplasty followed by stenting referred to as in-stent restenosis.^{2,3} When compared with coronary bypass graft surgery, patients treated with angioplasty have lower initial costs and fewer complications. However, reports indicate that six months to three years post-PTCA, angioplasty patients require more revascularization procedures and more frequently experience angina. Therefore, long-term studies report that restenosis reduces most of the cost benefit of angioplasty. In the United States, the societal cost of restenosis is estimated to be between \$800 million and \$2 billion annually.⁶⁻⁸

Elastic recoil, neointimal hyperplasia, and late contraction, or remodeling, have all been suggested as the primary mechanisms of restenosis. Recoil and remodeling are the mechanical collapse and constriction of the treated coronary artery. Neointimal hyperplasia is a proliferative response to overstretch balloon injury and consists largely of extracellular matrix synthesis by modified smooth muscle cells. This proliferative response to injury mimics scar tissue formation seen in other tissues.⁷⁻¹⁰

Coronary stents, which are frequently implanted at the time of angioplasty (Figure 1), have reduced the restenosis rate by 22 to 32%. Stenting can serve as a mechanical scaffold to prevent the effect of immediate and late vascular collapse, but does not eliminate restenosis due to tissue proliferation, and may actually stimulate neo-intimal hyperplasia. Coronary stents are a purely mechanical means of preventing immediate recoil and late remodeling, thus creating a larger lumen than PTCA. This larger lumen may afford more area of growth for the proliferating cells that migrate through the stent, thereby facilitating restenosis. In-stent restenosis occurs in patients who undergo stent implantation and is influenced by certain patient characteristics; lesion morphology, and procedural technique. Cardiologists have attempted to treat in-stent restenosis with a variety of different techniques including balloon angioplasty, additional stenting or supplementing repeat balloon angioplasty with excimer laser, high-speed rotational atherectomy, and directional atherectomy. Despite these efforts, repeat in-stent stenosis occurs in 54 to 66% of cases. Therefore, clinical researchers, trying to reduce restenosis, are interested in identifying a method, such as radiation therapy to use in conjunction with angioplasty and stenting.^{7,8,11,12}

1. The stent is premounted on the balloon catheter and positioned within the blocked area of the vessel.



2. Once the balloon and stent are in the correct position, the balloon is inflated, deploying the stent. One or more stents may be expanded in the vessel, depending on how many are needed.



3. The stent will remain in place permanently, keeping the vessel open.



Figure 1: A stent is placed in approximately 75% of all angioplasty procedures and in-stent restenosis develops in about 20 to 30% within six months.

Since radiation has been effective in the treatment of other hyperplastic disorders, both benign and malignant, clinical researchers thought that locally applied radiation might also be effective for the treatment of coronary artery restenosis.¹³ Local ionizing radiation has significantly reduced neointimal proliferation in animal models. The theoretical benefit of radiation resides in its lethal effect on rapidly dividing smooth muscle cells and the inhibition of the recruitment and proliferation of adventitial myofibroblasts.^{8,10} Catheter-based ionizing radiation and radioactive stents, which deliver either gamma (g) or beta (b) radiation to the affected vessels, are the two intra-coronary radiation therapy techniques currently used or being clinically investigated to reduce restenosis.⁷

Description

Catheter-Based γ -Brachytherapy Systems

Prior to the γ -radiation catheter-based procedure, an angiogram and an intravascular ultrasound study are performed to evaluate the vessel size and lesion length. To optimize final angiographic results, in-stent restenotic lesions are treated most commonly with cutting balloon or conventional balloon angioplasty and less commonly with excimer lasers, rotational atherectomy, or stenting. A closed-end noncentering catheter is then inserted into the lesion and situated to span the lesion length. The radiation oncologist inserts a 0.76-mm diameter ribbon containing sealed sources of ¹⁹²Iridium (¹⁹²Ir) into the positioning catheter. Angiography is used to confirm that the source covers the entire lesion length plus a 5-mm overlap of normal or uninjured segments on each end. The ribbon is removed after approximately 15 to 25 minutes, the duration required to administer the prescribed dose to the adventitial border.^{9,11,14}

Catheter-Based β -Brachytherapy Systems

The Galileo™ and Beta-Cath™ are catheter-based systems designed to deliver β -radiation to the target lesion. The Galileo system utilizes a double-lumen centering catheter, which incorporates a spiraling balloon in order to center the radiation source within the lumen and allow distal coronary perfusion. The catheter is marked with 2 radiopaque bands to delineate the treatment zone. A 0.018-inch diameter flexible source wire, encapsulated with Phosphorus-32 (³²P) in the distal end, is used to deliver the radiation dose. A closed lumen within the centering balloon catheter serves as the conduit for the source wire.^{15,16} Following balloon dilatation, the centering catheter is advanced to the lesion site, and the markers are optimally placed to straddle the balloon or stent-treated lesion segment. The centering balloon is then inflated with normal saline, and a contrast medium is injected through the guiding catheter to visualize the flow through the side branches and the distal artery. The inflated balloon permits passive side branch and distal coronary artery perfusion during treatment. An inactive wire is advanced into the centering catheter, its optimum placement is determined and the inactive wire is withdrawn. The active wire is then advanced to the same location and verified angiographically. The computerized source delivery unit calculates the required radiation exposure time, which is based on the desired radiation dose. Following the delivery of the desired radiation dose, typically 1 to 10 minutes, the active wire is withdrawn.^{15,16}

Unlike the Galileo system, which uses an inflated balloon to center the radiation dose, the Beta-Cath

system utilizes an over-the-wire delivery catheter. The closed-ended, flexible coronary catheter has one lumen for hydraulically conveying the train of radiation sources, a second lumen for reversed fluid flow, and a third through-lumen for passage of a 0.014-inch diameter guide wire. The catheter is marked with 2 radiopaque marker bands, 30-mm apart, which are located at the distal end of the catheter where the radioactive sources settle when deployed. The radiation source train is comprised of 12 tiny stainless steel canisters containing the radioisotope ⁹⁰Strontium/Yttrium (⁹⁰Sr/Y). The radiation source train is bounded by 2 gold markers, which allow visualization of the source train with fluoroscopy. A transfer device, which is attached to the catheter, holds the radioactive source train and is equipped with a switching system and a gate. The switch allows forward flow of sterile water to either transfer the sources to the catheter end or return them to the transfer device.^{17,18} After balloon angioplasty and successful dilatation of the artery, the balloon catheter is removed and the existing guide wire and guiding catheter are used to direct the radiation catheter. The radiation catheter is inserted over the guide wire and advanced until the two markers bound the angioplasty site. After fluoroscopy is conducted to verify optimal placement, the gate of the transfer device is opened and the source train is then hydraulically transported down the catheter. The source train is maintained at the distal end of the lumen source with minimal pressure and fluid flow for approximately 3 to 4 minutes. After therapy, the switching system is reversed and the sterile water pressure pushes the seed train back into the transfer device.^{17,18}

Radioactive Stents

To minimize in-stent restenosis, radiation may also be delivered to an affected vessel via radioactive stents. In the studies reviewed, the radioisotope Phosphorus-32 (³²P), a pure beta-particle emitter, was embedded beneath the stent surface. In one study, activity levels of 0.75 to 12 microcuries (mCi) delivered a total dose to the tissue at 0.5-mm from the stent surface of approximately 8 to 140 Gray (Gy) over a 28-day duration. Radioactive stents are delivered via the femoral artery in a technique similar to that used to implant non-radioactive stents. After the lesion is pre-dilated with an angioplasty balloon, a stent delivery system is advanced to the target lesion. The 15-mm long stent is pre-mounted on a 20-mm compliant balloon so that 2.5-mm of the length of the delivery balloon emerges beyond each stent edge. Stent deployment is achieved by inflating the delivery balloon to a recommended pressure of 8 to 10 maximum atmospheres. To maximize the final lumen dimension, further dilation may be performed with a larger and usually shorter balloon at a higher pressure. Intravascular ultrasound studies are performed after high-pressure inflation to ensure optimal placement.¹⁹⁻²¹

Postoperative Care: Patients receive routine care following angioplasty, including treatment with ticlopidine and aspirin, following either catheter-based brachytherapy or the implantation of radioactive stents.

Evaluation of Evidence

Catheter-Based Brachytherapy Systems

Waksman et al.¹¹ and Teirstein et al.¹⁴ randomized restenotic patients to gamma-brachytherapy (n=65 and n=26, respectively) or placebo (n=65 and n=29, respectively) following stent implantation. At six month follow-up, both studies reported that restenosis rates were significantly lower in the irradiated group (19% and 17%, respectively) compared with the placebo group (58% and 54%, respectively). Between 6 and 12 months, Waksman et al. reported a 9.3% increase in target lesion revascularizations and a 7.6% increase in target vessel revascularizations in the irradiated group only.¹¹ Teirstein et al. also reported that the restenosis rate increased by 16% in brachytherapy patients between 6 months and 3 years; however, the 3-year restenosis rate remained significantly lower in brachytherapy patients than placebo patients (33% versus 64%, P<0.05).¹⁴ Major Adverse Clinical Events (MACE) were significantly lower in the radiation group compared with the placebo group at 6 months (29% versus 68%, P<0.001) and 3 years (23% versus 55%, P=0.01, respectively). Leon et al.⁵ detailed the outcome of a triple-blind, randomized, controlled trial, designated Gamma-One. Gamma-One utilized the Checkmate System, recently approved by the FDA, for the delivery of gamma radiation. In this study, 252 patients were randomly assigned either to a treatment group that received radiation after the obstruction within a stent had been corrected or to a control group. In the control group, the inactive wire, which does not deliver radiation, was deployed. In this triple-blind study, the patient, the interventional cardiologist, and the evaluators of follow-up studies, were unaware of the assigned treatment. According to the authors, there was a large treatment benefit for patients who received brachytherapy, with a 41 percent relative reduction (as compared with the placebo group) in the recurrence of obstruction requiring revascularization of the target lesion. A companion benefit was reported in the composite primary end

point of major adverse cardiac events; which included death, the need for emergency coronary bypass surgery, myocardial infarction, and the need for revascularization of the target. However, there was a high incidence of delayed obstruction of stents due to thrombosis in the group that received radiation.

Appendix II summarizes data from two randomized controlled trials and a single case series that investigated the effects of catheter-based g-brachytherapy following interventional procedures in patients with arterial stenosis.

In another study which used the recently FDA approved beta radiation delivering system (Beta-Cath System) 22 for brachytherapy, patients were randomly assigned to brachytherapy or placebo after receiving revascularization treatment for in-stent stenosis. In this study, unlike the Gamma-One trial, the implantation of new stents was avoided, and adjunctive antiplatelet therapy was given for at least 90 days after the procedure. A total of 476 patients underwent randomization in this triple-blind study, and among the 242 patients assigned to receive brachytherapy, only 51 (21%) received new stents. In Gamma-One, by contrast, 111 of the 131 patients in the brachytherapy group (85%) received new stents. In the Beta-Cath System study, no thrombotic events occurred in the radiation group during 240 days of follow-up. At eight months, restenosis had occurred in 14 percent of the stented segments in patients who had received radiation, as compared with 41 percent of the controls.¹

A small early case series (n=21) demonstrated that catheter-based g-brachytherapy was safe and feasible.²³ The authors reported a 1-year MACE-free survival rate of 80.9% following brachytherapy. However, in the absence of a control group, this early trial does not allow for definitive conclusions regarding the efficacy of brachytherapy.

The Proliferation Reduction with Vascular Energy Trial (PREVENT) was the only randomized controlled trial of b-brachytherapy found in the peer-reviewed medical literature. PREVENT had 105 patients with de novo lesions, restenotic lesions, or restenotic in-stent lesions enrolled. Following balloon angioplasty or stenting, patients were randomized to placebo radiation (n=25) or three varying radiation doses (n=80). At six month post-radiation, restenosis rates were significantly lower in the radiation group at the target site (8% versus 39%; P=0.012) and at the target site plus adjacent segments (22% versus 50%, P<0.05). At 12-month follow-up, significantly fewer target lesion revascularizations were required in brachytherapy patients (6%) compared with the control group (24%, P<0.05). However, seven myocardial infarctions (MI) occurred in the brachytherapy group after hospitalization, whereas none of the control group suffered late occlusive events. According to the authors, the incidence of late thrombosis greatly diminished the clinical benefit of brachytherapy that might have been expected by the impressive reduction in angiographic stenosis.¹⁵

As a counterpart to the Washington Radiation for In-Stent Stenosis Restenosis Trial (WRIST)¹¹ randomized controlled study, Waksman et al.²⁴ investigated b-brachytherapy in a case series. At six months, the angiographic and clinical data of treated b-WRIST patients (n=50) were compared with the results obtained in g-WRIST placebo patients. Compared with g-WRIST control patients, angiography demonstrated that late luminal loss and the loss index were significantly lower in b-WRIST patients than control patients. Additionally, MACE (34% versus 66%, respectively) and angiographic restenosis (34% versus 72%, respectively) were significantly lower in the b-WRIST group (P>0.01). However it was noted that late total occlusion, which occurred in five patients, was a major limitation of radiation.²⁴

In a case series, Costa et al.²⁵ evaluated the incidence of late thrombotic events in 108 patients with de novo lesions following b-brachytherapy. The treatment protocol varied between patients; stents were implanted in some patients and two different brachytherapy systems were utilized to deliver radiation at different doses. Since a high percentage of irradiated patients experienced late thrombotic events (6.6%), the authors assert that further studies should address whether radiation is the key factor in the pathogenesis of late thrombosis.²⁵

In two case series, Meerkin et al.²⁶ and King et al.¹⁷ utilized ⁹⁰Sr/Y brachytherapy to treat ischemic patients (n=30 and n=23, respectively) with single de novo lesions of a native coronary vessel in two case series. Angiographic restenosis developed in 3 of 30 patients (10%) in the first study and 3 of 20 patients (15%) in the second. King et al. reported that one restenosis was a total occlusion, which may have been an early thrombotic event.¹⁷

In a recent report by Verin et al.¹ 181 patients were randomly assigned to receive 9, 12, 15, or 18 Gy of radiation delivered by a centered yttrium-90 source after successful balloon angioplasty of a previously untreated coronary stenosis. Adjunctive stenting was required in 28 percent of the patients. The primary end point was the minimal luminal diameter six months after treatment, as a function of the delivered dose of radiation. At the time of follow-up coronary angiography, the mean minimal luminal diameter was 1.67 mm in the 9-Gy group, 1.76 mm in the 12-Gy group, 1.83 mm in the 15-Gy group, and 1.97 mm in the 18-Gy group (P=0.06 for the comparison of 9 Gy with 18 Gy), resulting in restenosis rates of 29 percent, 21 percent, 16 percent, and 15 percent, respectively (P=0.14 for the comparison of 9 Gy with 18 Gy). At that time, 86 percent of the patients had had no serious cardiac events. In 130 patients treated with balloon angioplasty without a stent, restenosis rates were 28 percent, 17 percent, 16 percent, and 4 percent, respectively (P=0.02 for the comparison of 9 Gy with 18 Gy). Among these patients, there was a dose-dependent enlargement of the lumen in 28 percent, 50 percent, 45 percent, and 74 percent of patients, respectively (P<0.001 for the comparison of 9 Gy with 18 Gy). The rate of repeated revascularization was 18 percent with 9 Gy and 6 percent with 18 Gy (P=0.26).¹

Appendix III summarizes the findings of studies investigating catheter-based intracoronary b-radiation.

Radioactive Stents

In a small (n=23) case series, 17% of patients implanted with radioactive stents developed in-stent stenosis at 6 months and 13% of patients required repeat revascularization.²¹ Angiography demonstrated that implanted patients experienced a significant loss in minimum lumen diameter relative to the post-procedure minimum lumen diameter (P<0.0001). The authors also reported an "edge," or "candy wrapper," effect, defined as a decrease in mean diameter 5-mm distal and proximal to the stent edges, which was statistically significant.

Albiero et al.¹⁹ conducted a case series to evaluate the safety and efficacy of radioactive stents with varying dose levels. At six-month follow-up, a high intra-lesion restenosis rate was noted (range, 41 to 52%) that was not statistically different between dose levels. The authors attributed the high intra-lesion restenosis rate to a loss of lumen diameter at the stent edges. The precise mechanism by which this edge, or candy wrapper effect occurs remains poorly understood. Albiero et al. conjecture that this exaggerated proliferative response may be the result of low-dose radiation combined with vessel injury. To evaluate whether higher-level radioactive stents implanted with a non-aggressive stent technique could eliminate this candy wrapper effect, Albiero et al.²⁰ conducted a second comparative study. When the results from the two studies were compared, the data demonstrated that the high-dose/non-aggressive technique more effectively reduced neo-intimal hyperplasia than the low-dose/aggressive strategy ($4.4 \pm 5.6\text{-mm}^3$, $15.1 \pm 14.1\text{-mm}^3$, respectively; P<0.01). The rate of focal restenosis at the stent edges was not significantly different between the two studies. The authors concluded that although a higher initial stent activity level and a reduction in the balloon-induced injury reduced plaque growth, this technique did not solve the problem of edge stenosis associated with radioactive stents. Appendix IV summarizes the findings of studies investigating radioactive stents for the treatment of in-stent restenosis.

Patient Selection Criteria

Specific patient selection criteria have not been fully established at this time. Removable source catheter-based brachytherapy is indicated at this time only for in-stent restenotic lesions within native coronary artery.

The following study exclusion criteria have been used when enrolling patients into brachytherapy study protocols and their role in risk benefit outcomes in these population subsets should be further clarified:

- Contraindication to aspirin, ticlopidine, or stainless steel
- Prior chest brachytherapy
- Pregnancy
- Life-threatening coexisting condition
- Evidence of myocardial infarction within 3 days prior to brachytherapy
- Severe peripheral vascular disease
- Anticipated difficulty with follow-up
- Serum creatinine > 2.0 mg/dL
- Left ventricular ejection fraction < 40%
- Unprotected left main coronary artery disease

- Lesion angulation > 45°
- Intraprocedural angiographic evidence of thrombus, spasm, or dissection
- Multiple lesions in the same vessel
- Bifurcation or aorto-ostial lesions

Note: NRC currently does not allow the treatment of bifurcation lesions or extremely large lesions where fragments would require overlap and thereby double dosing of segments.

Issues of Clinical Controversy

Study Design: Currently, randomized evidence for the prevention of restenosis in patients with in-stent restenosis is limited to the catheter-based g-brachytherapy. Although one randomized study of catheter-based b-radiation has been conducted, patient selection criteria were heterogeneous, the treatment protocol prior to randomization was nonstandard, and patients were randomized to three different radiation doses or placebo. Trials of radioactive stents are limited to single-arm studies with small patient populations.

The majority of brachytherapy trials consist of small case series conducted at a limited number of treatment centers. The total number of patients who have participated in the published trials is small, and both clinical and angiographic follow-up have been short. Although three-year follow-up data have been published for the SCRIPPS trial, clinical follow-up in the other trials did not exceed 12 months. Longitudinal studies are lacking; patients were followed for six months in most studies. Patient selection criteria were not standard. Enrolled patients had de novo lesions, restenotic PTCA lesions, or restenotic in-stent lesions in aortocoronary bypass grafts or native coronaries. Trial results applied to a mixed group of patients who presented with stenosis, rather than a specific subset of patients. Treatment protocols varied between trials; some patients were administered radiation in conjunction with balloon dilation alone, or balloon dilatation combined with stenting, atherectomy, or excimer laser angioplasty. The optimum isotope and dose is yet to be identified for catheter-based radiation techniques. Researchers generally agree that further well-designed, large, randomized, controlled trials are required to determine the long-term effects of radiation on restenosis.¹³

Optimum Radiation Isotope and Dosing: The optimal radiation source has yet to be identified. Raizner et al.¹⁵ points out that both b- and g-radiation have their advantages and limitations. As compared with g-radiation, b-radiation has a more limited penetrability that may have inherent safety advantages. On the other hand, b-radiation may be ineffective, due to lesser penetration of the artery wall, particularly in stented arteries.^{15,27} The homogeneity of the distribution dose achieved in the vessel wall with radiation brachytherapy is problematic. Both b- and g-brachytherapy administer a relatively broad radiation dose to the vessel wall since the radiation dose rapidly declines at small increases in distance from the source state that b-emitters demonstrate a more rapid dose falloff than g-emitters.^{17,28}

Detailed, randomized, dose-finding studies have not been performed for g-radiation and only one has been performed for b-radiation. In studies, the prescribed doses generally vary from a mean dose of 12 to 18 Gy at a distance of 2-mm from the source while, due to geometrical factors, the actual delivered doses may be significantly higher or lower in different parts of the vessel. Kuntz and Baim¹² state that the importance of finding the optimal dose is underscored by the suggestion that doses less than 10 Gy may be stimulatory, as was found in one porcine study, or affect vascular contraction adversely. Current radiation techniques administer low doses to deeper vascular structures and just beyond the end of the indwelling source. If such areas were exposed to the mechanical trauma of a balloon injury beyond the edge of the radiation source, this might explain the intense candy wrapper effect seen at the ends of some radioactive stents or irradiated arterial segments. The minimum radiation dose that will prevent excessive hyperplasia without interfering with the healing process has yet to be determined.

Geographic Miss and Edge Effect: Geographic miss refers to treatment failure caused by an insufficient dose of radiation administered to the full extent of the treatment area. In such cases, a portion of the treatment zone may escape radiation or be inadequately irradiated due to a misalignment of the radioactive source with the lesion or miscalculation of the lesion size.^{8,29} Sabaté and colleagues analyzed the incidence and causes of geographic miss in the treatment of 50 patients with b-brachytherapy after PTCA.²⁹ Angiograms of the irradiated segments were studied prior to the procedure and at six-month follow-up. Geographic miss, or a combination of injury and low-dose radiation, was observed in 22 edges (31.9%), which were induced by balloon dilatation (n=13) or additional stent

implantation (n=9). Geographic miss was due primarily to procedural complications that extended the treatment beyond the margins of the irradiated segment. Late loss was significantly higher in geographic miss edges (0.84 ± 0.6 -mm) than in fully irradiated segments (0.15 ± 0.4 -mm) and uninjured edges (0.09 ± 0.4 -mm, $P < 0.0001$). Edge, or candy wrapper, restenosis at the ends of the treatment zone may suggest a stimulatory effect of subtherapeutic radiation doses or the failure to deliver the prescribed radiation dose to an appropriate target depth in an injured target vessel segment.¹² Edge restenosis rates were significantly higher in geographic miss edges (40.9%) than within the irradiated segment (10%) or in the uninjured edges (1.9%; $P < 0.001$). Therefore, the authors concluded that the combination of injury and low-dose b-radiation induces a harmful outcome.²⁹

Raizner et al.¹⁵ also reported that, although b-radiation dramatically inhibited the restenotic process at the lesion site, narrowing occurred at or adjacent to the edge of the radiation zone. In some cases, "geographic miss" caused restenosis. However, in other patients, edge narrowing developed despite the fact that the radiation treatment seemed to overlap the zone appropriately. Angiographic analysis of the target site at six months demonstrated restenosis in only 8% of the target lesions versus restenosis in 22% of the target sites plus adjacent segments. The authors stated that minimizing edge narrowing must be accomplished to maximize the clinical benefit of b-brachytherapy.

Late Thrombosis: There may be an increase in the incidence of myocardial infarction after percutaneous coronary revascularization in patients who receive intracoronary brachytherapy, possibly as a result of late thrombosis. A review of both randomized and nonrandomized studies of intracoronary brachytherapy found that 9% of the patients who received radiation had late thrombosis, as compared with less than 2% of the patients who did not receive radiation.³⁰ It has been hypothesized that late thrombosis is caused by the pronounced delay in endothelialization that occurs after exposure to radiation. Current trials are examining whether prolonged antiplatelet therapy and less repeated stenting can prevent this complication and most investigators now believe this to be less than 2%.

Waksman et al.³⁰ report that late thrombotic occlusion, occurring 30 days or more after brachytherapy, is a new phenomenon associated with the use of catheter-based radiation. The authors note that thrombotic occlusion following balloon angioplasty usually occurs within 24 hours after the procedure. Stenting is associated with subacute thrombosis, generally within 30 days of implantation, which is well controlled by antiplatelet therapy. To evaluate the incidence of late total occlusion in brachytherapy patient, the investigators reviewed the records of 473 patients with in-stent restenosis who were enrolled in various radiation protocols, whether randomized to placebo versus radiation or entered into registries. The study included 165 control patients and 308 irradiated patients. Patients completed at least six months of angiographic follow-up and received antiplatelet therapy for one month. Late total occlusion was significantly higher in irradiated patients (28/308, 9.1%) than the control group (2/165, 1.2%; $P < 0.0001$). Multivariate analysis determined that new stenting was the main predictor of late total occlusion. The late total occlusion rate among newly stented patients was 14.6%, whereas the total late occlusion rate in patients devoid of new stents was 3.8%.³⁰

Although the exact mechanism is unknown, Raizner et al. speculate that brachytherapy may delay the formation of "protective" neointima, thus affording an opportunity for exposed stent material or a disrupted lesion that may become a cause for subsequent coronary thrombosis.¹⁵ Researchers conjecture that minimizing the use of new stenting in brachytherapy patients may reduce late thrombosis. Additionally, the benefit of prolonged antiplatelet therapy requires further analysis in future brachytherapy trials. Further studies are required to define the true incidence and origin of late thrombosis, as well as the factors that contribute to it.^{15,25,30}

Effect on Vascular Remodeling: Researchers theorize that b- and g-radiation prevent neointimal proliferation by killing more rapidly dividing smooth muscles cells. However, Sabaté et al. indicate that the effect of brachytherapy on vascular remodeling is largely unknown.¹⁰ Therefore, the authors used intravascular ultrasound imaging to determine the evolution of coronary vessels dimensions in 21 patients following b-radiation and successful balloon angioplasty. The enrolled patients had single de novo lesions; treatment was delivered with the Beta-Cath System at 12, 14, or 16 Gy. Volumetric calculations demonstrated that, in the irradiated segments, mean external elastic membrane (EEM) and plaque volumes increased significantly (451 ± 128 to 490 ± 159 -mm³ and 201.2 ± 59.0 to 241.7 ± 74.0 -mm³, $P = 0.01$), whereas luminal volume remained unchanged (250.8 ± 91.0 to 249.2 ± 102.0 -mm³). The edges showed an increase in mean plaque volume (26.8 ± 12.0 to 32.6 ± 10.0 -mm³; $P = 0.0001$) and no net change in mean EEM volume (71.4 ± 24.0 to 70.9 ± 24.0 -mm³), resulting in a decrease in mean

luminal volume (44.6 ± 16.0 to 38.3 ± 16.0 -mm³; $P=0.01$). The authors concluded that, in the irradiated segments, the increase in luminal volume was primarily due to vessel enlargement, or an adaptive increase of EEM volume, rather than plaque reduction. Compared with the pattern of remodeling within the irradiated segment, the edge segments demonstrated a significant decrease in mean luminal volume due to an increase in plaque volume without a net change in EEM volume.¹⁰

A potential limitation of radiation therapy is the possibility that favorable short-term remodeling could lead to late deleterious aneurysm formation. Although the incidence and prognosis of aneurysm formation after radiation is largely unknown, Sabaté et al. reported one case (5%) of aneurysmatic formation at a six month follow-up.¹⁰ Condado et al. reported that four patients (20%) developed aneurysms within two months of γ -radiation.²³ Further longitudinal clinical trials are needed to substantiate the pattern of vascular modeling reported in this short-term study.

All but one of the trials have used a composite clinical end point that includes revascularization of the target lesion. In each of the studies, the reduction in the occurrence of this end point appeared to be driven entirely by the reduction in the need for revascularization of the target lesion. Because angiography was performed routinely at six months in each of the trials and clinical follow-up was conducted at 9 to 12 months, the reduction in the need for revascularization of the target lesion may well have resulted from the protocol-mandated angiography. As has been documented in previous angiographic trials, if cardiologists identify a restenotic lesion on protocol-mandated angiography, they are likely to redilate it.³¹

Safety

Food and Drug Administration (FDA)

The FDA approved the Cordis Checkmate[®] System and the Beta-Cath[™] System in November, 2000. According to the FDA, the two systems were shown to be safe and effective in reducing the need for additional interventions for the treatment of in-stent stenosis.³²

However, intracoronary brachytherapy may be associated with a number of other complications. Weeks to months after the administration of intracoronary brachytherapy, restenosis may occur at the proximal and distal edges of the irradiated zones. Mitogenic stimulation by low-level radiation that penetrates beyond the targeted treatment areas raises the specter of delayed oncogenesis in neighboring soft tissue and has been implicated in the constriction of vessels at the margins of irradiated stents, the so-called "candy wrapper" or "edge" effect.^{1,19} Coronary pseudoaneurysms were reported in one study,²³ and technical problems, such as loss of radioactive seeds or stents, may potentially occur. Secondary cancer and coronary arteriopathy have occurred years after external-beam brachytherapy for illnesses such as Hodgkin's disease and breast cancer. However, little is known about the likelihood of these complications in the case of intracoronary brachytherapy, due to the small number of clinical trials, which have been published, and the limited follow-up data available. These issues must be fully resolved with carefully designed clinical trials, the results of which could justify the evidence-based expansion of indications for a promising therapy for coronary and other vascular disease.

Cost Effectiveness

It has been reported that a 55 year-old male with symptomatic, single-vessel coronary disease treated by PTCA would have a quality-adjusted life expectancy of about 19.25 years and an expected lifetime treatment cost of \$52,500.³³ Analysis of the economic outcome of the STRESS-I trial by Cohen et al., has demonstrated that, compared with PTCA, primary stenting was associated with significantly higher initial hospital charges (\$9,738 vs \$7,505; $p < .001$), mainly because of a significantly longer hospital stay (7.5 vs 4.8 days; $p < .001$) and higher catheterization laboratory charges (\$4,705 vs \$3,643; $p < .001$).³⁴ Follow-up hospital charges during the next year were lower for stenting than for PTCA alone (\$1,918 vs \$3,359; $p = .21$). Nonetheless, cumulative one-year medical care charges remained higher for patients undergoing initial stenting (\$11,656 vs \$10,865).³⁴ However, recent data suggest that stented patients are routinely discharged one day after the procedure. There is no national coverage policy for catheter-based brachytherapy or radioactive stents and the direct cost effectiveness of brachytherapy treatment is not available at present. At present, catheter based brachytherapy using the Cordis Checkmate[™] System, the Beta-Cath[™] System or the Galileo[™] System are reimbursed by the Medicare program as an outpatient procedure.³⁵

Future of the Procedure

Preliminary results of the Stents and Radiation Therapy Trial (START) demonstrated that b-radiation reduced the frequency of repeat blockages by as much as 66%, according to the study's principal investigators. START, a multi-center, placebo-controlled study to evaluate the safety and effectiveness of b-radiation for the treatment of in-stent restenosis, enrolled 476 patients at centers in North America and Europe. At eight-month follow-up, patients treated with b-radiation had a significant reduction in major adverse cardiac events, as well as a 34% reduction in the number of repeat procedures. A 66% reduction in restenosis was reported within the stent itself. Of the patients who were implanted with new stents, no cases of clinical stent thrombosis were recorded.

Patients are currently being enrolled in the Galileo Intimal Hyperplasia Inhibit with Beta In-stent (INHIBIT) registry, from which data will be analyzed to evaluate the safety and efficacy of the Galileo™ Intravascular Brachytherapy for the treatment of in-stent restenosis. This multi-center registry will include data from patients with in-stent restenosis who underwent brachytherapy with the Galileo™ system for the development of restenosis following a successful interventional cardiology procedure, including PTCA, stent, atherectomy, or laser angioplasty.

Researchers are investigating modifications to the existing ³²P radioactive stents to reduce problematic edge stenosis, or the candy wrapper effect. Scientists are proposing the use of a "hot-ends" stent, which has a higher activity level at its proximal and distal ends. This higher activity level might reduce edge restenosis related to tissue proliferation and/or remodeling since the area of irradiation is extended beyond the balloon-injured area outside the stent. The use of a "cold-edge" stent, which is longer than current stents and is devoid of radiation at the stent edges, is also under consideration. Researchers postulate that the cold-edge stent might diminish the edge effect related to negative remodeling. Intravascular ultrasound analyses demonstrated that negative remodeling was the principle mechanism of edge restenosis in radioactive stents with an activity of 12 to 21 mCi implanted using a nonaggressive strategy in a study conducted by Albiero et al.²⁰

Until recently, only three placebo-controlled trials examining catheter-based intracoronary brachytherapy have been published. The SCRIPPS trial and the WRIST trial randomly assigned patients who underwent percutaneous coronary revascularization for restenosis to receive either placebo or iridium-192 (gamma radiation). The PREVENT trial randomly assigned patients to receive placebo or phosphorus-32 (beta radiation). Results from these trials demonstrate that catheter-based intracoronary brachytherapy reduces the rates of restenosis, but questions were raised regarding potential increases in the rates of myocardial infarction secondary to late thrombosis.

Given the absence of effective interventional treatments and the reported efficacy of catheter-based g-radiation in two randomized trials, g-radiation should be considered a treatment option for native coronary arteries with in-stent restenosis following successful PTCA for the purpose of preventing coronary artery restenosis. Due to a lack of data from well-designed longitudinal randomized clinical trials, catheter-based g-brachytherapy in patients with non-stented lesions is not yet supported by sufficient strong, scientific data to consider it safe and efficacious. Catheter-based b-brachytherapy for the treatment of native coronary arteries to prevent restenosis in stented and de novo lesions is an evolving technology that shows considerable promise; however, more scientific evidence needs to be published to support this technology as safe and efficacious. Radioactive stents for the treatment of de novo or restenotic lesions due to high intralumenal restenosis rates and high late luminal losses proximal and distal to the stent edges should currently be considered investigational treatments that require more evidence from well-designed, randomized controlled trials. Thus, many questions need to be answered before intracoronary brachytherapy receives widespread acceptance. Intracoronary brachytherapy is a new, exciting technology that is still in its infancy. Until these questions are answered, physicians should remain cautious in their use of intracoronary brachytherapy for the prevention and treatment of restenosis. Limited availability of trained radiation oncologists may impact the widespread use of this emerging technology.

Drug eluting stents are currently under investigation and may serve as competitive technology. Preliminary data from a series of pre-clinical studies using a drug eluting stent (consisting of a timed-release polymer containing Actinomycin D) demonstrated a marked reduction in the growth of cells at the site of drug eluting stent in comparison to stent placement without the drug. Histologic data indicated a significant reduction in hyperplasia (the re-growth of cells at the treated site) as compared to the control stent. Drug eluting stent systems are expected to begin human clinical studies with this stent

in the second half of 2001.³⁶ In July 2001, the FDA approved the first stent designed exclusively for small vessels in patients presenting with abrupt and threatened abrupt closure due to unsuccessful interventional therapy. The MULTI-LINK PIXEL stent is approved in de novo (first time) and restenotic (re-occurring) native coronary artery lesions.³⁷

Conclusions

Catheter-based g-brachytherapy in patients with de novo or non-stented restenotic lesions is not yet supported due to absence of data from well-designed longitudinal randomized clinical studies and because of lack of sufficiently strong, long-term scientific and clinical data.

Catheter-based b-brachytherapy for the treatment of native coronary arteries to prevent restenosis in de novo lesions is an evolving technology that shows considerable promise; however, more scientific and clinical evidence needs to be published to support this technology as safe and efficacious in this patient population.

Radioactive stents for the treatment of de novo or restenotic lesions due to high incidence of late luminal losses, proximal and distal to the stent edges, should currently be considered investigational treatments that require further technological adaptations of current radioactive stent platforms and more evidence from well-designed, randomized controlled trials.

Recommendations

Application of brachytherapy has been proposed as a treatment and for the prevention of coronary artery restenosis. Research on the effectiveness and long-term outcomes of intracoronary brachytherapy is lacking at this time. The best current evidence is for the short-term safety and efficacy of the, FDA approved, catheter-based g-brachytherapy for the treatment of restenosis following conventional therapy. The FDA has also approved catheter-based b-brachytherapy. While it is tempting to endorse these treatments due to the seriousness of the disease and the recent FDA approval of the technology, a strong recommendation would be premature. Fundamental questions remain to be answered concerning patient selection criteria, optimal radiation dose, effectiveness outside the research setting, and long-term outcomes. It is recommended that physicians discuss the potential risks and short-term benefits of these treatments with the patients. At the present time, both catheter-based g and b - brachytherapy should be used only in controlled settings that generate data on the intervention's safety and efficacy.

The use of radioactive stents is restricted to clinical trials, and the FDA has not approved their use. Results of trials using radioactive stents have been limited to single-arm studies with small sample sizes and short outcome horizons. Therefore, the use of radioactive stenting cannot be recommended outside of clinical trials.

Current evidence does not support the recommendation of either catheter or stent-delivered intracoronary brachytherapy for the prevention of restenosis of primary (de novo or non-stented) coronary artery stenosis.

Appendix I: Methodology

Search Strategy: Studies related to intracoronary brachytherapy were identified by a search in the MEDLINE, Current Contents, and FDC Reports databases utilizing the keywords radioactive stents, intracoronary brachytherapy, intracoronary radiation, and restenosis. The search was conducted for studies published between 1997 and July 2001 and supplemented by a manual search of references from selected published articles. The preliminary results of additional studies were found in abstract form; however, pending publication in the peer-reviewed medical literature, data from these preliminary studies have not been reviewed for this report.

Literature Review: Clinical and angiographic outcomes were used as endpoints to evaluate the safety and efficacy of intracoronary brachytherapy following angioplasty and stenting. Researchers reported the rate of myocardial infarctions, deaths, or repeat revascularizations as major adverse clinical events (MACE). The percentage of target lesion revascularizations, consisting of coronary angioplasty or surgical bypass, were reported when revascularizations were required due to $\geq 50\%$ diameter stenosis of the irradiated segment. Nontarget-lesion revascularization rates, or revascularization rates of an epicardial vessel that did not contain the target lesion, were also reported in some studies. Some

researchers defined binary stenosis of the target vessel as angiographically diagnosed stenosis $\geq 50\%$ of the luminal diameter of the stent and/or stent margin proximal and distal to the radiation source.

Appendix II: Catheter-Based Intracoronary Brachy Therapy Radiation

Key: f/u, follow-up; γ , gamma; grp(s), group(s); Gy, Gray; ^{192}Ir , 192 Iridium; IVUS, intravascular ultrasound study; MACE, major adverse clinical events; pt(s), patient(s); RCT, randomized controlled trial; TLR, target lesion revascularization; TVR, target vessel revascularization; tx, treatment.

Authors/Study Design	Study Population	Results	Conclusions/Comments/Limitations
<p>Leon et al (2001) (Gamma-one Trial)</p> <p>Multi-center, double blind, randomized trial of intracoronary radiation therapy for treatment of in-stent restenosis.</p>	<p>n=252</p> <p>Pts. with in-stent restenosis randomized to receive iridium-192 (n=131) or similar-appearing non-radioactive placebo (n=121).</p>	<p>At 9 months follow-up the primary end-point, a composite of death, myocardial infarction and the need for repeat revascularization occurred in 53 patients assigned to the placebo group (43.8%) and 37 patients assigned to iridium-192 (28.2%, p=0.02). Late thrombosis occurred in 5.3% of the iridium-192, as compared with 0.8 % of the placebo group (p=0.07), resulting in more late myocardial infarctions in the iridium-192 group (9.9% vs. 4.1%, p=0.09).</p>	<p>Intracoronary irradiation with iridium-192 resulted in lower rates of clinical and angiographic restenosis. It was also associated with a higher rate of late thrombosis, resulting in an increased risk of myocardial infarction.</p>
<p>Waksman et al. (2000a) γ-WRIST Investigators)</p> <p>Washington Hospital Center, Washington, DC</p> <p>Prospective, double-blind, RCT evaluating safety and effectiveness of γ-radiation therapy compared with placebo as an alternative for pts requiring tx for in-stent restenosis; f/u, 12 mos.</p>	<p>n=130</p> <p>Pts with in-stent restenosis in native coronaries or aortocoronary bypass grafts randomized to ^{192}Ir ribbon (n=65) or placebo (n=65); 15 Gy; additional stents implanted as required; repeat angiography and IVUS at 4 to 8 mos post-radiation.</p>	<p>At 6 mos. Irradiated pts required significantly less TLR and TVR (13.8% and 26.2%; respectively) than placebo pts (63.1%, P=0.001; 67.7%, P=0.0001, respectively). Angiographic binary restenosis rate significantly lower in the irradiated group (19% vs 58%, P=0.001). MACE significantly lower in the irradiated group (29.2% vs 67.7%, P<0.001).</p> <p>Between 6 and 12 mos, TLR increased by 9.3% and TVR increased by 7.6% in the irradiated group only. Greatest radiation tx benefit was within the stent; significantly higher later luminal loss observed in the segment including the stent edges (0.36 \pm 0.74) vs the segment only including the stent (0.22 \pm 0.84) (P=0.04).</p>	<p>A 6 mos, the angiographic and clinical benefits of irradiation surpassed those of placebo. However, the increase in the revascularization rate between 6 and 12 mos in the irradiated group suggests that radiation may delay the biological processes and that a late "catch-up" phenomena or late thrombosis may ultimately minimize the long-term benefit of radiation. Additionally, late luminal loss occurred at the irradiated stent edges. Authors conjecture that treating longer margins may reduce the stenosis rate at the edges. Longitudinal trails are needed to document long-term results of radiation.</p> <p>Limitations: Small study population limits the generalizability and statistical power of the results; nonstandard tx protocol.</p>
<p>Teirstein et al. (2000)</p> <p>Scripps Clinic and Research Foundation, La Jolla, CA</p> <p>Multi-center, double-blind, RCT evaluating ^{192}Ir γ- brachytherapy vs placebo for tx of pts w/restenotic stented coronary arteries; f/u, 3 yrs.</p>	<p>n=55</p> <p>Pts with restenotic coronary arteries that either already contained a stent (62%) or were candidates for stent placement (38%), randomized to ^{192}Ir (n=26) or placebo (n=29); 800-3000 cGy; single stents implanted in all pts; additional stents implanted if required</p>	<p>At six mos, restenosis rates were significantly lower in ^{192}Ir pts (17% vs 54%; P=0.01). At 3 yrs f/u, TLR was significantly lower in the ^{192}Ir grp (15.4% vs 48.3%, P<0.01). Restenosis either within the stent or at its border was significantly lower in irradiated pts (33.3% vs 63.6%; P<0.05) at 3 yrs.</p> <p>In the sub-grp of pts who did not undergo TLR, a small (0.37 mm, P=0.15) late loss in the minimal lumen diameter occurred in irradiated pts</p>	<p>At 3 yrs, TLR and dichotomous restenosis, either within the stent or at its border, was significantly lower in ^{192}Ir pts. Although the clinical benefits of radiation appear durable, a small amount of angiographic loss was observed between 6 mos and 3 yrs.</p> <p>Increase in restenosis rate in tx pts from 17% to 33% over 3-yr duration raises concerns about the prognosis. A longer f/u period is required</p> <p>Limitations: Patient selection criteria not homogenous; some pts had in-stent stenosis while others did not; nonstandard tx protocol; more diabetic pts in placebo grp; more asymptomatic pts in placebo grp refused 3-yr angiography, which may have increased the restenosis rate recorded</p>

		(n=17), while the placebo group (n=10) remained unchanged. In the irradiated group, TLR was reduced by 74% at 6 mos and 68% at 3 yrs. Angiographic restenosis was reduced by 69% at 6 mos and 48% at 3 yrs due to small reductions in luminal diameter.	in the placebo arm; small study population limits the generalizability and statistical power of the results.
		MACE was significantly lower in tx group (23.1% vs 55.2%; $P=0.01$) at 3 yrs	
Condado et al. (1997)	n=21	At 30 to 60 days post-radiation, angiography demonstrated total occlusion in 2/22 arteries (9%), a new pseudoaneurysm in one artery, and significant dilatation at the tx site in two additional vessels. At \geq six mos f/u, all 20 remaining arteries demonstrated patency; calculated late luminal loss was 0.27 ± 0.56 -mm, and late loss index was 0.19. Clinical events at 1 yr included MI in 1 pt, repeat angioplasty in 3 pts, and persistent angina in 7 pts.	Preliminary results indicate that γ -radiation, after coronary intervention, is feasible and associated with an acceptable degree of complications. According to the authors, lower restenosis rates are achieved with brachytherapy compared with conventional tx. However, the presence of total occlusion at 2 radiation treated sites at 30 and 38 days is a potential concern. Longitudinal trials are needed to document long-term results.
Hospital Miguel Perez-Carrefio, Centro Medico Caraca, Venezuela	Pts with unstable angina and at least one high-grade stenotic lesion that required PTCA; majority of lesions (77.3%) were de novo; stents implanted in 2 pts; 1 pt underwent rotational atherectomy; radiation delivered with ^{192}Ir wire at 25 Gy (n=9), 20 Gy (n=11), and 18 Gy (n=1)		Limitations: Uncontrolled design; nonstandard tx protocol; small study group limits the generalizability to larger population; historical controls not adequate for accurate comparisons.
Case series evaluating the safety, feasibility, and effectiveness of γ -radiation for tx of stenotic lesions; f/u, 1 yr			

Appendix III: Catheter-Based Intracoronary Brachytherapy with β -Radiation

Key: β , beta; Gy, grays; EEM, external elastic membrane; grp(s), group(s); IVUS, intravascular ultrasound; MACE, major adverse clinical events; MI, myocardial infarction; MLD, minimal lumen diameter; NS, not significant; ^{32}P , $^{32}\text{Phosphorous}$; PTCA, percutaneous transluminal coronary angioplasty; PREVENT, Proliferation Reduction with Vascular Energy Trial; p(s); patient(s); TLR, target lesion revascularization; TVR, target vessel revascularization; $^{90}\text{Sr/Y}$, $^{90}\text{Strontium/Yttrium}$.

Authors/Study Design	Study Population	Results	Conclusions/Comments/Limitations
Raizner et al. (2000a) for the PREVENT Investigators Baylor College of Medicine, Houston, TX Prospective RCT evaluating safety and effective-ness of β -brachytherapy vs placebo in pts with de novo or restenotic lesions treated by stenting or angioplasty; f/u, 12 mos	n=105 Pts with de novo (70%) or restenotic PTCA or in-stent lesions (30%) randomized to controls (n=25) or 16 Gy (n=26), 20 Gy (n=27), or 24 Gy (n=27) β -radiation; pts underwent balloon angioplasty (39%) or stenting (61%) prior to brachytherapy with a ^{32}P encapsulated wire.	At 6-mos, significantly lower late loss index in irradiated pts vs controls ($11 \pm 36\%$ vs $55 \pm 30\%$, respectively; $P<0.00001$). Significantly lower restenosis rates in the ^{32}P group at the target site (8% vs 39%; $P=0.012$) and at the target site plus adjacent segments (22% vs 50%, $P=0.018$). Edge restenosis at the radiated target sites increased the angiographic restenosis rate by 14%. At 12 mos, clinical examination found no significant difference in MACE (death, MI, and TLR) for irradiated pts vs control pts (16% vs 24%, $P=NS$). TLR required in significantly fewer irradiated pts (6% vs 24%, $P<0.05$). Post-hospitalization MIs occurred in 7/80 brachytherapy pts while none occurred in	Brachytherapy appears to be safe and effective in reducing neointima within the target site. However, arterial stenosis adjacent to the target site and unexpected late thrombo-occlusive events reduced the overall clinical benefit of brachytherapy. Since new stents were implanted in 6/7 radiation pts who suffered post-hospitalization MIs, the authors speculated that reducing the implantation of new stents might minimize the occurrence of late thrombotic events. Longitudinal studies are required to determine long-term effects. Limitations: Study not sufficiently powered to demonstrate statistically significant differences in the overall MACE event rates; heterogeneous pt selection criteria; nonstandard tx protocol.

		control pts.	
<p>Waksman et al. (2000b)</p> <p>(β-WRIST Investigators)</p> <p>Vascular Brachytherapy Institute, Washington Hospital Center, Washington, DC</p> <p>Case series investigating the safety and efficacy of β-brachytherapy for in-stent restenosis compared with retrospective data of γ-WRIST placebo pts; f/u, 6 mos.</p>	<p>n=50</p> <p>Pts with in-stent restenosis in previously stented native coronaries or aortocoronary bypass grafts treated with ⁹⁰Yttrium wire (20.6 Gy); prior to radiation therapy, pts were treated with balloon dilation (n=3), excimer laser angioplasty (n=5), or rotational atherectomy (n=27); additional stents implanted in 18 pts.</p>	<p>No procedural or in-hospital adverse events or complications related to radiation at 30 days. At 6 mos f/u, MACE occurred in 17/50 pts (34%); restenosis confined to the borders of the stent developed in 22% of pts (9/41); in-lesion restenosis, which extended >5 mm proximal and distal to the irradiated segment, occurred in 14/41 pts (34%). TLR performed in 28% of pts (14/50). Late total occlusion occurred in 4/18 pts in whom additional stents were implanted (22%) and 1/32 pts without additional stents (3%).</p> <p>Compared with γ-WRIST control pts, late loss (0.37 ± 0.8 mm vs 1.01 ± 0.65-mm, respectively; P=0.0002) and the loss index (0.28 ± 0.71 vs 0.75 ± 0.46, respectively; P=0.001) were significantly lower in β-treated pts.</p>	<p>MACE (34% vs 66%, respectively) and angiographic restenosis (34% vs 72%, respectively) were significantly lower in the β-radiation group than the γ-WRIST control group (P>0.01). High rate of late thrombosis, 2 to 6 mos post-procedure, was a major limitation of radiation therapy, especially in pts with additional stents. Longitudinal randomized studies are required to determine long-term effects.</p> <p>Limitations: Uncontrolled study design; heterogeneous pt selection criteria; nonstandard tx protocol; small study size limits generalizability of results; comparison to historical controls not adequate to draw accurate conclusions.</p>
<p>Costa et al. (1999)</p> <p>Dijkzigt University Hospital, Rotterdam, The Netherlands</p> <p>Case series documenting the incidence of late thrombotic events after β-radiation in pts with de novo lesions; f/u, 15 mos.</p>	<p>n=108</p> <p>Pts with stable angina pectoris, single vessel disease, and de novo lesions treated with Beta-Cath system (n=76; 32 stents, 44 balloon angioplasty) or Guidant system (n=32; 13 stents, 19 balloon angioplasty); prescribed radiation dose ranged from 12 to 18 Gy at 2-mm from the source or 35 Gy 0.5-mm from the source.</p>	<p>All patients discharged without complication. One patient suffered subacute thrombosis 15 days after stenting, possibly as a result of ticlopidine withdrawal 12 days post-procedure. Of 91 pts (84%) who completed at least 2 mos of clinical f/u, 6 pts (6.6%) experienced sudden thrombotic events 2 to 15 mos post-procedure (2 balloon angioplasty, 4 stents).</p>	<p>According to the authors, the incidence of late thrombotic events in brachytherapy pts is higher than nonirradiated pts treated with balloon angioplasty or stents. Further studies should address whether radiation promotes late thrombosis. Longitudinal studies are required to determine long-term effects.</p> <p>Limitations: Uncontrolled study design; nonstandard tx protocol; small study size limits generalizability of results; comparison to historical controls not adequate to draw definite conclusions.</p>
<p>Meerkin et al. (1999)</p> <p>Montreal Heart Institute, Montreal, Quebec, Canada</p> <p>Case series evaluating lumen changes in pts with de novo lesions treated with β-brachytherapy; f/u, 6 mos.</p>	<p>n=30</p> <p>(age 18-80 yrs) with angina or proven ischemia and single de novo lesion in a native coronary artery;</p> <p>⁹⁰Sr/Y source train at 12, 14, or 16 Gy; stents implanted in 2 pts during the initial angioplasty; stents implanted in 2 additional pts early after the initial procedure due to acute vessel closure and chest pain.</p>	<p>Six-mo angiography demonstrated acute gain in MLD of 1.27 ± 0.39-mm; NS late luminal loss (0.02 ± 0.60-mm) and loss index (0.09 ± 0.46). Binary angiographic restenosis in 3/30 pts (10%). TLR performed in 3/30 pts (10%), TVR in 5/30 pts (17%). In the 26 nonstented vessels, six mos IVUS demonstrated NS differences in mean MLD, mean EEM area, or % cross-sectional area narrowing.</p>	<p>β-radiation resulted in a low restenosis rate with negligible late luminal loss by angiography. By IVUS, β-radiation inhibited neointima formation, with no reduction of total vessel area at six-mo f/u. Longitudinal studies are required to determine long-term effects.</p> <p>Limitations: Uncontrolled study design; nonstandard tx protocol; small study size limits statistical power and generalizability of results.</p>
<p>King et al. (1998)</p> <p>Emory University School of Medicine, Atlanta, GA</p>	<p>n=23</p> <p>(age 18-80) with ischemia, de novo stenosis of a native coronary vessel, reference vessel diameter 2.5 to 3.5-mm, lesion length ≤15-mm, stenosis severity >60%; 12,</p>	<p>No in-hospital or 30-day morbidity or mortality. At six mos, there were no deaths or MIs. TLR performed in 2/20 pts (10%) at six mos. Six-mos arteriography demonstrated late luminal loss of 0.05-mm, late loss index of 4%, and restenosis</p>	<p>β-brachytherapy effectively reduced luminal renarrowing after angioplasty as compared with angioplasty alone. According to the authors, historical data demonstrate that β-brachytherapy lowers the loss index (4%) more effectively than angioplasty (43%). Longitudinal studies are required to determine long-term effects.</p>

<p>Case series investigating the safety and efficacy of β-brachytherapy after balloon angioplasty; f/u, six mos.</p>	<p>14, 16 Gy at 2-mm from the source; $^{90}\text{Sr}/\text{Y}$ successfully delivered to 21 pts with Beta-Cath system; postradiation stents implanted in 2 pts due to persistent stenosis.</p>	<p>rate of 15%. No significant differences in late luminal loss or late loss index between different dose groups ($P=0.58$). One restenosis was a total occlusion, which may have been an early thrombotic event. A second restenosis appeared to represent a nonhealed dissection.</p>	<p>Limitations: Uncontrolled study design; nonstandard tx protocol; small study size limits generalizability of results; historical controls not adequate for accurate comparisons.</p>
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Appendix IV: Radioactive Stents

Key: f/u, follow-up; %DS, % diameter stenosis; IRIS, Isostents for Restenosis Intervention Study; MLD, minimum lumen diameter; μCi , microcuries; NS, not significant; ^{32}P , ^{32}P phosphorous; pt(s), patient(s).

Authors/Study Design	Study Population/Protocol	Results	Conclusions/Comments
<p>Wardeh et al. (1999) University Hospital Rotterdam, Rotterdam, The Netherlands</p> <p>Nonrandomized, multi-center trial investigating ^{32}P radioactive stents in pts with single coronary artery disease; f/u, six mos.</p>	<p>n=26</p> <p>Ischemic pts with single native coronary lesions implanted with either Palmaz-Schatz or BX stent*; 0.75 to 1.5 μCi; single radioactive stents implanted in 18 pts; 4 pts required dual radioactive stents, and five pts were implanted with additional nonradioactive stents.</p>	<p>6-mo angiographic f/u in 23/26 pts (88%) demonstrated in-stent restenosis in 4/23 pts (17%). Revascularization performed in 3/23 pts (13%). MLD increased from 0.87 ± 0.28-mm pre-procedure to 2.84 ± 0.35-mm post-procedure ($P<0.0001$). MLD significantly decreased at f/u (1.85 ± 0.69; $P<0.0001$) compared w/post-procedure. Proximal and distal mean diameter, measured 5 mm from the stent edges, measured post-procedure and at f/u, also decreased significantly ($P=0.006$ and $P=0.0167$, respectively).</p>	<p>Although the implantation of radioactive stents is safe and feasible, the authors concede that results obtained with radioactive stents are similar but somewhat less favorable than the predicted restenosis rate of 12% and MLD of 2.05-mm achieved in trials with nonradioactive stents. The implantation of multiple stents may have increased the risk of restenosis; 3 of 4 pts with in-stent restenosis had multiple stents implanted.</p> <p>Limitations: Uncontrolled study design; nonstandard tx protocol, small study population limits the statistical power and generalizability of results; comparison to historical controls not adequate to draw accurate conclusions.</p>
<p>Albiero et al. (2000a) EMO Centro Cuore Columbus, Milan, Italy</p> <p>Single-center, nonrandomized, dose-response study to evaluate the safety and efficacy of ^{32}P radioactive stents with 3 increasingly higher activity levels; f/u, six mos.</p>	<p>n=82</p> <p>With de novo or restenotic lesions of a major, native coronary implanted with 0.75 to 3.0 μCi stents (Group 1, n=23), 3.0 to 6.0 μCi stents (Group 2, n=29), or 6.0 to 12.0 (Group 3, n=30); additional stents implanted as required.</p>	<p>At six mos f/u, no deaths occurred; 1 pt in Group 3 demonstrated subacute stent thrombosis. Repeat revascularization performed in pts with lesion restenosis. At 6 mos f/u, the intralesion restenosis rate was 52% in Group 1, 41% in Group 2, and 50% in Group 3 ($P=NS$). Pure intrastent restenosis rate was 16% in Group 1, 3% in Group 2, and 0% in Group 3. Restenosis in 1 or both edges of the stent or at the edges plus the first 1 to 4-mm inside the stent developed in 31 to 39% of lesions. Late luminal loss in the distal reference segment was significantly higher ($P=0.05$, 0.98-mm) in Group 3 than in Group 1 or 2 (0.44 and 0.52-mm, respectively).</p>	<p>Stents $>3 \mu\text{Ci}$ almost completely inhibited hyperplasia; however, an increased late luminal loss and restenosis in the first 1 to 3-mm proximal and distal to the stent edges was recorded. This phenomenon is referred to as the candy wrapper effect.</p> <p>Limitations: Uncontrolled study design; nonstandard tx protocol; heterogeneous patient selection criteria; small study population limits the statistical power and generalizability of results.</p>
<p>Albiero et al. (2000b) EMO Centro Cuore Columbus, Milan, Italy</p> <p>Case series to evaluate whether higher activity radioactive stents combined with nonaggressive stent implantation technique could eliminate stent edge restenosis; f/u, six mos.</p>	<p>n=40</p> <p>Pts with de novo or restenotic lesions of a major, native coronary artery, implanted with 12.0 to 21.0 μCi stents.</p>	<p>MLD increased from 0.96 ± 0.54-mm pre-procedure to 3.01 ± 0.47-mm post-procedure in Group 2; acute gain 2.05 ± 0.67-mm; intralesion restenosis in 30% of lesions; intrastent restenosis in 4% of lesions; total occlusion in 0%; restenosis at the stent edges in 26% of lesions. No MIs, deaths, or stent thromboses occurred.</p> <p>Intrastent plaque volume significantly lower with high-dose/nonaggressive technique compared with low-dose/aggressive</p>	<p>At six-mos, high-dose/nonaggressive technique more effectively reduced intrastent neointimal hyperplasia than low-dose/ aggressive technique; however, edge restenosis was problematic in both tx groups. High dose/nonaggressive stent implantation technique did not alleviate candy wrapper effect at stent edges.</p> <p>Limitations: Uncontrolled study design; heterogeneous pt selection criteria; small study population limits the statistical power and generalizability of results; comparison to historical data not adequate to draw accurate conclusions.</p>

		technique ($4.4 \pm 5.6\text{-mm}^3$ vs $15.1 \pm 14.1\text{-mm}^3$; $P<0.01$). Edge stenosis rate higher with low-dose/aggressive technique (33% vs 26%; $P=NS$).	
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