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Inhibition of Restenosis With β-Emitting Radiotherapy

Report of the Proliferation Reduction With Vascular Energy Trial (PREVENT)

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Background—Intracoronary γ- and β-radiation have reduced restenosis in animal models. In the clinical setting, the effectiveness of β-emitters has not been studied in a broad spectrum of patients, particularly those receiving stents.

Methods and Results—A prospective, randomized, sham-controlled study of intracoronary radiotherapy with the β-emitting ^{32}P source wire, using a centering catheter and automated source delivery unit, was conducted. A total of 105 patients with de novo (70%) or restenotic (30%) lesions who were treated by stenting (61%) or balloon angioplasty (39%) received 0 (control), 16, 20, or 24 Gy to a depth of 1 mm in the artery wall. Angiography at 6 months showed a target site late loss index of 11±36% in radiotherapy patients versus 55±30% in controls ($P<0.0001$). A low late loss index was seen in stented and balloon-treated patients and was similar across the 16, 20, and 24 Gy radiotherapy groups. Restenosis (≥50%) rates were significantly lower in radiotherapy patients at the target site (8% versus 39%; $P=0.012$) and at target site plus adjacent segments (22% versus 50%; $P=0.018$). Target lesion revascularization was needed in 5 radiotherapy patients (6%) and 6 controls (24%; $P<0.05$). Stenosis adjacent to the target site and late thrombotic events reduced the overall clinical benefit of radiotherapy.

Conclusions—β-radiotherapy with a centered ^{32}P source is safe and highly effective in inhibiting restenosis at the target site after stent or balloon angioplasty. However, minimizing edge narrowing and late thrombotic events must be accomplished to maximize the clinical benefit of this modality. **(*Circulation*. 2000;102:951-958.)**

Key Words: radiotherapy ■ radiation ■ restenosis ■ radioisotopes ■ stents ■ coronary disease

Radiation therapy with γ- and β-emitting sources inhibits restenosis after percutaneous coronary interventions.[1] Human trials with endovascular γ-radiation demonstrated reduced restenosis in patients with prior restenosis undergoing repeat coronary angioplasty followed by radiotherapy.[2,3] Nonrandomized pilot studies using endovascular β-radiation after balloon angioplasty showed a low late lumen loss and a low restenosis rate in patients with de novo lesions[4] and those with in-stent restenosis.[5]

The Proliferation Reduction with Vascular Energy Trial (PREVENT) is a randomized trial of intracoronary radiation with ^{32}P, a β-emitting source, in patients with restenotic and de novo lesions in whom preradiation treatment with stents or balloon angioplasty was allowed. As such, it represents a trial of β-emitting radiotherapy in a broad spectrum of patients undergoing percutaneous coronary interventions. The primary objective of this study was to demonstrate the safety and performance of intracoronary radiation therapy using an automated source-delivery unit and a source-centering mechanism (Guidant Vascular Intervention). Secondary objectives included evaluating the effectiveness of intravascular radiotherapy after stent implantation compared with balloon angioplasty alone and determining the relative effectiveness of 3 radiotherapy doses (16, 20, and 24 Gy).

Methods

This trial was conducted under a Food and Drug Administration Investigational Device Exemption for a trial of intracoronary radiation therapy. It was approved by the Institutional Review Boards or Ethics Committees and the Radiation Safety Committees of the participating institutions. The study was conducted at the 6 clinical sites listed in the authors' affiliations. The eligibility requirements are shown in Table 1.

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TABLE 1. Eligibility Requirements

Inclusion criteria

1. PTCA of a single, native coronary artery
2. Lesion types: de novo or restenotic
3. Treatment: balloon alone or stent implantation, at the operator's discretion
4. Lesion and vessel requirements: lesion length ≤15 mm; total treatment length (balloon or stent) ≤22 mm; reference vessel diameter ≥2.4 mm and ≤3.7 mm
5. Successful outcome of PTCA

Exclusion criteria

1. Patients receiving PTCA treatment to other coronary vessels within 60 days of the study procedure
2. Bifurcation lesions
3. Aorto-ostial lesions
4. Unprotected left main lesion ≥50% diameter stenosis
5. Dissection after PTCA that was not repaired by stent placement
6. Acute MI (creatine kinase ≥3×normal value) within 5 days
7. Cardiogenic shock
8. Prior therapeutic irradiation to the heart or target vessel area
9. Renal insufficiency
10. Unstable ventricular arrhythmias
11. Cancer or other serious medical illness, which could limit survival to <1 year
12. Previously diagnosed autoimmune disease

Radiation Delivery System

The intravascular radiation therapy system**,** dosimetry, and procedure have been described previously in detail.[6] Briefly, the system consists of 3 components. The source wire is a 0.018-inch flexible Nitinol wire, with the active ^{32}P source encapsulated in the distal 27 mm of the wire. The centering balloon catheter is a double-lumen catheter with a short monorail distal tip for a rapid exchange method of delivery and a spiral balloon, with nominal diameters of 2.5, 3.0, and 3.5 mm, which centers the source within the lumen while allowing side branch and distal perfusion (Figure 1).[7] The source delivery unit provides safe storage of the active wire and automated delivery and retrieval.

Procedure

After completing the angioplasty procedure, the centering catheter was advanced to the lesion site, and the markers were optimally positioned to straddle the balloon/stent-treated lesion segment. The centering balloon was inflated with normal saline, and a contrast injection was made through the guiding catheter to assess flow to the side branches and to the distal artery (Figure 2). An inactive wire was advanced into the centering catheter, its position was optimized, and it was withdrawn. Then the study wire (either active or placebo) was advanced to the same location as the inactive wire and verified angiographically.

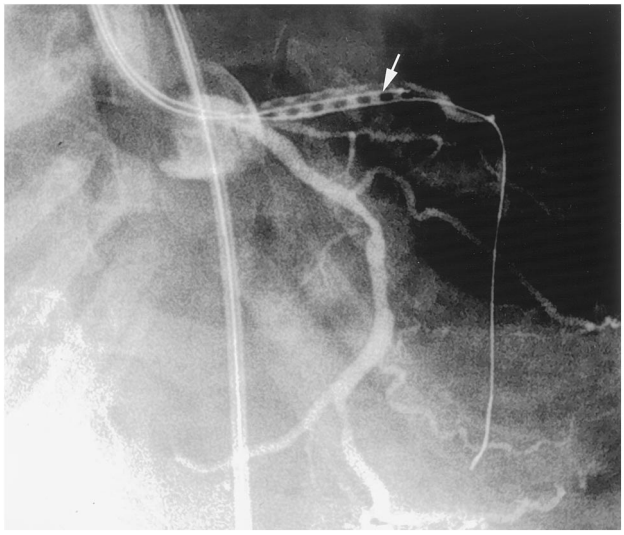

Figure 2. A centering balloon positioned in a left anterior descending coronary artery. With the balloon inflated (shown) the source is centered in the artery lumen (arrow). The inflated balloon allows passive side branch and distal coronary artery perfusion to accommodate prolonged treatment times.

Dosimetry

The radiation prescription was based on the average of the lumen diameters at the proximal and distal reference segments, as measured by intravascular ultrasound or online quantitative coronary angiography or as determined by the known percutaneous transluminal coronary angioplasty (PTCA) balloon or stent sizes. This value was entered into the source delivery unit, which then used source activity to calculate the dwell time needed to deliver the specified dose.

Randomization, Follow-Up, and Medication

Each patient was randomized to 1 of 4 radiation treatment groups: 0, 16, 20, or 24 Gy to 1 mm beyond the lumen surface. Only the radiation oncologist, medical physicist, and the radiation safety officer were not blinded to treatment assignment. Clinical follow-up

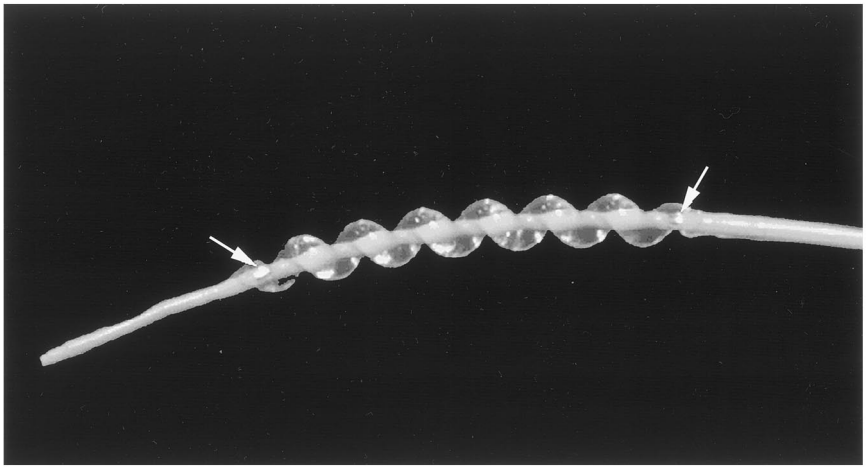

Figure 1. The rapid-exchange centering balloon catheter incorporates a spiral balloon to center the source. Radio-opaque markers identify the radiation treatment zone (arrows). A closed lumen within the shaft serves as the conduit for the source wire, which is delivered by the source-delivery unit.

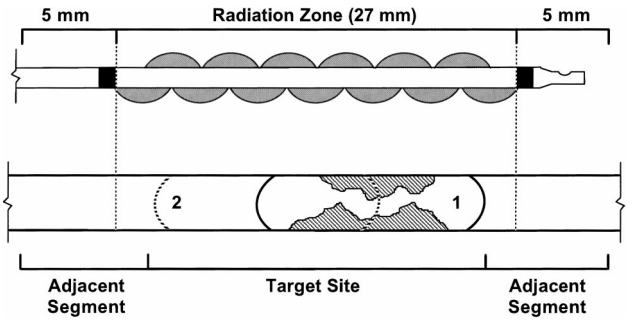

Figure 3. Schematic diagram of defined segments on quantitative coronary angiography. An example of a balloon is shown, which was inflated in 2 different positions (numbers 1 and 2) in the course of the procedure. The "target site" spans the length of these documented inflations.

was obtained at 1, 3, and 6 months. Angiographic follow-up was mandated after 6 months. All patients received 325 mg of aspirin for the duration of the study. Ticlopidine (250 mg BID) was prescribed for 4 weeks after the index procedure for patients who received a procedural stent.

Quantitative Coronary Angiography

After nitroglycerin administration, angiograms were obtained in ≥2 views at baseline (pre-PTCA), after the procedure, and at 6 months. Procedural and 6-month films were forwarded to the Core Angiography Laboratory at Baylor College of Medicine and were read in a blinded fashion using the CAAS II system (Pie Medical). Markers on the centering catheter identified the location of the radiation zone. The 6-month angiogram was analyzed with a side-by-side projection of the radiation treatment catheter to assure accurate identification of the radiation zone. Target site was defined as the segment of balloon and stent injury required to treat the target lesion. Adjacent segments were defined as the segments of artery outside the target site and extended to 5 mm beyond the radiation zone (Figure 3). Reference and minimal lumen diameters (MLD) and percent diameter stenosis of the target site and adjacent segment were determined. Acute gain, late lumen loss, and late loss index (expressed as a percent of acute gain) were calculated for the target site. Binary restenosis was defined as ≥50% diameter stenosis on the follow-up angiogram and was measured for target site alone and for target site plus adjacent segments.

End Points

All clinical events were reviewed and adjudicated by an independent Clinical Events Committee. The primary clinical end point was the combined short-term (in-hospital) and late (12 months) rate of major adverse clinical events (MACE). MACE were defined as the composite of death, myocardial infarction (MI; Q-wave and non–Q-wave), and target lesion revascularization (TLR; PTCA or coronary artery bypass grafting) for restenosis involving the target site. Secondary clinical end points included each of the individual MACE events, as well as target vessel revascularization (TVR) for restenosis involving the target site and adjacent segments. Angiographic end points were MLD, late lumen loss, late loss index, and binary restenosis at 6 months.

Statistical Methods

Analysis Population

The primary safety end point of the combined early and late rate of MACE was analyzed on a per protocol (successful procedure) basis. Three patients who were enrolled did not receive the randomized treatment because of equipment difficulties; they were excluded from analyses because none of them received any portion of the assigned radiation treatment.

The 3 radiation dose populations (16, 20, and 24 Gy) were pooled. Also, the 3 lesion types (de novo, PTCA restenosis, and in-stent restenosis) were pooled. Statistical differences were considered significant at $\alpha<0.05$.

TABLE 2. Baseline Clinical and Angiographic Charactistics

Characteristics	^{32}P Group (n=80)	Control Group (n=25)
Age, y	63±11	63±8
Male sex	51 (64)	19 (76)
Smokers	19 (24)	10 (40)
Diabetes mellitus	16 (20)	6 (24)
Hypertension requiring treatment	50 (63)	11 (44)
Hyperlipidemia requiring treatment	38 (48)	14 (56)
De novo lesion	54 (68)	19 (76)
Restenotic lesion	26 (33)	6 (24)
In-stent restenosis	19 (24)	6 (24)
Prior MI	28 (35)	14 (56)
CCS III or IV*	49 (69)	17 (71)
No. of diseased coronary arteries		
Single-vessel disease	52 (65)	18 (72)
Multivessel disease	28 (35)	7 (28)
Ejection fraction, %	60±11	58±16
Target vessel		
LAD	37 (46)	10 (40)
CFX	13 (16)	6 (24)
RCA	30 (38)	9 (36)
ACC/AHA lesion class	(n=76)	(n=25)
A	18 (24)	4 (16)
B_1	29 (38)	13 (52)
B_2	24 (31)	6 (24)
C	5 (7)	2 (8)

Values are mean±SD or n (%). CCS indicates Canadian Cardiovascular Society; LAD, left anterior descending; CFX, circumflex; RCA, right coronary artery; ACC, American College of Cardiology; and AHA, American Heart Association.

*n=71 in ^{32}P group and n=24 in control group.

Determination of Safety

The randomization was unbalanced (3:1) to detect any safety issues that would occur with radiation at a high frequency. Binary incidence rates, angiographic restenosis, target-related revascularization or failure, or combined nonspecific late ischemic end points were tested with χ^2 or exact contingency table analyses. Continuous variables were compared by Student's *t* test.

Results

A total of 105 patients were enrolled in the study and had a successful procedure; 25 were assigned to the control group and received a nonradioactive treatment wire (sham procedure), and 26, 27, and 27 patients were assigned to receive 16, 20, and 24 Gy, respectively.

The baseline clinical and angiographic characteristics of the treated and control patients are shown in Table 2. Overall, 73 patients (70%) had de novo lesions and 32 (30%) had restenotic lesions, which included those with in-stent restenosis (24%). The angioplasty procedure included placement of a new stent(s) in 64 patients (61%).

During centering balloon inflation, blood flow to the distal vessel and side branches was observed in 87% and 91% of

TABLE 3. MACE at 12 Months

	Radiotherapy (n=80)	Control (n=25)	P
MACE (death, MI, TLR)	13 (16)	6 (24)	NS
MACE (death, MI, TVR)	21 (26)	8 (32)	NS
Death	1 (1)	0 (0)	NS
MI	8 (10)	1 (4)	NS
Q-wave	2 (3)	0 (0)	
Non–Q-wave	6 (7)	1 (4)	
TLR	5 (6)	6 (24)	<0.05
PTCA	4 (5)	5 (20)	
CABG	1 (1)	1 (4)	
TVR	17 (21)	8 (32)	NS
PTCA	14 (17)	6 (24)	
CABG	2 (4)	2 (8)	

Values are n (%). CABG indicates coronary artery bypass grafting.

patients, respectively. Fractionation of the treatment was required in only 9 patients (9%) to relieve ischemia during inflation of the centering balloon.

Source wire activity ranged from 39 to 146 mCi (mean, 70±22 mCi). Dwell time ranged from 1.0 to 9.6 minutes (mean, 4.6±2.0 minutes). The time added to the angioplasty procedure to perform radiotherapy was 12±6 minutes (range, 4 to 31 minutes). The radiation survey reading taken 1 m from the approximate location of the source during active source dwell time was 0.46±0.35 mrem/h (range, 0.04 to 1.52 mrem/h).

The primary clinical end point was combined early (in hospital) and late MACE. In-hospital events occurred in 1 radiotherapy patient (1.3%; non–Q-wave MI) and 1 control patient (4.0%; non–Q-wave MI) (P=NS). No in-hospital death or postprocedure revascularization occurred.

Long-term (12-month) MACE (death, MI, and TLR) occurred in 13 radiotherapy patients (16%) and 6 control patients (24%; P=NS). If TVR is included, MACE occurred in 21 radiotherapy patients (26%) and 8 control patients (32%; P=NS).

The occurrences of individual MACE are shown in Table 3. One patient in the radiotherapy group (16 Gy) died suddenly 2.5 months after receiving a stent for the treatment of a restenotic lesion in the right coronary artery. Ticlopidine was prematurely discontinued 3 weeks after the procedure because of an allergic reaction. At autopsy, thrombotic occlusion within and proximal to the stent was noted in the absence of significant neointimal growth. Two in-hospital procedure-related non–Q-wave MIs occurred, one in each treatment group. Seven additional MIs occurred in the radiotherapy group. These occurred at 5 (non–Q-wave), 23 (Q-wave), 83 (non–Q-wave), 103 (non–Q-wave), 111 (non–Q-wave), 160 (Q-wave) and 188 (non–Q-wave) days after the index procedure. All 7 posthospitalization MIs were considered acute occlusive events; 6 were treated with thrombolytic therapy and 1 by direct PTCA. Angiography, which was performed in 6 of the 7 patients, showed definite thrombus in 3. No definite thrombus was seen in 3 others whose angiograms were performed several hours (2 patients) or 3 days (1 patient) after receiving thrombolytics. Each of these 3 patients had restenosis involving the adjacent segment. Six of the 7 patients with posthospitalization MIs received new stents at the index procedure. No late MIs occurred in the control group.

TLR for restenosis was significantly lower in the radiotherapy group (6%) than in the control group (24%; P<0.05). A trend existed toward a lower incidence of TVR in the radiotherapy patients (21% versus 32%), which was not significant by statistical criteria.

The results of the quantitative coronary angiography analysis are summarized in Table 4 and Figure 4. At the 6-month follow-up angiographic examination, late lumen loss was 0.22±0.6 mm for the radiotherapy patients compared with 1.1±0.7 mm for controls (P<0.0001), and the late loss index was 11±36% compared with 55±30% (P<0.00001). No coronary artery aneurysms or nonhealed dissections were seen on follow-up angiography.

Angiographic restenosis (≥50% diameter stenosis) of the target site was 8% for radiotherapy patients compared with

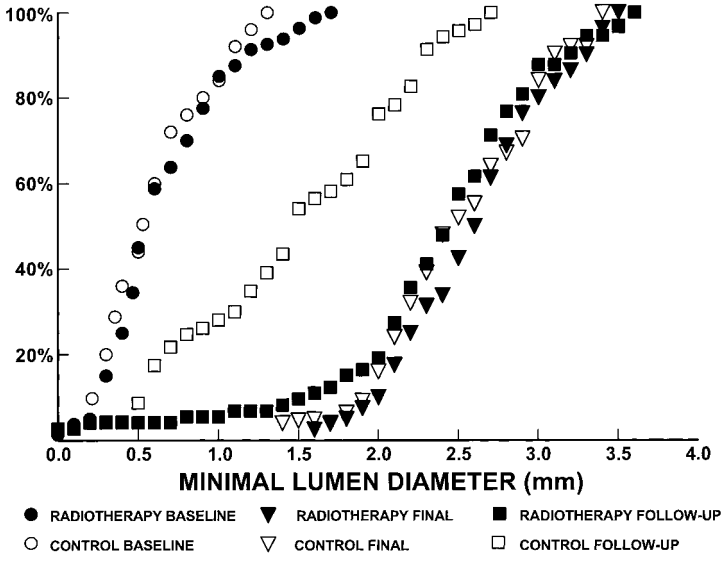

Figure 4. The cumulative distribution curves of the MLD before and after the index revascularization procedure and at 6-month follow-up angiography. The percentage on the vertical axis indicates the fraction of patients who presented with an MLD equal to or smaller than a given value on the horizontal axis. The curves are similar for the radiotherapy and control groups before and after the procedure. However, at 6 months, the control patients had regressed toward preprocedure MLD values, whereas the radiotherapy patients remained close to the postprocedure MLD curve.

TABLE 4. Quantitative Coronary Angiographic Analysis

	^{32}P Group (n=80)	Control (n=25)	*P*
Baseline			
Reference vessel diameter, mm	2.99±0.48	2.97±0.55	NS
MLD, mm	0.74±0.37	0.68±0.31	NS
Percent diameter stenosis, %	75±11	77±8	NS
Postprocedure			
Reference vessel diameter, mm	3.23±0.42	3.20±0.53	NS
MLD, mm	2.68±0.49	2.60±0.51	NS
Percent diameter stenosis, %	17±9	19±9	NS
At 6-month follow-up	(n=73)	(n=23)	
Reference vessel diameter, mm	3.08±0.45	2.98±0.53	NS
MLD, mm	2.44±0.74	1.55±0.70	<0.001
Percent diameter stenosis, %	21±20	49±20	<0.001
Change in MLD			
Acute gain, mm	1.9±0.6	1.9±0.4	NS
	(n=80)	(n=25)	
Late lumen loss, mm	0.2±0.6	1.1±0.7	<0.0001
	(n=73)	(n=23)	
Late loss index, %	11±36	55±30	<0.0001
	(n=73)	(n=23)	
Binary restenosis (>50%)			
Target site	6/73 (8%)	9/23 (39%)	0.0012
Target site plus adjacent segments	17/76 (22%)	12/24 (50%)	0.018

Values are mean±SD unless otherwise indicated.

39% for controls ($P=0.0012$). Restenosis of segments adjacent to the target site occurred in 11 radiotherapy and 3 control patients. Overall, restenosis of the target site plus adjacent segments occurred in 22% of the radiotherapy group and 50% of the control group ($P=0.018$).

Results in Stented Arteries

Quantitative coronary angiography showed no significant differences between patients who received stents (n=50) versus those who received balloon angioplasty (n=30) in late lumen loss (0.20±0.50 mm versus 0.25±0.74 mm; P=NS) or in late loss index (9±28% versus 13±46%; P=NS).

Results in 3 Radiotherapy Dose Groups

In patients with follow-up angiography who received 16 Gy (n=23), 20 Gy (n=25), and 24 Gy (n=25), no significant differences existed between groups in late lumen loss (0.12±0.49, 0.31±0.79, and 0.23±0.48 mm, respectively; P=NS), or in late loss index (4±28%, 18±50%, and 10±25%, respectively; P=NS).

Discussion

Endovascular radiotherapy has emerged as a promising method for reducing restenosis.[1–5] Animal investigations using the porcine coronary artery model of restenosis demonstrate a dramatic inhibition of neointima formation after balloon and stent injury after intravascular γ- and β-radiation.[8–16] In a landmark clinical trial, Teirstein and colleagues[2,17] showed a significant reduction in angiographic and clinical measures of restenosis in patients undergoing coronary intervention for restenotic lesions who received γ-radiation (^{192}Ir) compared with a control group.

Using a β-radiation source with more limited penetrability may have inherent safety advantages over γ-radiation sources. β-Radiation, however, has the potential limitation of lesser penetration of the artery wall, particularly in stented arteries.[18] King et al,[4] in a noncontrolled feasibility trial of β-radiation using ^{90}Sr, demonstrated a low late lumen loss and late loss index compared with historical controls in patients with de novo lesions treated with balloon angioplasty followed by radiation with a noncentered source. In clinical practice, however, most coronary interventions include stent implantation, and many coronary interventions are repeated in patients presenting with restenotic lesions.[19]

The present study was undertaken to explore the clinical advantages of an alternative, catheter-based β-radiation system that used a readily available isotope (^{32}P), a centering delivery catheter with perfusion capabilities, and an automated source-delivery unit. In addition, enrollment criteria were expanded to include a broader clinical spectrum of coronary disease, including both de novo (70%) and restenotic lesions (30%); the latter included in-stent restenosis (24%). It should also be noted that the protocol did not dictate the type of interventional procedure. This was left to the discretion of the operator and resulted in a new stent placement in 61% of lesions and balloon angioplasty alone in the other 39%.

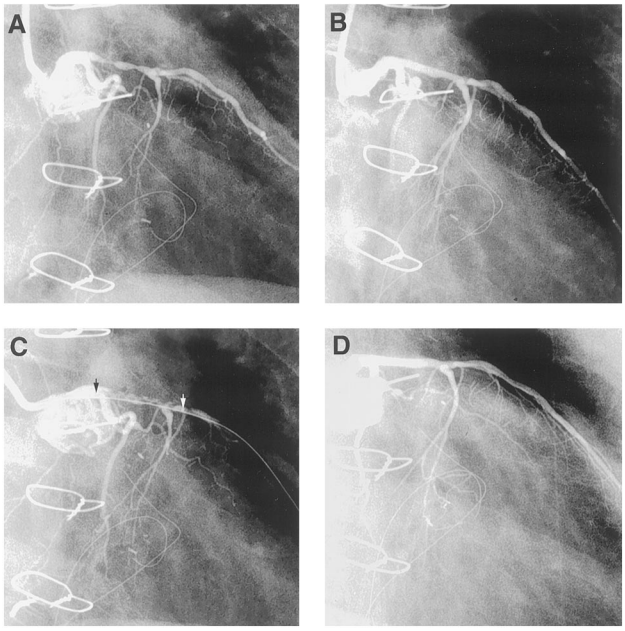

Figure 5. Arteriograms of a patient with in-stent restenosis who had undergone 3 prior interventional procedures, including rotational atherectomy. Despite these efforts, the proximal left anterior descending coronary artery was severely narrowed within the stent (A). After balloon angioplasty, an excellent procedural outcome was achieved (B), after which radiotherapy was applied (C; arrows indicate the radiation zone). At 6-month follow-up angiography (D), the previously recalcitrant restenotic artery has remained widely patent.

The study demonstrates the overall safety and feasibility of β-radiotherapy with this system for the prevention of restenosis. The lack of statistically significant differences in the overall MACE event rates between the 2 groups should not be construed as a negative finding because the study was not powered to show such differences. Individually, the rates of TLR were significantly lower with β-radiotherapy, and the rates of TVR showed a similarly beneficial trend.

The angiographic end points demonstrate a profound inhibition of restenosis within the target site in patients receiving radiotherapy compared with a sham-treated control group. Late lumen loss and the late loss index were reduced 80% by β-radiotherapy with ^{32}P. Angiographic restenosis at the target site was reduced by 79% and the need for revascularization because of target lesion restenosis was reduced by 74%. Importantly, no diminution of effectiveness in arteries in which stents were deployed before radiotherapy treatment seemed to occur. Further, individual instances of previously recalcitrant restenotic lesions, which were prevented from recurring by radiotherapy (Figure 5), underscore the potential utility of intracoronary radiotherapy to inhibit restenosis.

A unique centering catheter was used to center the source in the postangioplasty or stented lumen, facilitating specification of a particular dose at a circumferential layer within the artery wall while, at the same time, allowing perfusion to the distal artery and side branches. In this study, 3 doses (16, 20, and 24 Gy), representing a broad therapeutic spectrum, were used. The effectiveness of radiation to inhibit restenosis at the target site was comparably demonstrated for each of the doses used. This finding offers promise that the spectrum of therapeutic efficacy for radiotherapy is potentially quite wide.

A primary objective of this study was to assess the safety of radiotherapy with the system used. In this regard, 105 of 108 treatments (97%), both active and sham, were successfully administered. Fractionation of the treatment due to a reduction in coronary blood flow by the helical centering balloon was required in only 9% of applications. Only 2 patients had procedure-related clinical events (non–Q-wave MI; 1 patient in each group), which were due to stent-related side branch entrapment. Radiation survey readings in the room at the approximate site of the operator in attendance during active source dwell time were below those encountered during fluoroscopy.

Several potential radiation-related issues were identified in this study. Despite the dramatic inhibition of the restenotic process at the lesion site, which received the full beam of radiation, some patients developed narrowing at or adjacent to the edge of the radiation zone. In most instances in which edge narrowing was observed, a careful review of the procedural angiograms revealed evidence of balloon or stent injury that was incompletely covered by the radiotherapy treatment, which is consistent with the concept of a targeting error or "geographic miss" as the fundamental cause of this phenomenon (Figure 6).[20] As such, incorporating a broad margin of treatment beyond the segment of balloon or stent injury may lessen this phenomenon. In some patients, however, edge narrowing was observed despite radiation treatment that seemed to overlap the injury zone appropriately.

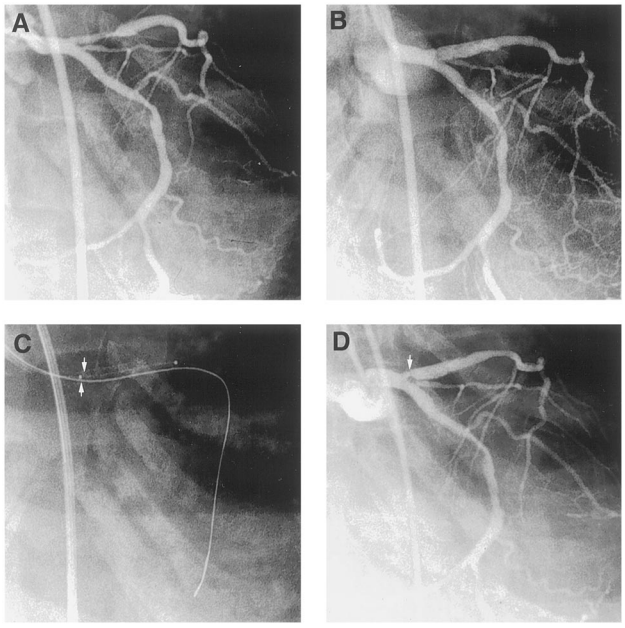

Figure 6. An example of edge narrowing due to geographic miss. This patient, who had a lesion in the proximal left anterior descending artery (A), had a stent placed beginning at the ostium of the artery (B). C, To avoid positioning the radiation catheter in the left main artery, the proximal end of the source (lower arrow) was brought to the edge of the stent (upper arrow), which provided no margin of radiotherapy. At 6-month angiography, edge narrowing was observed precisely at this site (D, arrow). Note that the distal end of the stent that received an adequate margin of radiotherapy shows no evidence of edge narrowing.

The net effect of edge narrowing was to substantially diminish the overall effectiveness of radiotherapy to inhibit angiographic and clinical measures of restenosis. When angiographic restenosis of the target site alone was analyzed, only 8% of target lesions restenosed. In contrast, when the target site plus adjacent segments was analyzed, the rate of angiographic restenosis in the radiotherapy group increased to 22%. Of note, even with restenosis related to edge narrowing included, the angiographic restenosis rate was still significantly below that observed in the control group (22% versus 50%; $P=0.018$). Similarly, TLR due to restenosis was needed in only 6% of radiotherapy patients. However, revascularization for restenosis at the target lesion or adjacent segments (TVR) was performed in 21% of radiotherapy patients.

An additional observation of this investigation was the occurrence of MI in 7 radiotherapy patients between the time of hospital discharge and 12-month follow-up. No such events occurred in control patients. All 7 MIs seemed to be acute events, which were treated with thrombolytic therapy (6 patients) or direct PTCA (1 patient). Six of the 7 patients had received new stents at the index procedure. These events contributed significantly to the diminution of clinical benefit that might have been anticipated by the impressive reduction in angiographic restenosis. A similar incidence of late thrombosis was recently reported for a group of patients treated in other γ- and β-source trials.[21,22] Although the proximate cause of these late thrombotic events is uncertain, it is reasonable to speculate that radiotherapy delays the formation of "protective" neointima, thus affording an opportunity for exposed stent material or a disrupted lesion to form a nidus for subsequent coronary thrombosis. Reducing the use of new stents in patients who are to receive radiotherapy may be an important strategy to minimize the occurrence of late thrombotic events.

During the time this study was conducted, the standard of care for anti-platelet therapy consisted of aspirin on a continuing basis and ticlopidine for 1 month for stented patients. None of the patients were on ticlopidine at the time a thrombotic event occurred. The possibility that longer-term use of anti-platelet agents would lessen the occurrence of these late thrombotic events is being explored.

Limitations of the Study

This study explored the safety and performance of β-radiation with ^{32}P in a broad spectrum of patients. In view of the limitation in sample size, definitive conclusions, positive or negative, about the efficacy of this radiotherapy to prevent restenosis are limited in scope. Nevertheless, a dramatic reduction of neointimal growth within the target site was demonstrable for this diverse patient group.

In a relatively small population of patients, statistically meaningful comparisons of subgroups are not possible. The subgroup analyses were performed to see if any trends were apparent between subgroups. No such trends were noted among dose subgroups. Additionally, stented patients did not seem to be less responsive than nonstented patients to the effects of radiotherapy.

Conclusions

Radiotherapy with a ^{32}P source wire using a centering catheter method and automated source-delivery unit seems to be safe and highly effective in reducing neointima within the target site in patients undergoing coronary angioplasty. The presence of a metallic stent in the coronary artery did not seem to limit the effectiveness of β-radiotherapy to diminish neointimal growth. There appears to be a wide therapeutic range of safe and effective dosing.

Two radiotherapy-related problems were identified, arterial narrowing adjacent to the edge of the target site and unexpected late coronary thrombo-occlusive events. The use of longer radiotherapy sources that provide a wide margin of treatment beyond the segment of injury may overcome the problem of edge narrowing. More prolonged use of anti-platelet agents and a reduced use of new stents may minimize the occurrence of late thrombotic events. Subsequent large-scale, multicenter trials incorporating these procedural changes will ultimately determine the overall benefit that can be achieved with β-radiotherapy in patients with restenosis.

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