8-20-2004

Dose Threshold for Clinical Success in Coronary brachytherapy: a nested case-control study

Harsimran Singh

Dose Threshold for Clinical Success in Coronary Brachytherapy: A Nested Case-Control Study

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Harsimran Sachdeva Singh
2004

DOSE THRESHOLD FOR CLINICAL SUCCESS IN CORONARY BRACHYTHERAPY: A NESTED CASE-CONTROL STUDY. Harsimran S. Singh, Ning Yue, Nassir Azimi, Kenneth B. Roberts, Ravinder Nath, and Steven Pfau. Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT

Intravascular brachytherapy is the primary treatment for coronary in-stent restenosis. We hypothesized that differences in dose delivered to target may contribute to treatment failures. We compared dose distribution between arteries that developed recurrent restenosis (treatment failures) and those that remained patent at nine-months (treatment success). A cohort of 207 patients receiving brachytherapy for coronary in-stent restenosis with four radiation delivery devices was followed to identify treatment failures and successes. This cohort was examined to establish which patient and lesion characteristics had an effect on outcome. A nested case-control construct was then used in which treatment failures (n=14) were compared 1:2 to treatment successes (n=28) matched by two variables: radiation delivery system and angiographic pattern of in-stent restenosis. At baseline, the groups had similar patient and lesion characteristics. The dose absorbed by 90% of the artery encompassed by the external elastic membrane (D_{90}EEM) was calculated using intravascular ultrasound (IVUS) images taken at 2-mm intervals along the treated lesion. Dose calculations were performed using dose kernel integration techniques; the dose kernels were generated from Monte Carlo simulations. The mean D_{90}EEM minimum dose in treatment failures was 7.46±1.98 Gy, while for treatment success the mean D_{90}EEM minimum dose was significantly higher: 8.87±1.13 Gy ($p=0.007$). Using a dose threshold of 8.4 Gy, a D_{90}EEM minimum dose $\leq$ 8.4 Gy occurred in 13 (93%) patients with treatment failure, but in only 9 (32%) with treatment success ($p\leq0.001$). No confounding variables were found to be statistically significant. In conclusion, current brachytherapy dose prescriptions result in significant inter- and intra-lesion variation in dose at the EEM. Arteries that receive $\leq$ 8.4 Gy at any point along the EEM are more likely to be treatment failures. IVUS guided dosimetry may be critical to assure adequate dose regardless of radiation delivery system.

ACKNOWLEDGEMENTS

In most everything in life, we must first acknowledge our family – without the wisdom and tolerance of my father, the compassion and nurturing of my mother, these pages would have been blank. To my parents, both my grandmothers, and my brother – I owe the world.

The individual most responsible for this research and for my education over the span of the past two years is Dr. Steve Pfau. He has been a fantastic mentor to work with – providing me with an appropriate mix of guidance, independence, and leadership. The primary directive of any research is to seek truth, and Dr. Pfau has always directed me to pursue this goal.

I would like to extend my most sincere thanks to my other mentors and collaborators on this project: including Dr. Kenneth Roberts in the Department of Radiation Oncology, Dr. Ravinder Nath and Dr. Ning "Jeff" Yue in the Division of Radiation Physics, and Dr. Nassir Azimi in the Division of Cardiology.

Finally, I would like to acknowledge Dr. John Concato for his teaching and statistical acumen, Carol Roberts and Mike Cabin for their data gathering assistance, Dr. John Forrest and the entire Office of Student Research for their advice and encouragement, and the Doris Duke Foundation for their monetary support.

TABLE OF CONTENTS

INTRODUCTION

Angioplasty is a standard non-surgical treatment of ischemia due to vascular stenosis most often caused by atherosclerosis. A major limitation of angioplasty has been restenosis (diameter renarrowing of ≥50% on angiographic follow-up) of the treated vessel. It can occur acutely or subacutely in 30 to 50% of coronary angioplasty cases – generally within the first ~3 months post-balloon dilation (1). The causes of restenosis after balloon angioplasty include neointimal hyperplasia, elastic vascular recoil, arterial dissection, thrombosis formation, and atherosclerotic remodeling (1,2).

For the past decade and a half, coronary interventions have included the placement of intravascular stents in addition to balloon angioplasty. From amongst the ~900,000 angioplasties, performed annually in the USA, ~70-80% include coronary stent placement. Stenting has been established to reduce angiographic and clinical restenosis when compared to percutaneous balloon interventions alone – by virtually eliminating the problem of elastic recoil and remodeling (3,4). However, restenosis after stenting continues to persist – 15-35% of patients develop restenosis of the affected site within the first 6-8 months after stent placement (3,5-7), with clinically driven repeat coronary revascularization necessary in 50-80% of those cases. (7-9). Given the prevalence of stenting/angioplasties and thus the overall disease burden of restenosis, a large amount of research has been invested over the past two decades in attempting to discern its pathophysiology and find ways to prevent and appropriately treat the problem.

In-Stent Restenosis

In-stent restenosis (ISR) is secondary to neointimal hyperplasia – an endovascular infiltration of inflammatory cells, fibroblasts, and myo-fibroblasts in response to the injury induced by angioplasty and stenting. Unlike the chronic pathology leading to atheroma formation, ISR may be localized or distributed over the length of the stent and is likely due

to a maladaptive response to vascular injury (10). The neointimal proliferation occurs in conjunction with macrophage and myo-fibroblast recruitment, presumably found within the tunica intima and also migrating from the tunica adventitia (11).

Several patient and lesion characteristics have been documented in the literature to affect ISR rates including: diabetes (12), long lesion length (13), small artery diameter (13), acute coronary syndrome (14), renal failure (12), and saphenous vein bypass grafts (15). Patterns of restenosis have been described by *Mehran et al* that encompasses lesion length as well as the relationship of tissue proliferation to the implanted stent. In-stent lesions are classified via an ordinal rank of Types I through IV – ranging from focal lesions of restenosis to total stent occlusion. This system captures the magnitude of the proliferative response and is shown to predict long term prognosis (16).

While ISR and specifically neo-intimal hyperplasia is a problem over the first 6-8 months post stenting, there may be no further regression in luminal diameter or clinical failure at one-year and beyond (17,18). The problem of ISR has been tackled through a variety of tactics in the past, including repeat angioplasties, ablative devices, laser ablation, and rotational artherectomy – all with minimal success in affecting recurrence rates and clinical course.

Radiation Therapy Theorized

The idea of radiation therapy for treating ISR in the vasculature was adapted from other fields of medicine relying upon radiation. For many years this modality has been used to inhibit growth of tumor cells and non-malignant hyperplasias (post-surgical keloids, heterotrophic bone formations, recurrent pterygium, etc). Brachytherapy literally means “local treatment” using radiation (as opposed to external beam radiation), thus limiting systemic side effects of diffuse radiation exposure. Given our present day understanding of the pathology behind atherosclerosis, intravascular brachytherapy (IVBT) was theorized to be of benefit by preventing endothelial/

intimal hyperplasia and/or matrix deposition after balloon injury – by either mediating apoptosis or inhibiting cellular proliferation (19).

Over the past decade, two classes of ionizing radiation have been investigated – 1) Gamma rays (low energy/high penetration) using 192-Ir and 2) Beta-particles (high energy/low penetration) using a variety of isotopes including 32-P, 90-Sr/90-Y, 188-Re, and 133-Xe. The radiation can be delivered either via a catheter-based system (ribbon, fixed-length wire, seed trains, and balloons – for radioisotopes in liquid phase) allowing temporary exposure or stent-based system for permanent implantation. Radiation may be delivered over a course ranging from 3 to 30 minutes depending on the dose required and isotope used.

Brachytherapy: Clinical Trials

Initial proof-of-concept and dosing for IVBT was established through animal studies after which it was attempted in humans. The first large scale randomized control trial for IVBT was SCRIPPS – a double blind trial (n=55) for in-stent restenosis and de-novo restenosis – showed a 70% reduction of restenosis rates (53.6% v. 16.7% by angiography) with IVBT v. placebo at 6 months; and a continuation of the effect at 3 years – 66.6% v. 33% restenosis. The SCRIPPS trial recently published a five-year follow-up of their patients – in which the clinical effectiveness of IVBT is shown to slightly diminish over time, but maintains improved clinical outcomes. This positive result led to a series of multi-center trials each supporting one of the three IVBT systems currently in use. 1) GAMMA-1 (20,21) was the premier multi-center double blind randomized control trial (n=252) for in-stent restenosis trailed the *Cordis - Checkmate system (192-Ir).* This study found a 36% reduction in major adverse cardiac events (MACE) in IVBT v. placebo (28.2% v. 43.8%). 2) START (22) was a significant multi-center trial that examined 472 patients in determining efficacy/safety of the *Novoste - BetaCath* balloon system (90-Sr/Y) for in-stent restenosis. They found 9-month revascularization rates to be 24% placebo v 16% Beta-VBT. 3) INHIBIT (23) further solidified Beta-IVBT's efficacy and safety. Examining 332 patients using

32-P source (*Guidant – Galileo)* with 20 Gy dose 1 mm into vessel wall, INHIBIT found a 66% reduction in restenosis rates at 9 months. The clinical and angiographic outcomes found in these three trials are presented in Figures 1 & 2. Given the positive results of these studies, in November 2000, two systems for delivery of coronary IVBT were approved by the Food & Drug Administration (FDA): the BetaCath system by Novoste and the Checkmate System by Cordis (24). A third system, Galileo by Guidant, was approved one-year later in November 2001 (23,25).

Brachytherapy Success & Reality

Over the past three years, brachytherapy has become established as the frontline treatment option for in-stent restenosis. While drug-eluting stents may prove to be viable alternatives for ISR in the future, IVBT has remained the only consistently proven treatment for ISR with decreased rates of repeat revascularization (26). As described above, three large multi-institutional, randomized control trials documented a 30-50% improvement in outcome compared to angioplasty alone, primarily driven by reduction in angiographic restenosis and the need for repeat revascularization (20-23).

To date very little data has emerged regarding the clinical application of IVBT in patients who receive treatment for ISR outside of clinical trials. The RENO registry provided multi-institutional outcomes on the use of the Novoste BetaCath system in Europe, providing insight into the more generalized application of this device. At 6-month follow-up, the rate of MACE in RENO was 18.7%, similar to the randomized control trial. RENO helps to prove that the clinical benefit of brachytherapy can be maintained outside of the strict environment of trial design (27,28), but there were two caveats to this study. First, the registry was limited to patients treated with the Novoste radiation system. Second, the analysis included patients with de novo lesions, which comprised 20% of the study population. To date there has been no study examining all three approved brachytherapy systems in a general population.

Despite this initial success, brachytherapy has not been the unconditional panacea for ISR. Depending on the trial, 15 to 29% of patients given IVBT will still fail treatment and require another revascularization procedure within 9-months (20,29,30). Certain risk factors associated with increased IVBT failure include diabetes (31,32), renal failure (33), and saphenous vein grafts (SVG) (34). There also have been inverse associations with age (35), lesion length (36), and minimal luminal diameter (MLD) (36).

Two complications related to brachytherapy treatment are edge restenosis and an increased risk for late thrombosis. Edge restenosis occurs when an inadequate dose is given to the edge of the stent, due to either dose fall out with inadequate dose prescriptions or due to "geographic misses" – where portion of the injured vessel are not accounted for when planning treatment. This problem can be counteracted by adequate coverage (37). Late thrombosis was a problem in initial studies, especially in patients who received additional stenting in addition to IVBT – however with long-term anti-thrombosis therapy this problem has been diminished (38,39).

Brachytherapy Dosing

One factor that may be related to brachytherapy outcomes is radiation dose. Few studies have explored the effects of ionizing radiation dose-distribution within the artery and different types of radiation sources (among the 3 FDA IVBT approved systems – different isotopes, Beta v. gamma sources) to clinical outcomes. Animal data has suggested that doses between 8 and 40 Gray (Gy) are effective (40-45), but steep dose gradients and concerns regarding toxicity have pushed clinical prescriptions to the lower limit of this range. Early clinical studies used ultrasound to prescribe at least 8 Gy to the external elastic membrane (EEM), but adjusted dose to avoid more than 30 Gy to the nearest part of the vessel (20,21).

At present, radiation prescriptions for IVBT are rather empiric. Dose (in Gray as a measure of absorbed energy in tissue per unit mass) is prescribed either at a fixed amount at a

standard depth (generally at 2 mm depth from a radiation line source) or to a histological target such as the EEM (radiolucent border on ultrasound). A minimal dose to the EEM in turn insures a minimal dose distribution to the intima, thought to be one putative biologic target in IVBT. While the exact cellular target for IVBT remains uncertain, in vitro data suggests that cells from the adventitia, media and neointima may all be involved (19,43,46). Current strategies have focused on delivering enough radiation to the entire vessel wall without exceeding vessel tolerance. As radiation dose from a line source decreases rapidly as a function of distance from that source, the vessel wall is exposed to a highly variable dose gradient – with additional variability between different isotopes and dose prescriptions (Figure 3). Dosing remains imprecise as the vascular anatomy and the position of the radiation source within the lumen are variable.

Current day dose prescriptions have evolved towards dosing regimens that are based on very few patient or lesion specific criteria. All three FDA-approved brachytherapy devices recommend dose prescriptions which are standardized to a fixed distance from the source, with small adjustments based on lumen size for the beta emitters. However, parameters such as plaque burden, plaque distribution (concentric v eccentric), vessel curvature, and catheter position all contribute to uneven dose distribution because they affect the variability in distance from the source to EEM (47,48). These factors result in variations of dose to target, which may ultimately impact the efficacy of this therapy.

STATEMENT OF PURPOSE & HYPOTHESIS

Over the past few years, brachytherapy has been clinically established to be a frontline treatment option for in-stent restenosis. Several multi-institutional, double blind randomized control trials have been conducted with 6 months to 5 years follow-up, all touting the effectiveness of IVBT for preventing MACE, repeat intervention, and site specific restenosis (as per angiography). However, there is minimal literature regarding the brachytherapy experience outside of clinical trials. Also, few studies have explored the role of radiation dose-distribution within the artery and its potential effect on the treatment efficacy of brachytherapy. The goal of this study is two fold:

1) *Determine clinical effectiveness of brachytherapy at our institution & examine patient/lesion characteristics that may affect outcomes.*

Yale New Haven Hospital's Endovascular Brachytherapy Center has been performing IVBT since November 2000 – and subsequently has a wealth of retrospective data that has not been formally explored. In this study, we reviewed our single-center experience with intra-coronary IVBT of 207 patients between November 2000 and November 2002 with subsequent 9-month clinical outcomes. We examined these patients' clinical data, including their specific IVBT regimen and angiographic/ultrasound parameters with their clinical outcomes within the first 8-9 months post-IVBT. By examining this cohort of patients, we hope to establish preliminary associations that assist in formulating parameters for dose prescription/distribution and radiation source selection for IVBT.

2) *Examine the relationship between de facto dose distribution and brachytherapy treatment success.*

Given the variation in vascular anatomy, plaque distribution & burden, catheter placement, and brachytherapy systems/isotopes used, we hypothesize that despite standardized dose prescriptions, patients are in reality receiving very different amounts of radiation, and this variability may lead to treatment failure. We used a nested case-control construct using intravascular ultrasound (IVUS) images to examine dose delivered to the EEM in patients across radiation devices who failed brachytherapy treatment compared to those who had a durable result. Treatment failures (n=14) were compared 1:2 to treatment successes (n=28) matched by two variables: radiation delivery system and angiographic pattern of in-stent restenosis**.** Our findings could lead to a refinement of dosing protocols and ultimately improvement in brachytherapy's treatment of ISR.

METHODS

A. Treatment Cohort Methodology

Cohort Study Population

We retrospectively examined the patient cohort who underwent intravascular brachytherapy at Yale New Haven Hospital between November 2000 and November 2002 – a total of 216 patients and 245 lesions. Brachytherapy was performed on all referred patients with clinical evidence of ischemia and ISR evident by cardiac catherization, aside from two patients for whom IVBT was aborted because of technical difficulties in radiation catheter placement. IVBT was administered by one of four devices: 1) *Novoste - BetaCath* system – Beta radiation using 90-Sr/Y; 2) *Cordis - Checkmate* – Gamma radiation using 192-Ir; and 3) *Guidant - Galileo* – Beta radiation using 32-P. 4) *Interventional Therapy* – Gamma radiation using 192-Ir as part of clinical trial. None of the patients in our study had received intravascular brachytherapy prior to this treatment. This study was approved by the Yale Human Investigation Committee in accordance with institutional guidelines.

Intervention and Brachytherapy Protocol

Diagnostic catheterization was performed separate from the intervention in the majority of cases. This allowed for decisions regarding appropriateness for brachytherapy, treatment planning and, device selection, especially early in the series when source length was a limiting factor in some cases. Anticoagulation was achieved using unfractionated heparin to achieve a target activated clotting time (ACT) of 300 seconds. Glycoprotein 2b/3a inhibitors were used only as a bailout strategy. All cases were completed with 8F-guiding catheters. Coronary intervention was performed using cutting balloon, rotational atherectomy, or balloon angioplasty. After the best angiographic result was obtained, IVUS was performed in all cases. If further intervention was indicated from ultrasound imaging, another IVUS run was performed

immediately prior to brachytherapy treatment. Lumen dimensions for the purposes of brachytherapy dose prescriptions were taken from MLD as designated by IVUS in all cases.

Several factors were used to determine the device for radiation delivery. Many patients in the first 6 months of the series were enrolled in research studies, which dictated device selection. Early in the series, the Checkmate device was used for the longest lesions, as the BetaCath was limited to a 40mm source (30mm injury length), and we avoided manual "stepping" of shorter sources because of inherent inaccuracies in delivered dose (49). Beta emitters were favored if patients became ischemic during the intervention or if it was the clinical impression of the operator that long dwell time would not be tolerated. Using this strategy, no cases required fractionation of treatment. Gamma sources were favored in arteries with heavy calcification, or where significant length of overlapping stents (>2-3mm) was present. In addition, we favored gamma sources for treatment of vein graft lesions because of the relative absence of data for beta-emitters in this anatomic subset. All patients were encouraged to continue dual antiplatelet therapy for at least six months. If a new stent was placed at the time of the brachytherapy procedure, we recommended 12 months of antiplatelet therapy.

Collection of Data & Analysis

This study was approved by the Yale Human Investigation Committee. We compiled a database including information from a) the patient's medical records – cardiac/medical histories, risk factors, comorbidities; b) angiography images – lesion and injury length, vessel diameter/degree of occlusion; c) IVUS images – MLD, dose-distribution within the vessels; d) Radiation treatment records – source type and dose prescription. Double entry of data was done to ensure accuracy.

Coronary angiograms were reviewed by two independent observers who classified lesions as per the ISR classification system described by *Mehran et al* (16):

Class I: Focal ISR group. Lesions are ≤10 mm in length and are positioned at the unscaffolded segment (i.e., articulation or gap), the body of the stent, the proximal or distal margin (but not both), or a combination of these sites (multifocal ISR)

Class II: "Diffuse intrastent" ISR. Lesions are >10 mm in length and are confined to the stent(s), without extending outside the margins of the stent(s).

Class III: "Diffuse proliferative" ISR. Lesions are >10 mm in length and extend beyond the margin(s) of the stent(s).

Class IV: ISR with "total occlusion." Lesions have flow grade of 0.

Patient Follow-up/Outcomes

Clinical outcomes were obtained for patients at 9 months by telephone contact with the patients and confirmed by their referring/primary physicians. As a quality control mechanism, the Yale Endovascular Brachytherapy Center uses a pre-established, standardized questionnaire to ask patients about their health status since undergoing brachytherapy – including whether or not they had stress testing, coronary artery bypass grafting (CABG), repeat percutaneous transluminal coronary angioplasty (PTCA), myocardial infarction (MI), and/or regular follow-up with a physician. This database was utilized as the major source of endpoint identification. From the 216 patients (245 lesions) treated with IVBT between November 2000 and November 2002, nine were lost to follow-up, leaving 207 patients (236 lesions) available for analysis– 96% follow-up. Patients lost to follow-up were double checked in the National Death Index to minimize selection bias. All cardiovascular endpoints were confirmed through the patients' referring cardiologists and/or primary care physicians.

B. Case-Control Methodology

Nested Case-Control Patient Selection

In order to perform detailed dosimetry, patients with reported MACE (that includes death, PTCA, CABG, and myocardial infarction) were identified from the Yale Endovascular Brachytherapy database who had received brachytherapy between November 2000 and June 2002. Follow-up angiography was reviewed to confirm treatment failure. Cases were eligible for inclusion as treatment failures if the target lesion treated was within a native coronary artery, and failure of the target lesion was confirmed by angiography as the cause of MACE. Cases with documented geographic miss were excluded (50).

Patients in our cohort who did not report MACE at 9 months were eligible as treatment successes. Treatment successes (controls) were then matched 2:1 to failure cases by two variables: 1) radiation delivery system and 2) angiographic pattern of ISR, according to the classification devised by Mehran et al (16).

IVUS Contours & Analysis

Images from the pre-radiation IVUS acquisition were printed every 2 mm throughout the lesion length (Figure 4). These images were scanned into an in-house computer calculation system and scaled to reflect their actual dimensions. Contours demarcating the EEM of the coronary vessel were drawn on each scanned image.

Figure 5 displays a typical EEM drawn on one of IVUS slices. The accuracy of this contouring was verified by two cardiologists. All steps of the dose distribution analysis were blinded to patient outcomes.

Dosimetry Calculations

The catheter-based radioactive source was assumed to be a line source with the radionuclide used in the treatment uniformly distributed over the length of the source and with the same length and strength as that used in the treatment. Dosimetric calculations were performed using a numerical integration method. Assuming that the point dose rate kernel per unit source strength of the radionuclide in interest is $k(\vec{r})$, the dose at a point of $\vec{r}$ is then (51):

$$D(\vec{r}) = \int_L k(\vec{r} - \vec{r}\,')\rho(\vec{r}\,')T d\vec{r}\,'$$

Where *L* is the length of radioactive source used in the treatment, *ρ(r)* is the source strength per unit length at the point *r* in the source, and *T* is the treatment time. The point dose rate kernels of various radionucliotides were obtained with Monte Carlo simulation in water. The doses were normalized to the prescription doses at the prescription points. The accuracy of the dose calculation was verified by the point-dose calculations at various points (other than the prescription points), comparing to the dose values provided by the manufacturers. It was assumed that the source was positioned where the IVUS catheter was located in the slice-based IVUS images, except for treatment catheters with a centering balloon in which case the source was assumed to be centered within the lumen. The longitudinal location of the source relative to IVUS slices was determined by comparing the IVUS images and corresponding angiograms.

Dose surface histogram (DSH) was calculated on the EEM for each examined slice (Figure 5) (52). The DSH was computed as follows: on each slice of interest, the EEM was divided into numerous points 0.001 mm apart from each other. The dose calculations were then performed on all the points. The calculated doses and percent of the points (representing EEM) were tabulated to form DSH. It should be noted that the dose calculations performed for DSH were only done on the contoured EEM lines, not on any points inside or outside the lines. Figure 5 shows a typical integral DSH. From the DSH on each slice of interest, the minimal dose that encompassed 90% of the EEM (D_{90}EEM) was determined. This is analogous to a parameter that

is predictive of success with cancer brachytherapy. Subsequently, the minimum, maximum, and average D_{90}EEM, were derived along the treated lesion.

C. Statistical Analysis

A composite outcome measure commonly referred to as MACE was utilized. Continuous data is presented as means with standard deviations, and discrete variables are presented as frequencies. Post-brachytherapy outcomes and bivariate analyses were described by Kaplan-Meier analysis, Pearson's Chi Square, and Independent T-test as required. Multivariate analysis was performed by conditional logistic regression to account for the controls matched to two variables. The multivariate model was restricted to four covariates to account for study size. SPSS 11.5 software was used to carry out statistical calculations.

D. Delineation of Work

As with most good research, our study was the joint effort of a group of dedicated individuals. The actual brachytherapy procedure was administered by a team consisting of Dr. Steven Pfau, Dr. Kenneth Roberts, and Dr. Ning Yue. The study concept was conceptualized by Dr. Steven Pfau, Dr. Kenneth Roberts, and Dr. Ning Yue. The epidemiological construct and study methodology was designed by Dr. Steven Pfau and Harsimran Singh. The dosimetry calculations described above were theorized and carried forth by Dr. Ravi Nath and Dr. Ning Yue. The IVUS delineation and angiography review (lesion typing) was performed by Harsimran Singh, Dr. Nassir Azimi, and Dr. Steven Pfau. The brachytherapy database (data collection) was made by Harsimran Singh. Cohort outcomes were obtained by Harsimran Singh, Mike Cabin, and Carol Roberts. Data analysis, statistical work, and team coordination was performed by Harsimran Singh. Data interpretation was performed by Harsimran Singh and Dr. Steven Pfau.

RESULTS

A. Patient Cohort Results

Patient demographics& Angiographic Characteristic:

Table 1 outlines the clinical characteristics of our study population. From amongst 207 patients, 152 (73%) were males whose ages ranged between 35-86 with a mean age of 63 and a corresponding 55 (27%) females with age range of 43-86 with a mean age of 67. The most prevalent clinical presentation that resulted in IVBT referral was unstable angina with 154 (74%). From the cohort, 149 (72%) had diagnosed hypertension, 152 (73%) hyperlipidemia, 66 (32%) diabetes (Type I and Type II), and 23 (5%) chronic renal insufficiency (defined by a baseline creatinine of > 1.5). Also, 82 (40%) patients had a previous myocardial infarction and 57 (27%) had undergone prior CABG.

Table 1. Cohort Characteristics & Outcomes (207 patients)

Pt Characteristics	
Male	152 (73.4%)
Average Age (years)	62.5 ± 12.6
Clinical Presentation	
Unstable Angina	154 (74.4%)
Stable Angina	23 (11.1%)
Positive Stress Testing	14 (6.8%)
Post-MI	12 (5.8%)
Other	4 (1.9%)
Risk Factor Profile	
Hyperlipidemia	152 (73.4%)
Hypertension	149 (72.0%)
Diabetes – Types 1 & 2	66 (31.9%)
Chronic Renal Insufficiency (Baseline Creatinine >1.5)	23 (11.1%)
Smoking	39 (18.8%)
Cardiac Family History (1st degree relative)	87 (42.1%)
Past Cardiac History	
Remote MI	82 (39.6%)
CABG	57 (27.5%)

Angiographic Characteristics

A total of 236 coronary lesions in 207 patients were treated with IVBT as listed in Table 2: the left anterior descending (LAD) in 78 (33%) lesions, circumflex (CFX) in 45 (19%) lesions, right coronary (RCA) in 73 (33%) lesions, ramus in 5 (2%) lesions, SVG in 33 (14%) lesions, and left internal mammary artery (LIMA) in 2 (1%). A total of 177 (75%) lesions were treated with cutting balloon or a combination of cutting balloon and standard balloon, and 48 (20%) lesions required additional stenting. The mean injury length for IVBT treatment was 22 mm.

Table 2: Vessel / Lesion Characteristics (n=236)

Variable	# of patients (%)
Vessel	
LAD	78 (33.1%)
CFX	45 (19.1%)
RCA	73 (30.9%)
SVG	33 (14.0%)
Ramus	5 (2.1%)
LIMA	2 (0.8%)
Average Injury Length (mm)	22.44 ± 10.28
Average MLD - post PTCA (mm)	3.07 ± 0.49
Primary PTCA Modality	
Cutting Balloon	177 (75.0%)
Rotational Atherectomy	17 (7.2%)
Balloon Only	38 (16.1%)
Additional Stenting	48 (20.3%)

Radiation Treatment

The Novoste BetaCath device was the most frequently used device, comprising 69% of cases (Table 3). This stems in large part from the fact that it was the first clinically available device, and was obtained by the Center in April of 2001. The Galileo device was available at Yale only as an investigational device during the period of this cohort, explaining the low number of patients treated with this device. Radiation dosing schemes were used as approved by the FDA for each individual system. Also outlined in Table III are the mean dose prescriptions for each brachytherapy system. Two patients had minimally shortened radiation treatment times due to ischemia (94% and 96% of prescription), while one patient had an increased treatment time (101% of prescription), due to difficulty in removing the radiation seeds.

Table 3: Brachytherapy System Used

Radiation System	Seed Train Length	Dose Prescription	Lesions Treated
Novoste (Beta – 90-Sr/Y)			
	30	23 Gy @ 2mm from source	34
	30	18.4 Gy @ 2mm from source	42
	40	23 Gy @ 2mm from source	38
	40	18.4 Gy @ 2mm from source	43
	60	23 Gy @ 2mm from source	4
	60	18.4 Gy @ 2mm from source	2

			163
Cordis Checkmate (Gamma – 192-Ir)	39	14 Gy @ 2mm from source	8
	39	8 Gy at furthest EEM	12
	55	14 Gy@ 2mm from source	8
	55	8 Gy at furthest EEM	28

			56
Interventional Therapy (Gamma – 192-Ir)	45	18 Gy @ 2 mm from source	13
Guidant Galileo (32-P)			
	60	20 Gy @ 1 mm into artery wall	4

Outcomes In-Hospital

There were no in-hospital deaths. Four lesions developed significant dissections during PTCA, all of which were treated successfully by additional stenting prior to IVBT. Two lesions were unable to be completely encompassed by IVBT due to tapering of the target vessel lumen diameter distal to the lesion. The IVUS catheter could not be passed into four lesions; in these cases MLDs were estimated from angiography alone. Two patients had enzymatic evidence of non-Q-wave myocardial infarction after the procedure. One patient with severe LV dysfunction and a large territory at risk had prophylactic placement of an intra-aortic balloon pump prior to the procedure. None of the patients required CABG surgery or emergent PTCA during their initial hospitalization. There was no incidence of subacute stent thrombosis.

Outcomes at 9-Month Follow-up

Table 4 summarizes the clinical outcomes obtained for our patient cohort at a mean time 9.1 months (± 2.8 months). 44 patients (21%) experienced MACE through our follow-up.

Table 4: Clinical Outcomes at 9 months (n=207)

Outcome Measure	# of patients (%)
MACE	44 (21.3%)
Repeat PTCA	21 (10.1%)
CABG	19 (9.2%)
MI	3 (1.4%)
Death	1 (0.5%)
No MACE	163 (78.7%)

The large majority of MACE was in patients requiring repeat revascularization (91%), evenly divided between PTCA and CABG. One patient with severe LV dysfunction died during the follow-up period. The one-year outcomes for our study population are illustrated in Figure 6 by means of a Kaplan Meier Survival Curve. Upon bivariate analysis of lesion and patient characteristics with outcomes (Tables 5 & 6), age (p=0.001), PTCA modality (0.037), and vessel type (p=0.002) were found to have a statistically significant effect upon outcome. An established diagnosis of hypercholesterolemia may eventually show a statistically significant effect on 9-month MACE with augmentation of the sample size (currently p= 0.156). Upon performing stepwise logistic regression with each independent variable, only age maintained statistical significance (p=0.001).

Table 5: Bivariate Analysis of Lesion Characteristics

Variable	MACE (n= 31)	No MACE (n=109)	Statistical P-Value
Age	58.24 ± 9.46	64.75 ± 12.88	0.001
Mean Lesion Length	23.40 ± 10.28	22.16 ±10.29	0.445
Mean MLD	3.07 ± 0.54	3.07 ± 0.48	0.990

Table 6: Bivariate Analysis of Patient/Lesion Characteristics

Variable	Variable Choices	Number of Patients	8-month freedom from event (%)	Statistical P-value
Gender				
	Male	152	77.0	0.301
	Female	55	83.6	
Age				
	≥65	98	87.8	0.001
	<65	109	70.6	
Hypertension				
	Yes	149	77.9	0.615
	No	58	81.0	
Hypercholesterolemia				
	Yes	152	76.3	0.156
	No	55	85.5	
Diabetes				
	Yes	66	75.8	0.472
	No	141	80.1	
Creatinine				
	> 1.5	23	70.0	0.254
	≤ 1.5	184	79.9	
Previous CABG				
	Yes	57	79.3	0.737
	No	150	77.2	
Previous MI				
	Yes	82	81.7	0.399
	No	125	76.8	
Type of Treatment Angioplasty				
	Cutting	177	79.1	0.037
	Balloon	17	76.3	
	Rotational Atherectomy	38	58.8	
Additional Stenting				
	Yes	48	73.7	0.650
	No	188	76.1	
Vessel				
	LAD	78	75.6	0.002
	CFX	45	62.2	
	RCA	73	89.0	
	SVG	33	78.8	
	Ramus	5	60.0	
	LIMA	2	0.0	

Section B. Case-Control Results

For the case-control segment of this study, only patients treated with brachytherapy between November 2000 and June 2002 were eligible. During this period, 145 patients (161 lesions) were treated for in-stent restenosis. The baseline characteristics of this cohort are reiterated in Table 7, and are consistent with those of the larger cohort described in Results Section A. During this period, five patients were lost to follow-up, leaving 140 patients available for analysis. At 9 months, 31 patients had reached significant MACE: 16 (11%) patients required repeat PTCA, and 14 (10%) patients needed CABG. Two patients were reported having an MI, and there was one death (Table 7).

Table 7. Cohort Characteristics & Outcomes (140 patients | 156 lesions)

Pt Characteristics	
Male	102 (73%)
Average Age (years)	64 (35-86 range)
Clinical Presentation	
Unstable Angina	112 (80%)
Stable Angina	10 (7%)
Positive Stress Testing	10 (7%)
Post-MI	6 (4%)
Other	2 (1%)
Risk Factor Profile	
Hyperlipidemia	100 (71%)
Hypertension	96 (69%)
Diabetes –	
Type II	36 (26%)
Type I	7 (5%)
Chronic Renal Insufficiency (Baseline Creatinine >1.5)	11 (8%)
Smoking	25 (18%)
Cardiac Family History (1st degree relative)	58 (41%)
Past Cardiac History	
Remote MI	55 (39%)
CABG	34 (24%)
Clinical Outcomes (at 9-months)	
MACE	31 (22%)
Repeat PTCA	16 (11%)
CABG	14 (10%)
MI	2 (1%)
Death	1 (1%)
No MACE	109 (78%)

Case-Control Patient Selection & Characteristics

All 31 clinical failures were reviewed for use in the dosimetry analysis. Four patients were excluded because the treatment segment was either a saphenous vein or internal mammary artery graft. Five patients were excluded because the point of failure was outside the treated segment. Two patients were excluded because of geographic miss. Of the remaining 20 patients, 6 were excluded from analysis because the EEM was not adequately visualized (at least 270 degrees identifiable in at least 90% of the IVUS images); this was most commonly related to shadowing from calcification or severe non-uniform rotational distortion. This left 14 patients with in-field failures of native coronary arteries with adequate IVUS imaging available for analysis (Figure 7).

Table 8. Variables Used to Match Controls with Cases

	Cases (n=14)	Controls (n=28)
Brachytherapy System		
Novoste (Beta – 90-Sr/Y)	4	10
Cordis Checkmate (Gamma – 192-Ir)	8	15
Interventional Therapy (Gamma – 192-Ir)	1	3
Guidant Galileo (Beta – 32-P)	1	0
Beta Radiation	5	10
Gamma Radiation	9	18
Lesion Type[A]		
Type I	3	7
Type II	5	11
Type III	6	7
Type IV	0	3
Types I & II	8	18
Types III & IV	6	10

Controls were then selected from the 109 patients who remained MACE-free at 9-months. All controls were native coronaries matched to failures in a 2:1 ratio; radiation delivery system and angiographic pattern of in-stent restenosis were the variables used to match cases to controls (Table 8).

Matching created 2 groups that were similar with regard to demographics, lesion length, final MLD (by IVUS), and PTCA treatment modality (Table 9). Chronic renal failure and diabetes were slightly more common in the controls than in the cases, and more additional stenting was performed in the control group compared to failures.

[A] Lesion typing system as designated by *Mehran: Circulation, 100(18): 1872-187.*

Table 9. Patient & Lesion Characteristics of Cases & Controls

	Cases (n=14)	Controls (n=28)
Patient Characteristics		
Male	12 (86%)	22 (79%)
Average Age (years)	60.00 ± 8.98	60.39 ± 12.88
Clinical Presentation		
Unstable Angina	13 (93%)	19 (68%)
Stable Angina	0 (0%)	1 (4%)
Positive Stress Testing	0 (0%)	4 (14%)
Post-MI	1 (7%)	4 (14%)
Risk Factor Profile		
Hyperlipidemia	11 (86%)	20 (71%)
Hypertension	11 (79%)	22 (79%)
Diabetes – Types I & II	3 (21%)	9 (32%)
Chronic Renal Insufficiency (Baseline Creatinine >1.5)	0 (0%)	1 (4%)
Smoking	3 (21%)	7 (25%)
Cardiac Family History (1st degree relative)	8 (57%)	15 (54%)
Past Cardiac History		
Remote MI	2 (14%)	16 (57%)
CABG	3 (21%)	1 (4%)
Treated Vessel		
LAD	5 (36%)	12 (43%)
CFX	5 (36%)	5 (18%)
RCA	4 (28%)	11 (39%)
Lesion Dimensions		
Average Injury Length (mm)	29.21 ± 11.73	26.71 ± 10.83
Average MLD post-PTCA (mm)	2.82 ± 0.43	2.89 ± 0.63
Primary PTCA Modality		
Cutting Balloon	12 (86%)	23 (82%)
Rotational Atherectomy	1 (7%)	2 (7%)
Balloon Only	1 (7%)	3 (11%)
Additional Stenting	3 (21%)	9 (32%)

Dose Distribution v. Clinical Outcomes

For every study patient, the D_{90}EEM was calculated for each IVUS slice along the entire length of radiation treatment, inclusive of the entire injury length. D_{90}EEM were then compiled to extrapolate the minimum, maximum, and average D_{90}EEMs for each lesion. An average of 22 slices was analyzed per lesion. A longitudinal display of D_{90}EEM for one lesion is illustrated below (Figure 8).

Figure 9 illustrates the minimum D_{90}EEMs plotted for all 42 patients. The mean minimum D_{90}EEM for the cases was 7.46 ± 2.07 Gy, while for the controls it was 8.87 ± 1.13 Gy. Upon bivariate analysis, minimum D_{90}EEM was found to be a statistically significant predictor of clinical success (p=0.007). All other patient and lesion characteristics were analyzed by bivariate analysis (selected variables shown in Table 10):

Table 10. Bivariate Analysis of Selected Variables Including Dose Distribution & Outcomes

	Cases (n=14)	Controls (n=28)	P-Value
Age (yrs)	60.00 ± 8.98	60.39 ± 12.88	0.919
Diabetes	3 (21%)	9 (32%)	0.469
Hyperlipidemia	11 (86%)	20 (71%)	0.306
Remote MI	2 (14%)	16 (57%)	0.008
Remote CABG	3 (21%)	1 (4%)	0.063
Lesion Length (mm)	29.21 ± 11.73	26.71 ± 10.84	0.496
MLD (mm)	2.82 ± 0.43	2.89 ± 0.63	0.393
Primary PTCA Modality			
Cutting Balloon	12 (86%)	23 (82%)	
Rotational Atherectomy	1 (7%)	2 (7%)	0.933
Balloon Only	1 (7%)	3 (11%)	
Average D_{90}EEM Dose (Gy)	10.50 ± 3.06	10.90 ± 1.70	0.586
Maximum D_{90}EEM Dose (Gy)	13.62 ± 5.97	14.24 ± 2.86	0.681
Minimum D_{90}EEM Dose (Gy)	7.46 ± 2.07	8.87 ± 1.13	0.007
Minimum D_{90}EEM Dose ≤ 8.4 Gy	13 (93%)	7 (33%)	
Minimum D_{90}EEM Dose > 8.4 Gy	1 (7.1%)	14 (67%)	<0.001

Only the presence of remote MI was found to be statistically significant (p=0.008). The maximum and average D_{90}EEM were neither numerically nor statistically different between the groups (figures not shown).

Using the dose distribution data displayed (Figure 9), a threshold for minimum dose of 8.4 Gy demarcates clinical success from failure reasonably well. Using this threshold, 13 (93%) of the cases had a minimum D_{90}EEM ≤ 8.4 Gy, while only 7 (33%) of the controls were below this minimum (p<0.001). A multivariate model was used including dose threshold, age, diabetes, remote MI, and lesion length. Minimum D_{90}EEM ≤ 8.4 Gy remained a significant predictor of clinical outcome with an odds ratio of 0.022 (CI of 0.002 to 0.300) when compared to minimum D_{90}EEM > 8.4 Gy. No other variable examined in our multivariate model was significant. Step-

wise, logistic regressions were also performed examining every variable in the multivariate analysis (Table 11). Only minimum D_{90}EEM retained its statistical significance.

Table 11. Logistical Regression Model of Select Variables for Clinical Success

	Odds Ratio	Lower 95% Limit OR[A]	Upper 95% Limit OR
Minimum D_{90}EEM Dose			
≤ 8.4 Gy	0.022	0.002	0.300
> 8.4 Gy	1.000	1.000	1.000
Age			
< 65	0.371	0.054	2.555
≥ 65	1.000	1.000	1.000
Diabetes			
Yes	1.000	1.000	1.000
No	0.315	0.041	2.402
Remote MI			
Yes	1.000	1.000	1.000
No	0.194	0.025	1.518
Lesion Length			
< 25 mm	1.000	1.000	1.000
≥ 25 mm	0.603	0.082	4.447

[A] OR indicates odds ratios.

DISCUSSION

Cohort Analysis Documenting Brachytherapy's Effectiveness:

We present our single-institution experience with coronary brachytherapy over the first two years since FDA approval in November of 2000. When applied to a broad group of patients with ISR, using a variety of delivery devices, intracoronary brachytherapy is safe and effective. Our 9-month MACE rate of 21.3% corresponds well with clinical outcomes reported in the radiation groups of the three hallmark randomized control trials: GAMMA-1 (28% at 9-months) (20,21), START (18% at 6-months) (22), and INHIBIT (22% at 6-months) (23). All patients were treated with prolonged dual anti-platelet therapy, and there were no instances of late stent thrombosis. While the larger Novoste based RENO registry in Europe has been reported (27,53), our registry is unique in that it incorporates experience with all the currently available devices and is limited strictly to patients treated for in-stent restenosis.

Several important lessons can be learned from the transition from initial clinical trials to a more general experience. First, when patients generally excluded from clinical trials are examined, there is no significant change in overall outcome. In our series, patients with SVG (14%) lesions, multivessel treatments (14%), total occlusions (9%) and chronic renal failure (11%), would have been excluded from randomized trials. Still, our cohort maintained treatment efficacy in spite of 36% of the total being "high risk" patients. Second, universal treatment with dual antiplatelet therapy resulted in elimination of the clinical entity of late thrombosis that was seen in earlier clinical trials (39,54,55). Without complete angiographic follow-up, however, the incidence of "subacute" late thrombosis (i.e. clinically silent total occlusion of the target vessel) could not be excluded. Finally, other procedural parameters that have been related to worse outcomes in prior studies, such as additional stenting at the time of brachytherapy (27), had no effect on outcome in our series (see table 5).

In bivariate and multivariate analysis of continuous variables, age was found to be a statistically significant inverse predictor of outcome. This finding is consistent with observations made by Ajani (35), as well as in the RENO registry (27). The reasons for the improved outcome in the elderly are not entirely clear; one hypothesis suggests that the ability for cellular regeneration and proliferate response to injury diminishes with age (35). Lesion length and smaller MLD were not related to clinically driven revascularization, although other studies have suggested that these factors are important in target vessel restenosis (36). Bivariate analysis of dichotomous variables failed to uncover any other significant relationships to outcome, similar to other studies of both diabetes (31,32), and chronic renal insufficiency (33). Use of cutting balloon was associated with better outcome, similar to the findings of the RENO registry in addition to several other studies (56-58). It has been suggested that precise limitation of injury with the cutting balloon may improve IVBT results by reducing the likelihood of geographic miss.

Certain limitations inherent in observational research must be considered when interpreting our findings. While clinical endpoints are the most important effect of any therapy, we were unable to precisely differentiate between target lesion failure, target vessel failure, and non-target vessel failure in many cases because of lack of complete angiographic reexamination. Nevertheless, there is a paucity of published data about IVBT in a non-controlled case mix, and even less information derived from a 'real world' utilization of all three available IVBT devices.

Yale Endovascular Brachytherapy Center's philosophy of using all available devices is a unique feature of this cohort. Early in the series device selection was primarily dictated by lesion length, but in several instances we allowed treatment with a secondary device when the initial device could not be negotiated into the target lesion. Furthermore, we believe strongly that appropriate device selection prevented severe ischemia during treatment and any need for dose fractionation. Ultimately this philosophy of device selection based on lesion characteristics will result in improved clinical outcomes, however too many of the patients in this particular cohort

had the device dictated by availability of source train length. Our more recent experience is that all devices now have the ability to treat injury lengths of 50mm, and the lesion characteristics that affect isotope-specific dose delivery such as calcium, overlapping stents, vessel curvature, involvement of bifurcations, and saphenous vein graft target will dictate device selection in order to most completely deliver dose to target.

The recent entry of drug-eluting stents into the US market will hopefully reduce the overall incidence of in-stent restenosis. At present, brachytherapy is the treatment of choice for ISR because it is proven, effective, and safe. Ongoing randomized trials of drug-eluting stents for restenosis may provide alternatives for this patient population, and ultimately the relative utilization of these modalities will be driven by efficacy, ease of application, and economics. Experiences from trials of IVBT have driven changes in practice that have further refined the protocol for IVBT treatment, leading to improved short-term and long term outcomes. Technical improvements in catheter design and familiarity with the use of this modality have improved its penetration into the overall interventional practice. Based on this data as well as that from other broad registries, it is likely that brachytherapy will remain an important part of the interventional landscape for the foreseeable future.

Case Control Suggesting a Dose Threshold for Clinical Success:

The second goal of this study was to explore the possibility of dose distribution playing a role in dictating clinical success. To our knowledge, this is the first study of coronary brachytherapy examining the relationship between actual delivered dose and clinical outcomes in a cohort of patients treated with a variety of radiation delivery devices, isotopes, and dose prescription algorithms. We used a standardized method to assess dose delivery across radiation devices in order to establish the relationship between delivered dose and outcome after IVBT. This study is also the first to suggest that there is a relationship between delivered dose and

revascularization rates in coronary brachytherapy for in-stent restenosis regardless of device used to deliver that dose.

Other investigators have examined the relationship between dose and outcome, but those studies have differed in two important ways. First, all have focused on a single delivery device and isotope. Second, these studies have primarily examined the relationship between dose and intimal tissue volume as assessed by IVUS (59-62). Although intimal tissue volume can be a surrogate for clinical outcomes in most of these prior studies the need for repeat revascularization was low, suggesting that changes in intimal tissue volume were not an appropriate correlate for the clinical effectiveness of coronary brachytherapy. Verin et al did show a relationship between angiographic restenosis and dose prescription using an Sr90 source (63). In de novo lesions treated with balloon angioplasty alone, dose prescriptions were 9, 12, 15, or 18Gy that resulted in angiographic restenosis rates of 29, 21, 16 and 15 percent. This translated into an improvement in clinical outcome, with a revascularization rate of 18% in the lowest dose group and 6% in the highest dose group. Unfortunately, this study did not include an IVUS examination, so that the relationship was between outcome and dose prescription rather than delivered dose. Furthermore, this study was of de novo lesions rather than in-stent restenosis.

A series of studies from Waksman's group have addressed the issues of dose with gamma emitters. In an IVUS based analysis of long, diffuse ISR treated with brachytherapy, both volume of intimal hyperplasia and minimum lumen area at follow-up were related to target distances (64). Although specific dosimetric analysis was not performed, a fixed dose prescription (15 Gy at 2mm) was used, so that longer source to target distances would have resulted in lower dose to the EEM. In a comparison of two dose prescriptions (15 or 18 Gy at 2mm), Waksman and colleagues showed that by IVUS parameters (60) or by angiographic restenosis and MACE (65), higher dose prescriptions were associated with better outcomes.

The optimal dose and target for brachytherapy for in stent restenosis was not rigorously examined in the pivotal clinical trials. Animal data suggests a dose-response in intimal growth

after balloon over-stretch injury in porcine coronary arteries, with the lowest doses (3.5 Gy) resulting in increased intimal growth, but higher doses (up to 14 Gy) showed a progressively beneficial effect (43,66). In the first series of patient treatments, dose prescriptions were as high as 25Gy at a distance of 1.5mm from the Ir^{192} source (67). Due to the lack of centering, estimates for maximum dose delivered to the vessel surface were as high as 92.5Gy. Concern for toxicity to the vessel at these doses led to the use of IVUS based prescription algorithms to limit "near field" doses to 30 Gy in the earliest randomized trials of gamma emitters (20,68). Randomized trials of beta emitters (23,69) did not use IVUS guided dosimetry, and have not performed IVUS analysis of delivered dose. For these isotopes (Sr^{90} and P^{32}) steeper dose gradients would result in high lumen doses relative to Ir^{192}. None of the current dose prescription algorithms take into account source to target distance, i.e. the variability of distance to the EEM from the lumen.

Our finding that a dose threshold of 8.4 Gy at the EEM exists is the first time that such a high dose has been associated with clinical success. In the SCRIPPS trial, angiographic late loss was significantly decreased when the adventitial border received at least 8 Gy (62). Because of small numbers, however, this paper was not able to relate dose to clinical failure. Further, it is important to note that this threshold exists across devices in our study. Although in other diseases there may be some difference in biologic effect related to dose rate of a specific isotope, these differences may not be as important in the coronaries (70).

The study is limited because of relatively small numbers and its retrospective design. Furthermore, the patients were not consecutive, but selected primarily based on the interpretability of the IVUS images. Other important determinants of dose delivery, such as degree of vascular calcification, curvature, and degree of stent overlap were not included as variables in this analysis. We limited our analysis to patients who suffer "in-field" failure, which does not account for all patients who require target vessel revascularization after coronary brachytherapy. Another limitation of the current study is the assumption that the line source location was assumed to be synonymous with the IVUS catheter.

In early studies, intravascular brachytherapy focused on dose in an effort to balance concerns of toxicity with proof of efficacy. These studies, both in animals and patients, suggested a dose response, and the concern for vascular toxicity led to IVUS guided dose prescriptions in the first randomized clinical trials primarily to avoid excessive "near field" doses. IVBT has resulted in remarkably consistent improvement in outcomes regardless of isotope, and dose prescriptions are standardized using only visual estimates of lumen diameter for dose adjustment. Abandoning routine IVUS improves short term time and cost efficiencies in the catheterization laboratory, but at a great loss of artery specific information that is important to clinical outcome. The data in our study argues that we should not settle for dose algorithms that are 'sufficient' to allow a 20-40% failure rate; rather further refinement of our dosing strategy is necessary. The improved image quality and general availability of IVUS, as well as future developments in intravascular imaging, should push this field to refine dose prescription to maximize benefit while minimizing potential toxicity. We believe that this study adds to the body of existing evidence that shows how improved outcomes in coronary brachytherapy are related to dose. Vessel and plaque anatomic data obtained by IVUS should be used in all patients undergoing brachytherapy to determine an optimal dose prescription.

REFERENCES

1. Mintz G.S., Popma J.J., Pichard A.D., Kent K.K., Satler L.F., et al. Arterial Remodeling after Cornary Angioplasty: A Serial Intravascular Ultrasound Study. Circulation 1996;77:361-371.
2. Pakala R., Willerson J.T., Benedict C.R. Effcet of Serotonin, Thromboxane A2, and Specific Receptor Antagonists on Vascular Smooth Muscle Cell Proliferation. Circulation 1997;96:2280-2286.
3. Fischman D.L., Leon M.B., Baim D.S., Schatz R.A., Savage M.P., et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496-501.
4. Serruys P., De Jaegere P., Kiemeneij F. A Comparison of Balloon Expandable Stent Implantation with Balloon Angioplasty in Patients with Coronary Arter Disease. N Engl J Med 1994;331:489-494.
5. Elezi S., Kastrati A., Neumann F.J., Hadamitzky M., Dirschinger J., et al. Vessel size and long-term outcome after coronary stent placement. Circulation 1998;98:1875-80.
6. Elezi S., Kastrati A., Wehinger A., Walter H., Schuhlen H., et al. Clinical and angiographic outcome after stent placement for chronic coronary occlusion. Am J Cardiol 1998;82:803-6, A9.
7. Ajani A.E., Kim H.S., Waksman R. Clinical trials of vascular brachytherapy for in-stent restenosis: update. Cardiovasc Radiat Med 2001;2:107-13.
8. Mehran R., Mintz G.S., Satler L.F., Pichard A.D., Kent K.M., et al. Treatment of in-stent restenosis with excimer laser coronary angioplasty: mechanisms and results compared with PTCA alone. Circulation 1997;96:2183-9.
9. Reimers B., Moussa I., Akiyama T., Tucci G., Ferraro M., et al. Long-term clinical follow-up after successful repeat percutaneous intervention for stent restenosis. J Am Coll Cardiol 1997;30:186-92.
10. Hoffmann R., Mintz G.S., Dussaillant G.R., Popma J.J., Pichard A.D., et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation 1996;94:1247-54.
11. Komatsu R., Useda M., Naruko T. Neointimal Tissue Response at Sites of Coronary Stenting in Humans. Circulation 1998;99:44-51.
12. Abizaid A., Kornowski R., Mintz G.S., Hong M.K., Abizaid A.S., et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardiol 1998;32:584-9.
13. Hirshfield J., Schwartz J., Jugo R., MacDonald R., Goldberg S., et al. Restenosis after Coronary Angioplasty: A Multivariate Statistical Model to Relate Lesion and Procedural Variables to restenosis. J Am Coll Cardiol 1991;21:16-25.
14. Myler R., Shaw R., Stertzer S. Reoccurence after Coronary Angioplasty. Cathet Cardiovasc Diagn 1987;13:77-86.
15. Platko W., Hollman J., Whitlow P., Franco I. Percutaneous Transluminal Angioplasty of Saphenous Vein Graft Stenosis: Long-Term Follow-up. J Am Coll Cardiol 1989;14:1645-1650.
16. Mehran R., Dangas G., Abizaid A.S., Mintz G.S., Lansky A.J., et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872-8.
17. Kuroda N., Kobayashi Y., Nameki M. Intimal Hyperplasia Regression from 6 to 12 Months after Stenting. Am J Cardiol 2002;89:869-874.

18. Kimura R., Yokoi H., Nagawa Y. Three Year Follow-up After Implantation of Coronary-Artery Stents. N Engl J Med 1996;334:561-568.
19. Waksman R., Rodriguez J.C., Robinson K.A., Cipolla G.D., Crocker I.R., et al. Effect of intravascular irradiation on cell proliferation, apoptosis, and vascular remodeling after balloon overstretch injury of porcine coronary arteries. Circulation 1997;96:1944-52.
20. Leon M.B., Teirstein P.S., Moses J.W., Tripuraneni P., Lansky A.J., et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med 2001;344:250-6.
21. Teirstein P.S., Massullo V., Jani S., Popma J.J., Russo R.J., et al. Three-year clinical and angiographic follow-up after intracoronary radiation : results of a randomized clinical trial. Circulation 2000;101:360-5.
22. Waksman R., Bhargava B., White L., Chan R.C., Mehran R., et al. Intracoronary beta-radiation therapy inhibits recurrence of in-stent restenosis. Circulation 2000;101:1895-8.
23. Waksman R., Raizner A.E., Yeung A.C., Lansky A.J., Vandertie L. Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. Lancet 2002;359:551-7.
24. Sapirstein W., Zuckerman B., Dillard J. FDA approval of coronary-artery brachytherapy. N Engl J Med 2001;344:297-9.
25. Tripuraneni P. Coronary artery radiation therapy for the prevention of restenosis after percutaneous coronary angioplasty, II: Outcomes of clinical trials. Semin Radiat Oncol 2002;12:17-30.
26. Teirstein P.S., Kuntz R.E. New frontiers in interventional cardiology: intravascular radiation to prevent restenosis. Circulation 2001;104:2620-6.
27. Urban P., Serruys P., Baumgart D., Colombo A., Silber S., et al. A multicentre European registry of intraluminal coronary beta brachytherapy. Eur Heart J 2003;24:604-12.
28. Coen V., Serruys P., Sauerwein W., Orecchia R., Von Rottkay P., et al. Reno, a European postmarket surveillance registry, confirms effectiveness of coronary brachytherapy in routine clinical practice. Int J Radiat Oncol Biol Phys 2003;55:1019-26.
29. Waksman R., White R.L., Chan R.C., Bass B.G., Geirlach L., et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation 2000;101:2165-71.
30. Ajani A.E., Waksman R., Cheneau E., Cha D.H., McGlynn S., et al. The outcome of percutaneous coronary intervention in patients with in-stent restenosis who failed intracoronary radiation therapy. J Am Coll Cardiol 2003;41:551-6.
31. Gruberg L., Waksman R., Ajani A.E., Kim H.S., White R.L., et al. The effect of intracoronary radiation for the treatment of recurrent in-stent restenosis in patients with diabetes mellitus. J Am Coll Cardiol 2002;39:1930-6.
32. Moses J.W., Moussa I., Leon M.B., Teirstein P.S., Fish R.D., et al. Effect of catheter-based iridium-192 gamma brachytherapy on the added risk of restenosis from diabetes mellitus after intervention for in-stent restenosis (subanalysis of the GAMMA I Randomized Trial). Am J Cardiol 2002;90:243-7.
33. Gruberg L., Waksman R., Ajani A.E., Kim H.S., White R.L., et al. The effect of intracoronary radiation for the treatment of recurrent in-stent restenosis in patients with chronic renal failure. J Am Coll Cardiol 2001;38:1049-53.
34. Waksman R., Ajani A.E., White R.L., Chan R.C., Satler L.F., et al. Intravascular gamma radiation for in-stent restenosis in saphenous-vein bypass grafts. N Engl J Med 2002;346:1194-9.
35. Ajani A.E., Waksman R., Cheneau E., Cha D.H., Pinnow E., et al. Elderly patients have a favorable outcome after intracoronary radiation for in-stent restenosis. Catheter Cardiovasc Interv 2002;56:466-71.

36. Ajani A.E., Waksman R., Cha D.H., Gruberg L., Satler L.F., et al. The impact of lesion length and reference vessel diameter on angiographic restenosis and target vessel revascularization in treating in-stent restenosis with radiation. J Am Coll Cardiol 2002;39:1290-6.
37. Kim H.S., Waksman R., Cottin Y., Kollum M., Bhargava B., et al. Edge stenosis and geographical miss following intracoronary gamma radiation therapy for in-stent restenosis. J Am Coll Cardiol 2001;37:1026-30.
38. Waksman R., Bhargava B., Mintz G.S., Mehran R., Lansky A.J., et al. Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis. J Am Coll Cardiol 2000;36:65-8.
39. Waksman R., Ajani A.E., White R.L., Pinnow E., Dieble R., et al. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS). Circulation 2001;103:2332-5.
40. Verin V., Popowski Y., Urban P., Belenger J., Redard M., et al. Intra-arterial beta irradiation prevents neointimal hyperplasia in a hypercholesterolemic rabbit restenosis model. Circulation 1995;92:2284-90.
41. Wiedermann J.G., Marboe C., Amols H., Schwartz A., Weinberger J. Intracoronary irradiation markedly reduces neointimal proliferation after balloon angioplasty in swine: persistent benefit at 6-month follow-up. J Am Coll Cardiol 1995;25:1451-6.
42. Weinberger J., Amols H., Ennis R.D., Schwartz A., Wiedermann J.G., et al. Intracoronary irradiation: dose response for the prevention of restenosis in swine. Int J Radiat Oncol Biol Phys 1996;36:767-75.
43. Waksman R., Robinson K.A., Crocker I.R., Gravanis M.B., Cipolla G.D., et al. Endovascular low-dose irradiation inhibits neointima formation after coronary artery balloon injury in swine. A possible role for radiation therapy in restenosis prevention. Circulation 1995;91:1533-9.
44. Waksman R., Robinson K.A., Crocker I.R., Gravanis M.B., Cipolla G.D., et al. Intracoronary radiation decreases the second phase of intimal hyperplasia in a repeat balloon angioplasty model of restenosis. Int J Radiat Oncol Biol Phys 1997;39:475-80.
45. Salame M.Y., Verheye S., Crocker I.R., Chronos N.A., Robinson K.A., et al. Intracoronary radiation therapy. Eur Heart J 2001;22:629-47.
46. Forrester J.S., Fishbein M., Helfant R., Fagin J. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. J Am Coll Cardiol 1991;17:758-69.
47. Sabate M., Marijnissen J.P., Carlier S.G., Kay I.P., van der Giessen W.J., et al. Residual plaque burden, delivered dose, and tissue composition predict 6-month outcome after balloon angioplasty and beta-radiation therapy. Circulation 2000;101:2472-7.
48. Yue N., Roberts K.B., Pfau S.E., Nath R. Dose distributions in bifurcated coronary vessels treated with catheter-based photon and beta emitters in intravascular brachytherapy. Med Phys 2003;30:1628-36.
49. Wallace S.A., Schumer W., Horrigan M. Monte Carlo dosimetry of a tandem positioned beta-emitting intravascular brachytherapy source train. Med Phys 2002;29:544-9.
50. Sabate M., Costa M.A., Kozuma K., Kay I.P., van der Giessen W.J., et al. Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy. Circulation 2000;101:2467-71.
51. Nath R., Yue N., Liu L. On the depth of penetration of photons and electrons for intravascular brachytherapy. Cardiovasc Radiat Med 1999;1:72-9.
52. Carlier S.G., Marijnissen J.P., Coen V.L., Sabate M., van der Giessen W.J., et al. Comparison of brachytherapy strategies based on dose-volume histograms derived from quantitative intravascular ultrasound. Cardiovasc Radiat Med 1999;1:115-24.

53. Coen V.L., Knook A.H., Wardeh A.J., van der Giessen W.J., De Pan C., et al. Endovascular brachytherapy in coronary arteries: the Rotterdam experience. Cardiovasc Radiat Med 2000;2:42-50.
54. Teirstein P., Reilly J.P. Late stent thrombosis in brachytherapy: the role of long-term antiplatelet therapy. J Invasive Cardiol 2002;14:109-14.
55. Derntl M., Syeda B., Beran G., Schukro C., Denk S., et al. Prevention of stent thrombosis following brachytherapy and implantation of drug-eluting stents. J Interv Cardiol 2002;15:477-83.
56. Adamian M., Colombo A., Briguori C., Nishida T., Marsico F., et al. Cutting balloon angioplasty for the treatment of in-stent restenosis: a matched comparison with rotational atherectomy, additional stent implantation and balloon angioplasty. J Am Coll Cardiol 2001;38:672-9.
57. Ajani A.E., Kim H.S., Castagna M., Satler L.F., Kent K.M., et al. Clinical utility of the cutting balloon. J Invasive Cardiol 2001;13:554-7.
58. Braun P., Stroh E., Heinrich K.W. Rotablator versus cutting balloon for the treatment of long in-stent restenoses. J Invasive Cardiol 2002;14:291-6.
59. Morino Y., Kaneda H., Fox T., Takagi A., Hassan A.H., et al. Delivered dose and vascular response after beta-radiation for in-stent restenosis: retrospective dosimetry and volumetric intravascular ultrasound analysis. Circulation 2002;106:2334-9.
60. Ahmed J.M., Mintz G.S., Waksman R., Mehran R., Leiboff B., et al. Serial intravascular ultrasound assessment of the efficacy of intracoronary gamma-radiation therapy for preventing recurrence in very long, diffuse, in-stent restenosis lesions. Circulation 2001;104:856-9.
61. Maehara A., Patel N.S., Harrison L.B., Weissman N.J., Bui A.B., et al. Dose heterogeneity may not affect the neointimal proliferation after gamma radiation for in-stent restenosis: a volumetric intravascular ultrasound dosimetric study. J Am Coll Cardiol 2002;39:1937-42.
62. Teirstein P.S., Massullo V., Jani S., Popma J.J., Mintz G.S., et al. A subgroup analysis of the Scripps Coronary Radiation to Inhibit Proliferation Poststenting Trial. Int J Radiat Oncol Biol Phys 1998;42:1097-104.
63. Verin V., Popowski Y., de Bruyne B., Baumgart D., Sauerwein W., et al. Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding Study Group. N Engl J Med 2001;344:243-9.
64. Ahmed J.M., Mintz G.S., Waksman R., Weissman N.J., Leiboff B., et al. Serial Intravascular Ultrasound Analysis of the Impact of Lesion Length on the Efficacy of Intracoronary gamma-Irradiation for Preventing Recurrent In-Stent Restenosis. Circulation 2001;103:188-191.
65. Waksman R., Cheneau E., Ajani A.E., White R.L., Pinnow E., et al. Intracoronary radiation therapy improves the clinical and angiographic outcomes of diffuse in-stent restenotic lesions: results of the Washington Radiation for In-Stent Restenosis Trial for Long Lesions (Long WRIST) Studies. Circulation 2003;107:1744-9.
66. Kaluza G.L., Raizner A.E., Mazur W., Schulz D.G., Zymek P.T., et al. Dose-response study of intracoronary beta-radiation with 32P in balloon- and stent-injured coronary arteries in swine. Cardiovasc Radiat Med 2001;2:225-30.
67. Condado J.A., Waksman R., Gurdiel O., Espinosa R., Gonzalez J., et al. Long-term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty and intracoronary radiation therapy in humans. Circulation 1997;96:727-32.
68. Teirstein P.S., Massullo V., Jani S., Popma J.J., Mintz G.S., et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med 1997;336:1697-703.

69. Popma J.J., Suntharalingam M., Lansky A.J., Heuser R.R., Speiser B., et al. Randomized trial of 90Sr/90Y beta-radiation versus placebo control for treatment of in-stent restenosis. Circulation 2002;106:1090-6.
70. Giap H., Tripuraneni P., Teirstein P., Massullo V. Theoretical assessment of dose-rate effect in endovascular brachytherapy. Cardiovasc Radiat Med 1999;1:227-32.

ABBREVIATIONS

IVBT	=	intravascular brachytherapy
ISR	=	in-stent restenosis
EEM	=	external elastic membrane
IVUS	=	intravascular ultrasound
CABG	=	coronary arterial bypass grafting
PTCA	=	percutaneous transluminal coronary angioplasty
MI	=	myocardial infarction
MACE	=	major adverse cardiac events
FDA	=	Food & Drug Administration
DSH	=	dose surface histogram
ACT	=	activated clotting time
LV	=	left ventricular
MLD	=	minimal luminal diameter
D_{90}EEM	=	minimal dose that encompasses 90% of the external elastic membrane

FIGURES

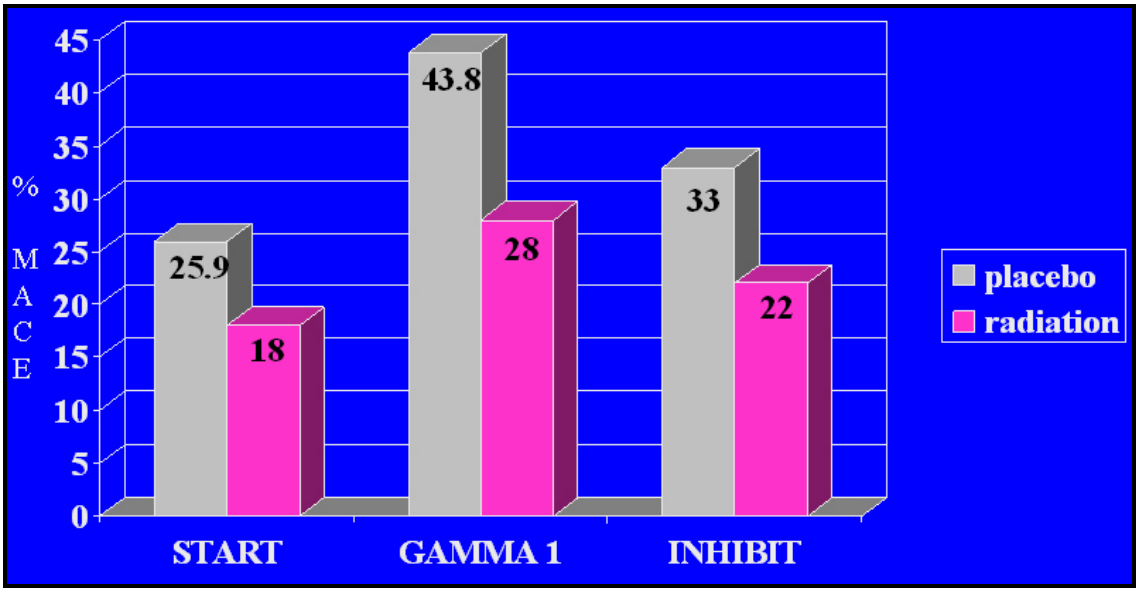

Figure 1. Clinical Outcomes of Brachytherapy Trials: This chart compares the percentage of major adverse cardiac events (MACE) between placebo and brachytherapy groups of three multi-center randomized control trials.[A]

[A] ***Leon, M.B., et al., N Engl J Med, 2001. 344***
Waksman, R., et al., Circulation, 2000. 101(16).
Waksman et al., Lancet, 2002. 359(9306)

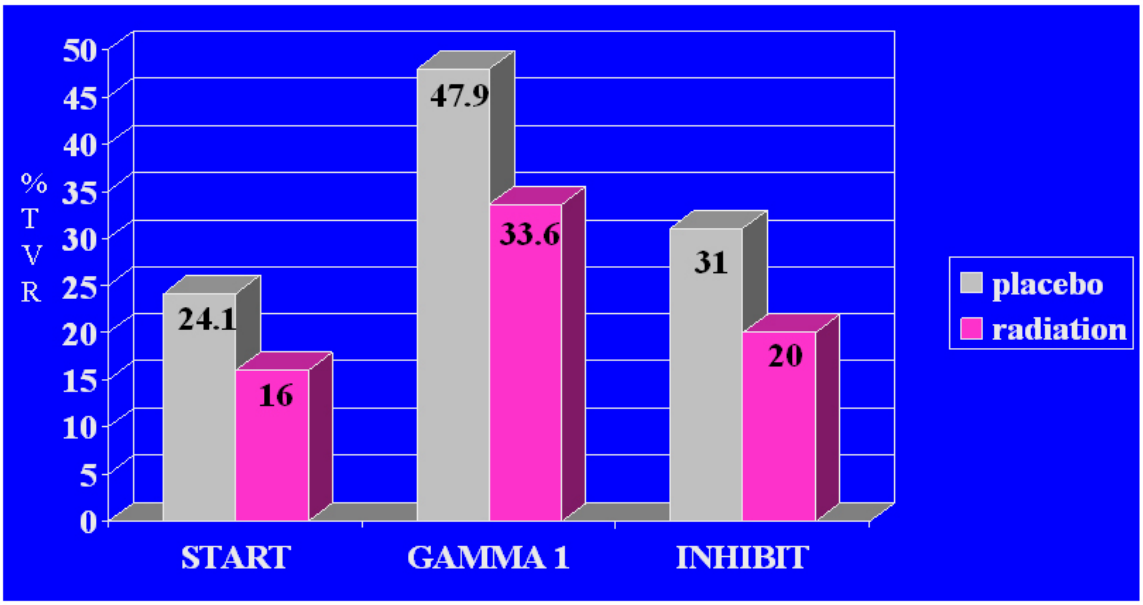

Figure 2. Angiographic Outcomes of Brachytherapy Trials: This chart compares the percentage of target vessel revascularization (TVR) between placebo and brachytherapy groups of three multi-center randomized control trials.[A]

[A] ***Leon, M.B., et al., N Engl J Med, 2001. 344***
Waksman, R., et al., Circulation, 2000. 101(16).
Waksman et al., Lancet, 2002. 359(9306)

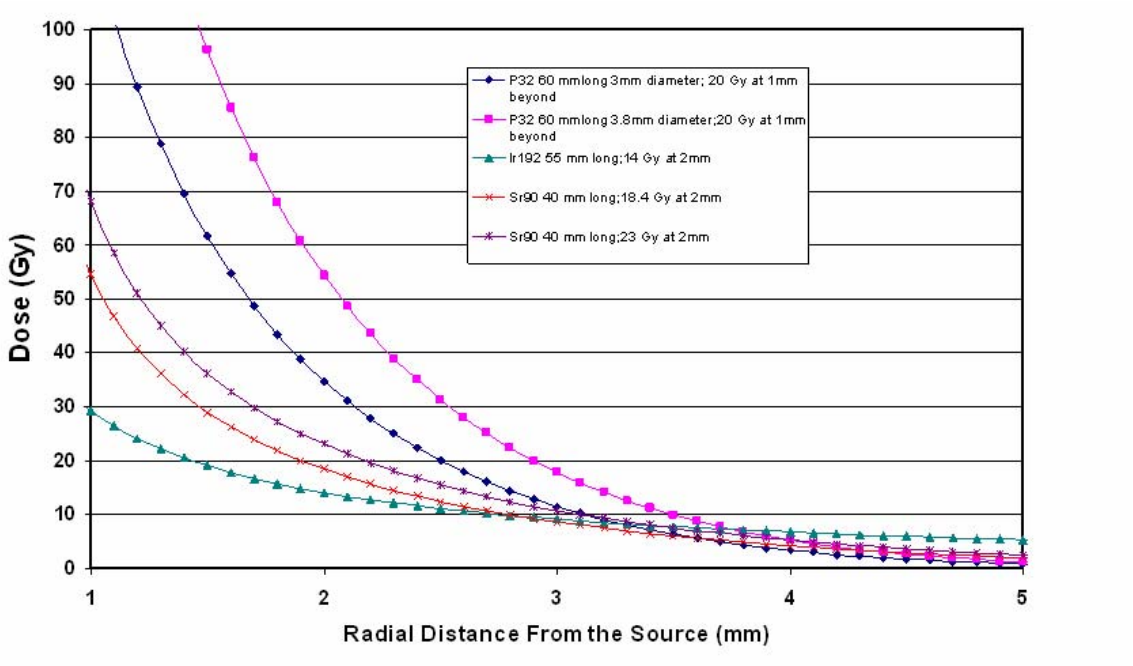

Figure 3. This figure illustrates theoretical dose variation for several different dose prescriptions and isotopes. It shows the de facto dose delivered is highly variable upon the distance to the target site.

Figure 1. IVUS Segments Across Target Vessel: Caricture shows basic premise of obtaining 2mm IVUS images across the span of the irradiated lesion.

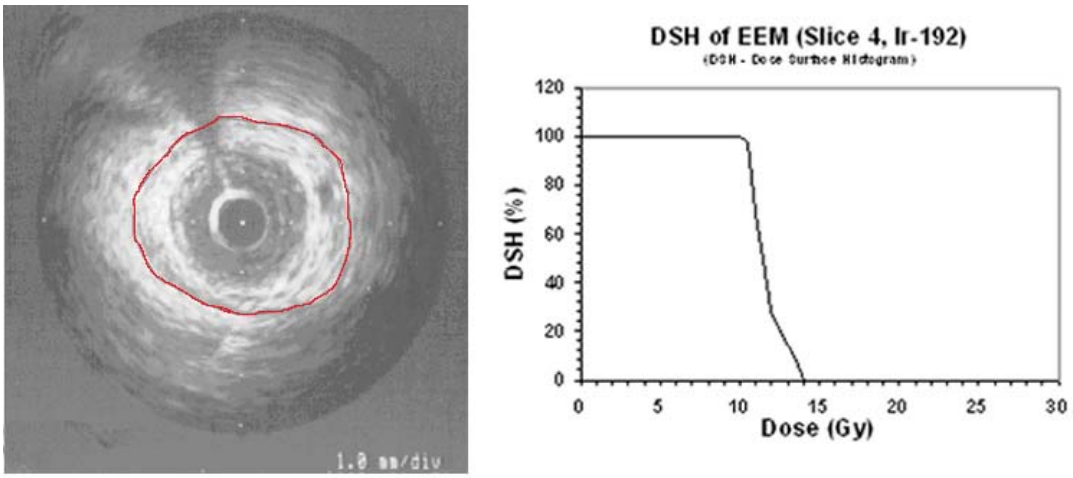

Figure 2. Sample IVUS with Dose Histogram: The external elastic membrane (EEM) outlined on a typical IVUS slice and its corresponding dose surface histogram (DSH).

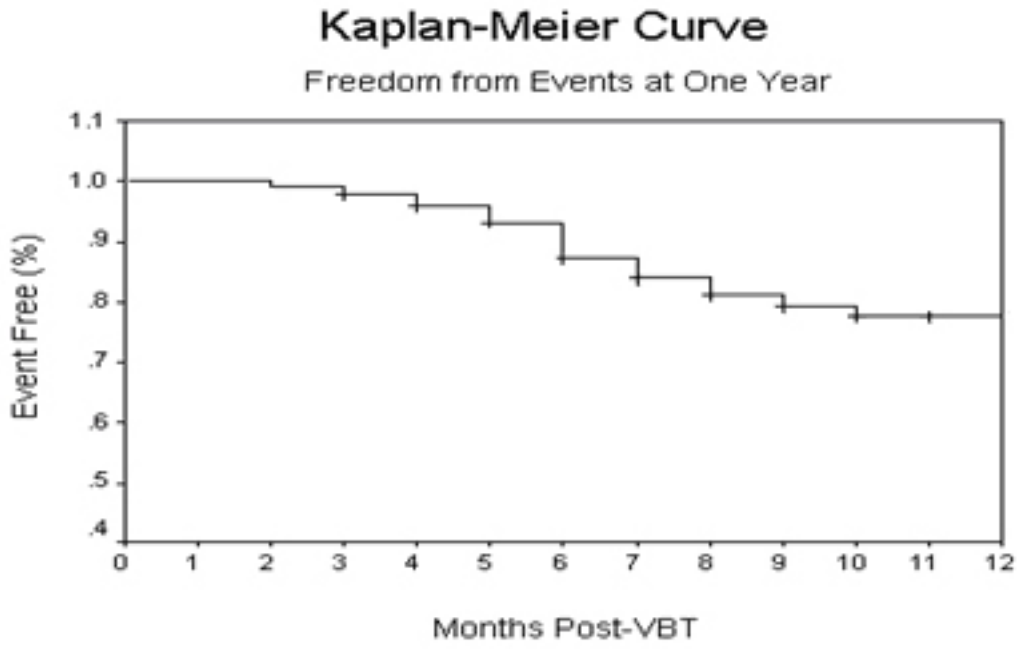

Figure 3. Kaplan-Meier survival curve over one year of the study cohort.

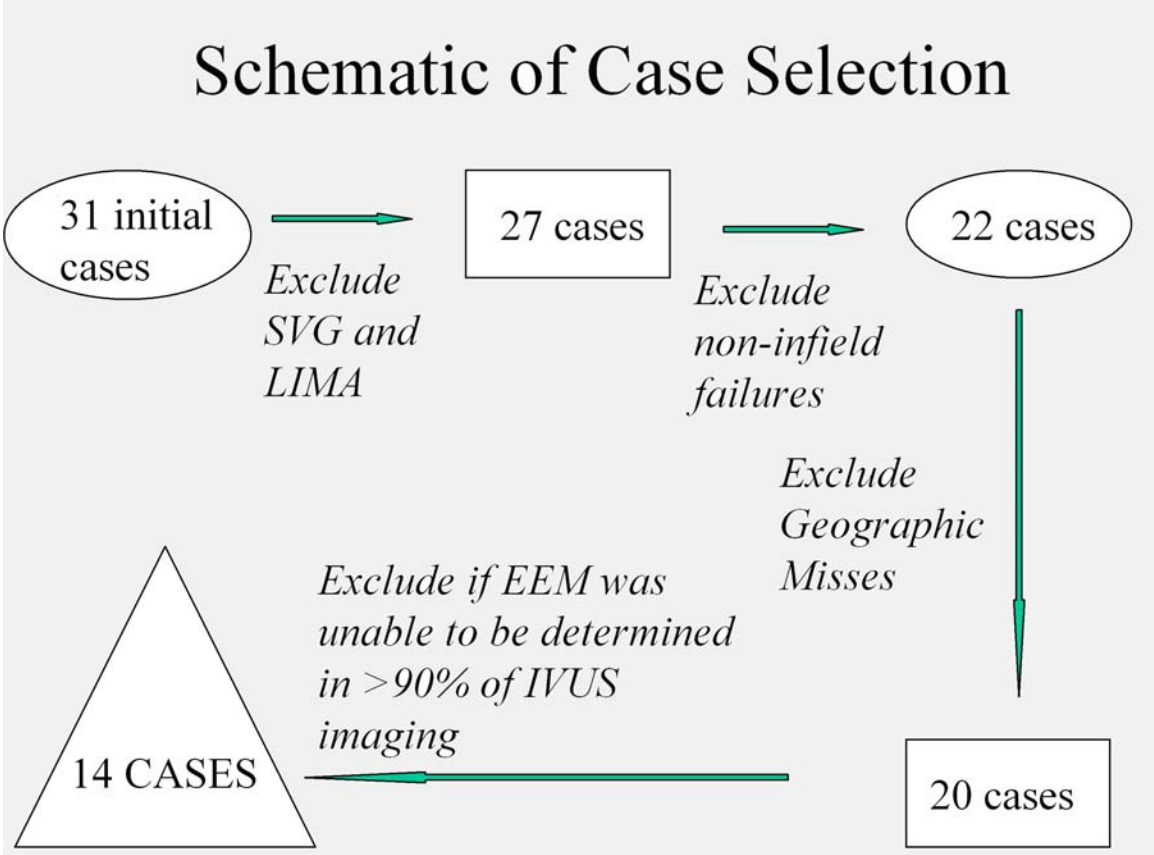

Figure 4. Schematic of Case-Control: Details the inclusion and exclusion criteria used to select patients eligible for case-control study.

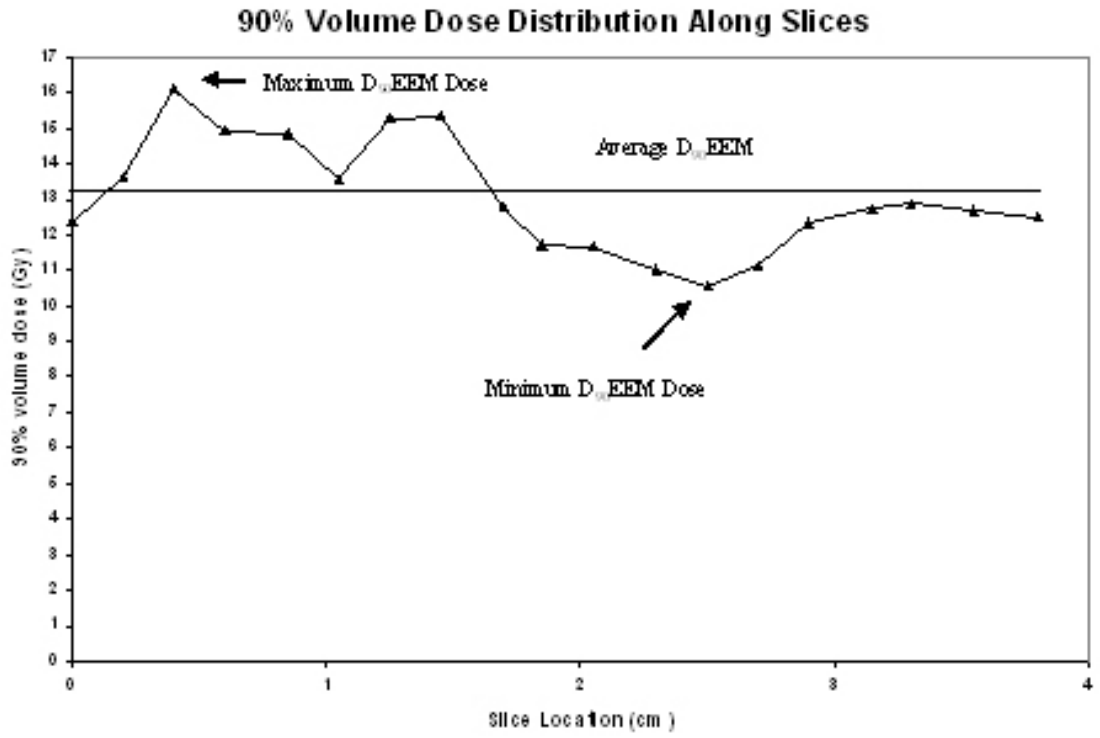

Figure 5. Dosing for a Single Vessel: A longitudinal display of the dose absorbed by 90% of the artery encompassed by the external elastic membrane (D90EEM) in intravascular ultrasound IVUS slices every 2 mm across a treated lesion. The maximum, mi

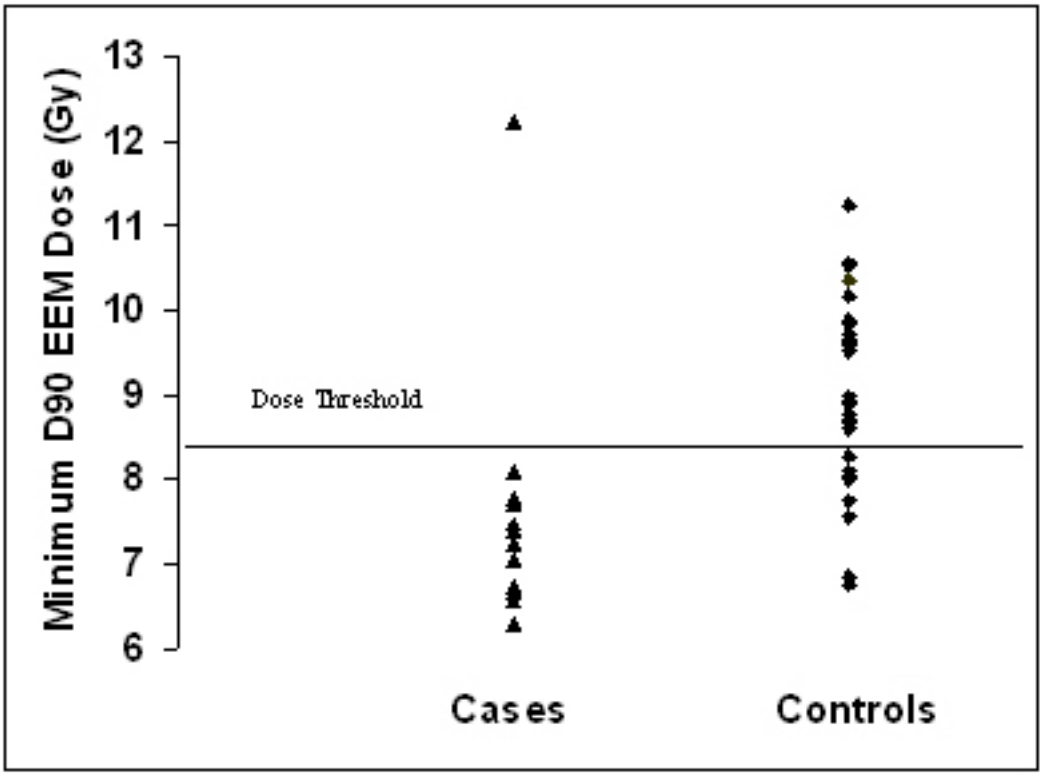

Figure 6. Dose Threshold: Distribution of the minimum dose absorbed by 90% of the artery encompassed by the external elastic membrane (D90EEM) for each study patient. Triangles represent cases (treatment failures). Diamonds represent the matched co