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Geographic Miss

A Cause of Treatment Failure in Radio-Oncology Applied to Intracoronary Radiation Therapy

Manel Sabaté, MD; Marco A. Costa, MD; Ken Kozuma, MD; I. Patrick Kay, MBChB; Willem J. van der Giessen, MD, PhD; Veronique L.M.A. Coen, MD; Jurgen M.R. Ligthart, BSc; Pedro Serrano, MD; Peter C. Levendag, MD, PhD; Patrick W. Serruys, MD, PhD

Background—A recognized limitation of endovascular β-radiation therapy is the development of new stenosis at the edges of the irradiated area. The combination of injury and low-dose radiation may be the precursor of this phenomenon. We translated the radio-oncological concept of "geographic miss" to define cases in which the radiation source did not fully cover the injured area. The aims of the study were to determine the incidence and causes of geographic miss and evaluate the impact of this inadequate treatment on the outcome of patients treated with intracoronary β-radiation.

Methods and Results—We analyzed 50 consecutive patients treated with β-radiation after percutaneous coronary intervention. The prescribed dose ranged between 12 and 20 Gy at 2 mm from the source axis. By means of quantitative coronary angiography, the irradiated segment (IRS) and both edges were studied before and after intervention and at 6-month follow-up. Edges that were injured during the procedure constituted the geographic miss edges. Twenty-two edges were injured during the intervention, mainly because of procedural complications that extended the treatment beyond the margins of the IRS. Late loss was significantly higher in geographic miss edges than in IRSs and uninjured edges (0.84 ± 0.6 versus 0.15 ± 0.4 and 0.09 ± 0.4 mm, respectively; $P<0.0001$). Similarly, restenosis rate was significantly higher in the injured edges (10% within IRS, 40.9% in geographic miss edges, and 1.9% in uninjured edges; $P<0.001$).

Conclusions—These data support the hypothesis that the combination of injury and low-dose β-radiation induces deleterious outcome. **(*Circulation*. 2000;101:2467-2471.)**

Key Words: geographic miss ■ radioisotopes ■ balloon ■ angioplasty ■ stents ■ angiography ■ restenosis

Endovascular radiation therapy is a novel technique aimed at preventing restenosis after percutaneous coronary intervention.[1–3] Radiation can be delivered to the coronary artery by means of catheter-based systems or radioactive stents.[4] A potential drawback of this treatment is the development of new stenotic lesions at both edges of the irradiated segment (IRS). This so-called "edge effect" was originally described after high-activity (>3 μCi) radioactive stent implantation.[5,6] However, this phenomenon is not exclusive to radioactive stents and may also affect coronary segments treated by means of catheter-based systems.[7] The pathophysiology of the edge effect may be the result of vessel wall injury[8–10] concomitant with low-dose radiation at the edges of the irradiated area.[11,12] In radio-oncology, the term to define a cause of treatment failure due to low dose was coined by the Manchester Clinic as "geographic miss." In such cases, a small part of the treatment zone has either escaped radiation or been inadequately irradiated because the total volume of the tumor was not appreciated and hence an insufficient margin was taken.[13] This concept is translated in interventional cardiology to define those coronary segments that were injured but received low-dose radiation. Typically, this phenomenon occurs when the edges of the IRS, where, by definition, the dose is rather low, are injured.

The aims of the study were (1) to determine the incidence and causes of geographic miss in the treatment of patients with intracoronary β-radiation by use of a catheter-based system and (2) to evaluate the impact of this inadequate treatment on the angiographic outcome of these patients.

Methods

Patient Selection

We retrospectively analyzed 50 consecutive patients treated at our institution with catheter-based β-radiation by means of the Beta-Cath system (Novoste Corp). Patients included in the radiation protocol were those with objective signs of ischemia and presence of

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From the Thoraxcenter, Heartcenter, and Academisch Ziekenhuis Dijkzigt (M.S., M.A.C., K.K., I.P.K., W.J.v.d.G., J.M.R.L., P.S., P.W.S.), and the Daniel den Hoed Cancer Center (V.L.M.A.C., P.C.L.), Rotterdam, Netherlands.

Correspondence to P.W. Serruys, MD, PhD, Professor of Interventional Cardiology, Head of Department of Interventional Cardiology, Bd 408, Heartcenter, Academisch Ziekenhuis Rotterdam, Erasmus University, PO Box 2040, Dr Molewaterplein 40, 3015 GD Rotterdam, Netherlands. E-mail serruys@card.azr.nl

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significant de novo lesions (n=39) or recurrent in-stent restenosis (n=11). A detailed description of the radiation system has been reported elsewhere.[14] The radiation source train consists of a series of 12 cylindrical seeds that contain the radioisotope $^{90}Sr/^{90}Y$ sources and is bordered by 2 gold radiopaque markers separated by 30 mm.[14]

Procedure

The medical ethics committee of our institution approved the investigational use of β-radiation, and all patients signed an informed consent form. Percutaneous intervention was performed according to standard clinical practice. Typically, coronary lesions were treated initially with balloon angioplasty (BA). After successful BA, the target coronary segment was irradiated. This could be followed by additional stent implantation when clinically indicated. Lesion length measured on average 11.4±4 mm, the mean balloon length was 20.0±3 mm, and the number of balloon inflations was 2.9±1.6. Patients received aspirin (250 mg) and heparin (10 000 IU IV) at the initiation of the procedure, and an additional dose of heparin was administered to maintain the activated clotting time >300 seconds. After the procedure, aspirin was continued indefinitely. In patients who also received stent implantation, ticlopidine was initiated and continued for ≥15 days after the procedure. The radiation dose was prescribed at 2 mm from the source axis. The prescribed dose for the treatment of de novo lesions was randomly assigned to 12, 14, or 16 Gy for protocol requirements. For the treatment of in-stent restenotic lesions, the prescribed dose was 16 or 20 Gy if the reference diameter, by quantitative coronary angiography (QCA), measured ≤3.25 mm or >3.25 mm, respectively. The mean dwell time to deliver these doses was 143±44 seconds.

Definitions

The IRS was defined as the area encompassed by the 2 gold markers of the radiation source train. It was identified on angiography by a contrast injection with the source in place. The edges of the IRS were defined as the 5-mm-long segments proximal and distal to the angiographic location of the gold markers. The edges that were touched by the angioplasty balloon or received new stent implantation during the procedure were defined as geographic miss edges, because they represent injured segments receiving low-dose radiation. Uninjured edges were those that were not traumatized during the intervention. To determine whether the edges of the IRS were injured, a few steps were followed: during the procedure, every balloon inflation or additional stent implantation was filmed in the same projection, as was the radiation source. This approach allowed us the correct matching of the cine films in the offline analysis. Either cine loop showing balloon inflation, stent implantation, and radiation source may be displayed simultaneously on the screen with the Rubo DICOM Viewer (Rubo Medical Imaging). ECG tracing is also displayed in either cine loop. By selecting those frames in the same part of the cardiac cycle, we were able to define the location of the radiation source relative to the injured area.

QCA Analysis

The IRS and both edges were analyzed by QCA before and after intervention and at 6-month follow-up. All angiograms were evaluated after intracoronary administration of nitrates. The offline analysis of 2 orthogonal projections was performed by means of the CAAS II analysis system (Pie Medical BV). Calibration of the system was based on dimensions of the catheters not filled with contrast medium. This method of analysis has been previously validated.[15–17] The following QCA parameters were computed in the IRS and both edges: minimal luminal diameter (MLD), which was computer defined; reference diameter, which was obtained by an interpolated method[15–17]; and percentage diameter stenosis. Binary restenosis was defined in every area as diameter stenosis >50% at follow-up. Acute gain was defined as MLD after treatment minus MLD before intervention. Late loss was defined as MLD after treatment minus MLD at follow-up. Relative late loss was defined as late loss divided by reference diameter.[18]

Statistical Analysis

To compare continuous variables between IRS, geographic miss edges, and uninjured edges, 1-way ANOVA with post hoc analysis for multiple comparisons was performed. Unpaired Student's *t* test was performed to compare continuous variables between proximal and distal geographic miss edges and between patients in whom the geographic miss was induced by balloon dilatation or stent implantation. To compare the binary restenosis between groups, the χ^2 test was performed. All tests were 2-tailed, and a value of $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Fifty irradiated coronary arteries and 100 edges in 50 patients were eligible for the study. However, 26 edges were excluded because of the ostial location of the proximal end of the source in the right coronary artery (n=12) or overlapping of 1 of the edges with side branches (n=14). Thus, finally, 74 edge areas and 50 IRSs were studied. Mean age was 55.3±9 years, and 38 patients (76%) were male. Smoking was the most frequent coronary risk factor, involving 33 patients (66%), followed by dyslipidemia in 27 patients (54%) and hypertension in 24 patients (48%). Eight patients (16%) were diabetic. The left anterior descending coronary artery was treated in 21 patients, the left circumflex in 10, the right coronary artery in 18, and a saphenous vein graft in 1. Twelve patients received a stent in a bailout situation.

Incidence and Causes of Geographic Miss

Geographic miss was observed in 22 edges (31.9%) induced by balloon dilatation (n=13) or additional stent implantation (n=9). The remaining 51 edges (68.9%) were defined as uninjured edges. The location of the geographic miss was in the proximal edge in 11 patients (50%) and in the distal margin in 11 patients (50%). The following reasons were responsible for this phenomenon: (1) development of procedural complications that extended the treatment beyond the margins of the IRS (unexpected geographic miss, n=9); (2) lack of availability of a longer radiation source (>30 mm) in patients with diffuse recurrent in-stent restenosis in whom radiation was given on a compassionate-use basis (n=8); and (3) lack of accurate matching; ie, the injured segment from previous balloon inflations was not appropriately covered by the source (n=5). An example of a patient with geographic miss induced by a balloon dilatation in the proximal margin is depicted in Figure 1.

QCA Analysis

QCA data are presented in the Table. As expected, IRSs demonstrated, on average, a higher acute gain than both injured and uninjured edges. However, geographic miss edges presented, on average, with significantly higher late loss and relative late loss. Restenosis was demonstrated in 5 cases (10%) within the IRS, in 9 cases (40.9%) in the geographic miss edges, and in 1 case (1.9%) in the uninjured edges ($P<0.001$). No difference in the pattern of the late loss between the 3 areas was observed in de novo lesions compared with recurrent in-stent restenotic lesions (Figure 2). In the geographic miss edges, 4 edge restenoses (44%) were located at the proximal edges, whereas the other 5 (56%)

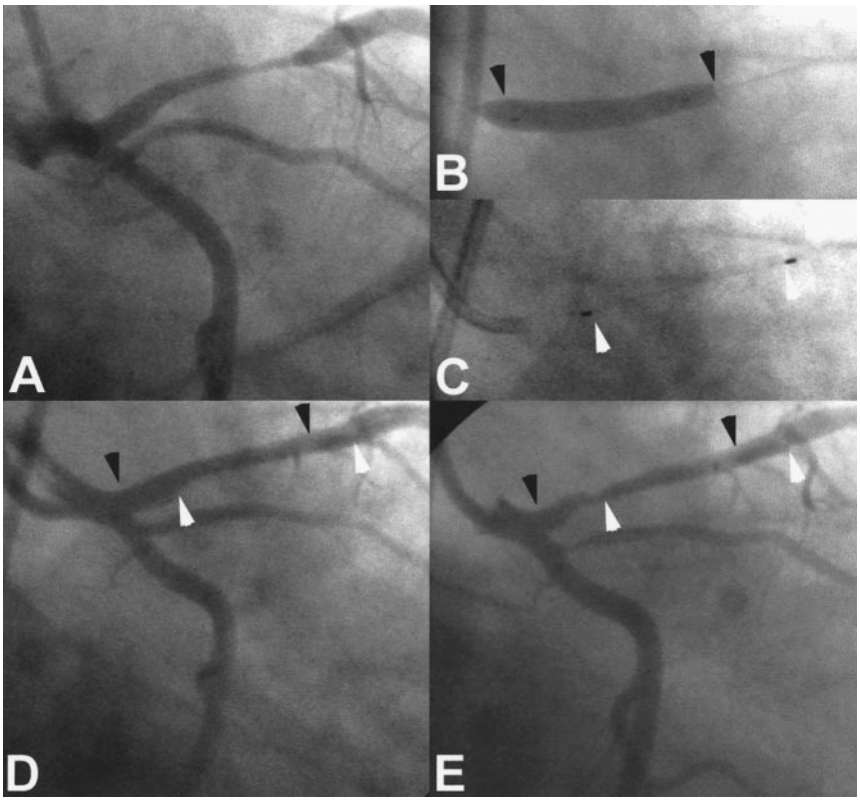

Figure 1. Geographic miss induced by balloon dilatation. A, Lesion located in proximal segment of left anterior descending coronary artery. B, Balloon dilatation performed during intervention (black arrowheads indicate area injured by balloon). C, Radiation source train in place. Irradiated area is delimited by gold markers (white arrowheads). D, Final result: proximal traumatized edge presented a residual type B dissection. E, At 6-month follow-up: obvious reduction in lumen at geographic miss edge.

were located at the distal edges. Mean relative late loss was comparable between those edges, with geographic miss located proximal or distal to the IRS (0.31±0.2 versus 0.34±0.2, respectively; P=NS). Those edges in which the geographic miss was due to additional stent implantation presented, on average, higher acute gain than those due to balloon dilatation (0.70±0.4 versus 0.21±0.3, respectively; P=0.005). However, mean late loss and mean relative late loss were comparable between both causes of geographic miss (0.95±0.9 mm and 0.36±0.3, respectively, after stent versus 0.77±0.3 mm and 0.30±0.1 after balloon dilatation; both P=NS).

Discussion

This study reports on the initial experience of our center with the use of intracoronary β-radiation. By means of a careful retrospective angiographic analysis of all patients treated with the same radiation system, we sought to define the effect of the injury on those areas located at the margins of the source where the delivered dose is potentially rather low. Up to 31.9% of the patients presented with the predefined technical error, called geographic miss. This concept requires the concurrence of 2 conditions: low-dose radiation and injury. Any other clinical situations that do not include both conditions cannot be called geographic miss. For instance, (1) the effect of injury on coronary segments not being irradiated (proximal or distal to an IRS but in areas in which the calculated dose is almost 0) should fall into the category of normal restenotic process; (2) the effect of low-dose radiation in areas that have not been injured may be defined as the pure radiation edge effect, because in intracoronary radiation, the

QCA Data

	IRS (n=50)	Geographic Miss Edges (n=22)	Uninjured Edges (n=52)	*P*
MLD before intervention, mm	1.20±0.3	2.02±0.6	2.10±0.6	<0.0001
MLD after intervention, mm	2.02±0.4	2.43±0.5	2.12±0.6	0.01
MLD at follow-up, mm	1.87±0.5	1.59±0.6	2.02±0.5	0.006
Reference diameter, mm	2.69±0.6	2.50±0.6	2.55±0.7	NS
%DS before intervention, %	54.9±13	19.8±14	17.9±11	<0.0001
%DS after intervention, %	28.4±9	19.9±10	20.8±11	0.0003
%DS at follow-up, %	33.3±11	44.3±22	24.3±10	<0.0001
Acute gain, mm	0.81±0.4	0.41±0.4	0.01±0.3	<0.0001
Late loss, mm	0.15±0.4	0.84±0.6	0.09±0.4	<0.0001
Relative late loss	0.06±0.1	0.32±0.2	0.02±0.1	<0.0001

%DS indicates diameter stenosis. Data are mean±SD.

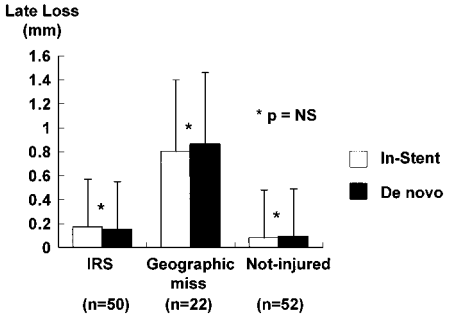

Figure 2. Difference in late loss between IRS, geographic miss edges, and uninjured edges. De novo lesions and in-stent restenosis demonstrated same degree of late loss between 3 groups.

edges of any IRS will always receive low-dose radiation; and (3) finally, the effect of a full prescribed dose on segments presenting with or without injury is the situation in which the physician may be able to irradiate (with full dose) the entire injured segment and include some uninjured margin. A key issue in the definition of geographic miss is to define those segments receiving a low dose. These may vary between systems and sources used. With the Beta-Cath system, the longitudinal distance of the 100% isodose is 26 mm. Because the β-emitting $^{90}Sr/^{90}Y$ has an acute falloff of dose related to the distance,[19] the last 2 mm within the markers of the source should be considered as having received a lower than prescribed dose. In fact, the dose received at 1 mm from the 100% isodose is 86% of the prescribed dose, and at 2 mm, 60% of the prescribed dose (inner part of the gold marker). At 3 mm, the dose is 30% of the prescribed dose; at 4 mm, 13% of the prescribed dose; and at 5 mm, 5% of the prescribed dose. We defined the IRS as the segment encompassed by the 2 gold markers, which included the last 2 mm within the markers with a lower than prescribed dose (up to 60% of the prescribed dose). By this definition, late loss and restenosis rate were significantly lower than those of the injured edges (analyzed from the inner part of the gold marker). Furthermore, the 5 cases of restenosis within the IRS were located at the site of the initial MLD. These results may reflect the fact that the dose at these last seeds of the source was high enough to avoid the edge effect after the edges had probably been injured during the procedure, especially when a 20-mm-long balloon was used. Thus, the region receiving a low dose may be defined, for this system and source, as the 5-mm-long segment located 2 mm farther from the 100% isodose boundary, that is, beyond the inner part of the gold marker. In this regard, we believe that the injury should be completely restricted to the segment of the 100% isodose curve of the radiation source (26 mm) and that the last 2 mm at both extremities of the source and within the gold markers may be considered relatively but probably not completely safe. Finally, any injured segment covered by or beyond the gold marker (up to 5 mm) must be considered to be at high risk of failure at follow-up.

From the perspective of these findings and future technical developments in the field, the following recommendations are advisable. Filming every single balloon inflation performed during the procedure would allow one to define the injured area. More than ever, tenacious attention to detail in positioning the radiation catheter encompassing the entire injured area must be mandatory. The development of longer sources (>30 mm) would allow one to treat diffuse lesions and completely cover those areas in which an extension of the treatment was indicated because of procedural complications. Equally, the use of online QCA in the decision-making would avoid appreciation errors due to visual assessment of the target area and subsequent underestimation or overestimation of balloon lengths. Finally, the selection of the most suitable fluoroscopic projections (eg, less foreshortening, no overlapping) would avoid errors in the quantification of the region of interest.

The facts that the locations of most of the restenoses were in geographic miss edges and that late loss in those areas was unexpectedly high must raise an alarm about the deleterious effect of the combination of injury and low-dose radiation. This hypothesis may be supported by the fact that the late loss observed in those injured edges is higher than that reported in recent clinical trials after either BA or stent implantation[20,21] and higher than that demonstrated in the uninjured edges. Balloon overstretch injury has been used as an experimental model to study the restenosis process.[8–10] The response of the vessel wall to injury involves both neointimal hyperplasia[8,9] and vessel remodeling.[10,22,23] The stimulatory effect of low-dose radiation after BA on smooth muscle cell proliferation has been reported previously.[11] In the low-dose radiation group of this swine model (10 Gy), neointima was composed of smooth muscle cells, with a marked increase in inflammatory cells and less medial and intimal fibrosis than in the higher-dose groups (15 and 20 Gy) and the control group. It was suggested that at low dose, inadequate fibrosis was induced to prevent effective smooth muscle cell migration and to act as a diffuse barrier for mediators of chemotaxis, chemokinesis, and cellular proliferation.[11] Similarly, after low-activity radioactive stent implantation (1 μCi) in a porcine model, neointimal hyperplasia was significantly greater than that after nonradioactive control stents.[12] If ongoing intravascular studies reveal that edge restenosis is mainly due to plaque increase, the former hypothesis that at a low dose, inadequate medial and intimal fibrosis to avoid migration and proliferation predominates may become a plausible explanation. Conversely, if negative remodeling is the main contributor to the lumen loss, the excess of inflammatory cells demonstrated at low dose may be responsible for subsequent adventitial fibrosis and vessel shrinkage. The development of the so-called “candy wrapper” after radioactive stent implantation[5] may represent the clinical paradigm of the combined deleterious effect of low-dose radiation and injury. The latter is secondary to the angioplasty balloon used for predilatation and postdilatation of the radioactive stent. In this regard, a higher balloon-to-artery ratio was associated with the presence of this phenomenon.[5]

Future trials must address the benefit of new technical developments in the field (use of square deployment balloons; hot-end, cold-end stents[6]; longer sources with smaller radiation delivery catheters) to minimize the impact of injury at the edges after either radioactive stent– or catheter-based systems.

Study Limitations

In this study, only 1 type of radiation delivery catheter using the β-source $^{90}Sr/^{90}Y$ was evaluated. Thus, the effect of either other catheter-based systems using centering balloons and different sources or the γ-radiotherapy on the geographic miss edges cannot be extrapolated from our results.

The actual dose at the margins of the radiation source has not been calculated. A low dose at these edges was assumed because the isotope $^{90}Sr/^{90}Y$ demonstrates an acute falloff related to the distance from the 100% isodose boundary.[19]

This angiographic study was aimed at defining the concept and the clinical implications of the geographic miss. To define the mechanism of the unexpectedly high late loss and the correlation between radiation dose and plaque extent at the margins of the IRS, intravascular ultrasound studies must be carried out.

The location of the segment receiving a low dose may vary between systems and sources. Thus, the confidence margin to be taken may vary accordingly.

The position of the source relative to the various balloon inflations was assessed by comparing still frames at the same part of the cardiac cycle from cineangiograms performed in the same projections. However, small inaccuracies in the definition of the IRS and the edges, derived from the axial movement of the radiation source during the cardiac cycle, cannot be completely ruled out.

This study was not placebo-controlled. Thus, the effect of the sham source on the balloon-injured coronary segments has not been determined.

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References

1. Waksman R, Robinson KA, Crocker IR, 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;91:1553–1559.
2. Wiederman JG, Marboe C, Amols H, et al. Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model. *J Am Coll Cardiol*. 1994;23:1491–1498.
3. Verin V, Popowski Y, Urban P, et al. Intra-arterial β-irradiation prevents neointimal hyperplasia in a hypercholesterolemic rabbit restenosis model. *Circulation*. 1995;92:2284–2290.
4. Waksman R, Serruys PW. *Handbook of Vascular Brachytherapy*. London, UK: Martin Dunitz Ltd; 1998.
5. Albiero R, Adamian M, Kobayashi N, et al. Acute and intermediate-term results of ^{32}P radioactive β-emitting stent implantation in patients with coronary artery disease: the MILAN dose response study. *Circulation*. 2000;101:18–26.
6. Serruys PW, Kay IP. I like the candy, I hate the wrapper: the ^{32}P radioactive stent. *Circulation.* 2000;101:3–7.
7. Sabaté M, Serruys PW, Giessen WJ, et al. Geometric vascular remodeling after balloon angioplasty and β-radiation therapy: a three-dimensional intravascular ultrasound study. *Circulation*. 1999;100:1182–1188.
8. Schwartz RS, Huber KC, Murphy JG, et al. Restenosis and proportional neointimal response to coronary artery injury: results in a porcine model. *J Am Coll Cardiol*. 1992;19:267–274.
9. Steele PM, Chesebro JH, Stanson AW, et al. Balloon angioplasty: natural history of the pathophysiological response to injury in a pig model. *Circ Res*. 1985;57:105–112.
10. Lafont A, Guzman LA, Whitlow PL, et al. Restenosis after experimental angioplasty: intimal, medial, and adventitial changes associated with constrictive remodeling. *Circ Res*. 1995;76:996–1002.
11. Weinberger J, Amols H, Ennis RD, et al. Intracoronary irradiation: dose response for prevention of restenosis in swine. *Int J Radiat Oncol Biol Phys*. 1996;36:767–775.
12. Carter AJ, Laird JR, Bailey LR, et al. Effects of endovascular radiation from β-particle–emitting stent in porcine coronary restenosis model: a dose-response study. *Circulation*. 1996;94:2364–2368.
13. Paterson R. *The Treatment of Malignant Disease by Radiotherapy*. London, UK: Edward Arnold (Publishers) Ltd; 1963.
14. Hillstead RA, Johnson CR, Weldon TD. The Beta-Cath system. In: Waksman R, Serruys PW, eds. *Handbook of Vascular Brachytherapy.* London, UK: Martin Dunitz Ltd; 1998:41–51.
15. Haase J, Escaned J, van Swijndregt EM, et al. Experimental validation of geometric and densitometric coronary measurements on the new generation Cardiovascular Angiography Analysis System (CAAS II). *Cathet Cardiovasc Diagn*. 1993;30:104–114.
16. Di Mario C, Hermans WR, Rensing BJ, et al. Calibration using angiographic catheters as scaling devices: importance of filming the catheters not filled with contrast medium. *Am J Cardiol*. 1992;69:1377–1378.
17. Serruys PW, Foley DP, de Feyter PJ. *Quantitative Coronary Angiography in Clinical Practice.* Dordrecht: Kluwer Academic Publishers; 1994.
18. De Jaegere P, Serruys PW, Bertrand M, et al. Angiographic predictors of recurrence of restenosis after Wiktor stent implantation in native coronary arteries. *Am J Cardiol*. 1993;72:165–170.
19. Amols HI, Zaider M, Weinberger J, et al. Dosimetric considerations for catheter-based and gamma emitters in the therapy of neointimal hyperplasia in human coronary arteries. *Int J Radiat Oncol Biol Phys*. 1996; 36:913–921.
20. Serruys PW, de Jaegere P, Kiemeneij F, et al, for the BENESTENT Study Group. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med*. 1994;331:489–495.
21. Fischman DL, Leon MB, Baim DS, et al, for the Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement in the treatment of coronary artery disease. *N Engl J Med*. 1994;331: 496–501.
22. Mintz GS, Popma JJ, Pichard AD, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation*. 1996;94:35–43.
23. Di Mario C, Gil R, Camenzind E, et al. Quantitative assessment with intracoronary ultrasound of the mechanisms of restenosis after percutaneous transluminal coronary angioplasty and directional coronary atherectomy. *Am J Cardiol*. 1995;75:772–777.