# EARLY RESULTS AND TECHNICAL SHORTCOMINGS IN INTRAVASCULAR BRACHYTHERAPY OF CORONARY ARTERIES: A RADIOTHERAPIST'S POINT OF VIEW.

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# EARLY RESULTS AND TECHNICAL SHORTCOMINGS IN INTRAVASCULAR BRACHYTHERAPY OF CORONARY ARTERIES: A RADIOTHERAPIST'S POINT OF VIEW.

VROEGE RESULTATEN EN TECHNISCHE BEPERKINGEN VAN INTRAVASCULAIRE BRACHYTHERAPIE IN CORONAIRE ARTERIEN: EEN RADIOTHERAPEUTISCH GEZICHTSPUNT.

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Aan mijn ouders

CONTENTS

# INTRODUCTION

# INTRODUCTION

## Coronary Artery Disease and Restenosis

The coronary arteries originate as branches of the ascending aorta and constitute the principal blood supply of the myocardium. The left coronary artery (LCA) gives rise to the left anterior descending (LAD) and the left circumflex (LCX) arteries. The LAD gives rise to septal and diagonal branches and the LCX to the obtuse marginal branches. The right coronary artery (RCA) gives rise to marginal branches and bifurcates into the posterior descending artery (PDA), and posterolateral branches. The PDA gives rise to septal branches.

The left and right coronary arteries surround the epicardial surface as a ring-loop system in two orthogonal planes defined by the fibrous skeleton of the heart. The RCA and the LCX run around the atrioventricular groove and form a circle between atria and ventricles at the base of the heart. Perpendicular to this plane the LAD and the PDA constitute a semicircle around the interventricular groove and encircle the left ventricular apex. In case of dominance of the left coronary system, the LCX gives rise to the PDA.

The coronary arterial wall is composed of different layers of tissue: the intima, the media and the adventitia. The inner coat of the vessel wall is the endothelium; a single layer of cells which forms a smooth surface providing interaction of blood constituants with the vessel wall. A thin layer of connective tissue and an elastic membrane - the internal elastic lamina - separate the intima from the media. The media consists mainly of smooth muscle cells and elastic fibers and is surrounded by a second elastic membrane, the external elastic lamina. The outer layer of the vessel wall is called the adventitia and contains collagen fibers, nerve fibers and vasa vasorum, small vessels which supply blood to the artery itself.

Atherosclerosis is the narrowing of an artery due to progressive accumulation of plaque, as a result of cholesterol deposits and other fatty materials on the walls of the arteries, white blood cell (macrophage) accumulation and smooth muscle cell growth. This thickening and hardening of the arterial walls is the basic mechanism for the development of coronary artery disease (CAD). [55] Progressive narrowing or stenosis of coronary arteries may lead to ischemia of the heart, causing angina pectoris and ultimately a myocardial infarction. Risk factors predisposing a person to CAD are hypertension, hyperlipidemia, smoking, diabetes, obesity, male sex, advancing age, physical inactivity, stress and genetic factors.

CAD is the leading cause of death in industrialized countries. The different treatment modalities of CAD are medical treatment (medication and life style changes), interventional treatment (percutaneous transluminal

coronary angioplasty, atherectomy, stent implantation) and surgery (coronary artery bypass graft). Indications for percutaneous interventions (PCI) have expanded during the past two decades, largely at the expense of medical therapy rather than surgery. Single vessel CAD remains the principle indication for PCI (> 80% of cases), but recently there has been a shift towards two-vessel and three-vessel disease.

In 1964 Dotter and Judkins performed the first percutaneous transluminal angioplasty (PTA) in a femoral artery. [22] Andreas Gruentzig performed the same technique in a coronary artery in 1977, the first percutaneous transluminal coronary angioplasty (PTCA). [35] Balloon angioplasty is a technique in which a balloon catheter is advanced in an artery over a previously inserted guidewire. The deflated balloon is positioned in the stenotic part of the artery and subsequently inflated with contrast fluid until fully expanded. A high pressure is exerted on the vessel wall for a period of seconds to minutes; the internal pressure may exceed $10^6$ Pa (10 atm). This results in compression and fracture of the atherosclerotic plaque, stretching of the vessel wall and frequently causes dissections that may extend into media and adventitia. All these mechanisms will improve the blood flow in the treated artery.

Worldwide more than one million procedures of PTCA are performed each year. [107] Despite the fact that a PTCA is successful in 95% of the cases and the complication rate is very low, restenosis remains the major limitation of this technique. Restenosis rates are reported to be 30-60% for conventional balloon angioplasty. [34,40,68,92] Restenosis is the result of damage to intima and media during PTCA, inducing a wound healing process with hyperproliferation and negative remodeling (constriction). Elastic recoil of the artery, local thrombus formation, neointimal cellular proliferation and vascular remodeling are factors contributing to a progressive narrowing of the residual lumen. [29,62,69,85,92] Elastic recoil mainly occurs within the first few minutes following balloon angioplasty and is responsible for about 30% decrease in vessel diameter. The early thrombotic process at the PTCA site, governed by platelets, inflammatory cells and thrombin, sets the stage for subsequent smooth muscle cell migration and matrix deposition. Neointimal hyperplasia is caused by proliferation and migration of smooth muscle cells and myofibroblasts and by deposition of an extracellular matrix by the smooth muscle cells. [36,37,57,62] This phenomenon starts within 48 hours after balloon angioplasty and causes progressive neointimal thickening over the following months. Vascular (negative) remodeling takes place over a period of several months and results in a shrinkage of the artery. It is the predominant contributing factor to restenosis; it is responsible for about 70% of late lumen loss, after balloon angioplasty. [62]

**Prevention of Restenosis**

Restenosis is defined as the narrowing of the vessel lumen resulting in a hemodynamic compromise. In clinical practice, using angiographic assessment, the definition of restenosis is a reduction of ≥ 50% of the lumen diameter compared to the adjacent normal segments. Many potential methods to prevent restenosis have been investigated, but only few have proven to be effective.

Initial pharmacologic therapies including anticoagulants, ACE inhibitors, corticosteroids, cholesterol lowering agents, aspirine and other antiplatelet agents to reduce the restenosis rate were disappointing. [24,26,60,66,71,73,89,91,95,96,105,108] Recently encouraging results were obtained with a monoclonal antibody, that is blokking the GP IIb/IIIa receptor and inhibits platelet aggregation and adhaesion. The EPIC-trial not only showed a decrease in acute and late complications, but also a significant reduction of clinical events (repeat revascularization) at 6 months. This was not correlated with a change in angiographic restenosis. [32,102,106] The EPILOG study [103] and the CAPTURE study [101] resulted in a significant improvement during the first 30 days after PTCA, but this difference was not sustained after 6 months. The results of the ERASER [104] and EPISTENT [53] trials, using GP IIb/IIIa receptor blokkers, combined with stent implantation were variable. In ERASER IVUS-measured intimal hyperplasia did not differ between groups.

Directional, rotational and laser atherectomy are debulking techniques designed to provide an increased arterial lumen size. These devices have been tested in clinical trials against balloon angioplasty, but no reduction in restenosis has been demonstrated. [1,12,13,78]

Endovascular stents are usually made of stainless steel and are placed in the artery by a self-expanding mechanism or, more commonly, by expanding with a balloon. Stent implantation following PTCA minimizes the elastic recoil and vascular remodeling, but does not reduce neointimal cellular proliferation. In fact, the stent struts stimulate the proliferative response, leading to neointima formation within the stent. [23] This is called in-stent restenosis. In clinical trials stent implantation has proven to reduce the restenosis rate significantly, compared to balloon angioplasty. In the STRESS and BENESTENT trials respectively a 24% and 31% reduction in restenosis rate was achieved after implantation of a single Palmaz-Schatz coronary stent for short lesions. [28,47,48,87,112]

Restenosis, however, remains significant after coronary stenting, especially in diabetic patients, after stenting for restenotic lesions, in long lesions and in small vessels. [54,61]

Local delivery of drugs has been attempted to decrease late neointimal proliferation. This technique requires a combination of a catheter providing acceptable delivery efficiency and a pharmacologic agent effective in decreasing restenosis at the delivered dose. The most important limitation is that the pharmacologic agent does not persist in the tissue for a long time. [17] New technologies are under development.

Another form of local drug delivery are the drug-eluting stents. These stents are coated with a polymer layer containing an antirestenotic agent. The delivery efficiency is higher and the application time is prolonged. A randomized clinical trial comparing heparin-coated stents with uncoated stents did not reveal a significant difference between both groups. [38,39,125] The first significant reduction of in-stent restenosis was demonstrated for a stent coated with an antimitotic agent (rapamycin), the sirolimus-coated stent. The multicenter, randomized, double-blind, controlled clinical RAVEL trial compared implantation of Sirolimus-coated BX Velocity balloon expandable stents with bare BX Velocity stents. At 6 months follow-up the restenosis rate was 0% in patients who received a coated stent and 26.6% in those with a uncoated stent. [64,88] In another multicenter, randomized, double-blind trial, SIRIUS trial, similar results were obtained. [50,65] Trials using paclitaxel-coated stents also showed promising results. [31,33,70] and many other clinical trials are still in progress.

The use of intravascular brachytherapy to prevent restenosis wil be discussed in a following section.

More technologies under investigation include sonotherapy (ultrasound) [77], photodynamic therapy [58,80], and gene therapies [81].

**Ionizing Radiation and Brachytherapy**

Radiotherapy can be administered in two different ways: external beam irradiation (teletherapy) by means of a linear accelerator or brachytherapy using radioactive sources, which are placed close to or inside the tissue to be irradiated. Brachytherapy comprises different techniques: interstitial means the sources are implanted in the tissue, for intracavitary or intraluminal the sources are placed in a natural body cavity and a surface mould can apply the sources to the skin. Brachytherapy can be delivered at different dose rates: low dose rate (LDR) 0.4 to 2 Gy/hour, medium dose rate (MDR) 2 to 12 Gy/hour and high dose rate (HDR) more than 12 Gy/hour (usually around 150 Gy/hour). An interstitial treatment can be a temporary application or a permanent implant (LDR).

The amount of radiation given to a patient is quantified as the amount of energy absorbed by the patient from the radiation. The unit of absorbed dose (energy absorbed / unit mass of medium) is Gray (1 Gy = 1 J/kg). An older

unit, the Rad (radiation absorbed dose) is equal to 0.01 Gy. The actual physical quantity of radioactive material is called the activity. It is defined as the number of desintegrations per time unit and measured in curies: 1 Ci = 3.7 x $10^{10}$ desintegrations / second.

Ionizing radiation used for medical purpose is most commonly X-rays, γ-rays or electrons. γ-rays are a type of high-energy electromagnetic radiation. As γ-rays have no mass and no charge they are deeply penetrating; they deliver a significant dose to the surrounding tissues and can cause a significant exposure to the personnel. Extra room shielding is required, lead is the preferred shielding material for γ-radiation. Electrons are negatively charged β-particles, of which the hazard depends on their energy. They are characterized by a short, finite range of penetration and a rapid deposit of energy in tissue. The external exposure hazard is mainly to the skin. β-radiation can easily be shielded by 1-2 cm plastic.

**History of Brachytherapy**

The history of brachytherapy started shortly after the discovery of X-rays by Konrad von Roentgen in 1895. Radium was discovered in Paris in 1898 by Marie en Pierre Curie. The first report on brachytherapy was from Alexander Graham Bell, the inventor of the telephone, who suggested to insert the radioactivity in "the heart of the cancer". Within five years the first successful brachytherapy for cancer had been histologically proven; two cases of basal cell carcinoma of the face. In 1905 an American surgeon performed a radium-application with a primitive afterloading system, to treat a malignant tumor. The number of medical radium applications increased rapidly.

The beginnings of dosimetry occurred around 1904 with a proposal for a gamma-ray unit of intensity/activity. Terminology varied, but the milligram-hour was the most popular radium unit, until the general acceptance of the röntgen as a unit for both X-rays and gamma rays (ICRU 1937 recommendation).

Radium sources, generally tubes , needles or small capsules, remained in widespread clinical use until the 1960s. The most important dosimetry proposal in the radium era was the "Manchester system" of Paterson & Parker in the 1930s, which was used as a worldwide standard for more than 30 years. The most important disadvantage of radium-226 is the disposal of obsolete sources of such long-lived radioactive material (half-life 1600 year).

In 1948 cobalt-60 needles and in 1953 an afterloading system with plastic tubes en gold-198 seeds were introduced. The afterloading technique was further developed at the "Memorial Hospital" in New York, with the use of caesium-137 en iridium-192, especially for the treatment of cervix carcinoma.

In France after 1955 at the "Institut Gustave Roussy" new techniques were developed using iridium-192 en caesium-137: afterloading "guide gutters" for implantation of iridium "hairpins" in head and neck tumors and skin malignancies. Afterloading techniques with plastic tubes and iridium wires were adapted in 1961 to be implanted in large tumors at different anatomic sites. In 1965 a new dosimetry system, the "Paris system" was designed for single-plane, double-plane and volume implants with radioactive wires of equal activity. Simultaneously a new technique was introduced for intracavitary treatment of gynecological tumors: a plastic cervicovaginal mould for application of iridium-192 or caesium-137 sources.

In 1961 the "Memorial Hospital" in New York started developing the high dose rate (HDR) remote afterloading technique, using small cobalt-60 sources with high activity. Movement of these sources in the applicators could simulate line sources with variable lengths. As the treatment was delivered in a shielded room and the personnel could operate the machine outside the room, exposure of personnel to radiation could be avoided. This was an important change in radioprotection.

Today, brachytherapy is a standard treatment modality used for certain types of gynecological tumors, breast carcinoma, head and neck tumors, bronchial and oesophageal tumors. Remote controlled afterloading devices place temporarily small sealed radioactive sources in specially designed applicators, after these have been correctly positioned in the body. This way there is no exposure of the medical staff to ionizing radiation. Modern imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) can be used for delineation of the tumor volume. The source positions and dwell times can be optimized by using a dedicated treatment planning system, in order to maximize the dose to the tumor and minimize the dose to the surrounding normal tissues.

**Intravascular Brachytherapy**

Clinical experience showed radiotherapy to be a potent inhibitor of cellular proliferation, in benign as well as in malignant diseases. Examples of benign proliferative disorders successfully treated with radiotherapy are keloïd [15,25,45], heterotopic ossification after surgery [56,86], gynecomastia [19], pterygium [11,16] and desmoid-aggressive fibromatosis [49,79]. These disorders are treated with radiation doses between 7 and 10 Gy in one or more fractions, inhibiting the fibroblast proliferation. Other benign diseases, such as Peyronie's disease [8,63], Graves' ophthalmopathy [72,83], macular degeneration [27,30] and cerebral arteriovenous malformations [14,21,93,126] need doses up to 20 Gy.

Hypothetical mechanisms of action of radiation in the treatment of benign conditions are inhibition of cellular proliferation, reduction of acute inflammation and immunomodulatory effects through the regulation of endothelial cell growth and cytokine production. In benign diseases randomized trials are rare, justification for the clinical use of radiation in these diseases mainly comes from single-center retrospective experiences.

Injury to the arterial wall as a result of angioplasty causes a series of morphological and functional changes, aimed at restoring the functional and structural integrity, similar to a wound healing process. Such as keloid formation in skin wounds, excessive healing following PTCA can cause restenosis. Interruption of this exhuberant healing process during inflammatory and repair processes could reduce the incidence and severity of restenosis. As radiation has been succesfully used in the treatment of various benign proliferative disorders, it was a proposed solution to prevent restenosis. The key target cell type for radiation therapy has not been identified yet, it is still under investigation. The concept of intravascular brachytherapy (VBT) is to apply radiation following the angioplasty procedure to the injured segment of the artery, by means of a radioactive source inserted in the vessel lumen, in order to prevent restenosis. VBT can be delivered either by removable sources (catheter-based systems) or a permanent implant (radioactive stent). Catheter-based systems can use both $\gamma$ and $\beta$-emitting sources, delivered manually or automatically, and the prescribed dose is delivered in a short time (HDR). Radioactive stents, coated with a $\beta$-emitting isotope, deliver radiation over a very long period of time (LDR) after implantation. In the past few years a large variety of radiation sources and different intravascular brachytherapy delivery systems have been developed. Currently $Ir^{192}$, $Sr^{90}/Y$, $Y^{90}$, $P^{32}$ and $Re^{188}$ are isotopes frequently in use for VBT. [119]

In 1992 the first clinical experience of VBT was conducted in Germany; patients who had undergone an angioplasty in a femoropopliteal artery were treated with a $^{192}Ir$ point source of 10 Ci in a flexible catheter, using a microSelectron HDR afterloader. [52] The results were quite successful [84], but the technique used was not suitable for treatment of coronary arteries; that required a thin and very flexible source and delivery catheter.

Experimental work was carried out in the US in porcine coronary restenosis models. These animal studies have demonstrated the effectiveness of $\gamma$-radiation [59,115-117,122-124] and $\beta$-radiation [6,7,41-43,82,113,118] in reducing neointimal hyperplasia after angioplasty. In Geneva a flexible pure $\beta$-emitting $^{90}Y$ source wire and a centering catheter were designed. These were tested in animal experiments, in rabbit iliac and carotid arteries, showing encouraging results. [110]

Clinical experience in human coronary arteries was initiated in 1994 by Condado, who treated 21 patients with a manually delivered $^{192}Ir$ wire in a non-centered catheter. [20] Verin at al. initiated a feasibility study of 15

patients, treated with the β-emitting $^{90}Y$ source wire and centering catheter. [111] Both studies demonstrated that the delivery of radiation in coronary arteries was feasible and safe, though the restenosis rate remained relatively high in the second trial.

SCRIPPS I was the first randomized clinical trial aimed to determine the effectiveness of γ-radiation ($^{192}Ir$) for the treatment of in-stent restenosis. [97-100] The significant reduction in restenosis rate obtained in this trial encouraged investigators to design further studies. WRIST [120] and GAMMA I [51] were both large randomized trials that confirmed the efficacy of γ-radiation in patients with in-stent restenosis. The LONG WRIST trial showed positive results for longer in-stent restenotic lesions, though the treatment seemed to be somewhat less effective than in the prior WRIST study. [3] In a registry trial (LONG WRIST HD) a higher radiation dose had been administered in patients with similar lesions and compared to the previous trial the higher dose had improved the results. [2,3]

In parallel a number of trials were investigating the safety and effectiveness of β-radiation in reducing restenosis in coronary arteries. After performing a pilot trial with the $^{90}Y$-source in Geneva a dose finding study was initiated in patients with short de novo lesions, showing a decrease in restenosis rate with dose escalation. [109] The same source was used in the BETA WRIST registry and seemed to be very effective also for in-stent restenosis. [114] The results of a feasibility study [44] with a $^{90}Sr/Y$ source lead to the largest randomized vascular brachytherapy trial, the Betacath trial, designed for de novo lesions. This trial did not show any clinical benefit. The angiographical results showed a significant decrease in restenosis rate at the lesion site, but not when the edges of the treated segment were taken into account. This edge-effect appeared mostly in the stented patients, who even showed an increase in restenosis rate after radiation. This trial was the first to report late thrombotic occlusions, which seemed to be resolved by prolonging the antiplatelet therapy. [46] The same Beta-Cath™ System was used in the randomized START trial for in-stent restenosis, resulting in a significant decrease of restenosis rate. In order to try to minimize the edge-effect the START 40 registry trial was initiated. Treating similar lesions with a longer source further decreased the restenosis rate. [94] The Galileo™ System with a $^{32}P$ source was first used in the feasibility study PREVENT [76], followed by the randomized INHIBIT trial for in-stent restenosis, which also showed a significant benefit of radiation. [75]

Radioactive stents did not improve the clinical results. They seem to reduce intimal hyperplasia in a dose-related manner within the stent, but a high restenosis rate occurred at the edges of the stent [4,5,121], the so called "candy-wrapper" effect. [90]

**Dosimetry for Catheter-based Coronary Brachytherapy**

The goal of radiation is to deliver a sufficient radiation dose to all target cells, without exceeding the normal tissue tolerance. The target cells may be near the luminal surface or in the adventitia, between 0-4 mm from the radiation source. In addition, diseased vessels usually have an asymmetric luminal wall thickening. Based on animal data and human trials the biologic window for successful treatment is between 8 and 40 Gy. This means the dose fall off, as a function of distance from the radiation source, cannot exceed 5/1 over a distance of 4 mm. [9]

The source requirements for VBT via temporary insertion of radioactive sources are listed below and would best be met by a low-energy γ-emitter or a high-energy β-emitter. [9,10]

- The source should be able to deliver a single fraction of 10 to 30 Gy to a variable length of artery, with an inner diameter of 2-5 mm and 0.5-3 mm of wall thickness.
- The high radiation dose volume should be confined to the PTCA site, with a minimal dose to normal vessels, myocardium and patient whole body.
- As short treatment time decreases the probability of thrombosis and cardiac complications, the dose rate should be higher than 2 Gy/min to keep the treatment time shorter than 15 minutes.
- The source dimensions must be compatible with the angiography catheter.
- The source should have a diameter of less than 0.5 mm, the appropriate stiffness to be pushed through more than 100 cm artery and the flexibility to negociate the multiple bends.

Radiation dosimetry for coronary brachytherapy remains a difficult problem because of the short distances from the source and the high dose gradients. Task group No. 60 of the American Association of Physicist in Medicine has published recommendations for dosimetry and calibration procedure. [67]

**Treatment Planning and IVUS for Coronary Brachytherapy**

The dose rate delivered to the arterial wall depends on vessel diameter and location of the source within the vessel lumen. Angiography provides high-resolution images of the vessel lumen, used to determine the diameter and guide the placement of intracoronary devices. The lumen diameter can be visually estimated by comparison with the guiding catheter with known diameter or can be measured more precisely using the quantitative coronary angiography (QCA) program. Intravascular ultrasound (IVUS) permits to evaluate both vessel wall morfology

and lumen. IVUS images provide detailed information of plaque, neointima and media, required for treatment planning. The distance from the radiation source, assumed to be in the same position as the IVUS catheter, to structures of interest can be measured in different cross-section images. [9] This type of dosimetry was applied in the SCRIPPS [97] and GAMMA I [51] trials to determine the dose prescription. Complete 3-dimensional information available from an ECG-gated IVUS pull-back device can be used for dosimetry, to evaluate the doses in specific volumes of the vessel wall. A dose-volume histogram (DVH) describes the cumulative dose distribution in a defined volume and summarizes the dose distribution in a graphic form. Because a DVH contains no information about the spacial dose distribution, it should be used in conjunction with the isodoses displayed on the 2-dimensional IVUS cross-sections. IVUS guided dosimetry could improve the knowledge of the mechanisms of action of brachytherapy and can be very helpful to compare trials using different sources and dosimetry strategies. [18] Recently the EVA GEC ESTRO Working Group published recommendations for dose prescription, and how to record and report endovascular brachytherapy applications. [74]

**Overview of Thesis**

The introduction describes the problem of restenosis in coronary artery disease and the therapeutic options to prevent it.

In Part I of this thesis we evaluated clinical results. Chapter 1 describes the clinical results of patients treated in Rotterdam, who were included in the BERT trial. More extensive clinical data of patients entered in various trials and the different brachytherapy systems used at that time are presented in Chapter 2. Finally Chapter 3 gives the results of a large European registry, confirming the positive trial results in routine clinical practice.

Part II focusses on the role of intravascular ultrasound (IVUS) in coronary brachytherapy, as a tool for dosimetry (Chapter 4) and as an imaging technique to help to understand the mechanisms of action of brachytherapy (Chapter 5).

In Part III we looked deeper into the dosimetry of two very specific clinical situations. Because of a trend towards treating longer and more complex lesions we evaluated the accuracy of the manual multisegmental irradiation, performed in 33 patients included in the European registry (Chapter 6). In Chapter 7 the question "can a bifurcation be irradiated adequately and if so, how to do it?" was addressed.

Part IV considers the late effects on different organs, the carcinogenic effects and a review of the literature of radiation induced coronary artery disease.

To conclude the effectiveness of vascular brachytherapy is reviewed through the different trials, limiting factors are discussed, as well as alternative therapies.

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# PART I

## Results of clinical trials.

# CHAPTER 1

Endovasculaire bestraling ter preventie van restenosering na PTCA:
praktische uitvoering, veiligheid en resultaten.

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Cardiologie 6: 128-135, 1999.

# Endovasculaire bestraling ter preventie van restenosering na PTCA: praktische uitvoering, veiligheid en resultaten

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*Objective.* To evaluate the safety and feasibility of low-dose irradiation following percutaneous transluminal coronary angioplasty (PTCA) in single de novo lesions of native coronary arteries, in order to decrease the restenosis rate.
*Material and methods.* Prospective multicentre clinical trial. From April to December 1997, 31 patients were treated with intracoronary irradiation following PTCA, according to the Beta Energy Restenosis Trial-1.5 (BERT-1.5), at the Thoraxcentre of the University Hospital Rotterdam, in co-operation with the Department of Radiation Oncology of the Daniel den Hoed Cancer Center/University Hospital Rotterdam. All patients treated (21 males and 10 females, aged 39-75 years) had severe symptoms of angina, despite medication. Following a successful PTCA procedure, the site of angioplasty was irradiated using an encapsulated β-emitting Sr-90 source. A hydraulic transport system moves the source to the distal end of the catheter positioned at the PTCA site. One patient could not be irradiated due to a mechanical obstruction.
*Results.* During PTCA, the diameter stenosis improved from 50-87% to 1-55%. The administered radiation dose was set at randomisation: ten patients received 12 Gy, nine patients 14 Gy and eleven patients 16 Gy at 2 mm from the source axis. In seven patients a stent placement was indicated at the treated segment following irradiation for substantial residual stenosis due to recoil. Complications did not occur. For the whole group of thirty patients, a follow-up period of six months has been reached. At one-month follow-up, 27 out of thirty patients showed symptomatic improvement. At three months follow-up, all but two patients had decreased anginal symptoms. With coronary angiography six months after treatment, restenosis could be visualised in eight of the thirty irradiated patients (29%).
*Conclusion.* The results of the thirty patients treated according to the BERT-1.5 trial confirmed the safety of endovascular irradiation following PTCA. After a follow-up period of three months, the symptoms of all but two patients had improved. After a follow-up period of six months a coronary angiography showed a restenosis rate of 29%. (Cardiologie 1999;6:128-135.)

Jaarlijks worden wereldwijd een miljoen coronaire angioplastieken (coronaire dotterprocedures) uitgevoerd, waarvan ongeveer 14.000 in Nederland (telling 1995). Hoewel een percutane transluminale coronaire angioplastiek (PTCA) in 95% van de gevallen zonder complicaties succesvol kan worden uitgevoerd, worden de middellangetermijnresultaten van PTCA bij 30-50% van de patiënten gecompromitteerd door restenose binnen een periode van zes tot negen maanden.[1-3]

Een PTCA veroorzaakt een beschadiging van de tunica intima en media en oprekking van het gedeelte van de circumferentie van het vat waarop geen atheromateuze plaque vastzit, waardoor een wondhelingsproces op gang komt, vergelijkbaar met andere weefsels. In dit wondhelingsproces spelen verschil-

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*Figuur 1. Microscopisch aspect van intimahyperplasie. Histologisch vergelijkbaar type proliferatie: A: na ballonangioplastiek; B: in cutaan litteken; C: na aanleg synthetische vasculaire graft. (Uit: Forrester et al.[4])*

lende factoren sequentieel een rol in het optreden van restenose: plaatjesaggregatie, infiltratie van inflammatoire cellen en vrijkomen van groeifactoren, modulatie en proliferatie van de gladde-spiercellen, synthese van proteoglycanen en modulering van de extracellulaire matrix. Door het samenspel van deze verschillende factoren treedt geleidelijk een vernauwing op van het residuele lumen (figuur 1).[4]

De resultaten van klinische onderzoeken naar een mogelijke reductie van de restenosefrequentie met farmaca zijn over het algemeen teleurstellend gebleken.[5-10]

Recenter werden gunstiger resultaten gerapporteerd van een monoclonaal antilichaam dat door blokkade van de GP IIb/IIIa-receptor de aggregatie en adhesie van bloedplaatjes inhibeert. Zo werd in het EPIC-onderzoek een significante reductie aangetoond van het heroptreden van ischemie tot een periode van zes maanden na PTCA.[11,12] Andere onderzoeken toonden een significante verbetering in de eerste periode van dertig dagen na PTCA, maar dit verschil werd niet meer teruggevonden na zes maanden.[13,14] De resultaten van onderzoeken met GP IIb/IIIa-receptorblokkers, gecombineerd met het gebruik van stents, leveren ook wisselende resultaten op (ERASER[15] en EPISTENT [Lincoff, persoonlijke mededeling, Atlanta, 1998]).

Het plaatsen van een coronaire stent in aansluiting aan PTCA heeft een beperkte maar gunstige invloed. Het is de enige techniek waarvan bewezen is dat ze de restenosefrequentie vermindert tot ongeveer 17%. Zo werd in de STRESS- en BENESTENT-onderzoeken na het plaatsen van een enkelvoudige Palmaz-Schatz coronaire stent de kans op restenose met 30% gereduceerd. Het effect van de stent op restenose is zuiver mechanisch;[16-20] door implantatie ervan dilateert het lumen van het bloedvat meer dan na PTCA alleen. Een stent voorkomt het remodelleren (krimpen) van het vat, maar heeft geen remmend effect op de proliferatie van gladde-spiercellen. Door vergroting van de capaciteit van de arterie wordt de tolerantie voor intimahyperplasie verbeterd.[4]

Ondanks uitgebreid klinisch onderzoek werd tot op heden geen methode ontwikkeld om de proliferatieve component van restenose te inhiberen. Het gebruik van antiproliferatieve farmaca wordt beperkt door de systemische toxiciteit, terwijl lokale toediening ter plaatse van de PTCA, een methode die systemische effecten voorkomt, zich nog in een experimentele fase bevindt.

Radiotherapie is de meest recente behandeling die wordt onderzocht in combinatie met PTCA. Na meer dan honderd jaar klinische ervaring staat vast dat radiotherapie de celproliferatie, zowel bij benigne als maligne aandoeningen, efficiënt remt. Voorbeelden van benigne proliferatieve aandoeningen die succesvol worden behandeld met radiotherapie zijn keloïdvorming in littekens, heterotope botaanmaak na totale heupprothese, pterygium, ziekte van Peyronie en desmoïdtumoren.[21-25]

Deze benigne proliferatieve aandoeningen worden behandeld met een stralingsdosis van 7 tot 10 Gy in één of meerdere fracties, waarmee een efficiënte inhibitie van de fibroblastenactiviteit wordt bereikt, zonder invloed op de normale heling.

Dit artikel doet verslag van de behandeling van de eerste patiënten in Nederland met intracoronaire radiotherapie ter voorkoming van restenose na PTCA.

## Materiaal en methoden

### *Onderzoekopzet*

In de periode van april tot en met december 1997 werden in het Thoraxcentrum van het Academisch Ziekenhuis Rotterdam, in samenwerking met de afdeling Radiotherapie van de Daniel den Hoed Kliniek, 31 patiënten behandeld met PTCA, gevolgd door intracoronaire bestraling.

Deze patiënten werden behandeld in het kader van de Beta Energy Restenosis Trial-1.5 (BERT-1.5), een klinisch onderzoek naar de veiligheid en effectiviteit van lage-dosis-bestraling na PTCA voor een enkelvoudige coronaire stenose, met als doel de restenose te remmen. Het Thoraxcentrum Rotterdam is het enige Europese instituut dat deelneemt aan dit prospectieve multicentrumonderzoek, naast Emory

**Tabel 1.**
Overzicht van de 31 patiënten behandeld in het kader van de BERT-1.5 trial.

| Patiënt | AP[1] | Coronair segment[2] | AP 1 maand | AP 3 maanden | AP 6 maanden | Restenose angiografie[3] | TLR[4] |
|---|---|---|---|---|---|---|---|
| 1 | CCS 3 | LAD 7 | 0 | 0 | CCS 1 | 0 | 0 |
| 2 | oap 1c | LAD 8 | CCS 1 | 0 | 0 | 0 | 0 |
| 3 | CCS 2 | LCX 13 | CCS 1 | CCS 1 | 0 | 0 | 0 |
| 4 | CCS 3 | RCA 2 | CCS 1 | CCS 1 | CCS 2 | 0 | 1 |
| 5* | oap 2b | RCA 3 | 0 | | 0 | 0 | 0 |
| 6 | CCS 3 | LAD 7 | 0 | 0 | 0 | 0 | 0 |
| 7 | CCS 3 | RCA 2 | CCS 4 | CCS 4 | oap 2b | 1 | 1 |
| 8 | CCS 4 | LAD 7 | CCS 3 | 0 | 2 | 0 | 0 |
| 9 | CCS 4 | LCX 13 | 0 | | 0 | 0 | 0 |
| 10 | CCS 3 | RCA 1 | 0 | 0 | 0 | 1 | 0 |
| 11 | CCS 2 | LAD 7 | 0 | 0 | 0 | 0 | 0 |
| 12 | CCS 2 | LAD 6 | CCS 3 | CCS 2 | CCS 2 | 0 | 0 |
| 13 | CCS 3 | LAD 7 | 0 | 0 | 0 | 0 | 0 |
| 14 | CCS 3 | RCA 1 | 0 | 0 | oap 3b | 1 | 1 |
| 15 | CCS 2 | LAD 6 | 0 | 0 | CCS 2 | 1 | 1 |
| 16 | CCS 3 | LAD 7 | 0 | 0 | 0 | 0 | 0 |
| 17 | CCS 2 | LCX 13 | CCS 1 | CCS 1 | CCS 2 | 0 | 1 |
| 18 | CCS 3 | LCX 13 | 0 | 0 | 0 | 0 | 0 |
| 19 | CCS 4 | LAD 6 | 0 | 0 | 0 | 0 | 0 |
| 20 | oap 2b | LCX 13 | 0 | 0 | 0 | 0 | 0 |
| 21 | CCS 3 | LAD 7 | CCS 2 | CCS 2 | CCS 2 | 0 | 0 |
| 22 | CCS 3 | LCX 13 | 0 | | CCS 2 | 1 | 0 |
| 23 | oap 1c | LAD 6 | 0 | 0 | 0 | | |
| 24 | CCS 2 | LAD 7 | 0 | 0 | 0 | 0 | 0 |
| 25 | CCS 2 | RCA 1 | 0 | 0 | 0 | 0 | 0 |
| 26 | CCS 3 | LCX 11 | 0 | CCS 2 | CCS 3 | 1 | 1 |
| 27 | CCS 4 | LAD 7 | 0 | | | | |
| 28 | CCS 3 | LAD 7 | 0 | 0 | 0 | 1 | 0 |
| 29 | CCS 3 | RCA 1 | 0 | 0 | CCS 3 | 1 | 1 |
| 30 | CCS 3 | RCA 1 | 0 | | CCS 2 | 0 | 0 |
| 31 | CCS 3 | LAD 7 | CCS 3 | | 0 | 0 | 0 |

* Eén patiënte werd niet bestraald.
[1] AP=angina pectoris; CCS=Canadian Cardiovascular Society Classification voor stabiele angina pectoris; oap=Braunwald classification voor onstabiele angina pectoris.
[2] LAD=arteria coronaria sinistra, ramus descendens anterior; RCA=arteria coronaria dextra; LCX=arteria coronaria sinistra, ramus circumflexus.
[3] 0=geen restenose; 1=restenose (stenose >50%).
[4] TLR=targetlaesie revascularisatie: 0=geen, 1=re-PTCA.

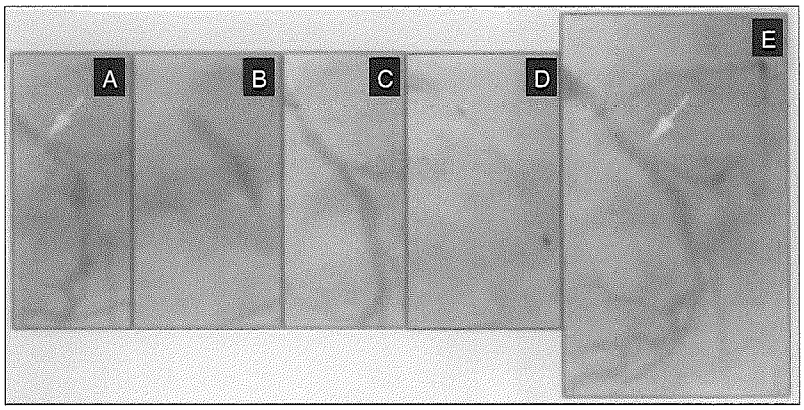
University in Atlanta (Georgia, USA), Rhode Island Hospital in Providence (Rhode Island, USA) en Montreal Heart Institute (Montreal, Canada). In totaal werden 84 patiënten opgenomen in dit onderzoek.

Het onderzoek werd opgezet door de Novoste Corporation, die een systeem heeft ontwikkeld dat toelaat ingekapselde bronnen met strontium-90 (Sr-90), een β-straling emitterende nuclide, op te slaan en via een katheter tot op de plaats van PTCA te verplaatsen (Transfer Device). Het doel van dit onderzoek is:

a. de veiligheid te onderzoeken van drie verschillende doses bestraling (12 Gy, 14 Gy en 16 Gy op 2 mm van de bronas) toegediend na PTCA en
b. na zes maanden angiografisch de restenosefrequentie van deze patiënten te vergelijken met een historische controlegroep uitsluitend behandeld met angioplastiek (Lovastatin Restenosis Trial).[26]

*Patiënten*

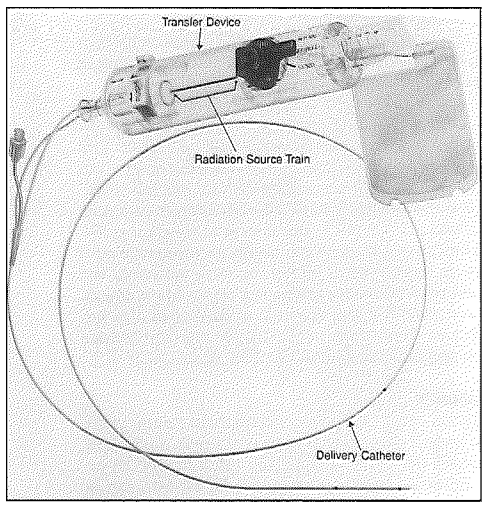
De groep van 31 behandelde patiënten bestond uit 21 mannen en 10 vrouwen, in leeftijd variërend van 39 tot 75 jaar. Bij alle patiënten was er sprake van ernstige angina pectoris ondanks medicamenteuze therapie. De ernst van de angina pectoris werd gescoord volgens de Canadian Cardiovascular Society Classification voor stabiele angina pectoris (CCS) en volgens




*Figuur 2. Verschillende fasen in de behandeling volgens de BERT-1.5 trial: A. stenose voor PTCA; B. ballondilatatie; C. resultaat na PTCA; D. bestraling, radioactieve bronnen tussen de duidelijk zichtbare gouden markers; E. angiografie met definitief resultaat.*

de Braunwald Classification voor onstabiele angina pectoris (oap).

De groep bestond uit zeven patiënten met CCS 2, 16 patiënten met CCS 3 en vier patiënten met CCS 4, twee patiënten met oap 1c en twee patiënten met oap 2b (tabel 1). Een van deze laatste twee patiënten werd uitgesloten van het onderzoek: wegens mechanische weerstand kon de bestralingskatheter niet worden opgevoerd tot de plaats van PTCA, zodat op klinische gronden werd besloten tot plaatsing van een stent.




*Figuur 3. Novoste Beta-Cath™ System: Transfer Device en bestralingskatheter.*

*Intracoronaire bestraling met β-emitterende bron*

De PTCA werd verricht conform de conventionele ballonkathetertechniek met, indien nodig, verschillende opeenvolgende inflaties van de ballon tot een succesvol angiografisch resultaat werd bereikt. Daarna werd de angioplastiekkatheter verwijderd.

Voorafgaand aan de bestraling dient de Beta Cath-katheter te worden getest op lekkage en doorgankelijkheid. Deze endovasculaire brachytherapiekatheter wordt vervolgens via de 'guide wire' opgevoerd en exact gepositioneerd op de plaats van de PTCA (figuur 2).

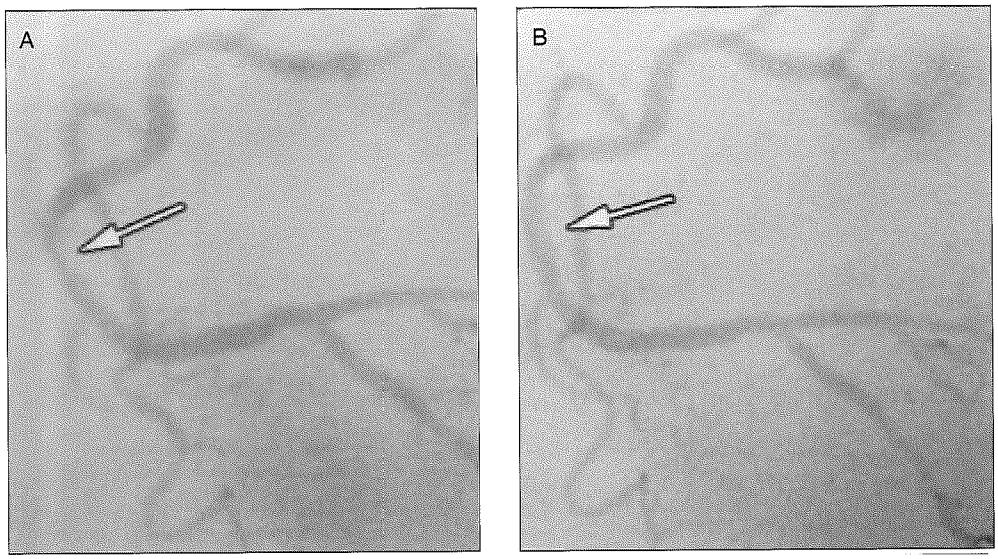
De radioactieve bron bestaat uit een serie van 12 ingekapselde Sr-90-zaadjes met elk een lengte van 2,5 mm; de totale lengte van de brontrein bedraagt 30 mm, met een activiteit van 3,7 GBq. Met de Transfer Device (figuur 3) kan de radiotherapeut de bronnen verplaatsen naar het distale uiteinde van de katheter en terug door middel van een hydraulisch transportsysteem met fysiologisch zout.

Na de bestraling wordt de katheter verwijderd en wordt opnieuw een controleangiografie verricht. Dankzij het gebruik van een β-bron kan het personeel van het katheterisatielaboratorium tijdens de hele procedure aanwezig blijven, zodat de patiënt nooit alleen wordt gelaten.

## Resultaten

*Behandeling*

Voorafgaand aan de behandeling toonde de coronaire angiografie een diameterstenose van 50 tot 87% ten opzichte van de referentiediameter van het bloedvat (gemiddeld 3,02±0,60 mm), met een laesielengte van maximaal 15 mm. De stenosen waren gelokaliseerd in de ramus descendens anterior van de linker coronaire arterie bij 16 patiënten, in de rechter coronaire arterie bij acht patiënten, en in de ramus circumflexus




*Figuur 4. Coronaire angiografie bij patiënt #7: A. voor behandeling; B. drie maanden na behandeling.*

van de linker coronaire arterie bij zeven patiënten. De PTCA-procedure bestond uit één tot negen inflaties van de ballon, met een maximale druk van 6-18 bar.

De toe te dienen stralingsdosis werd bepaald bij randomisatie: tien patiënten kregen 12 Gy, tien patiënten 14 Gy (één patiënte werd niet bestraald) en elf patiënten 16 Gy. De duur van de bestraling bedroeg 159 sec voor 12 Gy, 185 sec voor 14 Gy en 212 sec voor 16 Gy. Na de bestraling was het nodig bij zeven patiënten een stent in te brengen wegens residuele stenose, en bij twee patiënten werd een tweede stent geplaatst in een aangrenzend segment. Ook bij de niet-bestraalde patiënte werd een stent geplaatst; deze patiënte werd uitgesloten van de verdere follow-up. De totale duur van de procedure varieerde van 54 tot 177 min. Tijdens en na de procedure deden zich geen complicaties voor.

De minimale lumendiameter (MLD) van de behandelde laesies bedroeg gemiddeld 1,06±0,30 mm voor dilatatie en 2,21±0,39 mm op het einde van de behandeling. De residuele diameterstenose na ballondilatatie, eventuele stentplaatsing en bestraling was gemiddeld 27±10%.

*Follow-up*

Bij de eerste klinische controle na een maand werd bij 27/30 patiënten een verbetering van de klachten vastgesteld, bij twee patiënten namen de klachten echter toe (#7 en #12), en bij één patiënt bleven de klachten onveranderd (tabel 1).

Patiënten #7 en #12 ondergingen beiden na twee tot drie maanden een controleangiografie in verband met persisterende klachten. Het met PTCA en bestraling behandelde segment was in beide gevallen goed doorgankelijk (figuur 4).

Na een follow-up-duur van drie maanden bleek er bij de meeste patiënten geen verdere verandering in het klachtenpatroon te zijn opgetreden (tabel 1).

Naast de klinische controle werd na zes maanden ook een controleangiografie verricht (tabel 1). De gemiddelde MLD bij follow-up was 1,77±0,68 mm voor een gemiddelde referentiediameter van 3,04±0,44 mm. De gemiddelde 'late loss index' bedroeg 0,40±0,85. Van de 28 evalueerbare patiënten ontwikkelden 8 (29%) een restenose op angiografie. In functie van de graad van angina pectoris en de ernst van de stenose werd bij vijf van deze patiënten een revascularisatie verricht van het bestraalde segment. Twee patiënten met klachten ondanks een niet-significante stenose van het bestraalde segment werden ook opnieuw behandeld met PTCA.

**Discussie**

Hoewel een PTCA in de meerderheid van de gevallen zonder complicaties succesvol wordt uitgevoerd, worden de middellangetermijnresultaten ervan gecompromitteerd door restenose bij 30-50% van de patiënten binnen een periode van zes tot negen maanden na de behandeling. Het plaatsen van een coronaire stent na PTCA is de enige techniek die de re-

**Tabel 2.**
Overzicht van de klinische onderzoeken.

| Referentie | Aantal patiënten | Bron | Dosisprescriptie | Restenose (%) | LLI (%)* | Follow-up-duur (maanden) |
|---|---|---|---|---|---|---|
| Liermann et al. | 30 | Ir-192 | 12 Gy op oppervlak van het lumen | 11 | | 33 (7-84) |
| Condado et al. | 21 (22 laesies) | Ir-192 | 20-25 Gy op de intima (1,5 mm) | 29 | 26 | 36 |
| Teirstein et al. | 26 | Ir-192 | ≥8 Gy meest distale LEE** ≤30 Gy meest proximale LEE** | 17 | 12 | 26 |
| | 29 | Placebo | | 54 | 38 | 26 |
| King et al. (BERT-1.5) | 23 | Sr-90 | 12 Gy, 14 Gy, 16 Gy op 2 mm van de bron | 15 | 4 | |
| Bonan et al. (BERT-1.5) | 30 | Sr-90 | idem | 10 | Negatief | |
| Verin et al. | 15 | Y-90 | 18 Gy op oppervlak van het lumen | 40 | 50 | 6 |

* LLI=late loss index (late loss/acute winst); ** LEE=lamina elastica externa.

stenosefrequentie kan verminderen, in sommige onderzoeken tot 17%. Het effect van de stent is zuiver mechanisch, maar heeft geen remmend effect op de intimahyperplasie.[16-20]

Het concept van het gebruik van radiotherapie ter preventie van neo-intimahyperplasie is gebaseerd op het remmend effect van radiotherapie op de celproliferatie, zowel bij benigne als maligne aandoeningen. De klinische ervaring heeft aangetoond dat verschillende benigne proliferatieve aandoeningen, zoals onder andere keloïdvorming in littekens, succesvol kunnen worden behandeld met relatief lage doses radiotherapie.

In verschillende dierexperimentele onderzoeken werd zowel met gebruik van een gammastraling emitterende Ir-192-bron als met een β-straling emitterende Sr-90-bron een gunstig effect aangetoond van intravasculaire bestraling op de neo-intimahyperplasie na PTCA of stent. In sommige onderzoeken kon ook een dosis-responsrelatie worden vastgesteld, terwijl acute of subacute vaatbeschadigingen niet werden vastgesteld, ook niet bij hogere doses.[27-34]

Popowski et al. ontwikkelden een centreringskatheter voor het gebruik van een Sr-90-bron,[35,36] waarmee zij in een konijnenmodel een reductie van vaatrestenose met een dosis van 18 Gy, gedoseerd op het oppervlak van het lumen, zonder acute of subacute complicaties konden aantonen.[37] Door gebruik te maken van een centreringskatheter wordt de radioactieve bron centraal in het lumen gepositioneerd, zodat een meer homogene dosisverdeling over de vaatwand wordt bereikt.

Een overzicht van de tot op heden gepubliceerde klinische onderzoeken wordt gegeven in tabel 2.

Het eerste klinische onderzoek werd in 1990 gestart door Liermann et al. In dit onderzoek werden dertig patiënten met een recidiverende stenose of occlusie in het femoropopliteale traject behandeld met percutane transluminale angioplastiek (PTA), gevolgd door plaatsing van een stent en radiatie. Na een mediane follow-up-duur van 33 maanden werd bij slechts 3/28 patiënten (11%) restenosering vastgesteld.[38,39]

Het eerste klinische onderzoek waarin coronaire arteriën werden behandeld met radiatie na PTCA met een Ir-192-bron, werd gepubliceerd door Condado et al. Angiografisch werd een restenose vastgesteld bij 6/21 patiënten na een follow-up van twee jaar. Van de tien patiënten die werden bestraald tot een dosis van 25 Gy, ontwikkelden vier een coronair aneurysma. De overige patiënten kregen een dosis van 20 Gy toegediend op 1,5 mm van de bronas.[40-42]

Teirstein et al. hebben een prospectief gerandomiseerd klinisch onderzoek opgezet, waarbij 55 patiënten met restenose werden behandeld met PTCA en stentimplantatie. Bij 26 patiënten werd deze procedure gevolgd door intracoronaire radiotherapie met Ir-192, en bij 29 patiënten werd een dummyprocedure verricht. Een significante reductie van het restenosepercentage werd gezien bij de bestraalde groep (17%), in vergelijking met 54% bij de niet-bestraalde groep.[43-45]

Gedeeltelijke resultaten van de BERT-1.5 trial werden in maart 1998 bekendgemaakt door King en Bonan, na zes maanden follow-up van resp. 23 en 30 patiënten, behandeld met het Novoste Beta-Cath-systeem.[46,47] Het betreft hier alleen enkelvoudige de-novo-laesies in de coronaire arteriën, behandeld met PTCA gevolgd door intracoronaire radiotherapie, waarbij de dosis (12, 14 of 16 Gy op 2 mm van de bronas) door randomisatie wordt bepaald. Het betreft hier hetzelfde onderzoek als waarin de huidige dertig patiënten uit Rotterdam werden behandeld. De eerste resultaten van dit onderzoek toonden een restenosepercentage van resp. 15 en 10, in vergelijking met resp. 42 en 43 in een historische controlegroep (Lovastatin Restenosis Trial).[26]

De resultaten bij onze dertig patiënten, behandeld met PTCA gevolgd door intracoronaire bestraling in

het kader van de BERT-1.5 trial, tonen tot op heden geen complicaties, noch tijdens de hospitalisatie, noch tijdens een follow-up-periode van drie maanden. Na drie maanden follow-up was er bij alle patiënten, behalve twee, sprake van een subjectieve verbetering van de angina-pectoris-klachten.

Na een follow-up van zes maanden werden ook geen complicaties gezien, maar bij controleangiografie werd een restenosering gezien bij 29% van de patiënten. Indien deze resultaten worden gegroepeerd met die van de andere deelnemende centra, bedraagt het restenosepercentage over de totale groep van 84 patiënten 24%, inclusief de restenosen aan de rand van het bestralingsgebied [R. Bonan, referaat AHA 1998].

Het enige andere onderzoek dat gebruikmaakt van een β-bron in coronaire arteriën, werd gepubliceerd door Verin et al.; in dit onderzoek werd voor het eerst gebruikgemaakt van een centreringskatheter. De patiënten in dit onderzoek werden behandeld voor een de-novo of recidiverende stenose van een coronaire arterie. Dit onderzoek laat geen reductie van restenose zien.[48-50]

Het doel van de BERT-1.5 trial was in de eerste plaats om de uitvoerbaarheid en veiligheid van deze behandeling te onderzoeken. Hieruit kunnen dan ook geen conclusies worden getrokken betreffende de effectiviteit van de behandeling. Hiervoor zullen we moeten wachten op de resultaten van de gerandomiseerde, placebo-gecontroleerde, dubbelblinde 'Beta Cath trial', waarin ons centrum ook participeert. In dit internationale multicentrumonderzoek zullen in totaal naar verwachting 1100 patiënten worden gerandomiseerd tussen β-bestraling of 'placebo-bestraling' na PTCA.

## Conclusie

Zowel dierexperimentele als klinische onderzoeken tonen een gunstig effect van intravasculaire radiotherapie op de restenosefrequentie na angioplastiek, zonder fatale of ernstige complicaties tot op heden. De follow-up van de meeste onderzoeken, die overigens niet gerandomiseerd zijn, is vrij kort.

De resultaten bij de dertig patiënten behandeld met PTCA, gevolgd door intracoronaire bestraling, in het kader van de BERT-1.5 trial in het Thoraxcentrum van het Academisch Ziekenhuis Rotterdam, tonen tot op heden geen complicaties, noch tijdens de hospitalisatie, noch tijdens een follow-up-periode van zes maanden. Een controle-coronaire-angiografie na zes maanden toonde restenosering bij 29% van de patiënten. Een langere klinische follow-up is echter noodzakelijk om eventuele late complicaties van deze behandeling op te sporen.

Prospectieve gerandomiseerde onderzoeken zijn nodig om te bepalen wat in de toekomst de plaats van de radiotherapie zal zijn bij de preventie van restenose na angioplastiek. Langdurige follow-up is noodzakelijk om late complicaties ten gevolge van deze behandeling te evalueren. ■

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# CHAPTER 2

Endovascular brachytherapy in coronary arteries: the Rotterdam experience.

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# Endovascular brachytherapy in coronary arteries: the Rotterdam experience

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**Abstract**

**Purpose:** The use of endovascular coronary brachytherapy to prevent restenosis following percutaneous transluminal coronary angioplasty (PTCA) began in April 1997 at the Department of Interventional Cardiology of the Thoraxcenter at the University Hospital of Rotterdam. This article reviews the more than 250 patients that have been treated so far.

**Methods and Materials:** The Beta-Cath System (Novoste), a manual, hydraulic afterloader with 12 $^{90}$Sr seeds, was used in the Beta Energy Restenosis Trial (BERT-1.5, $n=31$), for compassionate use ($n=25$), in the Beta-Cath System trial ($n=27$) and in the Beta Radiation in Europe (BRIE, $n=14$). Since the Beta-Cath System has been commercialized in Europe, 57 patients have been treated and registered in RENO (Registry Novoste). In the Proliferation Reduction with Vascular Energy Trial (PREVENT), 37 patients were randomized using the Guidant-Nucletron remote control afterloader with a $^{32}$P source wire and a centering catheter. Radioactive $^{32}$P coated stents have been implanted in 102 patients. In the Isostent Restenosis Intervention Study 1 (IRIS 1), 26 patients received a stent with an activity of 0.75–1.5 μCi, and in the IRIS 2 (European $^{32}$P dose response trial), 40 patients were treated with an activity of 6–12 μCi. In two consecutive pilot trials, radioactive stents with non-radioactive ends (cold-end stents) and with ends containing higher levels of activity (hot-end stents) were implanted in 21 and 17 patients, respectively.

**Results:** In the BERT-1.5 trial, the radiation dose, prescribed at 2 mm from the source train (non-centered), was 12 Gy (10 patients), 14 Gy (10 patients) and 16 Gy (11 patients). At 6-month follow-up, 8 out of 28 (29%) patients developed restenosis. The target lesion revascularization rate (TLR) was 7 out of 30 (23%) at 6 months and 8 out of 30 (27%) at 1 year. Two patients presented with late thrombosis in the first year. For compassionate use patients, a restenosis rate (RR) of 53% was observed. In the PREVENT trial, 34 of 37 patients underwent an angiographic 6-month follow-up. The doses prescribed at 0.5 mm depth into the vessel wall were 0 Gy (8), 28 Gy (9), 35 Gy (11) and 42 Gy (8). TLR was 14% in the irradiated patients and 25% in the placebo group. One patient developed late thrombosis. In the IRIS 1 trial, 23 patients showed an RR of 17% (in-stent). In the IRIS 2 trial, in-stent restenosis was not seen in 36 patients at 6-month follow-up. However, a high RR (44%) was observed at the stent edges.

**Conclusions:** The integration of vascular brachytherapy in the catheterization laboratory is feasible and the different treatment techniques that are used are safe. Problems, such as edge restenosis and late thrombotic occlusion, have been identified as limiting factors of this technique. Solutions have been suggested and will be tested in future trials. © 2000 Elsevier Science Inc. All rights reserved.

*Keywords:* Radiation; Intravascular brachytherapy; Restenosis; Coronary vessel

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## 1. Introduction

Coronary artery diseases remain the major cause of death in industrialized countries. Worldwide, more than one million procedures of percutaneous transluminal coronary angioplasty (PTCA) are performed each year. Despite the fact that PTCA is successful in 95% of the cases and that the complication rate is very low, long-term results show a high rate of restenosis: 30–50% within the first year [1–3].

PTCA causes damage to the intima and media, inducing a wound healing process with hyperproliferation and negative remodeling, causing restenosis. Different factors play a sequential role in this process: platelet aggregation, infiltration of inflammatory cells and release of growth factors, modulation and proliferation of smooth muscle cells, synthesis of proteoglycans and modifications of extracellular matrix. Mechanisms involved in restenosis are the elastic recoil of the artery, local thrombus formation, vascular remodeling and neointimal cellular proliferation. All these different factors contribute to a progressive narrowing of the residual lumen [4].

Results of clinical trials, using drugs to reduce the restenosis rate (RR) were disappointing [5–10]. Recently, encouraging results were obtained with a monoclonal antibody that blocks the GP IIb/IIIa receptor and inhibits platelet aggregation and adhesion. The EPIC-trial showed a significant reduction of ischaemia in a period of 6 months following PTCA [11,12]. Other trials resulted in a significant improvement during the first 30 days after PTCA, but this difference was not sustained after 6 months [13,14]. The results of the trials using GP IIb/IIIa receptor blockers combined with stent implantation have been variable (ERASER [15] and EPISTENT [16] trials).

Stent implantation following PTCA minimizes the elastic recoil and vascular remodeling, but does not reduce neointimal cellular proliferation. In fact, stent implantation tends to induce an increased proliferative response. The use of stents in clinical trials has proven to reduce the RR to around 20–30%. For example, in the STRESS and BENESTENT trials, a 30% reduction in the recurrence of RR was achieved after implantation of a single Palmaz–Schatz coronary stent for short lesions [17–21]. Nevertheless, the RR remains high after stent implantation in long lesions and small vessels.

Despite extensive clinical research no treatment has been proven to inhibit the proliferative component of restenosis. Systemic toxicity is the limiting factor for the use of antiproliferative drugs. Local drug delivery at the PTCA site is one way to prevent systemic side effects, but in its current stage is still experimental.

Radiotherapy is the most recent treatment tested in combination with PTCA. Clinical experience for more than 100 years has shown radiotherapy to be a potent inhibitor of cellular proliferation, in benign as well as malignant diseases. Examples of benign proliferative disorders successfully treated with radiotherapy are keloid, heterotopic bone formation after surgery, pterygium, Peyronie's disease and desmoid-aggressive fibromatosis. Benign proliferative disorders are treated with radiation doses between 7 and 10 Gy in one or more fractions, inhibiting the fibroblast proliferation [22–26].

Animal studies have demonstrated the effectiveness of γ- and β-radiation in reducing neointimal hyperplasia after angioplasty. The use of radioactive stents has also shown a reduction of restenosis in animals [27–34]. The encouraging results from these preclinical studies has initiated different clinical trials with γ- and β-radiation.

## 2. Materials and methods

In April 1997 trials using β-endovascular coronary brachytherapy were started at the Department of Interventional Cardiology of the Thoraxcenter at the University Hospital of Rotterdam. Since then, more than 250 patients have been treated for different indications, including prevention of restenosis of de novo or restenotic lesions and treatment specifically for in-stent restenosis. In close conjunction with the Department of Radiotherapy at the Daniel den Hoed Cancer Center, University Hospital of Rotterdam, 193 patients were irradiated using a catheter-based technique. Of these patients, 104 underwent radioactive stent implantation (Table 1).

### 2.1. Catheter-based techniques

#### 2.1.1. Beta-Cath system

The manual, hydraulic afterloader of Novoste (Fig. 1) has been used in different multicenter trials including the BERT-1.5 trial, the Beta-Cath System trial and the BRIE trial. The same device was also used in a compassionately for patients with recurrent in-stent restenosis. The company started the RENO registry when the device became commercially available in Europe. The source used in the RENO registry is a pure β-emitting nuclide, a line source containing 12 or 16 seeds Strontium-90 ($^{90}$Sr) with an

Table 1

| Technique | Number of patients |
|---|---|
| *Catheter-based devices* | *193* |
| BERT-1.5 trial | 31 |
| Compassionate use Novoste | 25 |
| Beta-Cath System trial | 29 |
| BRIE trial | 14 |
| RENO registry | 57 |
| PREVENT trial | 37 |
| *Permanent implant of radioactive stents* | *104* |
| IRIS 1 trial | 26 |
| IRIS 2 trial | 40 |
| Cold-end stents | 21 |
| Hot-end stents | 17 |

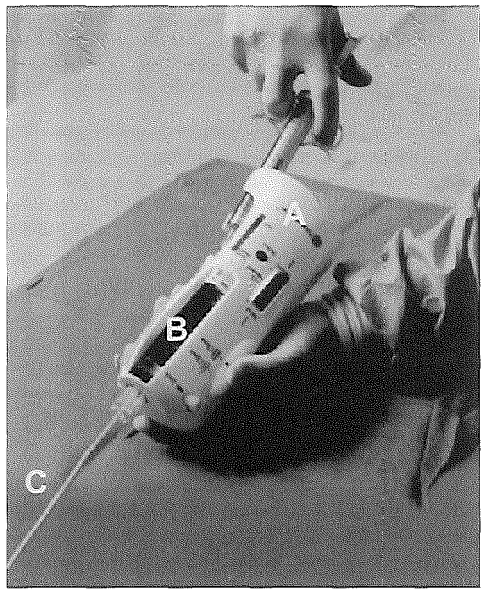


Fig. 1. Beta-Cath System: manual, hydraulic afterloader of Novoste. (A) Transfer device. (B) Radiation source train. (C) Delivery catheter.

active length of 30 or 40 mm, respectively. Each cylindrical seed is 2.5 mm long and is encapsulated in stainless steel. The seeds are stored in the Novoste Transfer Device and the hydraulic manual afterloading device uses sterile water to move the sources in a closed lumen of the Novoste radiation delivery catheter.

Balloon angioplasties were performed according to standard clinical practice. To obtain a successful angiographic result multiple balloon inflations were necessary in some of the patients.

Prior to radiation, the Beta-Cath catheter was tested for potential leaks and successful transfer of the source train. The delivery catheter, a 5 Fr triple lumen over-the-wire or monorail non-centered catheter, was advanced over the guide-wire and positioned at the site of PTCA. A proximal and distal radiopaque marker at the distal part of the catheter delineated the position of the source train, which allowed precise positioning at the PTCA site. The radiation oncologist uses the transfer device to advance the sources to the distal end of the catheter and later retrieve them when the radiation is complete. Then the catheter is removed and a final angiography is made. In case of residual stenosis or dissection, a stent was implanted after irradiation. Because of the low radiation hazard due to the use of β-radiation emitting isotopes, lab personnel can remain in the cath lab at the time of the radiation procedure.

*2.1.2. Guidant-Nucletron afterloader*

A remote-controlled afterloader (Fig. 2) has been used for the PREVENT trial. The afterloader stores and shields the radioactive source wire and houses the dummy wire. The source is a pure β-emitting $^{32}P$ line wire, 27 mm of active length. The radiation delivery catheter is a 3.9 Fr monorail catheter with a closed end lumen, preventing the source wire from coming into contact with blood. The helical balloon (Fig. 2) is designed to center the source wire and potentially allows distal and side branch perfusion during treatment. For precise positioning at the PTCA site, the two radiopaque markers defining the treatment area are used. First a dummy wire is used to verify the patency of the catheter lumen and to correctly position the radioactive wire between the two radiopaque markers. Then the dummy wire is automatically retrieved and the radioactive wire is then sent into the catheter. The computer calculates the treatment time based upon the reference vessel diameter and the prescribed dose.

*2.2. Radioactive stents*

*2.2.1. Isostent*

The Fischell IsoStent is a stainless steel stent with $^{32}P$ embedded beneath the surface of the stent. The first stents were Palmaz–Schatz IsoStent, and later the BX IsoStent (Fig. 3) was used. The radioactive stent is provided mounted on a currently approved stent delivery system (balloon) with an integral sheath. To prevent radiation exposure to the operator the stent is covered with a protective plastic lucent shield (Fig. 3). These stents are 15 mm long with a variable activity of 0.75–1.5 μCi in the IRIS 1 trial and 6–12 μCi in the IRIS 2 (European $^{32}P$ dose response) trial. Implantation of one or two stents in tandem was permitted.

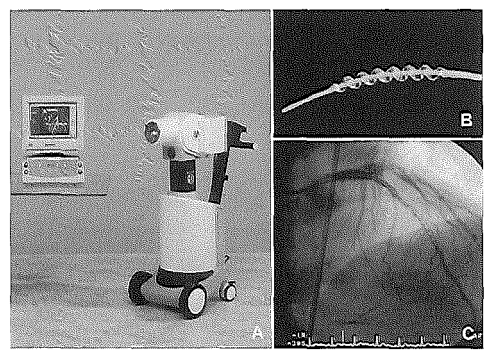


Fig. 2. Remote controlled afterloader of Guidant-Nucletron. (A) Afterloader and planning computer. (B) Centering catheter. (C) Angiography with centering catheter allowing perfusion.

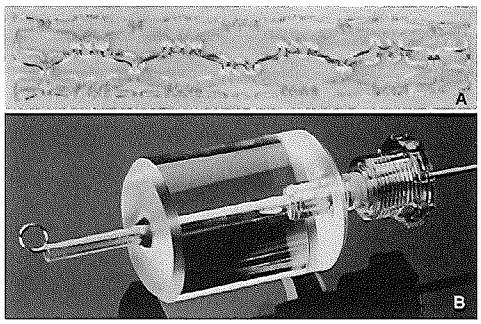


Fig. 3. (A) BX IsoStent. (B) Protective lucent shield.

*2.2.2. Isostent with cold ends*

The $^{32}P$ coated stent is 25 mm long with an active length of 13.6 mm. The total activity of this active part is 3–12 μCi, which is 0.2–0.9 μCi/mm. At the proximal and distal end a 5.7-mm segment is nonactive (0.1 μCi).

*2.2.3. Isostent with hot ends*

This $^{32}P$ coated stent has a total length of 18 mm. It consists of a central part of 14 mm long with an activity of 0.3–0.6 μCi/mm (total activity 4.5–9 μCi). The proximal and distal edges are 2 mm long with an activity of 1.3–2.6 μCi/mm.

## 3. Results

### *3.1. Catheter based trials*

*3.1.1. Beta energy restenosis trial: BERT-1.5*

In this prospective multicenter feasibility (non-randomized) study, 31 patients were included. In 23 patients, the lesion was located in the left coronary artery; 8 were in the right coronary artery. The reference diameter varied between 2.18 and 4.69 mm. The mean lesion length was 13±4 mm. A PTCA was performed in all patients, followed by provisional stenting in eight patients (26%). In one patient atherectomy was performed prior to PTCA. After PTCA brachytherapy was delivered using the Beta-Cath System described previously. The radiation dose was prescribed at a distance of 2 mm from the source axis: 10 patients were randomized for 12 Gy, 10 patients for 14 Gy and 11 patients for 16 Gy. In one patient of the 12 Gy group, the sources could not be retrieved into the transfer device. The catheter was removed with the radioactive source in situ and put into the bail-out box. This emergency procedure prolonged the radiation time and a dose of 16 Gy was delivered instead of 12 Gy. In the 14 Gy group, radiation was not completed in one patient; the lesion could not be crossed with the radiation delivery catheter. The angiographic follow-up at 6 months resulted in an RR of 29% (8/28); 2 out of 6 patients with de novo stent implantation and 6 out of 22 patients treated with balloon angioplasty alone. Target lesion revascularization rate (TLR) was 23% (7/30) at 6 months and 27% (8/30) at 12 months. No in hospital complications were seen. A late thrombosis occurred in two patients within 12 months. The first patient developed ventricular fibrillation at 3 months, and at 6 months angiography showed a total occlusion due to restenosis and thrombosis. This patient had two stents implanted with a total length of 41 mm, radiation did not cover the whole stent length. The second patient had a persistent dissection 10 months after PTCA, without restenosis. A third patient developed late thrombosis at 15 months; IVUS showed a malopposed stent, without restenosis. Late stent malopposition occurring after intracoronary beta-radiation was detected by intravascular ultrasound [35]. Two patients developed a myocardial infarction between 6 and 12 months after treatment.

*3.1.2. Compassionate use with the Beta-Cath system*

The Beta-Cath System was used as the brachytherapy afterloader for the compassionate use of irradiating 25 patient with recurrent in-stent restenosis. The mean lesion length was 16±7 mm, in six cases the lesion was longer than 20 mm. The average recurrence rate of restenosis was 2.4±0.7. All patients were treated with a standard PTCA procedure, and in most cases combined with atherectomy, achieving an 89% procedural success rate. Two patients developed a distal dissection after laser debulking, leading to a transient occlusion of the vessel: a non-Q wave infarction occurred in one case and a re-angioplasty was performed in the other patient [36]. The dose of brachytherapy delivered after PTCA was prescribed at a distance of 2 mm from the source axis, according to the vessel lumen diameter: 16 Gy for a lumen diameter ≥2.70–≤3.35 mm and 20 Gy for a lumen diameter >3.35–≤4.00 mm. The 6-month clinical follow-up was achieved in 18/25 patients, with a 6-month angiography in 17 patients. The overall RR and the TLR were, respectively, 53% (9/17) and 44% (8/18). In 8/18 (44%) patients, review of the treatment films showed a geographical miss; in 5 patients the injured area was not adequately covered by the radioactive source and in 3 patients an additional stent had to be implanted following radiation for distal dissection. The RR was 75% in the geographical miss areas compared to 33% of the non-geographical miss areas. In radiotherapy the term "geographical miss" describes the part of the target volume that has been inadequately irradiated, due to underestimation of the tumor volume or insufficient treatment margins. It is one of the causes of treatment failure. In endovascular brachytherapy, this term is used for cases where the radiation source does not fully cover the injured area.

*3.1.3. Beta-Cath system trial*

In this prospective multicenter double-blind randomized trial, safety and efficacy of β-radiation will be evaluated in coronary arteries, following PTCA with or without stent implantation. The patients treated with PTCA alone and those treated with PTCA and provisional stenting are randomized separately between irradiation and placebo treatment. In the PTCA alone arm, bail-out stenting was performed if necessary following brachytherapy (radiation or placebo). We included 29 patients in this trial with single de novo lesions in native coronary arteries with a stenosis of at least 60% and less than 100%. The maximum length of the PTCA balloon and/or stent was 20 mm. The treatment consisted of a standard PTCA procedure followed by brachytherapy. The dose of radiation was 14 Gy for a lumen ≥2.70–≤3.35 mm and 18 Gy for a lumen >3.35–≤4.00 mm. The stent was implanted immediately post brachytherapy. Clinical follow-up is performed at 30 days, 8 months, 1 and 2 years. Patients undergo a control angiography 8 months after treatment.

*3.1.4. Beta radiation in Europe: BRIE trial*

In this prospective multicenter non-randomized trial, safety and efficacy of β-radiation will be evaluated in coronary arteries, following PTCA with or without stent implantation in one or two lesions in different vessels. We included 14 patients with one or two stenotic lesions in different native coronary arteries. Lesion characteristics were de novo or restenotic lesions with a stenosis of at least 50% and less than 100%. The treated length was limited to 24 mm for PTCA and the maximum stent length was 22 mm, mounted on a 24-mm balloon. Patients were treated with standard PTCA and followed by brachytherapy. The dose of radiation was again dependent on the vessel lumen diameter; i.e. 14 Gy for a lumen ≥2.70–≤3.35 mm and 18 Gy for a lumen >3.35–≤4.00 mm. When indicated a stent was implanted after brachytherapy. The clinical follow-up is performed at 30 days, 6 months, 1 year and patients undergo a control angiography 8 months after treatment.

*3.1.5. Registry Novoste: RENO*

Since the Beta-Cath System has been commercialized in Europe, 57 patients have been treated and registered in RENO. Patients with de novo or restenotic lesions as well as patients with relapsing in-stent restenosis, with more complex and diffuse disease, were treated. A standard revascularization procedure was performed, the use of mechanical or laser atherectomy devices was allowed. The dose of radiation was related to the vessel size: 14 Gy for a lumen diameter ≥2.5–≤3.5 mm, 18 Gy for >3.5–<4.00 mm and 20 Gy for ≥4.0 mm. Stented vessels radiation doses were increased by 2 Gy, taking into account the shielding effect of the metallic structure of the stent. The maximum length of the treated area advised in RENO is 30 mm. The 30-mm source is used for a treated area not longer than 20 mm; for a lesion between 20 and 30 mm, the 40 mm source is recommended. In eight patients, the lesion length exceeded 30 mm, with total lengths up to 70 mm. These patients were irradiated with the source in tandem position. The catheter had to be retrieved manually first, before the source was introduced again in juxtaposition to the previous source.

*3.1.6. Proliferation REduction with Vascular ENergy Trial: PREVENT-trial*

In this phase I pilot trial, 37 patients were included. All patients presented with single, de novo or restenotic lesions, and some with in-stent restenosis, in native coronary vessels with a lumen diameter between 2.4 and 3.7 mm. The maximal lesion length was 15 mm. Patients underwent a standard PTCA, in some cases followed by stent implantation. The maximum treated length (PTCA + stent) was 22 mm. In this trial, brachytherapy was delivered after stent implantation. One patient was not irradiated due to rupture of the centering balloon, probably due to stent struts. The dose was prescribed at 1-mm depth into the vessel wall. After randomization, the patients were allocated to four different dose levels, that is 0, 16, 20 or 24 Gy. Radiation was delivered in 28 patients: 28 Gy in 9 patients, 35 Gy in 11 patients and 42 Gy in 8 cases. A dummy procedure was performed in eight patients. The clinical follow-up was performed at 30 days, 6 months, 1 and 2 years. Patients underwent a control angiography 6 months after treatment. The clinical and angiographic 6-month follow-up was done in 34/36 patients. Two patients refused follow-up angiography. In the irradiated patient group, TLR was 14% (4/28) and angiographic RR 19% (5/26). In the placebo group these numbers were, respectively 25% (2/8) TLR and 63% (5/8) RR. In terms of complications, three patients developed thrombosis; two patients developed subacute thrombosis (within 30 days) and one developed late thrombosis. Subacute thrombosis occurred in two patients 14 days after treatment: one following PTCA, stenting and radiation (35 Gy), due to interruption of the antiplatelet therapy and the other following PTCA and radiation (35 Gy). Late thrombosis was seen in a patient 3 months after PTCA and radiation (35 Gy), IVUS showed persistent dissection.

*3.2. Radioactive stent trials*

*3.2.1. Isostent restenosis intervention study: IRIS-1*

In this phase I non-randomized multicenter safety/feasibility trial, 26 patients were included. Lesion characteristics were: single, de novo or restenotic lesions with maximal length of 28 mm, in native coronary vessels with a reference diameter between 3.0 and 3.5 mm. Following a standard PTCA procedure, 1 or 2 radioactive stents of 15 mm were implanted, 31 stents were placed in 26 patients. The first 5 patients received a $^{32}P$ Palmaz–Schatz Isostent, the other 26 stents were $^{32}P$ BX Isostents. The activity of the stents ranged between 0.75 and 1.5 μCi. In four patients, two radioactive stents were implanted, five patients received an

additional non-radioactive stent. The mean lesion length was 13 ± 4 mm and the mean reference diameter 2.93 ± 0.47 mm. The dose delivered at 1 mm from the stent surface, accumulated over a 100-day period, ranged between 500 cGy and 1000 cGy. At 6-month clinical follow-up, 81% of these patients were asymptomatic, no cases of death or myocardial infarction were reported. TLR was 12% (3/26). Angiographic control at 6 months was obtained in 23 patients, showing restenosis in 4 (17%). All restenosis occurred inside the stent, which means no "candy wrapper" effect was observed. In one patient only one radioactive stent was implanted, the other three patients received a radioactive and a non-radioactive stent. The only complication seen in these patients was the embolization of a second radioactive stent meant to be implanted distally from the first one.

*3.2.2. The European $^{32}P$ dose response trial: the Rotterdam contribution*

This phase I non-randomized multicenter safety/feasibility trial included patients with single, de novo or restenotic lesions, with a maximum length of 28 mm, in native coronary vessels (reference diameter 3.0–3.5 mm). In 40 patients, 42 radioactive stents were implanted following PTCA. The stents were $^{32}P$ BX Isostent of 15 mm long, with an activity of 6–12 μCi. In six patients an additional non-radioactive stent was implanted. The mean lesion length was 10 ± 3 mm with a mean reference vessel diameter of 2.98 ± 0.70 mm. At 4 months, angiographic control in 36 patients showed no in-stent restenosis, instead a high rate (44%) of target segment restenosis at the stent edges was observed. Three patients during the procedure developed a transient thrombotic occlusion of the stent, one of whom with a non-Q wave myocardial infarction.

*3.2.3. Cold-end and hot-end stents*

Cold-end stents and hot-end stents were implanted in 21 and 17 patients, respectively with a maximum length of lesions of 15 mm in vessels with a diameter of 3.0–3.5 mm. Implantation of more than one stent per patient was not allowed in these two pilot trials.

## 4. Discussion

Condado et al.'s [37,38] study represented the first use in humans of intracoronary radiation therapy, using γ-radiation ($^{192}Ir$). It was a single arm study without a control group. The RR was 29% (6/21). In the Scripps trial, 55 patients with restenosis following previous PTCA were randomized between placebo and irradiation ($^{192}Ir$). Results showed a significant reduction in RR in the irradiated group (17%) compared to placebo (54%) [39–42]. Two double-blinded randomized trials including a larger number of patients with in-stent restenosis, the single center WRIST trial and the multi-center Gamma-1 trial confirmed these results. The WRIST trial randomized 130 patients between placebo and $^{192}Ir$, showing a significant decrease in RR following radiation (19%) compared to the placebo group (58%) [43]. In the Gamma-1 trial 252 patients were randomized. The in-stent RR was 21.6% in the irradiated group versus 52% in the placebo group, the in-lesion RR (including the edges) was higher, respectively, 34% versus 56% [44].

At the present time results of the randomized trials using β-radiation are still unknown. Different safety-feasibility trials, using different types of β-sources, show variable results. In BERT-1.5 patients were treated with a $^{90}Sr$ source delivering different doses of radiation. The RR in 78 patients was 24%: 16.7% showed restenosis at the target lesion site and 7.7% developed a new lesion in the intervention area [45,46]. In PREVENT, patients were treated with a $^{32}P$ source and received one out of three different doses of radiation or placebo. In 71 out of 72 randomized patients (55 radiation and 17 placebo), radiation therapy was successfully completed. In the irradiated group 6% showed a restenosis at the target lesion site and 25% developed restenosis when including the adjacent segments. In the placebo group these numbers were, respectively, 33% and 44% [47]. The negative result from the safety-feasibility trial of Verin et al. [48], using a $^{90}Y$ source wire, was attributed to too low of a prescribed dose. A European dose finding study including 181 patients, using an $^{90}Y$ line source, was recently terminated, showing a clear dose–response relationship. The results were presented at the XXIst Congress of the European Society of Cardiology. Six-month follow-up was performed on 154 patients. The different dose levels were 9, 12, 15 and 18 Gy prescribed at 1-mm depth into the vessel wall. The RR for de novo lesions was, respectively, 27.5%, 15.8%, 17.5% and 8.3%. Overall the stented patients had a higher RR than the patients treated with balloon angioplasty only. In the highest dose group their RR was only 4.2%. Another encouraging result for β-radiation is the β-WRIST trial, in which 50 patients with in-stent restenosis were treated with the $^{90}Y$ source. The RR (22.5%) was comparable to the result of the 50 patients treated with $^{192}Ir$ in the WRIST trial [49].

For evaluation of endovascular brachytherapy using catheter-based techniques the following factors, among others, seem to be of relevance: centering versus non-centering catheters, radioactive source type, dose prescription, treatment time, dose rate, total body dose received by the patient, radiation exposure of the personnel and need for modification of catheterization laboratories due to the brachytherapy procedure. A detailed discussion on these brachytherapy treatment-related factors is, however, beyond the scope of the present paper.

The low RR in the irradiated area proves the effectiveness of radiation in inhibiting neointimal hyperplasia. An important concern in most of the trials at present and highlighted by many clinical investigators is the restenosis at the edges of the irradiated area. This phenomenon could possibly be attributed to inadequate coverage of the injured

area by radiation. The problem of edge restenosis may be decreased by adequately treating the target length of the vessel, which includes not only the stenotic lesion but also the barotraumatized segment (result of angioplasty and stent deployment balloons), i.e. increasing the margins, taking into account source movements, penumbra of the isodose lines and uncertainties in targeting. An important limiting factor in the use of β-radiation devices is the fixed length of the sources, limiting the application to patients with short lesions. The technique of tandem irradiation with manual positioning of the source has its inherent problems, because of potential overlap or underdosage at the site of the juxtaposition of the sources. As the use of coronary brachytherapy is increasing, treating patients with longer and more complex lesions in diffuse diseased arteries, there is a need for longer sources or preferably a stepping source accommodating a large range in treatment lengths.

Clinical trials using radioactive stents show a very high RR, especially at the stent edges. Besides the problem of a geographical miss, another hypothesis for the edge restenosis is the combination of injury and the possible stimulatory effect of low doses of radiation on neointima hyperplasia. Radioactive stents with cold and hot ends have been developed to analyze the phenomenon of restenosis at the stent edges and try to solve the problem.

The advantage of β-radiation is of course the low body radiation dose received by the patient and the low radiation exposure of the staff. It can be used without any modification of the catheterization laboratory and the short treatment time hardly prolongs the total duration of the procedure. γ-radiation in contrast, needs extra shielding, i.e. mobile shields in the room or shielding of the entire room. Also, treatment times are longer with γ- versus β-radiation and the radiation exposure of patient and staff is more relevant. The radiation exposure of the personnel, however, could easily be solved by developing a remote-controlled afterloader.

So far no major complications have been reported. In the Condado trial, two patients developed an aneurysm, asymptomatic and stable. Calculations demonstrated that these patients focally received a very high radiation dose. Recently, an increase in late thrombosis was reported (up to 10%), especially in patients who are re-stented at the time of brachytherapy. The current recommendation, therefore, is to prolong antiplatelet therapy for 6 months [50–52].

The results obtained in Rotterdam with the Novoste system varied between 29% RR in BERT-1.5 and 53% in the compassionate use patients. In this last group the bad results are probably due to patient selection and the high number of geographical miss cases. In the PREVENT trial, using the Guidant-Nucletron afterloader, irradiated patients demonstrated an RR of 19%. In the radioactive stent trials an RR of 17% (in-stent) was reported in the low activity stents (0.75–1.5 μCi), whereas the high activity stent group (6–12 μCi) showed an RR of 44% at the stent edges. Late thrombosis was reported in 6.6% of patients treated with catheter-based intracoronary β-radiation [51].

The integration of a vascular brachytherapy program in a busy catheterization laboratory seems feasible, but only in close cooperation with a department of radiotherapy. For the most part, β-brachytherapy is applicable in routine practice with minimal modifications of the catheterization laboratory procedures. The use of the various techniques appeared to be safe. Results are mixed but appear to be promising for the future. The follow-up period in most of the trials is far too short to make final statements on long-term effects of radiation as yet. There is still a long way to go in terms of dosimetry and uniformity in prescribing and reporting the radiation dose. Future trials will undoubtedly select patient groups that benefit most from radiation and the choice of the device will depend on safety and ease of procedure as well as on local logistics.

## 5. Conclusions

This article reviews more than 250 patients, treated with endovascular coronary brachytherapy at the Thoraxcenter in Rotterdam. Different catheter-based techniques with β-emitting radioactive sources and radioactive $^{32}P$ coated stents were used in various trials. Different restenosis and TLR rates were obtained depending on the technique used and the lesion type. The integration of vascular brachytherapy in a catheterization laboratory is feasible and the different treatment techniques used are safe. Problems, such as edge restenosis and late thrombotic occlusion, have been identified as limiting factors of these techniques. Solutions have been suggested and will be tested in future trials.

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# CHAPTER 3

RENO, a European postmarket surveillance registry, confirms effectiveness of coronary brachytherapy in routine clinical practice.

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# RENO, A EUROPEAN POSTMARKET SURVEILLANCE REGISTRY, CONFIRMS EFFECTIVENESS OF CORONARY BRACHYTHERAPY IN ROUTINE CLINICAL PRACTICE

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**Purpose: To assess, by a European registry trial, the clinical event rate in patients with discrete stenotic lesions of coronary arteries (*de novo* or restenotic) in single or multiple vessels (native or bypass grafts) treated with β-radiation.**

**Methods and Materials: Between April 1999 and September 2000, 1098 consecutive patients treated in 46 centers in Europe and the Middle East with the Novoste Beta-Cath System were included in Registry Novoste (RENO).**

**Results: Six-month follow-up data were obtained for 1085 patients. Of 1174 target lesions, 94.1% were located in native vessels and 5.9% in a bypass graft; 17.7% were *de novo* lesions, 4.1% were restenotic, and 77.7% were in-stent restenotic lesions. Intravascular brachytherapy was technically successful in 95.9% of lesions. Multisegmental irradiation, using a manual pullback stepping maneuver to treat longer lesions, was used in 16.3% of the procedures. The in-hospital rate of major adverse cardiac events was 1.8%. At 6 months, the rate was 18.7%. Angiographic follow-up was available for 70.4% of the patients. Nonocclusive restenosis was seen in 18.8% and total occlusion in 5.7% of patients. A combined end point for late (30–180 days) definitive or suspected target vessel closure was reached in 5.4%, but with only 2% of clinical events. Multivariate analysis was performed for major adverse cardiac events and late thrombosis.**

**Conclusion: Data obtained from the multicenter RENO registry study, derived from a large cohort of unselected consecutive patients, suggest that the good results of recent randomized controlled clinical trials can be replicated in routine clinical practice.** © 2003 Elsevier Science Inc.

**RENO, Restenosis, Coronary, Radiation.**

## INTRODUCTION

Coronary artery disease remains the major cause of death in industrialized countries. Worldwide, >1 million procedures of percutaneous transluminal coronary angioplasty (PTCA) are performed each year. Even though PTCA is successful in 95% of cases and the complication rate is very low, restenosis remains the major limitation of percutaneous coronary interventions (PCIs).

Restenosis is the result of damage to the intima and media during PTCA, inducing a wound healing process with hyperproliferation and negative remodeling (constriction). Elastic recoil of the artery, local thrombus formation, vascular remodeling, and neointimal cellular proliferation are factors contributing to a progressive narrowing of the residual lumen (1).

Restenosis rates in short, type A and B lesions are reported to be 30–50% for conventional balloon angioplasty (2–4). Stent implantation after PTCA minimizes the elastic recoil and vascular remodeling, but does not reduce neointimal cellular proliferation; in fact, it tends to induce an increased proliferative response. Stents have been proved in clinical trials to reduce the restenosis rate to around 15–30%. For example, in the Stent Restenosis Study (STRESS) and Belgium Netherlands STENT Study (BENESTENT) trials, a 30% reduction in

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the restenosis rate was achieved after implantation of a single Palmaz-Schatz coronary stent (Cordis, Johnson and Johnson Company, Warren, NJ) for short lesions (5, 6). Nevertheless, the restenosis rate remains high after stent implantation in long lesions and small vessels.

Intravascular brachytherapy (VBT) has been proved an effective mode of preventing restenosis after PCI (7–13). The promising results of clinical trials and commercial availability of coronary radiation devices have led to the use of VBT in daily routine application. The Registry Novoste (RENO) registry allows the reporting of results of VBT using the Beta-Cath coronary system (Novoste, Norcross, GA) in routine clinical practice.

## METHODS AND MATERIALS

Between April 1999 and September 2000, 1174 lesions were treated in 1098 consecutive patients in 46 centers in Europe and the Middle East with the Novoste Beta-Cath System and registered in RENO. All patients treated in routine clinical practice with this radiation device during the above-mentioned period were registered.

Patients with angina and/or objective evidence of ischemia due to an angiographically documented coronary artery lesion in a native vessel or bypass graft, who were candidates for percutaneous revascularization, were included in this registry. In patients with multivessel disease, only one lesion per vessel could be treated. The vessel diameter varied between 2.5 and 4.0 mm. All patients provided informed consent before inclusion.

The reference vessel diameter and lesion length were visually estimated. PTCA was performed according to standard clinical practice. To obtain a successful angiographic result (<50% residual stenosis), different approved PTCA techniques (balloon angioplasty, cutting balloon, mechanical or laser atherectomy, stent implantation) were applied.

After a successful PTCA procedure, the site of angioplasty was irradiated using source trains that consist of $\beta$-emitting $^{90}Sr/^{90}Y$ seeds with a stainless steel encapsulation. Each seed is 0.9 mm in diameter and 2.5 mm in length. The seeds are stored in the Novoste Transfer Device. This device incorporates a hydraulic, manual afterloading system, using sterile water to move the sources in a closed lumen of the radiation delivery catheter. Until January 2000, only source trains with 12 or 16 seeds were available that had active lengths of 30 or 40 mm, respectively. Investigators were instructed to pay attention to optimal positioning of the radiation source relative to the PTCA site to cover the entire interventional length, with a margin of at least 5 mm at each side. Interventional lengths >30 mm required multisegmental irradiation: a combination of two or three source train positions with one or two junctions. In March 2000, a 60-mm source train (24 seeds) became available, eliminating the junction of two 30-mm source trains. The delivery catheter (Beta-Cath, Novoste) is a 5F, triple-lumen, monorail, noncentered catheter. Before radiation, the Beta-Cath catheter was tested for fluid leakage and unhampered transfer of the dummy source train. The delivery catheter was advanced over the guidewire and positioned at the PTCA site. Proximal and distal radiopaque markers at the distal part of the delivery catheter delineated the position of the source train, allowing precise positioning at the PTCA site while providing sufficient margin. The radiation oncologist or technician uses the transfer device to advance the sources to the distal end of the delivery catheter and retrieve them when radiation is completed. Then, the catheter is removed, and a final angiogram is made.

The recommended radiation dose was determined by the vessel diameter and the presence of a stent. The dose has been prescribed at a distance of 2 mm from the source axis. The nominal diameter of the largest angioplasty balloon was considered to represent the reference diameter and was used for dose prescription. Without a stent, the dose prescription was as follows: 16.1 Gy for a maximal balloon diameter of ≥2.5 mm to <3.5 mm, 20.7 Gy for a balloon diameter of ≥3.5 to <4.0 mm, and 23 Gy for a balloon diameter of ≥4.0 mm. For in-stent restenosis or after stent implantation, the corresponding doses were 18.4, 23, and 25.3 Gy (i.e., 2.3-Gy extra to compensate for attenuation by the stent struts).

At discharge, per protocol, antiplatelet therapy was usually given for at least 3 months: aspirin with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily.

The primary end point of this registry trial was to assess the clinical success at 6 months, defined as procedural success without occurrence of major adverse cardiac events (MACE). Procedural success was achieved when at least 90% of the prescribed radiation dose had been delivered to the PTCA site and the final residual stenosis was not >50%. Geographic miss (14) was defined as incomplete coverage of the injured segment by the prescribed radiation dose; it was not evaluated according to a standard protocol. MACE included death, acute myocardial infarction (MI), or target vessel revascularization. Postprocedure measurements of creatine phosphokinase (CPK) and CPK-myocardial band isoenzymes were obtained 8 h after the procedure and every 6–8 h if the CPK was elevated. The highest level was recorded. Plasma CPK elevation to greater than twice the upper limit of normal and/or new Q waves on electrocardiography were scored as MI. Target vessel revascularization was defined as revascularization of a vessel that previously had undergone PCI by either coronary artery bypass grafting or repeat PTCA. Secondary end points were procedural success and clinical success at hospital discharge and at 12 months (optional). A follow-up coronary angiogram at 6 months was recommended.

The patient and lesion characteristics, indications for VBT, type of PCI and VBT performed, in-hospital events, and 6-month clinical and angiographic (if available) follow-up data were recorded. Case report forms were filled out and sent to the data coordinating center; no data monitoring was performed. An event committee evaluated and adjudicated all cases of death, MI, and MACE.

Categorical data are presented as absolute and relative frequencies. For continuous variables, the arithmetic mean ± standard deviations are given as summary measures. The anal-

Table 1. Baseline clinical characteristics

| Characteristic | All patients | ISR* | De novo* | Vein grafts | Native vessels | 60-mm RST* | Pullback* |
|---|---|---|---|---|---|---|---|
| Patients | 1098 | 878 | 188 | 67 | 1031 | 49 | 183 |
| Lesions | 1174 | 929 | 224 | 74 | 1100 | 56 | 208 |
| Mean age (y) | 62.0 ± 10.2 | 62.1 ± 10.4 | 61.2 ± 9.7 | 66.8 ± 9.9 | 61.7 ± 10.1 | 59.5 ± 9.2 | 62.0 ± 10.9 |
| Male gender | 840 (76.5) | 668 (76.1) | 149 (79.3) | 58 (86.6) | 782 (75.8) | 39 (79.6) | 153 (83.6) |
| Diabetes | 256 (23.5) | 209 (24.0) | 36 (19.3) | 21 (31.3) | 235 (23.0) | 9 (18.8) | 41 (22.7) |
| Hypertension | 688 (62.7) | 563 (64.1) | 98 (52.1) | 45 (67.2) | 643 (62.4) | 32 (65.3) | 108 (59.0) |
| Hyperlipidemia | 852 (77.8) | 700 (79.9) | 123 (65.4) | 52 (78.8) | 800 (77.7) | 44 (89.8) | 151 (82.5) |
| Smoking | 170 (15.9) | 118 (13.8) | 45 (24.7) | 6 (9.4) | 164 (16.3) | 10 (20.4) | 31 (17.4) |
| Unstable angina | 271 (26.9) | 203 (24.8) | 54 (32.3) | 26 (41.3) | 245 (25.9) | 14 (30.4) | 43 (26.4) |
| Prior MI | 395 (36.2) | 331 (37.9) | 52 (28.0) | 21 (31.8) | 374 (36.5) | 28 (57.1) | 85 (46.7) |
| Multivessel disease | 548 (50.0) | 433 (49.4) | 100 (53.2) | 62 (92.5) | 486 (47.2) | 28 (57.1) | 109 (59.9) |
| Estimated mean lesion length (mm) | 19.0 ± 11.8 | 19.4 ± 12.3 | 17.4 ± 9.5 | 17.8 ± 14.8 | 19.0 ± 11.6 | 31.0 ± 14.7 | 31.3 ± 18.7 |
| Estimated mean reference diameter (mm) | 3.2 ± 0.5 | 3.2 ± 0.5 | 3.2 ± 0.5 | 3.5 ± 0.62 | 3.2 ± 0.5 | 3.2 ± 0.4 | 3.2 ± 0.6 |
| Target lesion in native vessel | 1104 (94.1) | 876 (94.4) | 210 (93.8) | 4 (5.5) | 1100 (100) | 54 (96.4) | 191 (92.3) |
| Target lesion in bypass graft | 69 (5.9) | 52 (5.6) | 14 (6.3) | 69 (94.5) | 0 (0) | 2 (3.6) | 16 (7.7) |
| De novo lesion | 208 (17.7) | 12 (1.3) | 208 (92) | 14 (19.2) | 194 (17.6) | 10 (17.5) | 50 (24.2) |
| Restenotic lesion | 48 (4.1) | 4 (0.4) | 2 (0.9) | 4 (5.5) | 44 (4.0) | 3 (5.3) | 14 (6.8) |
| In-stent restenosis lesion | 913 (77.7) | 913 (97.6) | 14 (6.2) | 54 (74.0) | 859 (77.9) | 43 (75.4) | 143 (69.1) |

*Abbreviations*: ISR = in-stent restenosis; RST = radiation source train; pullback = multisegmental irradiation; MI = myocardial infarction. Data presented as the number of patients with the percentage in parentheses, unless otherwise noted.

* In at least 1 vessel.

ysis was performed according to the intention-to-treat principle. Multivariate analyses consisted of logistic regression analyses based on the 980 patients treated in a single vessel, with complete data for 17 baseline variables. Automatic backward selection procedures based on maximal likelihood were performed, preserving variables that significantly contributed to prediction ($p < 0.05$). Calculations were performed using Statistical Package for Social Sciences, version 10.0.7.

## RESULTS

The 6-month follow-up data were obtained for 1085 patients (98.8% of all included patients). Of these, 840 (76.5%) were men, and the mean age was 62.0 ± 10.2 years; 271 (26.9%) had unstable angina and 256 (23.5%) were diabetics. The target lesions were in a native vessel in 1104 (94.1%) and in a bypass graft in 69 (5.9%); 208 (17.7%) were *de novo* lesions, 48 (4.1%) restenotic, and 913 (77.7%) in-stent restenotic lesions. The mean estimated reference diameter was 3.2 ± 0.5 mm, and the mean estimated lesion length was 19.0 ± 11.8 mm (Table 1). A new stent was implanted at the time of the VBT procedure in 345 lesions (29.6%): 73.2% of *de novo* lesions and 18.4% of in-stent restenotic lesions (Table 2).

VBT was technically successful in 1114 lesions (95.9%). Clinical sites reported geographic miss in 71 cases (6.1%). A mean radiation dose of 18.8 ± 3.2 Gy was delivered at 2 mm from the source axis using a source train of 30 mm (16.4%), 40 mm (79.1%), or 60 mm (4.3%). A multisegmental irradiation, performing a manual stepping procedure for the longer lesions, was used in 191 procedures (16.3%). The mean dwell time was 3.4 ± 0.5 min, excluding the mutisegmental irradiation. Fractionation due to ischemia was required in 41 procedures (3.5%) (Table 2).

The in-hospital MACE rate was 1.8% (20 of 1098 patients); details are listed in Table 3. At 6 months, after a mean follow-up period of 6.3 ± 2.4 months, 85% of patients experienced improvement of angina and the MACE rate was 18.7% (205 of 1098 patients; Table 4). Angiographic follow-up at 6 months was available for 764 (70.4%) of 1085 patients (Table 4). A combined end point for late (30–180 days) definite or suspected target vessel closure (defined as the sum of angiographic total occlusion at follow-up, MI, and death) was reached in 59 (5.4%) of 1085 patients, but with only 2% of clinical events (death or MI) (Table 4).

In the subgroup analysis, diabetic patients ($n = 256$) had a similar outcome compared with that of nondiabetics ($n = 833$): in-hospital MACE rate 2% vs. 1.8%, 6-month MACE rate

Table 2. Procedure-related parameters

| Parameter | All patients | ISR* | De novo* | Vein grafts | Native vessels | 60-mm RST* | Pullback* |
|---|---|---|---|---|---|---|---|
| Multivessel procedure | 68 (6.2) | 46 (5.3) | 31 (16.5) | 6 (9) | 62 (6) | 7 (14.3) | 22 (12.0) |
| Nominal diameter of largest balloon† (mm) | 3.3 ± 1.0 | 3.3 ± 1.1 | 3.2 ± 0.6 | 4.03 ± 3.77 | 3.22 ± 0.45 | 3.3 ± 0.4 | 3.5 ± 2.3 |
| Atherectomy† | 26 (2.2) | 17 (1.8) | 9 (4.0) | 0 (0) | 26 (2.4) | 3 (5.4) | 5 (2.4) |
| Cutting balloon† | 177 (15.1) | 171 (18.4) | 8 (3.6) | 11 (14.9) | 166 (15.1) | 15 (26.8) | 21 (10.1) |
| New stent implanted† | 345 (29.6) | 170 (18.4) | 164 (73.2) | 24 (33.3) | 321 (29.3) | 20 (35.7) | 90 (44.1) |
| Technical success of VBT† | 1114 (95.9) | 880 (95.7) | 213 (96.4) | 67 (91.8) | 1047 (96.1) | 54 (96.4) | 199 (96.6) |
| Geographic miss† | 71 (6.1) | 55 (6.0) | 16 (7.2) | 4 (5.6) | 67 (6.1) | 2 (3.6) | 11 (5.3) |
| Mean radiation dose at 2 mm (Gy)† | 18.8 ± 3.2 | 19.0 ± 3.1 | 18.1 ± 3.4 | 20.1 ± 3.2 | 18.8 ± 3.1 | 20.7 ± 3.4 | 18.9 ± 3.0 |
| 30-mm source train† | 193 (16.5) | 136 (14.7) | 51 (22.9) | 22 (29.7) | 171 (15.6) | 1 (1.8) | 36 (17.5) |
| 40-mm source train† | 929 (79.3) | 753 (81.1) | 165 (74.0) | 51 (68.9) | 878 (80) | 7 (12.5) | 159 (77.2) |
| 60-mm source train† | 50 (4.3) | 39 (4.2) | 7 (3.1) | 1 (1.4) | 49 (4.5) | 48 (85.7) | 11 (5.3) |
| Pullback maneuver† | 191 (16.3) | 137 (14.8) | 44 (19.6) | 18 (24.3) | 173 (15.8) | 11 (19.6) | 191 (91.8) |
| Fractionated treatment† | 41 (3.5) | 33 (3.6) | 8 (3.6) | 4 (5.4) | 37 (3.4) | 0 (0) | 12 (5.8) |

*Abbreviations*: VBT = intravascular brachytherapy; other abbreviations as in Table 1.
Data presented as the number of lesions, with the percentage in parentheses, unless otherwise noted.
* In at least 1 vessel.
† Results per lesion.

20.3% vs. 18.2%, and late thrombosis rate 6.3% vs. 5.0%. The results in saphenous vein grafts were worse than in native vessels (Table 4).

The MACE rate was lower in patients treated with the 60-mm source train ($n$ = 49) than in those treated with the 30- and 40-mm source trains ($n$ = 1049): 12.2% vs. 19%. The MACE rate was relatively low in patients with in-stent restenosis (17.7%, $n$ = 878) and when a cutting balloon was used (11.1%, $n$ = 171).

In 183 patients, 191 lesions were treated with multisegmental irradiation because of lesion length, performing a manual stepping procedure. The mean estimated lesion length was 31.3 ± 18.7 mm. The mean radiation dwell time was 7.3 ± 1.3 min. The MACE rate was 27.9% vs. 16.8% in the nonmultisegmental irradiated patients.

Angiographic follow-up was performed in 177 of these patients (96.7%). The restenosis and late thrombosis rate were 37.1% and 9.8%, respectively, compared with 21.8% and 4.5% in the nonmultisegmental irradiated patients.

In patients irradiated with a geographic miss, the MACE

Table 3. In-hospital events

| Event | All patients | ISR* | De novo* | Vein grafts | Native vessels | 60-mm RST* | Pullback* |
|---|---|---|---|---|---|---|---|
| Any MACE | 20 (1.8) | 15 (1.7) | 6 (3.2) | 3 (4.5) | 17 (1.6) | 2 (4.1) | 6 (3.3) |
| Death | 3 (0.3) | 3 (0.3) | 1 (0.5) | 2 (3) | 1 (0.1) | 0 (0) | 2 (1.1) |
| MI | 9 (0.8) | 7 (0.8) | 2 (1.1) | 1 (1.5) | 8 (0.8) | 2 (4.1) | 3 (1.6) |
| TVR revascularization | 11 (1.0) | 8 (0.9) | 3 (1.6) | 1 (1.5) | 10 (1.0) | 0 (0) | 2 (1.1) |
| TVR by CABG | 2 (0.2) | 2 (0.2) | 0 (0) | 0 (0) | 2 (0.2) | 0 (0) | 0 (0) |
| TVR by PCI | 9 (0.8) | 6 (0.7) | 3 (1.6) | 1 (1.5) | 8 (0.8) | 0 (0) | 2 (1.1) |

*Abbreviations*: MACE = major adverse cardiac event; TVR = target vessel revascularization; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.
Data presented as the number of patients, with the percentage in parentheses.
* In at least 1 vessel.

Table 4. Clinical and angiographic follow-up

| | All patients | ISR* | De novo* | Vein grafts | Native vessels | 60-mm RST* | Pullback* |
|---|---|---|---|---|---|---|---|
| Any MACE | 205 (18.7) | 155 (17.7) | 47 (25.0) | 18 (26.9) | 187 (18.1) | 6 (12.2) | 51 (27.9) |
| Death (all causes) | 21 (1.9) | 18 (2.1) | 4 (2.1) | 8 (11.9) | 13 (1.3) | 1 (2.0) | 7 (3.8) |
| MI | 28 (2.6) | 21 (2.4) | 5 (2.7) | 2 (3.0) | 26 (2.5) | 2 (4.1) | 5 (2.7) |
| TVR revascularization | 179 (16.3) | 135 (15.4) | 40 (21.3) | 10 (14.9) | 169 (16.4) | 4 (8.2) | 42 (23.0) |
| TVR by CABG | 36 (3.3) | 29 (3.3) | 6 (3.2) | 2 (3.0) | 34 (3.3) | 1 (2.0) | 7 (3.8) |
| TVR by PCI | 146 (13.3) | 108 (12.3) | 34 (18.1) | 9 (13.4) | 137 (13.3) | 3 (6.1) | 36 (19.7) |
| Angiographic follow-up | 764 (70.4) | 602 (70.9) | 138 (79.3) | 41 (67.2) | 723 (72.7) | 32 (66.7) | 135 (76.3) |
| Restenosis (occlusive and non-occlusive) | 185 (24.5) | 141 (23.7) | 39 (28.9) | 13 (32.5) | 172 (24.1) | 5 (16.7) | 49 (37.1) |
| Restenosis (total occlusion) | 43 (5.7) | 32 (5.4) | 8 (5.8) | 3 (7.5) | 40 (5.6) | 1 (3.2) | 17 (12.6) |
| Composite end point late thrombosis | 59 (5.4) | 46 (5.2) | 10 (5.3) | 5 (7.5) | 54 (5.2) | 2 (4.1) | 18 (9.8) |
| Angiographic total occlusion | 42 (3.8) | 32 (3.6) | 8 (4.3) | 3 (4.5) | 39 (3.8) | 1 (2.0) | 17 (9.3) |
| MI | 18 (1.6) | 15 (1.7) | 1 (0.5) | 1 (1.5) | 17 (1.6) | 0 (0) | 1 (0.5) |
| Cardiac death | 4 (0.4) | 3 (0.3) | 1 (0.5) | 1 (1.5) | 3 (0.3) | 1 (2.0) | 1 (0.5) |

Abbreviations as in Tables 1 and 3.
Data presented as the number of patients, with the percentage in parentheses.
* In at least 1 vessel.

rate at 6 months was 19.7% vs. 18.6% in the adequately irradiated patients. The restenosis rate at 6 months, including total occlusions, was 28.8% vs. 24.2% and the late thrombosis rate was 12.9% vs. 4.7%, respectively. Table 5 shows the significant risk factors for MACE derived from the multivariate analysis. The risk of MACE was lower in older patients, in native vessels compared with saphenous vein grafts, in larger vessels, and when a cutting balloon was used for PTCA. The MACE rate was higher in patients with unstable angina, in longer lesions, and after implantation of a new stent. Multisegmental irradiation and geographic miss were not significant risk factors for MACE. For late thrombosis, the significant risk factors derived from the multivariate analysis are listed in Table 6. The risk in slightly decreasing with increasing age, is much higher in patients with an initial chronic total occlusion of the target lesion and in the case of a geographical miss. There was a strong trend toward a higher risk of thrombosis for patients in whom a new stent was implanted at the time of brachytherapy. Multisegmental irradiation did not increase the risk of late thrombosis.

Table 5. Multivariate predictors of MACE during follow-up

| Risk factor | *p* | Odds ratio | 95% Confidence interval |
|---|---|---|---|
| Age (1-yr older) | 0.03 | 0.98 | 0.981–0.998 |
| Balloon diameter (1-mm larger) | 0.01 | 0.61 | 0.41–0.90 |
| Cutting balloon use | 0.02 | 0.49 | 0.27–0.88 |
| Native vessel (not SVG) | 0.02 | 0.45 | 0.23–0.87 |
| Lesion length (1 mm longer) | 0.01 | 1.02 | 1.005–1.032 |
| New stent implanted | 0.009 | 1.61 | 1.13–2.29 |
| Unstable angina | 0.01 | 1.63 | 1.13–2.36 |

*Abbreviations*: MACE = major adverse cardiac event; SVG = saphenous vein graft.

A lack of procedural success was reported in 48 lesions (4.1%). In 28 cases (2.6%), the cause of failure was related to VBT: ischemia due to obstruction of coronary flow by the delivery catheter ($n$ = 3), inadequately functioning transfer device ($n$ = 5), catheter failure ($n$ = 14), unable to cross the lesion ($n$ = 4), arrhythmia ($n$ = 1), and unknown ($n$ = 1). In 20 lesions (1.8%), the PTCA result was not satisfactory, but VBT was successfully delivered.

## DISCUSSION

This study is the largest registry of consecutive patients with coronary artery disease treated with VBT. All patients treated in Europe during the registry period between April 1999 and September 2000 with the Novoste Beta-Cath System were registered.

Table 6. Multivariate predictors of late thrombosis during follow-up

| Risk factor | *p* | Odds ratio | 95% Confidence interval |
|---|---|---|---|
| Age (1-yr older) | 0.010 | 0.97 | 0.94–0.99 |
| Initial CTO target | 0.003 | 2.66 | 1.38–5.14 |
| Geographic miss | 0.010 | 2.80 | 1.23–6.35 |
| New stent | 0.051 | | |

*Abbreviation*: CTO = chronic total occlusion.

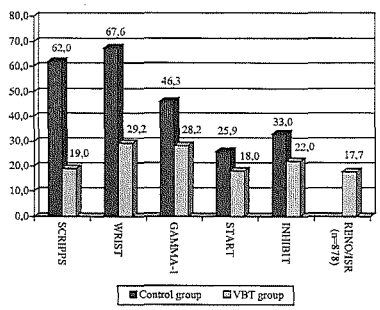


Fig. 1. Comparison of MACE rates (6–12 months) in randomized clinical VBT trials and RENO for in-stent restenosis. Inclusion and exclusion criteria were different among the various trials. MACE rate reported after a follow-up time varying from 6 to 12 months, depending on the trial.

Treatment was to be performed according to the good clinical practice of each participating center. This registry included patients with a high risk of restenosis, considering the prevalence of different risk factors, such as smoking, diabetes, hypertension, hyperlipidemia, and restenosis. Most patients (77.7%) were treated for in-stent restenosis. The 6-month clinical follow-up rate was extremely high (98.8%). The angiographic follow-up was similarly high and was obtained in 70.4% of patients, even though it was optional in this registry.

All trials, whether of $\beta$- or $\gamma$-radiation, demonstrated a benefit of radiation in patients with in-stent restenosis (9, 12, 13, 15, 16). In the SCRIPPS and GAMMA-I trials, the reduction in the restenosis rate was more important in the diabetic patients. The same trend was seen for diabetic patients in the subgroup analysis of RENO, with rates of 1.9% death, 2.6% acute MI, and 16.6% target vessel revascularization at 6 months. The 18.7% MACE rate at 6 months (17.7% for in-stent restenosis) compares favorably with the results of major randomized clinical trials for in-stent restenosis using either $\gamma$- or $\beta$-radiation (Fig. 1).

As expected, the MACE rate and restenosis rate were higher in vein grafts than in native vessels. In a recent randomized trial (17), the benefit of $\gamma$-radiation for in-stent restenosis in bypass grafts was demonstrated. Compared with the restenosis rate of 21% in the irradiated group after 6 months, the 32.5% rate obtained in RENO is rather disappointing.

The positive trends in the subgroup analysis also suggested a clinical benefit when longer source trains are used or when using a cutting balloon. These are available in a length of 10 or 15 mm, and it is assumed that their injury length is shorter than with a conventional angioplasty balloon of the same length, because they are anchored by the blades and do not slide during inflation, decreasing the risk of a geographic miss.

The geographic miss was site reported without using a standard protocol and therefore probably was underestimated. This may explain why no influence of geographic miss on the MACE rate could be demonstrated. The results could probably be improved further by irradiating with wider margins. In the current registry, a proximal and distal margin of 5 mm beyond the injured area was recommended. Taking into account that the PTCA injury exceeds the physical balloon length, the 50% dose falloff over the last seed (2.5 mm) of the source train, and the position uncertainty of the source (lack of landmarks and heart movement) (18), a 7.5–10-mm margin would be required to deliver the prescribed dose adequately to the whole injured length (19). In the Stents and Radiation Therapy 40 trial, the use of longer source trains, resulting in wider margins, reduced the incidence of edge restenosis and geographic miss compared with the initial Stents and Radiation Therapy trial. As determined by quantitative angiography, 46% had evidence of geographic miss. The restenosis rate among those patients was 32% compared with 18% for those whose injury length fell within the 90% isodose distribution ($p = 0.04$) (20).

According to the 6-month results, the multisegmental irradiation technique, although technically not satisfactory (21), can be performed safely with the Novoste Beta-Cath System. The follow-up events were acceptable, considering the lesion length and the high incidence of in-stent restenosis in the baseline population.

From this registry, no conclusions can be drawn concerning the radiation dose. The only dose-finding trial ever performed in coronary VBT was based on a $^{90}Y$ source wire and a centering delivery catheter, with a different dose prescription point. That trial showed a clear dose–response relationship (22). The dose prescription in this registry and in other trials using the Novoste Beta-Cath System was relatively low compared with trials using other radiation devices; however, because they demonstrated similar clinical results, the therapeutic window may be wide and there may be some gain in delivering a higher dose. The exact attenuation by stent struts is unknown; sparse data in literature vary between 10% and 15% (23–26). To simplify the dose calculation, a fixed dose of 2.3 Gy was recommended in the protocol, which means a 10–14% increase of the dose to compensate for the stent. This seems acceptable, taking into account the results of the published dosimetry studies. The question of adapting the dose prescription to the degree of calcification of the vessel wall has never been addressed in a clinical trial.

VBT was technically successful in 95.9% of lesions, and the in-hospital MACE rate was only 1.8%. Because of the low radiation hazard using $\beta$-radiation emitting isotopes, the personnel can remain in the cath-laboratory during the radiation procedure. It seems fair to conclude that coronary brachytherapy with $\beta$-radiation using a $^{90}Sr/^{90}Y$ source train is feasible and safe.

This registry recommended antiplatelet therapy for at least 3 months (aspirin with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily). Because late thrombosis was defined as a composite end point of angiographic total occlusion, any acute MI, or death, 5.4% was probably an overestimation; the clinically related events were low (0.4% death and 1.6% MI). Implantation of a new stent is not a significant risk factor for late thrombosis, although multi-

variate analysis showed a strong trend. A higher rate of late thrombosis after brachytherapy has also been reported in other trials (27), especially when a new stent was implanted at the time of brachytherapy. Antiplatelet therapy is now generally prescribed for at least 6 months, and more often 12 months.

This registry has certain limitations. No core laboratory was involved to analyze the fluoroscopic images of treatment procedure and follow-up. No accurate measurements were performed to assess any geographic miss. Additional treatment after irradiation was not registered. The late thrombosis rate could have been overestimated, because it was defined as a composite end point of angiographic total occlusion, any acute MI, or death.

The data derived from this largest cohort of unselected consecutive patients treated with VBT in the coronary arteries suggest that the excellent results of recent randomized, controlled, clinical trials, including patients with in-stent restenosis, can be replicated in "routine clinical practice." The results can probably be improved by using wider margins. The optimal radiation dose is still unknown but should be the subject of additional investigation.

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Appendix 1. Organization of the registry

| | |
|---|---|
| Steering Committee: | P. Urban (principal investigator)<br>A. Gerschlick<br>R. Bonan<br>D. Baumgart<br>A. Zeiher<br>R. Schilcher<br>L. Verhees |
| Data Coordination Center: | Wegscheider, Biometrie und Statistik GmbH, Berlin, Germany |
| Sponsor: | Novoste Europe SA/NV |

Appendix 2. List of participating centers

| Participating centers | Interventional Cardiologist | Radiation Oncologist |
|---|---|---|
| Lausanne, C.H.U.V. | Eeckhout | Coucke |
| Antwerp, UZA | Vrints | De Bal |
| Aalst, OLV | Wijns | Verbeke |
| Brussels, St Jean | Vandormael | Burette |
| Brussels, St Luc | Debbas | Scalliet |
| Dresden, Weisser Hirsch | Dörr | Herrmann |
| Eindhoven, Catharina | Bonnier | Schmeets |
| Hasselt, Virga Jesse | Benit | Brosens |
| Milan, Columbus | Colombo | Orecchia |
| München, Professor Silber | Silber | von Rottkay |
| Rotterdam, Thoraxcenter | Serruys | Levendag/Coen |
| Antalya, Akdeniz UH | Sancaktar | Garipagaoglu |
| Haifa, Rambam | Beyar | Rosenblatt |
| Tel Aviv, Ichilov | Miller | Ron |
| Mont Godinne UCL | Gurné | Vandeput |
| Erlangen, Universitätsklinikum | Ludwig | Strnad |
| Chemnitz, Herzzentrum | Kleinertz | Schubert |
| Hamburg, UKE | Brockhoff | Krüll |
| München, Klinikum Innenstadt | Klaus | Pöllinger |
| Dortmund, St. Johannes | Heuer | Donsbach |
| Glenfield General Hospital | Gershlick | Benghiat |
| Berlin, Charité Mitte | Rutsch | Buchali/Matnjani |
| Jerusalem, Shaari Zedek | Meerkin | Hayne |
| Essen, Universitätsklinikum | Baumgart | Sauerwein |
| Århus, Skejby | Thuesen | Overgaard |
| Kayseri, Erciyes | Basar | Karahacyoglu |
| Lübeck, Universitätsklinikum | Katus | Feyerabend |
| Bad Oeynhausen, Herzzentrum | Wiemer | Lindner |
| Hamburg, St Georg | Küchler | Ehnert |
| Kaiserslautern, Westpfalz-Klinikum | Glunz | Herbig |
| Aachen, Universitätsklinikum | vom Dahl | Schubert |
| Berlin, Benjamin Franklin | Schultheiss | Hinkelbein |
| Bochum, St. Joseph | Mügge | Kißler |
| Athens, Onassis | Voudris | Efstathopoulos |
| Varese, Circulo | Verna | Novario/Bianchi |
| Frankfurt, UNI | Auch-Schwelk | Schopohl |
| Nijmegen Acad. Ziekenhuis | Aengevaeren | Pop |
| Bochum, Augusta Krankenhaus | Altmaier | Dürscheidt |
| Vienna, AKH | Glogar | Pötter/Pokrajac |
| Milano, Humanitas | Presbitero | Orecchia |
| Potsdam, Ernst von Bergmann | Ohlmeier | Koch |
| Ioaninna University | Michalis | Tsekeris |
| Barcelona Clinico | Serra | Penaranda |
| London, King's College | Thomas | Calman |
| Hamburg, Mathey-Schofer | Schofer | Thelen |
| Saarbrücken, Klinikum | Görge | Treitz |

# PART II

## Role of intravascular ultrasound.

# CHAPTER 4

The role of intravascular ultrasound imaging in vascular brachytherapy.

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# The role of intravascular ultrasound imaging in vascular brachytherapy

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**Intracoronary brachytherapy has recently emerged as a new therapy to prevent restenosis. Initial experimental work was achieved in animal models and the results were assessed by histomorphometry. Initial clinical trials used angiography to guide dosimetry and to assess efficacy. Intravascular ultrasound (IVUS) permits tomographic examination of the vessel wall, elucidating the true morphology of the lumen and transmural components, which cannot be investigated on the lumenogram obtained by angiography.**

**This paper reviews the use of IVUS in the clinical studies of brachytherapy conducted to date. IVUS allows clinicians to make a thorough assessment of the remodeling of the vessel and appears to have a major role to play in facilitating understanding of the underlying mechanisms of action in this emerging field. The authors propose that state-of-the-art IVUS techniques should be employed to further knowledge of the mechanisms of action of brachytherapy in atherosclerotic human coronary arteries.** (Int J Cardiovasc Intervent 2000; 3: 3–12)

**Keywords:** brachytherapy – intravascular ultrasound – restenosis

## Introduction

On the verge of an exponential increase of the use of brachytherapy in interventional cardiology, it is appropriate to keep in mind that this new therapeutic modality is still in its infancy. The first case of brachytherapy was initiated in Europe as recently as 1992 by Liermann et al, in patients who had undergone a femoral percutaneous angioplasty.[1] Since radiotherapy has proven to be effective in treating the exuberant fibroblastic activity of keloid scar formation and other nonmalignant benign processes such as ocular pterygia,[2,3] it has been assumed that this adjunctive treatment could inhibit restenosis. Mechanisms involved in the restenosis process are elastic recoil of the artery, local thrombus formation, vascular remodeling with shrinkage of the vessel and an exuberant healing process with neointimal cellular proliferation and matrix synthesis.[4–6] Stent implantation minimizes elastic recoil and remodeling of vessels, but exacerbates the normal proliferative reaction in response to the traumatizing intervention.[7,8] Depending on the type of lesions treated, a significant restenosis rate of 15–50% remains the major hindrance to the success of stent therapy and is mainly caused by this exacerbated proliferative reaction.

Clinical coronary applications of brachytherapy were carried out after the experimental work achieved mainly in the United States by Wiedermann et al in New York,[9] Waksman et al in Atlanta[10] and Mazur et al in Houston.[11] They demonstrated a reduction of intimal hyperplasia in swine models of restenosis, initially using γ-radiation ($^{192}$Ir) and thereafter ß-sources.[12] In parallel, Verin et al in Geneva conducted experimental studies with the pure ß-emitter $^{90}$Y in carotid and iliac arteries of rabbits.[13] Concomitantly, Hehrlein et al demonstrated a marked reduction of neointima formation in rabbits with low-dose radioactive stents,[14] while Carter showed that the dose response of a ß-particle-emitting radioactive stent in a porcine coronary restenosis model was actually complex, presenting a bell-shape.[15] These groups provided compelling experimental evidence of efficacy of brachytherapy in the prevention of restenosis. In these studies, the short- and long-term results were evaluated by histomorphometry,

measuring the amount of neointima formation after balloon overstretch injury.

The objective of this review is to emphasize the potential of intravascular ultrasound (IVUS) imaging in guiding dose prescription, in assessing the results of brachytherapy in clinical trials as a surrogate of histomorphometry and in reviewing the different modalities which have been implemented so far.

## Intravascular ultrasound

### An update on its value in predicting restenosis

Coronary interventions depend mainly on imaging techniques as the source of guidance. Angiography alone provides a good representation of the complete coronary anatomy but a relatively poor image of the diseased vessel wall. Angiograms that are difficult to interpret are frequently encountered. These include images of ostial lesions, tortuous vessel segments, vessel overlap, intermediate lesions, dissections and thrombus. Although the value of angiography remains unquestioned, radiographic imaging depicts a two-dimensional silhouette of the arterial lumen. This 'lumenogram' is a limited standard on which to base therapeutic decisions.[16] Angiography demonstrates only lumen narrowing well, but is inherently limited in defining the distribution and extent of wall disease. Furthermore, angiography is insensitive to early atheromatous thickening of the arterial wall, partly owing to vascular remodeling that allows plaque to grow to occupy an average of 40% of the vessel cross-section before luminal encroachment occurs.[17] Plaque burden in reference segments that are considered angiographically normal can reach on average 35-40%.[18]

In the late Eighties, IVUS emerged as a promising imaging modality with which to assess vascular disease.[19] IVUS provides real-time tomographic images of vessel wall cross-sections, elucidating the true morphology of the lumen and transmural components of atherosclerotic arteries. The field of intravascular ultrasound imaging has led to improvements in the understanding of atherosclerotic disease and its response to various therapeutic interventions. However, a main thrust of this technique is the guidance of therapeutic interventions, and controversial data exist in the literature on the value of postintervention IVUS parameters to predict the restenosis rate. For percutaneous transluminal coronary angioplasty (PTCA), no criteria were found in the PICTURE study including 200 patients,[20] whereas Mintz et al found that the residual plaque burden measured with IVUS was an independent predictor of restenosis.[6] The final report of the GUIDE trial that showed the predictive value of IVUS plaque area and minimal lumen cross-section is still pending.[21] On the other hand, it has been demonstrated that, based on IVUS, it was safe to increase the nominal balloon-to-artery ratio.[22] A low rate (14 %) of clinical events at one year has been reported in a single-center nonrandomized study of 252 patients where the balloon sizes were based on the external elastic membrane diameters.[23] For stenting, a very recent combined analysis from three registries (MUSIC, WEST-II, ESSEX) and two randomized stent restenosis trials (ERASER and TRAPIST) ($n$ = 800 patients) has demonstrated that the IVUS criteria minimum lumen cross-sectional area (MLCSA), mean in-stent lumen area, stent length and lumen diameter were predictors of six-month in-stent restenosis, defined as luminal diameter stenosis >50% by quantitative angiography (QCA),[24] in agreement with other reports which demonstrated also the predictive value of an ostial lesion location and the preinterventional and residual lesion site plaque burden.[25-28] Finally, it remains also controversial whether IVUS guidance may decrease in-stent restenosis and improve event-free survival after an intervention.[29] In a study matching patients between two centers, one performing IVUS guidance, the other using only angiography, there was a significant decrease of the restenosis rate (9.2% versus 22.3%) at an early stage where the IVUS criteria implied aggressive dilatation using oversized balloons.[30] However, this led to a high incidence of vessel ruptures. IVUS criteria were modified, the balloon-artery ratio used was decreased to achieve a stent cross-sectional area (CSA) equal to or greater than the distal lumen CSA, and no further difference in the outcome of the patients was found between the angiographic and IVUS guidance groups.

IVUS guidance improved the minimal CSA in the stent at the end of the intervention in the MUSIC trial, and comparison of angiographic data with earlier studies demonstrated that the improvement of this minimal lumen diameter (MLD) (2.9 mm versus 2.5 mm) was associated with a lower restenosis rate (9.7% versus 20% respectively for the MUSIC and Benestent I).[31,32] When the IVUS criteria for optimal stent expansion are met, the restenosis rate is lower.[33] However, these criteria cannot be met in all patients, and the results of two randomized trials (RESIST and OPTICUS) comparing IVUS with angiographic guidance today show no difference in clinical and angiographic outcome at six-month follow-up.[34,35]

On the other hand, it has been demonstrated that the rate of target vessel revascularization in the randomized CRUISE trial was reduced from 15.3% to 8.5% ($P < 0.05$) in the arm with IVUS-guided stent implantation. The results of AVID, a large multicentre and randomized study including 800 patients, were recently revealed by Dr Russo at the TCT'99 meeting. IVUS was used in one arm to document the results of a stent implantation, and in the other arm to guide optimal stent implantation using the following criteria: (i) full apposition of stent struts; (ii) MLCSA >90% of the distal vessel CSA; and (iii) absence of major dissection. In the IVUS-guided arm, 42% of the patients required additional treatment. This led to a mean increase of the MLD of 0.3 mm and of the MLCSA of 1.27 mm$^2$ (+20.3%). At 12-month follow-up, the primary end-point (target lesion revascularization, TLR) was 12.4% in the IVUS-documented arm, and 8.4% in the IVUS-guided arm. This difference did not reach statistical significance ($P$ = 0.08). However, in subgroups, a strong benefit of IVUS guidance could be demonstrated, for example when treat-

ing saphenous bypass lesions (TLR 20.8 versus 5.1%; $P < 0.01$).

A major limitation of these studies is that there is no comparison between quantitative IVUS and quantitative angiographic guidance: only visual assessment of the angiographic results was carried out. Recently, the concordance between physiological (fractional myocardial flow reserve: FFRmyo), IVUS and QCA data has been reported. The best agreement was found between IVUS and FFRmyo, with a concordance rate of 91%. The concordance rate between QCA and IVUS was only 48%.[36]

Brachytherapy might be the ideal field in which to apply the unique characteristics of IVUS.[37] Indeed, with its potential for tomographic imaging of the complete arterial wall and quantification of different structures such as the volume of plaque or in-stent hyperplasia, IVUS might fill the gap between the experimental knowledge acquired from histology and the results of ongoing clinical studies.

### IVUS imaging

IVUS imaging is usually performed before an intervention, or after the placement of a stent, and the interpretation is based on the successive cross-sections obtained when moving the transducer manually. A comprehensive review of the clinical use of IVUS has recently been published by the study group of intracoronary imaging of the European Society of Cardiology.[38] A natural extension to cross-sectional ultrasound imaging is three-dimensional (3D) imaging. To obtain a 3D survey of the vessel, ultrasound images are acquired during the 'pull back' of the imaging catheter (20–30 frames per second). Typical velocity of the pull-back ranges from 0.5 to 1 mm/s. The sequence of images contains 3D information that can be presented in various ways. A common form of presentation is the longitudinal or sagital view, which shows one of the image planes perpendicular to the set of cross-sectional images. Since during the pull-back there is motion because of the movement of the heart, longitudinal scans may have a jagged appearance. Although this artifact does not impede the understanding of the vessel structure, the use of ECG-triggered pull-backs improves the reconstruction.[39] Recently, the fusion of biplane angiography and IVUS images has been described for true 3-D reconstruction of coronary segments for computation of parameters such as wall shear stress.[40]

### Dosimetry evaluation from IVUS

Assuming that the catheter containing the radioactive source is lying in the same position as the IVUS catheter, it is possible to measure the distance from the source to any vascular structure in one cross-sectional image, and to construct isodose plots when the activity and physical characteristics (dose fall-off with distance) of the source are known.[41] This is illustrated in Figure 1. Isodoses may also be superimposed on the sagital view of the pull-back. However, the evaluation of the overall dosimetry in the arterial wall from successive cross-sectional images is difficult. Dose–volume histograms (DVH) have been introduced in radiotherapy to condense the large body of information of the complete 3-D dose distribution data into a plot summarizing graphically the radiation distribution throughout the target volume and the anatomical structures of interest.[42,43] The present authors recently described the methodology for computing DVH for coronary brachytherapy from 3-D IVUS data[44] and the clinical applications will be illustrated in the review of the clinical trials which follows.

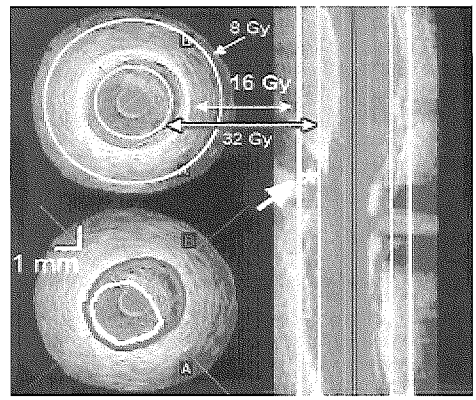


Figure 1
Lower left panel: a typical intravascular ultrasound (IVUS) cross-section demonstrating a mixed plaque from 11 to 5 o' clock, and highlighted luminal (in red) and external elastic lamina (EEL) (in green) contours. Upper left panel: isodoses of 8, 16 and 32 Gy corresponding to a $^{90}Sr$ β-source are superimposed on the IVUS $^{90}Sr/Y$. Right panel: longitudinal reconstruction of a 30 mm segment of a patient included in the BERT trial, acquired with an ECG-triggered pull-back device. The position of a side-branch is indicated by the arrow. The 32 and 16 Gy isodoses permit a quick evaluation of the dose delivered to the target, the adventitia, limited by the EEL.

## Overview of the use of IVUS in clinical brachytherapy trials

### The Venezuelan experience

Condado and colleagues in Venezuela introduced brachytherapy in human coronary arteries using a hand-delivered $^{192}Ir$ wire into a non-centered closed-end lumen catheter.[45] They explored the feasibility and safety of this approach in 22 lesions in 21 patients. The doses were prescribed at 1.5 mm from the source (single doses of 18 Gy, $n = 1$; 20 Gy, $n = 11$; 25 Gy, $n = 9$) using angiographic assessment. Although reported as positive, an unexplained early reduction of the minimal lumen diameter of 0.45 mm on average after only 24 hours might have blurred the real efficacy of the applied radiotherapy in these patients[37]

who presented no additional loss in MLD between 24 hours and six-month follow-up. However, doses of up to 92.5 Gy could have been delivered to the lumen wall because of the non-centered device.[37] This may well be over the vascular tolerance limits. Such a high dose could explain the observation that two patients experienced early total vessel occlusion, and four others developed an aneurysm at two-year follow-up. IVUS guidance could have stressed cases with over-dosage administration.

## The Geneva trial

In Geneva, Verin et al employed ß-irradiation in human coronary arteries using a radioactive wire ($^{90}Y$) in a centering balloon device.[46] The dose prescribed was 18 Gy at the surface of the balloon corresponding to the vessel luminal surface. No IVUS assessment was performed. The findings were disappointing, with a restenosis rate of 40% among the 15 studied patients. A retrospective analysis of the dose prescribed revealed that at a depth of 2 mm in the vessel wall, the dose was only ~2.7 Gy, probably below the nominal effective dose against the proliferating cells involved in the post-angioplasty restenosis process.[47]

## The SCRIPPS study

Shortly after Condado, Teirstein et al started to treat restenosis lesions with γ-therapy in a randomized placebo-controlled study. They demonstrated a substantial reduction of the angiographic restenosis rate (17% versus 54%) among 55 patients presenting with in-stent restenosis.[48] The recently published two-year follow-up data demonstrate the long-term efficacy of this new therapeutic modality: the target-lesion revascularization was significantly lower in the $^{192}Ir$ group (15.4% versus 44.8%; $P < 0.01$). Non-target-lesion revascularization was similar in the two groups (19.2% versus 20.7%). The composite end-point of death, myocardial infarction or target-lesion revascularization was significantly lower in $^{192}Ir$-treated versus placebo-treated patients (23.1% versus 51.7%; $P = 0.03$).[49]

A sealed $^{192}Ir$ γ-source in a non-centered catheter was used (Best Medical/Cordis Corp, Warren, NJ, USA). This study was the first where the dosimetry was based on IVUS measurements. A series of tomographic IVUS images were obtained with a motorized pull-back apparatus. The distance between the center of the ultrasound catheter (supposed equivalent to the source position) and the adventitial border (the target) was measured every 1 mm along the stented segment. As illustrated in Figure 2, the aim was to adjust the dwell time to administer 8 Gy to the target farthest from the source (A), provided that no more than 30 Gy was delivered to the closest target (B). The importance of IVUS has been clearly demonstrated in a retrospective subgroup analysis.[50] Late luminal loss and loss index were calculated for patients with diabetes, in-stent restenosis or minimum dose exposure of the target of 8.00 Gy. Two-factor analysis of variance was used to test for an interaction between patient characteristics and treatment effect. In the treated group ($^{192}Ir$), late loss was particularly low in patients with diabetes (0.19 versus 0.46 mm), in-stent restenosis (0.17 versus 1.02 mm) and also in patients who received a minimum radiation dose to the entire adventitial border of at least 8.00 Gy (0.06 versus 0.92). The loss index in this subgroup was 0.03. The two-factor analysis of variance demonstrated a significant interaction between treatment effect (late loss) and the subgroup characteristic of receiving a minimum dose of 8.00 Gy to the adventitial border ($P = 0.009$). This illustrates the usefulness of IVUS in clarifying results of a brachytherapy trial.

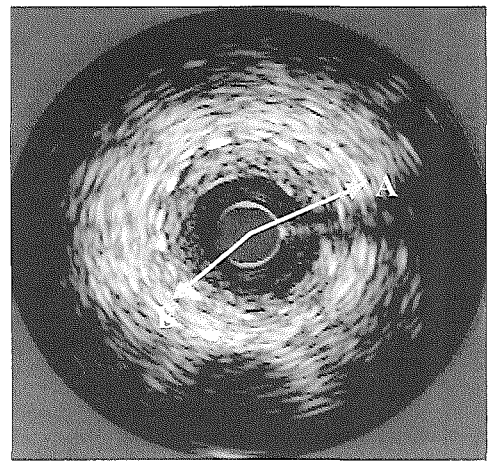


Figure 2
In the SCRIPPS study, IVUS was used in order to administer at least 8 Gy to the target (external elastic lamina) farthest from the source (A), provided that no more than 30 Gy was delivered to the closest target (B).

## The WRIST trials

The series of WRIST (Washington Radiation for In-Stent Restenosis) trials addressed different issues: native or saphenous (SVG) bypass in-stent restenosis, long lesions, ß- or γ-sources. They were initiated with a gamma ribbon source ($^{192}Ir$) or placebo ribbon. Dosage prescribed was 15 Gy at 2 mm from the source in vessels of 2.0–4.0 mm in diameter and at 2.4 mm for vessels >4.0 mm in diameter. The data recently presented for 130 patients (100 native, 30 SVG) have confirmed the efficacy of brachytherapy: the angiographic restenosis rate was significantly lower (19% versus 58%; $P < 0.001$) as were mortality, myocardial infarction and repeat target lesion revascularization combined end-points (29% versus 68%).[51]

In this series, IVUS was not used for dosage prescription, but was performed systematically after irradiation and at six-month follow-up for off-line analysis. From

these measurements, it could be demonstrated that the volume of intimal hyperplasia increased by 60 $mm^3$ in the placebo group, but that in the treated group it was only 2 $mm^3$, with patients even demonstrating a melting of the residual intimal hyperplasia left at the time of the procedure. IVUS was also useful for estimating the minimum and maximum dose administered to the lumen border (7.3 Gy and 45 Gy, respectively).

Initially performed with a γ-source, the expanding WRIST series has recently investigated ß-radiation (with the $^{90}Y$ source of the Boston Scientific brachytherapy system) for in-stent restenosis (beta-WRIST). With this system, which incorporates a balloon to center the source in the artery, 20.6 Gy was prescribed at 1 mm from the surface of the balloon. The preliminary results recently presented of the first 49 patients with six-month follow-up demonstrated a similar efficacy of ß-radiotherapy for in-stent restenotic lesions, with a 50% reduction in major adverse cardiac events, compared with historical controls from the γ-WRIST.[52]

## The BERT trial

The Beta Energy Restenosis Trial (BERT) was initially conducted in the United States. This study was designed to evaluate the feasibility and safety of the delivery of 12–16 Gy with a $^{90}Sr/Y$ source after balloon angioplasty of de novo lesions. A special device (Beta-Cath, Novoste Corp, Norcross, GA, USA) consisting of a hand-held hydraulic delivery system was used to send 12 encapsulated sources in a 5.4 F. catheter lying across the target lesion (total irradiated length: 30 mm). The results of the American arm in which delivery of ß-radiation was attempted in 23 patients were obtained with neither IVUS guidance nor IVUS documentation. A late loss of 0.05 mm, a late loss index of 4% and a restenosis rate of 15% were lower than in previous restenosis trials using similar angiographic methods.[53] In the Canadian arm initiated later, the 30 patients included were systematically documented by IVUS. QCA data were similar, and the IVUS findings after six-month follow-up were very recently reported[54]: there was no significant change in lumen area (5.7 ± 1.7 $mm^2$ post-treatment, 6.0 ± 2.6 $mm^2$ at follow-up), nor in external elastic lamina (EEL) area (13.7 ± 4.5 $mm^2$ post-treatment to 14.2 ± 4.7 $mm^2$). With these IVUS findings, it was suggested that ß-radiation inhibit neointima formation with no reduction of total vessel area at six-month follow-up. The authors' findings discussed in the following section, and based on 3-D ECG-triggered IVUS assessment of the treated area, are more in favor of an adaptative remodeling with an increase of the vessel size (EEL) and plaque.

## The Thoraxcenter experience

One of the first IVUS scanners was developed in the authors' institution.[55] IVUS is performed routinely and systematically in studies evaluating new antirestenotic strategies, even when it is not mandatory for the trial.

Three-dimensional image reconstruction and analysis systems have been introduced that can be used for complete quantitative analysis of IVUS images.[56–59] However, image artifacts that result from cyclic changes in coronary dimensions and from the movement of the IVUS catheter in the arterial lumen limit the accuracy of the 3-D boundary detection systems.[60] This led to the development of a new approach. In order to limit cyclic movement artifacts, an ECG-gated image acquisition workstation is employed which controls a dedicated pull-back device. The complete 3-D dataset of the coordinates of the automatically detected lumen (corresponding to the highly echogenic blood–vessel interface) and of the echogenic media–adventitia interface (EEL) over the complete length of the treated area can be used to study the change between baseline and six-month follow-up of lumen, plaque and vessel volumes. Dosimetry evaluation at the time of the iradiation is then feasible, when considering the source in the same position as the IVUS catheter.[44]

Analyzing 21 patients consecutively included in the European arm of BERT in the authors' institution, Sabate et al have recently demonstrated that over the 30 mm of the irradiated segments with the Beta-Cath delivery system, mean EEL and plaque volumes increased significantly (from $451 \pm 128$ $mm^3$ to $490 \pm 159 mm^3$ and from $201 \pm 59$ $mm^3$ to $242 \pm 74$ $mm^3$; $P = 0.01$ and $P = 0.001$, respectively), whereas luminal volume remained unchanged.[61] On the other hand, edges of the treated segments presented an increase in mean plaque volume with no net change in EEL, resulting in a decrease in mean luminal volume. This very meticulously conducted 3-D analysis could assess subtle changes in the remodeling of human irradiated coronary arteries. This would otherwise have only been possible in an animal study with serial histomorphometric assessment. Analyzing a total of 206 coronary subsegments of 2 mm lying in the treated area, it was possible to demonstrate that the independent predictors of the plaque volume at follow-up were the plaque volume post-treatment, the type of plaque and the minimal dose absorbed by 90% of the adventitial volume (DV90adv).[62]

From the 3-D IVUS dataset, it has been also possible to compute DVH to describe the cumulative distribution of dose over three specific volumes: at the level of the luminal surface, the EEL, and in the volume encompassed between the luminal surface and the EEL (plaque + media). On average, DVH derived from the authors' BERT cases demonstrate that the minimal dose in 90% of the adventitial volume (defined with a thickness of 0.5 mm from the EEL) was 37 ± 16 % of the prescribed dose; the minimal dose in 90% of the plaque + media volume was 58 ± 24% and of the luminal surface volume was 67 ± 31%. The minimal dose in the 10% most exposed luminal surface volume was 296 ± 42%.[63] Simulations of the use of a γ-emitter and/or a radioactive source train centered in the lumen have also been evaluated, with a comparison of the homogeneity of the dose distribution. A typical DVH is illustrated in Figure 3.

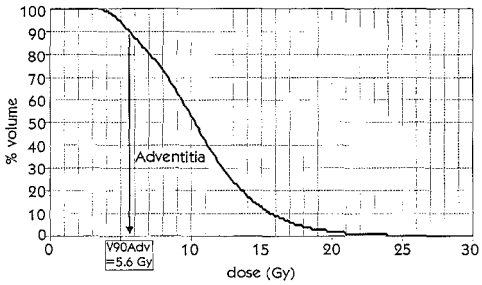


Figure 3
Example of the integral dose-volume histogram at the adventitia level of the patient illustrated in Figure 1, representing the fraction of volume (y-axis: % volume) receiving greater than or equal to a specific dose (x-axis: dose (Gy)). For this patient, 90% of the target volume for coronary brachytherapy, believed to be the adventitia, receives a dose of at least 5.6 Gy.

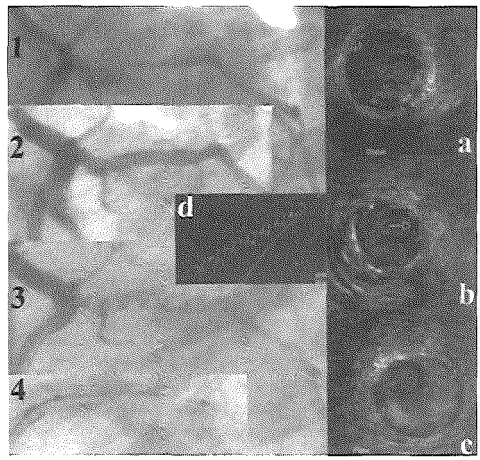


Figure 4
Panel 1 shows the lesion in the circumflex artery of a patient included in the PREVENT trial in the authors' institution. After stent implantation (panel 2), the helical balloon (panel d) used to maintain the $^{32}P$ wire in the center of the lumen permits the preservation of distal perfusion (panel 3). Its size was chosen using the IVUS stent diameter measured in panel b (3 mm). The dwelling time of the source (seen in panel 4) is calculated in order to give 16, 20 or 24 Gy at 2 mm in the vessel wall. The size of the vessel is calculated as the average of the distal (panel a) and proximal (panel c) intravascular ultrasound vessel size dimensions.

## Ongoing trials

There is a series of ongoing trials, recently reviewed by Waksman,[64] that is soon expected to shed light on the utility of brachytherapy for prevention of restenosis. Modalities of IVUS as used in these trials are very different. In PREVENT, conducted with a $^{32}P$ ß-source delivered with an automatic afterloader (Galileo™, Guidant Corp, Houston, TX, USA), the radioactive wire is centered in the target lesion (de novo or in-stent restenosis) in a helical balloon which preserves distal perfusion (Figure 4). The size of this balloon is based on the coronary dimensions derived from IVUS measurements at the minimal cross-sectional area in the lesion. Proximal and distal reference segments are measured to estimate the mean vessel diameter. This measurement is used to prescribe a dose of 16, 20 or 24 Gy at 2 mm in the vessel wall.

In GAMMA-I, a $^{192}Ir$ source or a placebo was manually delivered following successful treatment for in-stent restenosis in 252 patients. A dose greater than 8 Gy but less than 30 Gy was administered to the EEL, with a similar IVUS guidance to that used in the SCRIPPS trial. The angiographic outcome recently reported was a reduction at six-month follow-up of the angiographic restenosis rate from 52% for the placebo group to 21.6% for the irradiated group.

In the ARREST trial investigating the restenosis rate after PTCA and provisional stenting, a mechanical delivery of a $^{192}Ir$ source in a partially centering balloon (3.2 F.) is used. A dose greater than 8 Gy but less than 30 Gy is also prescribed to the adventitia based on IVUS measurements.

There are also studies in which the dose is administered at a given distance from the source, without the use of IVUS. In the BETA-CATH trial (ß- $^{90}Sr/Y$ source), it is 14 Gy in vessels >2.7 mm and <3.35 mm, and 18 Gy in vessels >3.35 mm and <4.0 mm; in the SMARTS trial, which is designed for small vessels (<2.75 mm), it is 12 Gy to a distance of 2 mm from a $\gamma$-$^{192}Ir$ source. In the ARTISTIC trial investigating patients with in-stent restenosis, the same mechanical delivery system of a $^{192}Ir$ source as in ARREST is used, but a dose of 12, 15 or 18 Gy is prescribed at 2 mm from the source. In the CURE study conducted with a balloon filled with $^{188}Re$, a dose of 13 Gy at 0.5 mm from the surface of the balloon is prescribed.

Positive results are not obtained only when using IVUS. The data of the Schneider/Boston Scientific ß-intracoronary irradiation dose-finding study very recently presented by Verin at the European Congress of Cardiology (Barcelona, August 1999) demonstrate that with 9–18 Gy at 1 mm tissue depth, there was a significant dose-related inhibitory effect on restenosis after PTCA and a beneficial effect on remodeling. The delivery of 18 Gy at 1 mm tissue depth resulted in a low overall restenosis rate of 8.3% and an even lower rate of 4.3% in those patients treated with balloon angioplasty and radiation alone. Measurements were based on QCA. However, Russo et al have compared the method of dosage using IVUS during the SCRIPPS trial to a method based on an angiographic model and a fixed-dose strategy.[65] From 119 IVUS pull-backs, the IVUS method would give mean minimal and maximal adventitial doses of 7.73 ± 0.69 Gy and 25.81 ± 5.26 Gy, and

10.9% of targets would receive <7 Gy, believed to be subtherapeutic. With the angiographic model, the mean minimal dose would be 7.51 ± 1.44 Gy, but 38.7% of patients would receive a minimal adventitial dose <7 Gy. With a fixed-dose strategy of 15 Gy delivered at 2 mm from the source, the mean minimal dose would be 8.59 ± 1.64 Gy, with 17.9% of patients receiving <7 Gy at the adventitia. However, with this strategy, 41.5% of targets would receive >30 Gy. This demonstrates that probably only IVUS permits the optimal dosimetry, adapted to the remodeling of the specific lesion of a patient.

## Limitations of IVUS for dosimetry

A major assumption made when using IVUS to assess the dosimetry is to consider that both the imaging catheter and the brachytherapy delivery system are following the same course in the treated coronary segment. Compared with a 5 F. (~ 1.7 mm) device such as the Beta-Cath, the IVUS catheter, which is smaller (2.9 F. ~ 1 mm), will be in a more eccentric position in the coronary lumen. However, no easy correction can be applied since the channel source in the delivery device is not in the center of the catheter. When using a centering balloon for the source such as in PREVENT or the Schneider Dose Finding Study, it is easy to calculate the center of gravity of the lumen of each slice from the 3-D IVUS dataset. However, even with the use of radiotherapy and IVUS catheters of the same size, or centered, it is not certain that when advanced sequentially in the arterial lumen, they will occupy the same position. Although both catheters should be on the shortest 3-D path in the lumen, coronary arteries have a complex curved geometry in space, and are partially deformed by the catheter lying in their lumen. Thus, catheters with differing rigidity will occupy different positions. These methodological limitations could be partially overcome with existing imaging wires which could be introduced in the lumen of the irradiation delivery catheter itself.[66] Another very interesting device, illustrated in Figure 5, has recently been developed. The unique characteristic of this catheter, designed for directional radiation (BRIGADE™, EndoSonics Corp, Rancho Cordova, CA, USA) is the combination of a solid-state IVUS imaging array proximal to the site in the delivery system where the source lies.[67] A second unique feature of this device is a gold attenuator surrounding the radioactive source asymmetrically, in order to direct preferentially radiation in eccentric plaques. The incorporation of the imaging possibilities allows for rotation of the system towards the most eccentric plaque. Clinical trials will soon be launched, after the demonstration of the feasibility of this new approach in an animal model.

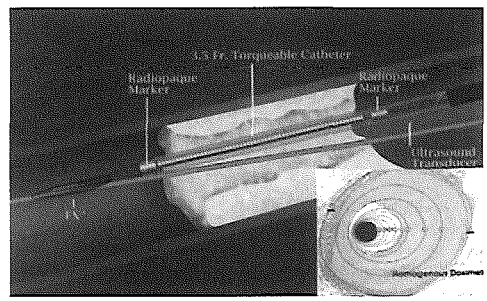


Figure 5
Illustration of a directional radiation catheter, including an asymmetric gold attenuator encompassing only the top half of the area where the source is positioned for coronary brachytherapy (between the two radiopaque markers). This configuration offers an asymmetric dose distribution which optimizes the dosimetry of eccentric lesions (panel). Optimal orientation of such a device can only be performed thanks to the incorporated intravascular ultrasound transducer attached proximally in this combined device.

## Conclusion

Radiation therapy bears some resemblance to antibacterial therapy, which requires the right dosage to achieve its therapeutic goal, without excessive toxicity related to overdose or incorrect targeting (classically called by the radiotherapist a 'geographical miss'). At the present stage, IVUS appears to be an indispensable tool for understanding the mechanisms of action of radiotherapy in the prevention of restenosis and in finding the target volume. The confounding and negative results of the early clinical studies, performed without IVUS guidance, support the need to at least document by IVUS the ongoing clinical trials, even when there is no direct guidance of dosage administration. To treat coronary arteries effectively, it seems necessary to evaluate the dose absorbed in different arterial structures since there is still controversy about the target volume to be irradiated. This cannot be appreciated with angiography, which gives only a lumenogram of the artery. Methods based on the determination of specific dose–volume histograms might be useful. Only the future will tell us whether angiography is a sufficient guideline to establish and apply the correct dose. The desire to simplify the methodological approach of brachytherapy in this early phase might be fatal for this technique in its infancy.

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# CHAPTER 5

Geometric vascular remodeling after balloon angioplasty and β-radiation therapy.
A three-dimensional intravascular ultrasound study.

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Circulation 100: 1182-1188, 1999.

# Geometric Vascular Remodeling After Balloon Angioplasty and β-Radiation Therapy

## A Three-Dimensional Intravascular Ultrasound Study

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***Background***—Endovascular radiation appears to inhibit intimal thickening after overstretching balloon injury in animal models. The effect of brachytherapy on vascular remodeling is unknown. The aim of the study was to determine the evolution of coronary vessel dimensions after intracoronary irradiation after successful balloon angioplasty in humans.

***Methods and Results***—Twenty-one consecutive patients treated with balloon angioplasty and β-radiation according to the Beta Energy Restenosis Trial-1.5 were included in the study. Volumetric assessment of the irradiated segment and both edges was performed after brachytherapy and at 6-month follow-up. Intravascular ultrasound images were acquired by means of ECG-triggered pullback, and 3-D reconstruction was performed by automated edge detection, allowing the calculation of lumen, plaque, and external elastic membrane (EEM) volumes. In the irradiated segments, mean EEM and plaque volumes increased significantly (451±128 to 490.9±159 $mm^3$ and 201.2±59 to 241.7±74 $mm^3$; $P=0.01$ and $P=0.001$, respectively), whereas luminal volume remained unchanged (250.8±91 to 249.2±102 $mm^3$; $P$=NS). The edges demonstrated an increase in mean plaque volume (26.8±12 to 32.6±10 $mm^3$, $P=0.0001$) and no net change in mean EEM volume (71.4±24 to 70.9±24 $mm^3$, $P$=NS), resulting in a decrease in mean luminal volume (44.6±16 to 38.3±16 $mm^3$, $P=0.01$).

***Conclusions***—A different pattern of remodeling is observed in coronary segments treated with β-radiation after successful balloon angioplasty. In the irradiated segments, the adaptive increase of EEM volume appears to be the major contributor to the luminal volume at follow-up. Conversely, both edges showed an increase in plaque volume without a net change in EEM volume. (***Circulation.*** **1999;100:1182-1188.**)

**Key Words:** balloon ■ angioplasty ■ ultrasonics ■ remodeling ■ radioisotopes

Restenosis after balloon angioplasty (BA) is the major limitation of the technique, occurring after 30% to 40% of procedures despite excellent acute results.[1] Excessive neointimal proliferation and extracellular matrix synthesis by modified smooth muscle cells in response to injury have been suggested as the main mechanisms of restenosis.[2,3] However, recent studies identified geometric vascular remodeling after BA as a concomitant contributor to the process of restenosis.[4,5]

Endovascular radiation appears to be a novel technique, which, by use of either β- or γ-isotopes, has inhibited intimal thickening after overstretch balloon injury in experimental models.[6–8] The theoretical benefit of radiation in preventing neointimal proliferation resides in its killing effect of more rapidly dividing smooth muscle cells.[9] Two randomized studies demonstrated substantial reductions in restenosis rate after treatment of in-stent restenosis.[10,11] The use of either β- or γ-radiation for treatment of de novo coronary lesions has been successfully tested in humans.[12,13]

The effects of brachytherapy on geometric vascular remodeling of de novo treated lesions are still unknown. By allowing direct measurement of the vessel wall, intravascular ultrasound (IVUS) imaging has been used to study the remodeling process in coronary arteries.[14–16] Recently, 3D IVUS reconstruction systems have been introduced, allowing the quantitative analysis of a particular segment of interest during an automated pullback.[17] Furthermore, to prevent artifacts caused by systolic-diastolic dimension changes of the coronary vessel wall, the pullback of the IVUS catheter can be performed with ECG gating.[18]

The purposes of this article were to (1) quantify the volumes of vessel structures by means of 3D reconstruction of IVUS images of coronary segments successfully treated by BA followed by β-radiation therapy, (2) determine the

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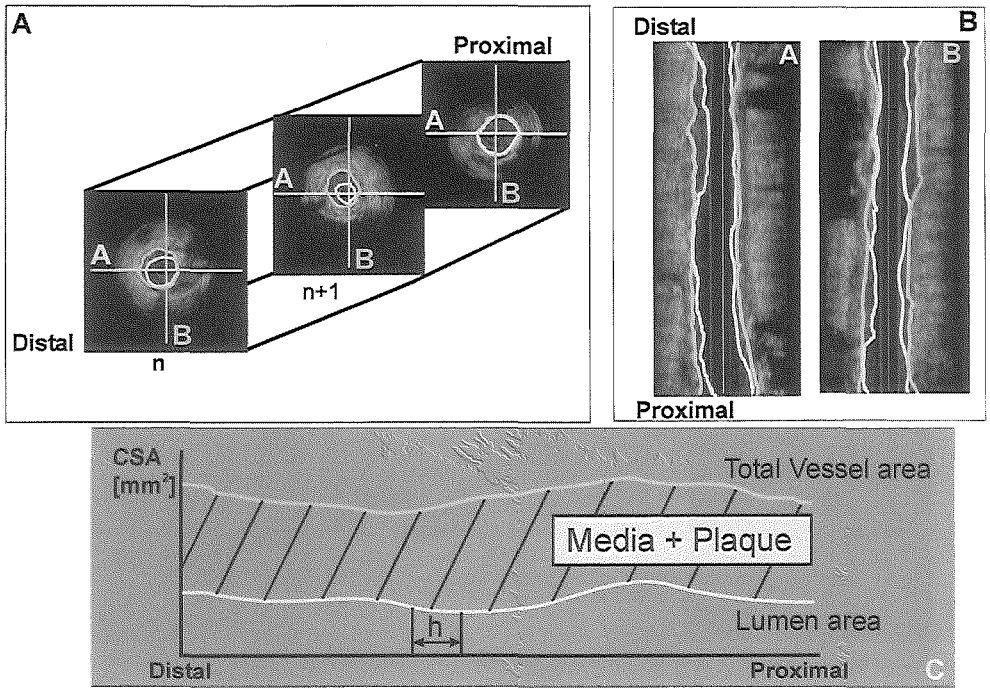


**Figure 1.** Overview of the applied analysis software package.[18,21] A, Schematic presentation of the IVUS catheter pullback. B, Two computed longitudinal perpendicular views. Corresponding cut-planes in A are represented by the letters A and B. C, Outcome of measurements. CSA indicates cross-sectional area; h, distance between 2 consecutive catheter positions (0.2 mm). Gray boundary lines represent total vessel contours; white lines, luminal contours.

evolution of these vessel parameters to define the pattern of vascular remodeling after coronary irradiation, and (3) evaluate the potential effect of brachytherapy on the remodeling at both edges of the irradiated area.

## Methods

### Patient Selection

Patients eligible for the study were those treated successfully with BA followed by intracoronary irradiation according to the Beta Energy Restenosis Trial (BERT)-1.5. The purpose of this trial was to evaluate the safety and efficacy of low-dose irradiation after BA with or without stent implantation in patients with single de novo lesions of native coronary arteries. The isotope selected was the pure β-emitting strontium 90, and patients were randomly assigned to receive doses of 12, 14, or 16 Gray. The inclusion and exclusion criteria of this trial have been previously reported.[13] The delivery of the radiation was performed by the use of the Beta-Cath System (Novoste Corp).[19] The radiation source train of this system consists of a series of 12 independent cylindrical seeds that contain the radioisotope sources and is bordered by 2 gold radio-opaque markers separated by 30 mm.[19]

### IVUS Image Acquisition Analysis System

The segment subject to 3D reconstruction was examined with a mechanical IVUS system (ClearView, CVIS, Boston Scientific Corp) with a sheath-based IVUS catheter incorporating a 30-MHz single-element transducer rotating at 1800 rpm (Ultracross, CVIS). The transducer is placed inside a 2.9F, 15-cm-long sonolucent distal sheath that alternatively houses the guide wire (during the catheter introduction) or the transducer (during imaging). The IVUS transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor developed at the Thoraxcenter, Rotterdam.[20] The ECG-gated image acquisition and digitization was performed by a workstation designed for the 3D reconstruction of echocardiographic images[20] (EchoScan, Tomtec). This workstation received input from the IVUS machine (video) and the patient (ECG signal) and controlled the motorized transducer pullback device. The steering logic of the workstation considered the heart rate variability and only acquired images from cycles meeting a predetermined range; premature beats were rejected. IVUS images were acquired coinciding with the peak of the R wave. If an R-R interval failed to meet the preset range, the IVUS catheter remained at the same site until a cardiac cycle met the predetermined R-R range. Then, the IVUS transducer was withdrawn 200 μm to acquire the next image.[17,18,20] Given the slice thickness of 200 μm and the length subject to the analysis of 40 mm (distance between the 2 gold markers of the radiation source and 5 mm both edges), 200 cross-sectional images per segment were digitized and analyzed. A Microsoft Windows-based contour detection program developed at the Thoraxcenter was used for the 3D analysis.[21] This program constructs 2 longitudinal sections from the data set and identifies the contours corresponding to the lumen-intima and media-adventitia boundaries (Figure 1). Corrections could be performed interactively by "forcing" the contour through visually identified points, and then the entire data set was updated.[21] Careful checking and editing of the contours of the 200 planar images was performed with an average of

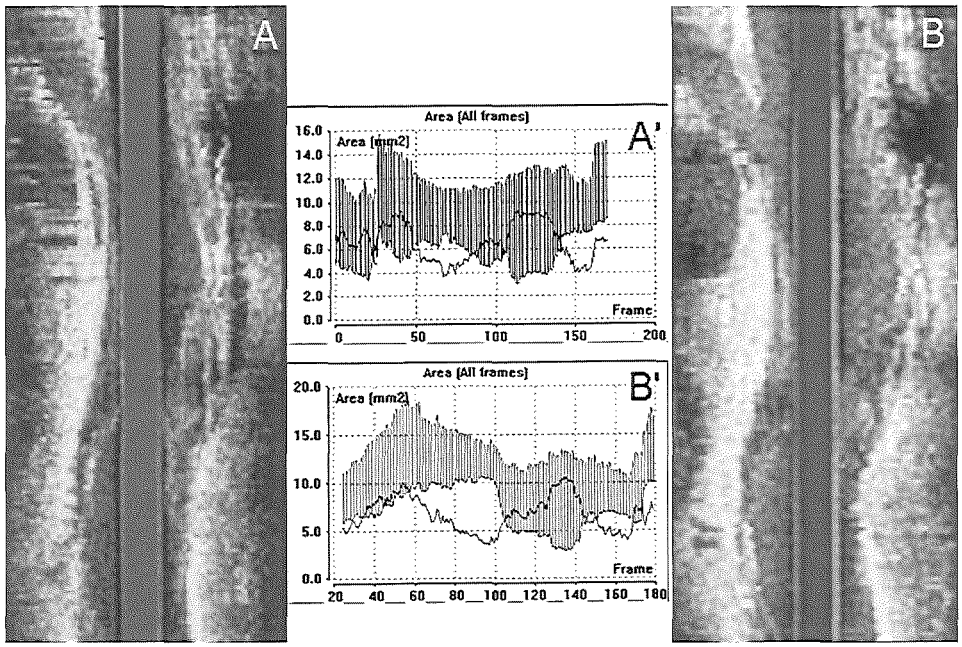


**Figure 2.** Longitudinal reconstruction of the IVUS cross-sectional images and subsequent volumetric calculations (middle charts) after irradiation (A and A') and at 6-month follow-up (B and B'). Note increase in scale at follow-up chart reflecting increase in total vessel volume.

60 minutes for complete evaluation. The area encompassed by the lumen-intima and media-adventitia boundaries defined the luminal and the external elastic membrane (EEM) volumes, respectively. The difference between EEM and luminal volumes defined the plaque volume. Volumetric data were calculated by the formula

$$V=\sum_{i=1}^{n} A_i \cdot H$$

where V is volume, A is area of EEM or lumen or plaque in a given cross-sectional ultrasound image, H is thickness of the coronary artery slice reported by this digitized cross-sectional IVUS image, and n is the number of digitized cross-sectional images encompassing the volume to be measured.[21] The feasibility and intraobserver and interobserver variabilities of this system have been previously reported.[17,22] The 3D analysis was performed by 1 investigator. Intraobserver variability was assessed by analyzing a series of 15 IVUS volumetric studies at least 3 months apart. Differences in EEM, plaque, and lumen volumes were as follows: $-0.4\pm1.0\%$, $-0.3\pm1.3\%$, and $-0.2\pm0.9\%$, and the intraclass correlation coefficients were $r=0.97$, $r=0.97$, and $r=0.98$, respectively.

To define the treated segment, a few steps were followed. First, an angiogram was performed after positioning the delivery catheter and the relation between anatomic landmarks and the 2 gold markers were noted. Typically, the aorto-ostial junction and the side branches were used as landmarks. The anatomic landmark closest to either of the gold markers was used as a reference point. During the IVUS analysis, this reference point was identified during a contrast injection with the IVUS imaging element at the same position as the gold marker of the source. At the same time, during the contrast injection, the image from the IVUS imaging element was recorded and the reference point identified. During the subsequent pullback, this reference point was recognized and used for selecting the area subject to the analysis: 30 mm for the irradiated segment analysis and 5 mm at both edges for the "edge effect" evaluation. In cases in which there were no angiographic landmarks bordering either of the 2 gold markers of the delivery catheter, the minimal luminal diameter identified during the IVUS pullback was used as the reference point. Then, the irradiated segment was defined by selecting slices encompassed within 15 mm proximal and 15 mm distal to the minimal luminal diameter. This approach was necessary only in 2 cases. At follow-up, correct matching of the region of interest was performed by comparing the longitudinal reconstruction with that after treatment (Figure 2).

## Procedure

The medical ethics committee of our institution approved the study, and all patients signed a written informed consent form. The patients received aspirin (250 mg) and heparin (10 000 IU IV) before the procedure. If the duration of the entire interventional procedure exceeded 1 hour, additional heparin was given to maintain the activated clotting time >300 seconds. In BERT-1.5, BA was performed according to standard clinical practice. After successful angioplasty, intracoronary $\beta$-radiation was performed as previously described,[13] and afterward, repeat angiography and IVUS pullback were carried out. On average, IVUS pullback was performed at $12\pm2$ minutes (9 to 15 minutes) after BA. A continuous motorized pullback at a speed of 0.5 mm/s was first carried out, followed by an ECG-gated pullback at a step size of 0.2 mm/step. Intracoronary nitrates were administered immediately before each of the IVUS pullbacks. A final angiogram after the IVUS study concluded the procedure. At 6-month follow-up, further IVUS analysis of the treated area was performed.

**TABLE 1. Baseline Characteristics. (n=21)**

| | |
|---|---|
| Male sex, n (%) | 16 (76%) |
| Mean age, y | 56±9 |
| Coronary risk factors, n (%) | |
| Smoking | 14 (67%) |
| Hypercholesterolemia | 11 (52%) |
| Family history | 11 (52%) |
| Hypertension | 10 (48%) |
| Diabetes | 4 (19%) |
| Treated vessel, n (%) | |
| Left anterior descending | 11 (52%) |
| Left circumflex | 6 (29%) |
| Right coronary artery | 4 (19%) |
| Prescribed dose, n (%) | |
| 16 Gy | 9 (43%) |
| 14 Gy | 4 (19%) |
| 12 Gy | 8 (38%) |

### Statistical Analysis

Quantitative data are presented as mean±SD. Volumetric data derived from the 3D reconstruction of the IVUS imaging were compared immediately after treatment and at follow-up by use of the 2-tailed, paired Student's *t* test. Linear regression analysis was performed to assess the relation between the change in EEM, lumen, and plaque dimensions. A value of $P<0.05$ was considered statistically significant.

## Results

### Baseline Characteristics

Thirty-one patients were included in BERT-1.5 at our institution. Eight patients who received stent implantation for important recoil or dissection after BA were excluded from the volumetric assessment. At follow-up, the 3D IVUS analysis was not performed in 2 patients: 1 patient refused and the other returned prematurely with unstable angina pectoris secondary to severe restenosis, and only a manual IVUS pullback preintervention was possible. Therefore, 21 patients with volumetric IVUS analysis after treatment and at follow-up formed the study population. The baseline characteristics of the patients are presented in Table 1.

### Clinical and Angiographic Follow-Up

At follow-up, 14 (66%) patients remained asymptomatic. Six patients had stable angina pectoris: Canadian Cardiovascular Society class 1 (n=1), class 2 (n=1), and class 3 (n=4). One patient was admitted prematurely because of unstable angina pectoris. The follow-up angiography demonstrated restenosis (>50% diameter stenosis on quantitative coronary angiography) in 5 (24%) patients. One restenotic patient demonstrated aneurysmatic formation within the irradiated area (Figure 3). The prescribed dose in restenotic patients was 12 Gray (n=1), 14 Gray (n=1), and 16 Gray (n=3).

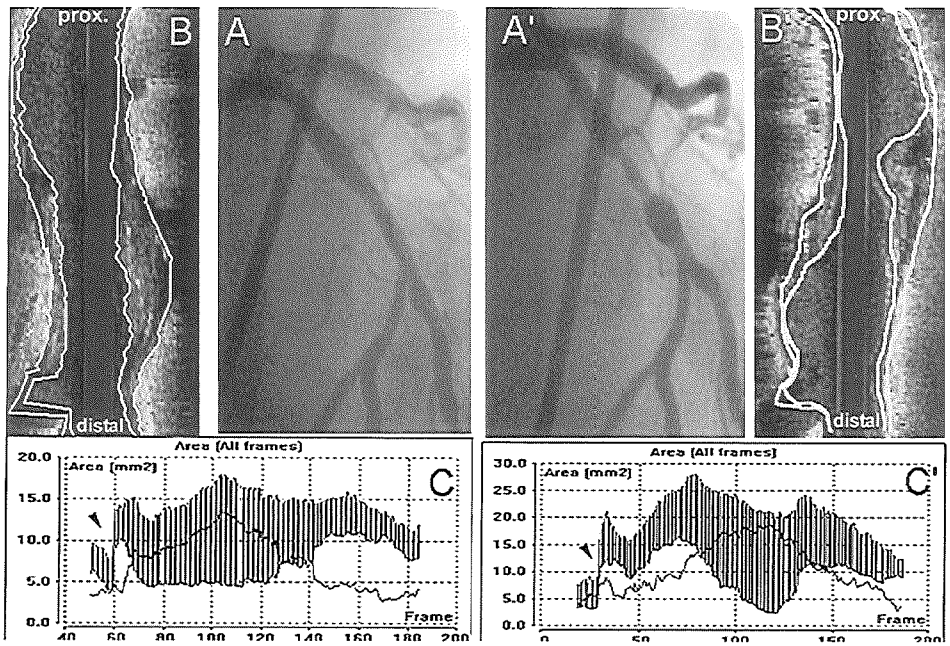


**Figure 3.** Angiography and 3D reconstruction of an irradiated segment (A, B, and C) that demonstrated restenosis and aneurysmatic formation at 6-month follow-up (A', B', and C'). Contour tracing has been manually corrected for distal side branch (black arrowheads in bottom charts). prox. indicates proximal.

**TABLE 2. IVUS Volumetric Analysis**

| Patient | Artery | Dose, Gray | LV Post | LV Follow-Up | ΔLV | EEM Post | EEM Follow-Up | ΔEEM | PV Post | PV Follow-Up | ΔPV |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | LAD | 12 | 143.2 | 148.4 | 5.2 | 321.4 | 371.9 | 50.5 | 178.2 | 223.5 | 45.3 |
| 2 | LAD | 14 | 297.6 | 289.2 | −8.4 | 605.5 | 634.8 | 29.3 | 307.8 | 345.5 | 37.7 |
| 3 | LCx | 16 | 206.2 | 222.8 | 16.6 | 399.3 | 426.1 | 26.8 | 193.2 | 203.2 | 10 |
| 4 | LAD | 12 | 201.6 | 186 | −15.6 | 313.1 | 315.4 | 2.3 | 111.5 | 129.5 | 18 |
| 5 | RCA | 14 | 281 | 213.4 | −67.6 | 493.5 | 486.1 | −7.4 | 212.5 | 272.4 | 59.9 |
| 6 | RCA | 12 | 228.1 | 197.9 | −30.2 | 458.7 | 442.4 | −16.3 | 230.6 | 244.5 | 13.9 |
| 7 | LCx | 12 | 192.1 | 257 | 64.9 | 352.5 | 439.5 | 87.0 | 160.4 | 182.4 | 22 |
| 8 | LAD | 16 | 169.6 | 176.8 | 7.2 | 323.9 | 359.3 | 35.4 | 154.3 | 182.5 | 28.2 |
| 9 | LAD | 14 | 231.2 | 246.3 | 15.1 | 470 | 489.8 | 19.8 | 238.8 | 243.5 | 4.7 |
| 10 | LCx | 16 | 333.2 | 278.9 | −54.3 | 487.2 | 470.3 | −16.9 | 154 | 191.4 | 37.4 |
| 11 | LCx | 16 | 392.5 | 490.9 | 98.4 | 718.5 | 806 | 87.5 | 325.9 | 315.1 | −10.8 |
| 12 | LAD | 12 | 272.6 | 193 | −79.6 | 452.9 | 498.2 | 45.3 | 180.3 | 305.2 | 124.9 |
| 13 | LCx | 12 | 326.4 | 321.2 | −5.2 | 578 | 676 | 98.0 | 251.6 | 354.8 | 103.2 |
| 14 | LAD | 12 | 154.8 | 187.8 | 33 | 276.8 | 337.1 | 60.3 | 122 | 149.3 | 27.3 |
| 15 | LAD | 16 | 237.6 | 216.6 | −21 | 332.1 | 334.2 | 2.1 | 94.5 | 117.6 | 23.1 |
| 16 | LAD | 16 | 341.2 | 229 | −112.2 | 605.3 | 520.4 | −84.9 | 264.2 | 291.4 | 27.2 |
| 17 | LCx | 16 | 210.1 | 278.2 | 68.1 | 412.6 | 600.7 | 188.1 | 205.7 | 322.5 | 116.8 |
| 18 | RCA | 16 | 176.6 | 219.3 | 42.7 | 415.1 | 430.1 | 15.0 | 238.5 | 210.8 | −27.7 |
| 19 | LAD | 16 | 234.2 | 225 | −9.2 | 446.9 | 463.2 | 16.3 | 212.7 | 238.3 | 25.6 |
| 20 | LAD | 14 | 119 | 108.5 | −10.5 | 315.7 | 296.1 | −19.6 | 196.7 | 187.6 | −9.1 |
| 21 | RCA | 12 | 501.4 | 548 | 46.6 | 694.4 | 912.2 | 217.8 | 193 | 364 | 171 |
| Mean | | 14.1 | 250.8 | 249.2 | −1.6* | 451.1 | 490.9 | 39.8† | 201.2 | 241.7 | 40.5‡ |
| SD | | 1.8 | 91.8 | 102.5 | 51.5 | 128.1 | 159.3 | 68.7 | 59.3 | 74.0 | 49.4 |

LAD indicates left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; LV, luminal volume; EEM, external elastic membrane volume; PV, plaque volume; and post, after treatment. All values in $mm^3$.

*$P$=NS; †$P$<0.01; ‡$P$<0.001.

## Irradiated Segment IVUS Analysis

Volumetric calculations of the EEM, lumen, and plaque at the site of irradiated coronary segments are presented in Table 2. A significant increase in mean EEM volume was observed at follow-up (451±128 to 490.9±159 $mm^3$; $P$=0.01) parallel to that in plaque volume (201.2±59 to 241.7±74 $mm^3$; $P$=0.001). As a result, mean luminal volume remained unchanged (250.8±91 $mm^3$ after treatment vs 249.2±102 $mm^3$ at follow-up; $P$=NS). Patients assigned to receive a dosage of 16 Gray showed no differences in terms of EEM, lumen, and plaque changes as compared with those assigned to receive 12 and 14 Gray. Changes in EEM and plaque volumes showed a significant and positive correlation ($r$=0.66; $P$=0.001). Similarly, changes in luminal volumes correlated significantly with those in EEM volumes ($r$=0.69; $P$=0.005) but not with those in plaque volumes ($r$=0.07, $P$=NS) (Figure 4). Sixteen (76.2%) patients showed a global increase in EEM volume (+61.3±60 $mm^3$), whereas 3 (14.3%) patients showed a reduction in plaque volume (−15.7±10 $mm^3$). Five (23.8%) patients demonstrated angiographic restenosis. In 2 of them, despite the

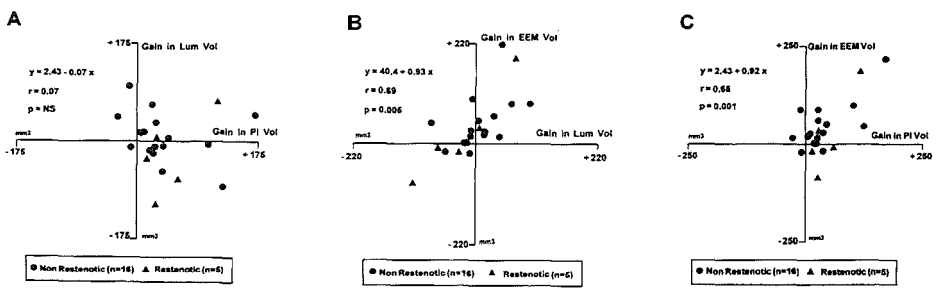


**Figure 4.** Linear regression analysis between changes in plaque and luminal volumes (A), EEM and luminal volumes (B), and EEM and plaque volumes (C). EEM Vol indicates EEM volume; Pl Vol, plaque volume; and Lum vol, luminal volume.

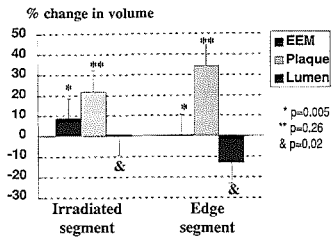


**Figure 5.** Comparison between patterns of remodeling in irradiated area and at edges.

absolute increase in EEM volume, a focal increase in plaque volume led to restenosis. The remaining 3 patients showed an increase in plaque concomitant to a decrease EEM volume.

Ten (47.6%) patients showed a global increase in luminal volume (+40.1±30 $mm^3$). In 8 of them, the increase in EEM volume (+85.7±75 $mm^3$) overcame the increase in plaque volume (+53.2±59 $mm^3$). In the other 2 patients, enlargement of EEM volume was observed concomitantly to decrease in plaque volume.

### "Edge Effect" IVUS Measurements

Significant angiographic reduction in luminal diameter involving the proximal edge of the irradiated area was observed in 1 patient at follow-up. Volumetric calculations demonstrated a significant mean increase in plaque volume (26.8±12 to 32.6±10 $mm^3$; $P=0.0001$) and no net change in mean EEM volume (71.4±24 to 70.9±24 $mm^3$; $P$=NS), resulting in a significant decrease of mean luminal volume at follow-up (44.6±16 to 38.3±16 $mm^3$; $P=0.01$). Changes in luminal volumes correlated significantly with those in EEM and plaque volume ($r=0.87$; $P<0.0001$ and $r=-0.51$; $P=0.03$; respectively). Conversely, changes in plaque did not correlate with those in EEM ($r=-0.03$; $P$=NS). At the edges, percentage of change in EEM and in luminal volume differed significantly from those within the irradiated segment (Figure 5). No differences in volumetric changes were observed regarding the 3 ranges of doses.

## Discussion

Previous studies with γ-radiation for the treatment of in-stent restenosis have demonstrated a reduction in the restenosis rate mainly as the result of a reduction in neointimal formation, as assessed by IVUS.[10,11] Our study provides the mechanistic interpretation of β-radiation on remodeling of de novo lesions treated with BA. On average, adaptive vessel enlargement is the main contributor to luminal volume at follow-up by accommodating the increase in plaque volume.

The importance of geometric remodeling after BA has been studied both in experimental models[5,23,24] and in humans.[14–16] Di Mario et al[15] reported that shrinkage of the vessel accounted for 68% of the late loss after BA. Similar results were obtained by and Mintz et al,[14] who reported 73% of late loss caused by chronic vessel constriction. A serial IVUS study[16] described a biphasic time course of the geometric remodeling after BA. Thus an initial adaptive vessel enlargement was observed up to the first month, followed by a late constriction phase during the next 5 months.

Only 5 (23.8%) patients demonstrated shrinkage of vessel volume 6 months after radiation, whereas the remaining 16 (76.2%) patients showed vessel enlargement. Furthermore, luminal volume appeared to increase in 10 (47.6%) patients. These results are in concordance with those obtained by Condado et al,[12] who reported a negative late loss in 10 (45%) of 22 patients treated with γ-radiation. We demonstrated that the increase in luminal volume was mainly due to vessel enlargement rather than plaque reduction, which was observed only in 2 patients.

The severity and depth of the arterial wall injury caused by the balloon overstretching might induce adventitial inflammation and subsequent fibrosis, which, in turn, might lead to contraction of the vessel.[24,25] The beneficial effect of intravascular radiation on the arterial remodeling after angioplasty may be explained by a reduction of either cell proliferation in the media and adventitia or the expression of α-smooth muscle actin in the adventitia, which is responsible for fibrotic scar formation after BA.[26] A potential concern regarding coronary brachytherapy is the fact that initially favorable adaptive remodeling would lead to late undesired aneurysm formation. The incidence of coronary aneurysm after BA or stent implantation, as defined as a coronary dilatation that exceeded the diameter of normal adjacent segments by 1.5 times,[27] ranges between 3.9% and 5.4% and has not been associated with angiographic restenosis or unfavorable clinical outcome.[28,29] The incidence and prognosis of aneurysm formation after radiation is unknown. In our cohort, 1 patient demonstrated this complication at 6-month follow-up. Condado et al[12] reported 4 (20%) cases of aneurysmatic formation within 2 months after γ-radiation. In 2 of them, a further increase of the size was observed at 6 and 8 months, respectively.[12]

An interesting finding was the concurrent vessel enlargement and focal plaque increase, as observed in 12 patients, resulting in restenosis in 2 of them. Inhomogeneity of dosing caused by the lack of centering might account for this paradox. Therefore the actual dose to the luminal surface and adventitia appeared to be highly variable between patients as calculated by means of dose-volume histograms.[30] A more homogeneous dose distribution might be achieved by use of a centering catheter or a γ-source.[30]

As opposed to the pattern of remodeling within the irradiated area, the edge segments demonstrated a significant decrease in mean luminal volume. A lack of adaptive remodeling concomitantly to an increase in plaque volume accounted for the residual luminal volume at the edges. The edge of the radiation source represents an area receiving low-dose radioactivity. It is hypothesized that a low activity could have a proliferative effect, especially when associated with injury induced by BA.[31]

### Study Limitations

This study was not placebo-controlled. Consequently, no conclusion about the effectiveness of β-irradiation in preventing neointimal formation can be extrapolated.

A potential source of error is germane to the presence of the IVUS catheter in the lumen. In relatively small vessels, this can result in vessel stretching, resulting in volumetric

overestimation. Alternatively, the distending pressure on the vessel may be substantially decreased by the presence of the catheter that fills a significant part of the lumen. This limitation could be especially relevant in studies evaluating only 1 cross-section at the narrowest part of the segment. However, in our cohort, none of the segments showing adaptive remodeling demonstrated any area in which the lumen were occluded by the IVUS catheter.

The method of selection of the area of interest is the best available. However, despite the meticulous procedure followed, a small inaccuracy cannot be completely ruled out. Ideally, new systems incorporating the IVUS imaging element on the delivery catheter would resolve this drawback.

The follow-up period of our cohort might be short, considering the fact that vascular irradiation may delay restenosis by 1 to 3 years.[32] Therefore the observed vessel enlargement might represent an early phase of the effect of β-radiation therapy after BA.

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# PART III

## Challenges in vascular brachytherpy.

# CHAPTER 6

Inaccuracy in manual multisegmental irradiation in coronary arteries.

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# Inaccuracy in manual multisegmental irradiation in coronary arteries

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**Abstract**

*Purpose*: Retrospective evaluation of the accuracy of manual multisegmental irradiation with a source train for irradiation of long (re)stenotic lesions in coronary arteries, following percutaneous transluminal coronary angioplasty (PTCA).

*Material and methods*: Thirty-six patients were treated with intracoronary irradiation following PTCA with manual multisegmental irradiation. These patients were included in the multicenter, multinational 'European Surveillance Registry with the Novoste Beta-Cath system' (RENO). In all 36 patients the target length (i.e. PTCA length plus 5-mm margin at each side) was too long for the available source train lengths (30 and 40 mm). In 33 patients the radiation delivery catheter was manually positioned twice and in three patients three times in series, trying to avoid any gap or overlap. The total number of junctions was 39. Following a successful PTCA procedure the site of angioplasty was irradiated using the Novoste Beta-Cath afterloader with a 5-F non-centered catheter which accommodates the sealed beta-emitting $^{90}Sr/^{90}Y$ source train or dummy source train. Radiation was delivered first to the distal part of the target length. Fluoroscopic images of this source position were stored in the computer memory. For irradiation of the proximal part of the target length, the delivery catheter had to be retracted over a distance equal to the source length used for the distal part. This was done by a continuous overlay video loop with ECG-gated replay of the image stored in the computer memory. The dummy source was used to position the delivery catheter so that the junction between both source positions was as precise as possible. Measurements of gap or overlap between the source positions were performed retrospectively on printed images. Doses were calculated, in accordance with the Novoste study protocol, at a distance of 2 mm from the source axis ( = dose prescription distance) in several points along the irradiated length.

*Results*: Interventional or PTCA length varied between 33 and 95 mm. The lesion sites were in the left anterior descending artery, ($n = 6$), right coronary artery ($n = 20$), left circumflex artery ($n = 6$) and one vein graft. The administered radiation dose was determined by the vessel diameter and the presence of a stent. This dose, prescribed at a distance of 2 mm from the source axis, varied between 16 and 22 Gy. No gap or overlap was seen between the two source trains in only two out of 39 cases. In 16 cases there was a gap ranging between 0.6 and 9.6 mm and 18 cases showed an overlap of 0.5–14.4 mm. In three patients the measurement was not possible. In case of a gap the minimal dose calculated at 2 mm from the source axis varies between 0 and 87% of the prescribed dose, depending on the distance between both sources. In case of overlap the maximal dose varies between 110 and 200% of the prescribed dose at 2 mm from the source axis.

*Conclusions*: The results show the inaccuracy of manual multisegmental irradiation using a source train in coronary arteries, causing unacceptable dose inhomogeneities at a distance of 2 mm from the source axis at the junction between both source positions. Moreover, a perfect junction will never be possible due to movement of the non-centered radiation delivery catheter in the vessel lumen, as applied in this study. Manual multisegmental irradiation is therefore not recommended. Using longer line sources or source trains or preferably an automated stepping source is a more reliable and safer technique for treatment of long lesions. 

*Keywords*: Coronary artery; Manual multisegmental irradiation; Intracoronary irradiation; Brachytherapy

## 1. Introduction

Coronary artery diseases remain the major cause of death in industrialized countries. Worldwide, more than 1 million procedures of percutaneous transluminal coronary angioplasty (PTCA) are performed each year. Despite the fact that a PTCA is successful in 95% of the cases and the complication rate is very low, the long-term results show a high rate of restenosis: 30–50% within the first year [9,10,16].

PTCA causes damage to intima and media, inducing a wound healing process with hyperproliferation and negative remodeling (constriction), causing restenosis. Elastic recoil of the artery, local thrombus formation, vascular remodeling and neointimal cellular proliferation are factors contributing to a progressive narrowing of the residual lumen [6].

Stent implantation following PTCA minimizes the elastic

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recoil and vascular remodeling, but do not reduce neointimal cellular proliferation; in fact, they tend to induce an increased proliferative response. Stents have proven in clinical trials to reduce the restenosis rate to around 20–30%. For example in the STRESS and BENESTENT trials a 30% reduction in restenosis rate was achieved after implantation of a single Palmaz–Schatz coronary stent for short lesions [5,11,12,23,24]. Nevertheless, the restenosis rate remains high after stent implantation in long lesions and small vessels.

Radiotherapy is the most recent treatment tested in combination with PTCA. Clinical experience over more than 100 years showed radiotherapy to be a potent inhibitor of cellular proliferation, in benign as well as in malignant diseases. Examples of benign proliferative disorders successfully treated with radiotherapy are keloïd, heterotopic bone formation after surgery, pterygium, Peyronie's disease and desmoid-aggressive fibromatosis. Benign proliferative disorders are treated with radiation doses between 7 and 10 Gy in one or more fractions, inhibiting the fibroblast proliferation [1,3,4,14,20].

Animal studies have demonstrated the effectiveness of γ- and β-radiation in reducing neointimal hyperplasia after angioplasty. The use of radioactive stents also showed a reduction of restenosis in animals [19,26–29,31–33]. The encouraging results of these preclinical studies initiated different clinical trials with γ- and β-radiation. Promising results of these clinical trials and commercial availability of some coronary radiation devices lead to the use of endovascular coronary radiation in routine clinical practice, in patients with a high restenosis risk. There is a trend towards treating more complex and longer lesions, despite the fact that only short source lengths (30–60 mm) are available, especially for β-radiation. Moreover, as most lesions treated in β-radiation trials were short (15–30 mm), no results of efficacy in preventing restenosis are available for longer lesions. Today the only technique available to treat long lesions with a β-source is to position a line source or source train in series. Only one of the endovascular radiation devices, the Galileo intravascular radiotherapy system (Guidant), permits automatic stepping of the source, a 20-mm long $^{32}P$ wire. So far the software of this afterloader allows three source positions and the longest centering balloon available for Galileo is 52 mm long. Taking into account margins and dose fall-off the PTCA length should not exceed 40 mm. In all other devices stepping has to be performed manually. In this article we evaluate the accuracy of manual multisegmental irradiation with a source train for treatment of long lesions in coronary arteries, following PTCA.

## 2. Material and methods

From September 1999 to June 2000, 36 patients were treated with intracoronary irradiation following PTCA, with manual multisegmental irradiation. These patients were included in the multicenter, multinational 'European Surveillance Registry with the Novoste Beta-Cath system' (RENO). In all 36 patients the target length (i.e. PTCA length plus 5 mm margin at each side) was too long for the available source train lengths (30 and 40 mm). In 33 patients the radiation delivery catheter was manually positioned twice and in 3 patients three times in series, trying to avoid any gap or overlap. The total number of junctions was 39.

Following a successful PTCA procedure the site of angioplasty, including a 5 mm margin at each side [17], was irradiated using source trains that consist of β-emitting $^{90}Sr/^{90}Y$ seeds with a stainless steel encapsulation. Each seed is 0.9 mm in diameter and 2.5 mm in length. Until January 2000, only the source trains with 12 or 16 seeds were available, which had active lengths of 30 or 40 mm, respectively. In practice, interventional lengths up to 95 mm were encountered. Interventional lengths exceeding 30 mm required a combination of two or three source train positions with one or two junctions. Later a 60-mm source train (24 seeds) became available, eliminating the junction of two 30-mm source trains.

The seeds are stored in the Novoste Transfer Device. This device incorporates a hydraulic manual afterloading system, using sterile water to move the sources in a closed lumen of the radiation delivery catheter. The delivery catheter (Beta-Cath catheter) is a 5-F triple lumen monorail non-centered catheter. Prior to radiation the Beta-Cath catheter is tested for leakage of fluid and unhampered transfer of the source train. The delivery catheter was advanced over the guidewire and positioned at the site of PTCA. A proximal and distal radiopaque marker at the distal part of the delivery catheter delineate the position of the source train, which allows precise positioning at the PTCA site. The radiation oncologist uses the transfer device to advance the sources to the distal end of the delivery catheter and retrieve them when radiation is completed.

According to the Novoste study protocol, the administered radiation dose was determined by the vessel diameter and the presence of a stent. The dose has been prescribed at a distance of 2 mm from the source axis. The nominal diameter of the angioplasty balloon was used for dose prescription. Without stent the dose prescription was as follows: 14 Gy for a maximum balloon diameter of $\geq 2.5$ mm– $< 3.5$ mm, 18 Gy for a balloon of $\geq 3.5$– $< 4.0$ mm and 20 Gy for a balloon of $\geq 4.0$ mm. For in-stent restenosis or after stent implantation the doses were 16, 20 and 22 Gy, respectively, i.e. 2 Gy extra to compensate for attenuation by the stent struts. The exact attenuation by stent struts is unknown, but sparse data in literature varies between 10 and 15% [2,13,15,34]. To simplify the dose calculation a fixed dose of 2 Gy was recommended in the Novoste protocol, which means an 11–14% increase of the dose to compensate for the stent. In March 2000, the National Institute of Standards and Technology (NIST) used a more accurate method

for calibration of the $^{90}Sr/^{90}Y$ source. The effect of the change is a 15% dose-rate increase. This means that all given doses in this paper are in reality 15% higher when using the new calibration values.

Radiation was delivered first to the distal part of the PTCA length. Fluoroscopic images of this source train position were stored as a video loop of one ECG cycle in maximal expiration. After radiation the source train was returned into the transfer device. The Beta-Cath delivery catheter was carefully retracted to cover the proximal part of the PTCA length. The dummy source train was used to position the catheter so that the junction between both source positions was as precise as possible, using the radiopaque gold markers of the source train and the dummy source train. Our intention was to abut the active ends of the sources. Fluoroscopy was performed in maximal expiration, while the stored fluoroscopy image of the first source position was visible on an overlay video loop, with ECG-gated replay.

Although the procedure of proximal source positioning using the overlay video loop appeared to be satisfactory in the cath lab, we decided to evaluate the accuracy of the manual positioning. Retrospectively careful measurements of gap or overlap between the source positions were performed on printed images, selecting the same ECG sequence and the maximal expiration image. The guiding catheter was used for calibration and the measurements were corrected for foreshortening. This correction was performed using the ratio between the calculated length of the source train taking into account the calibration and the length measured on the image.

In order to determine the effect of positioning errors for the dose in the gap or overlap the dose distribution around the junction of two $^{90}Sr/^{90}Y$ source trains was calculated with a self developed dosimetry computer program, written in Delphi, running on a Pentium PC. First the dose distribution for a 1-mm segment of a single Novoste seed was determined by using the ITS 3.0 Integrated TIGER Series of coupled electron/photon Monte Carlo code system. The relative dose distribution around the 1-mm segment was implemented in the dosimetry program as a look-up table with a 0.2-mm grid. For a given source geometry (gap or overlap) the program yielded an isodose pattern using a 0.1-mm grid as well as the point dose in a number of predefined points of interest (Fig. 1 and Table 1). The different source trains (30, 40 or 60 mm length) are modeled as a row of the 1-mm segments. In this point source approach the net error of a few percent in the dose at 2 mm from the source axis due to absorption and scattering by the neighboring seeds are neglected. This is justified by the fact that in practice the dose at 2 mm from the source axis is highly affected by the plaque thickness and plaque density (degree of calcification) [13]. Also, the effect of the small spacing between the seeds in the real source train are neglected because this effect, a ripple on the isodose, is only significant at a distance less than 1 mm from the source axis. All isodoses are normalized in the central plane to the dose at 2 mm from the axis of a simulated 30-mm source train. The accuracy of the dosimetry program was checked by comparing the calculated isodose pattern of a 30-mm Novoste source train with a measured isodose pattern (GAF chromic film) provided by Novoste. The deviation in the locations of the both the 100% isodose (at 2 mm from the source axis) and 50% isodose is less than 0.2 mm in the radial direction (central). At the edges of the source train the deviation in the locations of the 10 and 50% isodose along a line at 2 mm parallel to the source axis is 0.5 and 0.3 mm, respectively. This uncertainty in the calculated dose distribution is neglectable because in practice the mean longitudinal displacement of a floating (non-centered) catheter is about 1.1 mm [8]. In addition, a displacement in the radial direction is expected for this non-centered catheter.

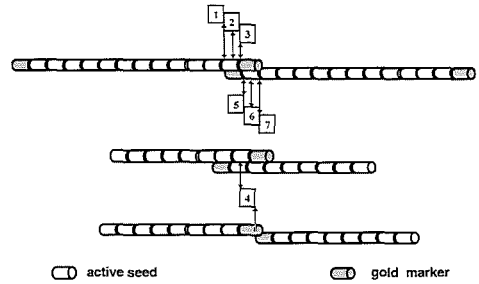


Fig. 1. Points related to the source, in which the dose was calculated.

As recommended by the EVA GEC ESTRO Working Group [17] the doses are reported at a distance of 2 mm from the source axis (= dose prescription distance) in several points along the irradiated length (Fig. 1):

| | |
|---|---|
| Dose point 1: | at 2.5 mm distal to the proximal end of the distal source |
| Dose point 2: | at 1.25 mm distal to the proximal end of the distal source |
| Dose point 3: | at the proximal end of the distal source |
| Dose point 4: | in the middle of the gap or overlap zone |
| Dose point 5: | at the distal end of the proximal source |
| Dose point 6: | at 1.25 mm proximal to the distal end of the proximal source |
| Dose point 7: | at 2.5 mm proximal to the distal end of the proximal source |

## 3. Results

Interventional length (length of the segment treated by balloon angioplasty, stenting and/or debulking techniques) varied between 33 and 95 mm. Of the treated lesions, six were located in the left anterior descending coronary artery (LAD), 20 in the right coronary artery (RCA), six in the left circumflex artery (LCX) and one in a vein graft.

Table 1
Summary of course of treatment and calculated doses

| Patient[a] | Segment[b] | Interventional length (mm) | Source distal (mm) | Dose distal (Gy) | Source proximal (mm) | Dose proximal (Gy) | Gap (mm) | Overlap (mm) | Dose 1 (Gy) | Dose 2 (Gy) | Dose 3 (Gy) | Dose 4 (Gy) | Dose 5 (Gy) | Dose 6 (Gy) | Dose 7 (Gy) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | LCX 13 | 46 | 30 | 22 | 40 | 22 | 9.6 | | 19.4 | 16.2 | 11.0 | 0.0 | 11.0 | 16.2 | 19.4 |
| 2 | LAD 6/7 | 57 | 40 | 16 | 40 | 16 | 1.8 | | 14.6 | 13.0 | 11.0 | 10.3 | 10.9 | 13.0 | 14.5 |
| 3 | LCX 13 | 46 | 30 | 16 | 30 | 16 | 2.4 | | 14.4 | 12.5 | 9.9 | 8.5 | 9.9 | 12.5 | 14.4 |
| 4 | LCX 13 | 38 | 30 | 16 | 30 | 16 | | 1.2 | 18.2 | 19.6 | 19.6 | 19.8 | 19.6 | 19.6 | 18.2 |
| 5 | RCA 2/3 | 72 | 40 | 16 | 40 | 20 | 0 | | 16.4 | 17.0 | 18.0 | 18.0 | 18.0 | 18.9 | 19.5 |
| 6 | RCA 4 | 56 | 40 | 20 | 40 | 20 | 8.4 | | 17.6 | 14.7 | 10.0 | 1.3 | 10.0 | 14.7 | 17.6 |
| 7 | LAD 6/7 | 70 | 40 | 16 | 40 | 20 | | 6.9 | 33.5 | 31.6 | 27.9 | 33.8 | 25.9 | 30.5 | 33.1 |
| 8 | RCA 1/2 | 70 | 40 | 18 | 40 | 18 | 0 | | 18.0 | 18.0 | 18.0 | 18.0 | 18.0 | 18.0 | 18.0 |
| 9 | LAD 7 | 40 | 30 | 16 | 30 | 16 | | 4.0 | 26.4 | 26.2 | 23.3 | 26.7 | 26.2 | 26.4 | 26.7 |
| 10 | RCA 1/3 | 34 | 30 | 18 | 30 | 20 | 5.8 | | 15.9 | 13.3 | 9.1 | 3.3 | 10.1 | 14.7 | 17.6 |
| 11 | RCA 1 | 63 | 40 | 16 | 40 | 20 | | 6.5 | 33.3 | 31.5 | 27.9 | 33.5 | 25.9 | 30.5 | 33.0 |
| 12 | RCA 2/3 | 38 | 30 | 20 | 30 | 20 | 4.2 | | 17.7 | 14.9 | 10.6 | 6.1 | 10.6 | 14.9 | 17.7 |
| 13 d | RCA 1/2 | 95 | 40 | 16 | 40 | 20 | 2.3 | | 14.5 | 12.8 | 10.6 | 10.0 | 12.1 | 15.6 | 17.9 |
| 13 p | | | 40 | 20 | 40 | 22 | | 6.6 | 38.8 | 36.4 | 31.8 | 39.2 | 30.8 | 35.9 | 38.6 |
| 14 | RCA 1/2 | 40 | 30 | 16 | 30 | 16 | | | | | | | | | |
| 15 | LAD 7/8 | 40 | 30 | 16 | 30 | 20 | | 0.7 | 17.8 | 19.4 | 20.7 | 20.5 | 20.1 | 20.8 | 20.6 |
| 16 | LCX 11/13 | 44 | 30 | 16 | 30 | 20 | | 2.8 | 25.1 | 27.2 | 26.0 | 27.2 | 24.4 | 27.1 | 26.5 |
| 17 | LAD 6/7 | 42 | 30 | 16 | 30 | 16 | 0.8 | | 15.1 | 14.3 | 13.4 | 13.3 | 13.4 | 14.3 | 15.1 |
| 18 | RCA 2/3 | 50 | 30 | 20 | 40 | 20 | 2.3 | | 18.0 | 15.8 | 12.7 | 11.2 | 12.7 | 15.8 | 18.0 |
| 19 | LCX 13 | 33 | 30 | 16 | 30 | 16 | | 0.7 | 17.1 | 18.0 | 18.3 | 18.3 | 18.3 | 18.0 | 17.1 |
| 20 d | RCA 1/4 | 90 | 40 | 16 | 40 | 20 | 4.6 | | 14.1 | 11.9 | 8.4 | 4.8 | 10.3 | 14.8 | 17.6 |
| 20 p | | | 40 | 20 | 40 | 20 | 6.4 | | 17.6 | 14.7 | 10.0 | 2.8 | 10.0 | 14.7 | 17.6 |
| 21 | RCA 3/4 | 35 | 30 | 16 | 30 | 16 | 2.8 | | 14.3 | 12.3 | 9.5 | 7.6 | 9.5 | 12.3 | 14.2 |
| 22 | LAD 7/8 | 50 | 40 | 16 | 40 | 16 | | 3.7 | 25.7 | 25.8 | 23.2 | 26.2 | 23.2 | 25.8 | 25.7 |
| 23 d | RCA 1/3 | 86 | 40 | 16 | 40 | 20 | | 10.5 | 34.0 | 31.7 | 27.9 | 35.5 | 25.6 | 30.7 | 33.6 |
| 23 p | | | 40 | 20 | 40 | 22 | 7.6 | | 17.6 | 14.7 | 10.0 | 1.8 | 11.0 | 16.2 | 19.4 |
| 24 | LCX 13 | 40 | 30 | 16 | 30 | 16 | | 8.5 | 30.0 | 27.7 | 23.9 | 31.0 | 23.9 | 27.7 | 30.0 |
| 25 | RCA 1/3 | 56 | 40 | 20 | 40 | 20 | | 7.6 | 37.3 | 34.6 | 29.9 | 38.2 | 29.9 | 34.6 | 37.3 |
| 26 | RCA 2/3 | 56 | 40 | 16 | 40 | 20 | 1.2 | | 15.0 | 14.2 | 13.4 | 13.6 | 14.3 | 16.6 | 18.4 |
| 27 | RCA 1/3 | 76 | 60 | 20 | 40 | 20 | | 9.6 | 37.6 | 34.7 | 29.9 | 39.2 | 29.9 | 34.7 | 37.6 |
| 28 | RCA 1/2 | 61 | 40 | 20 | 40 | 20 | | 14.4 | 37.6 | 34.7 | 29.9 | 39.9 | 29.9 | 34.7 | 37.6 |
| 29 | Vein graft | 59 | 40 | 20 | 40 | 20 | | | | | | | | | |
| 30 | RCA 1/2 | 65 | 60 | 20 | 30 | 20 | | 0.5 | 20.9 | 21.7 | 22.0 | 22.0 | 22.0 | 21.7 | 20.9 |
| 31 | RCA 1/2 | 60 | 40 | 20 | 40 | 20 | 1.2 | | 18.6 | 17.1 | 15.4 | 15.1 | 15.4 | 17.1 | 18.6 |
| 32 | RCA 1/2 | 60 | 40 | 22 | 40 | 22 | 0.6 | | 21.0 | 20.2 | 19.3 | 19.2 | 19.3 | 20.2 | 21.0 |
| 33 | RCA 2/3 | 60 | 40 | 16 | 40 | 20 | | | | | | | | | |
| 34 | RCA 1/2 | 50 | 40 | 20 | 40 | 22 | | 0.6 | 21.5 | 22.8 | 23.6 | 23.6 | 23.5 | 23.5 | 22.9 |
| 35 | RCA 1/2 | 53 | 40 | 20 | 40 | 20 | | 4.3 | 33.9 | 33.1 | 29.4 | 34.1 | 29.4 | 33.1 | 33.9 |
| 36 | LCX 11 | 60 | 40 | 16 | 40 | 14 | | 4.8 | 26.2 | 25.0 | 21.7 | 26.2 | 22.7 | 25.4 | 26.2 |

[a] d, distal; p, proximal.
[b] LCX, left circumflex artery; LAD, left anterior descending coronary artery; RCA, right coronary artery.

Radiation doses delivered to the distal segment were 16 Gy ($n = 20$), 18 Gy ($n = 3$), 20 Gy ($n = 10$) and 22 Gy ($n = 3$). The doses delivered to the proximal segment were 16 Gy ($n = 8$), 18 Gy ($n = 1$), 20 Gy ($n = 18$), 22 Gy ($n = 6$). In three patients treated with three source positions the dose to the middle segment was 20 Gy.

In 12 patients the 30-mm source was used twice, in 17 patients the 40-mm source and in two patients a combination of 30 and 40 mm. In two patients the 60-mm source train was combined with the 30 and 40 mm source, respectively. In three patients the 40-mm source was positioned three times.

No gap or overlap was seen between the two source trains in only two out of 39 cases. In 16 cases there was a gap ranging between 0.6 and 9.6 mm and 18 cases showed an overlap of 0.5–14.4 mm (Fig. 2). In three patients the measurement was not possible. In one patient the bending of the guide-wire was different in both images caused by the stiffness of the source in both positions. In another patient calibration was not possible as the catheter was not visible on the images. In the third patient the expiration was not maximal and the position of the diaphragm was not comparable on both images.

Dose calculations at 2 mm from the source axis show an underdosage varying between nearly 0 Gy and 19.2 Gy in case of a gap, depending on the distance between both sources, which is 0–87% of the prescribed dose. In case of overlap the maximal dose is 22 Gy for a 0.5-mm overlap and increases up to 39.9 Gy for a 14.4-mm overlap. This means that the overdosage varies between 110 and 200% of the prescribed dose at 2 mm from the source axis (Table 1).

## 4. Discussion

An important limiting factor in the use of endovascular irradiation, especially in β-radiation devices, is the current fixed and short source length, limiting the application to patients with short lesions. In γ-radiation the longest source

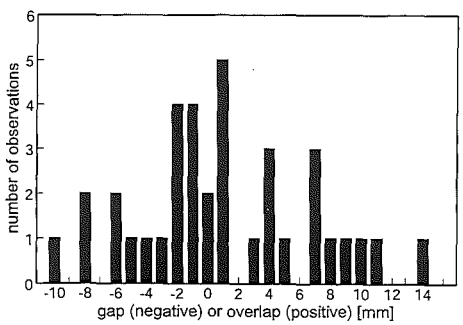


Fig. 2. Histogram showing the size of the gaps or overlaps and the number of times each has been observed.

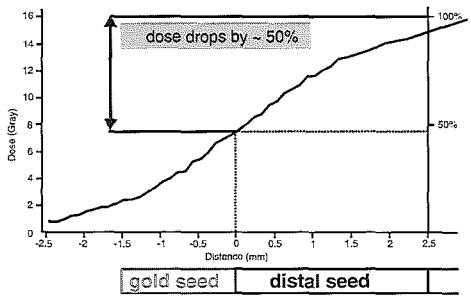


Fig. 3. Dose fall-off at the source edges starts at 2.5 mm within the edge of the source.

train available in the United States is 87 mm. The technique of manual multisegmental irradiation has its inherent problems, because of potential overlap or underdosage at the site of the juxtaposition of the sources.

The results of this series of patients demonstrate the inaccuracy of manual multisegmental irradiation in coronary arteries. The average deviation from a perfect junction, either gap or overlap, was 3.7 mm, with major consequences for the dose at 2 mm from the source axis delivered in this area.

The main reason for this lack of accuracy is the manual retrieval of the catheter to reposition the source.

Inaccuracies in source positioning are due to longitudinal movement of the source due to heart movement and in some cases to absence of anatomical landmarks. The longitudinal movement of the source may be diminished using a centering balloon catheter. But this movement can be an advantage, as it causes a wide dose fall-off which makes the junction less critical in terms of overdosage (Fig. 3).

Neither a gap, nor to much overlap seem to be desirable for a good treatment quality (Fig. 4). The long-term consequences are still unknown, as the experience is limited in terms of number of patients and follow-up time. In case of

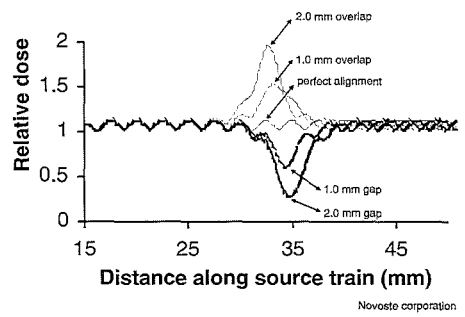


Fig. 4. Dose variations for respectively 1 and 2 mm gap or overlap compared to a perfect alignment of sources.

underdosage a result similar to that seen in geographical miss patients could be expected, resulting in a restenosis at the junction site (Fig. 5) [21]. In case of overlap the probability of serious long-term complications, such as aneurysm, necrosis, rupture or fibrosis of the vessel, is low as the high dose is delivered to a small tissue volume. Nevertheless, further and long-term follow-up of these patients is required to assess the long-term effects of this treatment technique.

The efficacy and safety of manual multisegmental irradiation has been evaluated by Waksman et al. [25] in 16 of 50 patients treated for diffuse in-stent restenosis and enrolled in the Beta-WRIST trial. Radiation was performed using a computerized afterloader with a 29-mm long $^{90}Y$ wire and a centering delivery catheter. The delivered radiation dose was 20.6 Gy prescribed at 1 mm from the surface of the balloon, for lesions $\geq$ 25 mm with manual multisegmental irradiation, with an overlap up to 3 mm. The calculated dose at the overlapped area did not exceed 70 Gy. After a follow-up period of 6 months there was no evidence of perforation or aneurysm at the overlapped segments. Besides the small number of patients, the follow-up time of 6 months is too short to evaluate long-term effects of radiation.

The use of coronary brachytherapy is increasing, treating patients with longer and more complex lesions in diffuse diseased arteries. The radiobiological mechanisms of vascular brachytherapy have not yet been understood completely and the target cells/structures have not been clearly identified. Clinical experience indicates that the target volume is the entire vessel wall in the coronary segment injured by the interventional procedures plus a safety margin on both sides, and not only the stenotic segment. The safety margin is recommended to be at least 5 mm in coronary arteries and 10 mm in peripheral vessels [18]. It has also to be considered that on both ends of the source the dose drops by 50% over the length of the last seed (Fig. 3). Longer radiation treatment lengths can be achieved by using either longer sources or a stepping source. The first solution means that sources of different lengths should be stored in the department, which is expensive and causes a lot of radioactive waste. The main disadvantage of such long sources is that dwell time and radiation dose cannot be adapted along the source length for variations in vessel diameter. As stepping source either a point source (2–3 mm length) or a short line source (10–20 mm length) can be used and the stepping can be performed manually or automatically. With a computerized stepping source one can achieve automatic and precise source movements, avoiding areas with over- or underdosing. The irradiated length can be precisely adapted to the interventional length, avoiding tight or excessive safety margins. Moreover, it offers the possibility to choose a different dwell time for each source position to adapt the dose according to the variations in vessel diameter. Multisegmental irradiation performed by lining up irradiations, as described in this paper, should be considered as a temporary solution. One should avoid underdosage between irradiations to reduce the risk for neointimal hyperplasia induced by a low dose of radiation [7,22,30].

## 5. Conclusions

The results of this study show the inaccuracy of manual multisegmental irradiation in coronary arteries, causing serious dose inhomogeneities at a distance of 2 mm from the source axis at the junction site between two source positions. Interpretation of clinical and angiographic results in terms of treatment efficacy will be very difficult in these patients, due to uncertainties in source position and related dosimetric consequences.

Moreover, a perfect junction will never be possible due to movement of the radiation delivery catheter in the vessel lumen. Manual multisegmental irradiation should not be recommended and used exceptionally as a temporary solu-

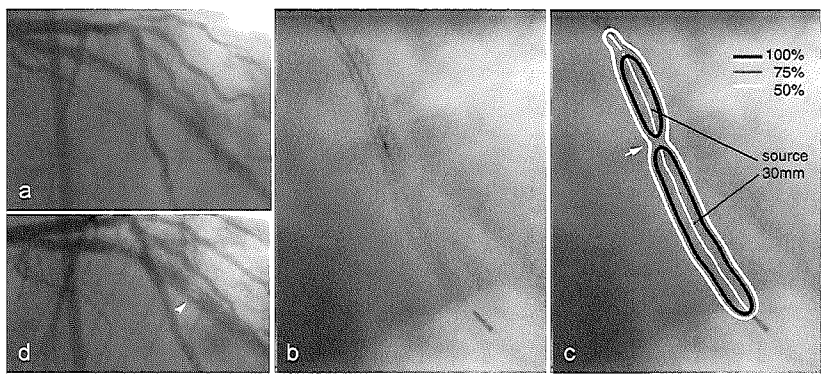


Fig. 5. (a) Long in-stent restenosis in segment LCX 13, treated with balloon angioplasty. (b,c) Thirty-millimeter source was used twice and measurement showed a gap of 2.44 mm. (d) Six months after treatment an angiogram showed a significant restenosis at the site of junction between source trains.

tion only in patients with very high risk of restenosis. Using longer line sources or source trains, or preferably a stepping source, is a more reliable and safer technique for treatment of long lesions.

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# CHAPTER 7

Optimal source position for irradiation of coronary bifurcations in endovascular brachytherapy with catheter based beta or Iridium -192 sources.

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# OPTIMAL SOURCE POSITION FOR IRRADIATION OF CORONARY BIFURCATIONS IN ENDOVASCULAR BRACHYTHERAPY WITH CATHETER BASED BETA OR IRIDIUM-192 SOURCES.

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**Abstract**

*Purpose*: Intracoronary brachytherapy after Percutaneous Transluminal Coronary Angioplasty (PTCA) is usually performed with catheter-based treatment techniques in a straight vessel segment. There is a growing interest for treatment of bifurcations, which requires consecutive positioning of the source in main vessel and side branch.

*Material and methods*: In-house developed software (*IC-BT doseplan*) is used to explore the optimal positioning of the source in modeled bifurcations with different shape for the source types available in our hospital, i.e. $^{90}Sr/^{90}Y$, $^{32}P$ and $^{192}Ir$. The results were summarised in a table that serve as positioning guide. The usefulness of these tables was tested on various clinical examples.

*Results*: Tabulated results for the modeled bifurcations yield an estimation of the distance between the sources (gap width) in relation to the geometry and source type: $^{90}Sr/^{90}Y$ gap range 3-8.5 mm, $^{32}P$ gap range 2-7 mm and $^{192}Ir$ gap range 3.5–8 mm. The average dose relative to 2 mm from the source axis is: $^{90}Sr/^{90}Y$ (mean±sd) 120±40%, $^{32}P$ 125±50% and $^{192}Ir$ 120±22%. The tables also provide the coarse location and value of maximum and minimum dose: $^{90}Sr/^{90}Y$ 220-60% , $^{32}P$ 230-55% and $^{192}Ir$ 170-85%. The data appear to be in agreement with the clinical examples.

*Conclusion*: Tabulated optimal gap widths are very useful for quick estimation of the required gap width for a given bifurcation and source type. In unfavourable geometries there is a risk of local underdosage. Individual treatment planning using a program such as *IC-BT doseplan* is then recommended.

## 1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is successful in 95% of the cases and the complication rate is very low, but the long-term high restenosis rate, 30-50% within the first year, is the major limiting factor of this treatment technique [4,5,10]. Restenosis is the result of damage to intima and media during PTCA. This includes a wound healing process with hyperproliferation and negative remodeling (constriction). Elastic recoil of the artery, local thrombus formation, neointimal cellular proliferation and vascular remodeling are factors contributing to a progressive narrowing of the residual lumen. [2]. Intravascular brachytherapy has proven to be an effective mode of preventing restenosis following PTCA. [7,8,12,15,16,18,19]

Promising results of several clinical trials and commercial availability of endovascular (coronary) radiation devices lead to the use of coronary radiation in clinical practice in patients with a high restenosis risk. However, most clinical trials included only short lesions in non-tortuous vessels, which could be treated with a single source position. In some trials, using radiation devices with long sources available, longer lesions were treated. Manual multisegmental irradiation was rarely performed in the major randomised trials. More recently there is a trend towards treating more complex lesions, such as long lesions and bifurcations. The radioactive source length and positioning should adequately cover the PTCA length. In clinical practice the source position is not very accurate due to lack of landmarks and heart contractions. To overcome this problem and to cover the injured length beyond the proximal and distal end of the PTCA balloon or stent a margin of at least 5 mm at each side of the PTCA or stent length and an accurate positioning of the source under fluoroscopy is recommended in order to avoid geographic miss. Geographic miss causing underdosing of the edges of the PTCA length leads to a higher restenosis rate at the edges than when these edges are adequately covered. [13,14] In the literature no data are available showing a relationship between high dose ($\geq$ 200% of the prescribed dose) delivered to the vessel wall and long-term complications. The only publication looking at efficacy and safety of manual multisegmental irradiation (maximal dose $\leq$ 70 Gy at a depth of 1 mm in the vessel wall) included only a small number of patients. Moreover, the follow-up time of 6 months was really too short to evaluate long term effects of radiation [6,17].

Irradiation of a bifurcation requires consecutive positioning of the source(s) in main vessel and side branch. The positioning of the source in the side branch relative to the source position in the main vessel depends on bifurcation geometry (angle between vessels) and source type (penetration depth). The distance between the proximal end of the source in the side branch and the source in the main vessel should be chosen carefully in

order to minimise under- or overdosage. Time pressure in the cathlab does not always allow for performing an individual treatment planning for each patient. A positioning guide readily available could keep the time between PTCA and irradiation as short as possible. Our initial goal therefore was to create guiding tables for different sources and various bifurcation angles for quick estimation of the gap width. The usefulness of these guiding tables was tested on clinical bifurcations and compared with individual treatment planning. It appeared that the tables provide a good approximation of the optimal gap width.

## 2. Material and methods

### *2.1. Treatment devices*

In the Erasmus MC–Thoraxcenter we have clinical experience with 3 treatment systems for intracoronary brachytherapy: the Novoste Beta-Cath™ System with a β-emitting $^{90}Sr/^{90}Y$ source trains of 40 and 60 mm length in 3.5 Fr non-centering catheters, the Guidant Galileo™ computerized afterloader with a 20 mm long β-emitting $^{32}P$ stepping source wire in 3.7 Fr centering catheters and the Cordis Checkmate™ manual afterloaders with γ-emitting $^{192}Ir$ source ribbons, 23, 39 and 55 mm in length in 3.7 Fr non-centering catheters.

### *2.2. Dosimetry software, IC-BT doseplan*

In order to calculate the radiation dose delivered to the vessel wall for a variety of sources, a computer program, called *IC-BT doseplan*, was developed. The computer code was developed in the Borland Delphi environment. The program runs on a Pentium 750 MHz pc and permits point dose calculations and plotting isodoses around the source configuration. For simple geometries the source and dose point coordinates are entered via keyboard or numerical input file. For entering real vessel geometry an image of the quantitative coronary angiography (QCA) in bitmap format is imported. The source and dose point coordinates are marked on the screen with the mouse. These coordinates are saved in a file that may be used and edited as an input file. An example of the input screen with an imported QCA image (fig.1a) and corresponding output screen with isodoses projected over lumen contours is shown in fig.1b. The pixel size is calibrated using the diameter of the guiding catheter. Once a source point is marked on the screen a circle with a predefined radius appears around that point. This is to assist the positioning of the next source coordinated at a fixed distance from the foregoing coordinate. In case of the Novoste Beta-Cath™ System the predefined distance is 2.5 mm, which is the length of each $^{90}Sr/^{90}Y$ seed. The distance between the source coordinates is considered as an individual seed or a segment of a line source (e.g. Guidant $^{32}P$-source). For dose calculation each source segment is subdivided into a number of point sources

(typically 2 point sources per millimeter in this study). The dose distributions around a mathematical isotropic point source were obtained from Monte Carlo simulation using the ITS 3.0 Monte Carlo code. The point source dose distribution for each source type is implemented as a look-up table with a 0.1 mm resolution. The calculation grid for isodoses and point dose calculations is 0.1 x 0.1 x 0.1 mm. The Monte Carlo results for point sources were verified by simulating a clinical source by a series of point sources and comparing the radial dose distribution with the data provided by the companies. The deviation for $^{90}Sr/^{90}Y$ and $^{32}P$ was less than ± 6% and ± 10% respectively, between 1 and 6 mm from the source axis. These maximal deviations are within the accuracy of the provided radial dose distribution and within the required accuracy for this study. In addition to the source and dose point coordinates a number of points or line segments may be added that indicate vessel contours or anatomical landmarks. These vessel contours or landmarks appear on the isodose plot (fig.1b).

*2.3. Idealized bifurcations in model calculations*

The basic forms of the modeled bifurcation have an inverted -Y or T geometry (fig.2). In the simple model calculations the real vessel morphology was ignored. The model of the bifurcation was a pipe like structure in a homogeneous water equivalent material. In fig. 2 both examples have a 60 degrees angle (Y-shape, left figure) and a 30 degrees angle (T-shape, right figure) between the main vessel and side branch.

Different dose points were defined to calculate the dose in the bifurcation (fig. 2):

point A: 2 mm from source axis in main vessel, half-way from bifurcation, where the contribution to the dose from side branch source is minimal and where no significant edge effects are expected.

point B: 2 mm from source axis in main vessel, opposite to side branch, at a fixed position near the origin of the bifurcation (Y-type) or at a position that follows the proximal end of source in side branch (T-type) when the source in advanced deeper into the side branch to increase the gap

point C: 2 mm from source axis in main vessel, at the side of branching vessel, at fixed position near the origin of bifurcation

point D: at about 1 mm depth in the vessel wall of the bifurcation, at the wedge formed by the branches

point E: 2 mm distal to point D and 2 mm from source axis in main vessel

point F: 2 mm distal to point D and 2 mm from source axis in side branch

point G: 2 mm from source axis at proximal end of source in side branch

point H: 2 mm from source axis in side branch, half-way from bifurcation, where the contribution to dose from source in main vessel is minimal and where no significant edge effects are expected.

All doses in points B through H are expressed as a percentage of the reference dose at a distance of 2 mm from the source axis [11] in the main vessel (point A). In the tube-like model point D always receives the maximum calculated dose. In a real vessel this wedge–like volume is more rounded and the dose at point D is an indication of the highest dose at the surface or in only a small volume. Therefore, the dose in points D, E and F are calculated separately, but reported as the mean of the relative doses. This is to compensate for the unrealistic high dose in point D and in that way yield an approximation of the mean dose in a small wedge-like volume formed by points DEF. The prescribed dose in point H (side branch) may be lower than the prescribed dose in point A (main vessel) depending of the lumen diameter. In the present study the doses in points A and H are equal, which is the case as the lumens have approximately the same diameter. However, with *IC-BT doseplan* the dosage in the individual vessel can be adapted according the actual protocol.

*2.4. Optimal gaps width tables*

Based on the sparse clinical experience available from literature, we suppose that for the present study, the dose distributions can be judged by the position of the 50% and 200% isodoses. In the model calculations the gap width was considered as optimal if the points A-H were within the 50 and 200 % isodose. In some cases an exceed of the maximum dose in small spots was allowed if underdosage in a signicant volume could be avoided.

*2.5. Verification results of model calculation on clinical examples*

To verify if the optimal gap widths obtained in the modelled bifurcations also apply for clinical bifurcations *IC-BT doseplan* was used to determine the gap width for a number of clinical examples for each treatment device. Fluoroscopic images of bifurcations were used as input for *IC-BT doseplan*. The vessel lumen was contoured and saved in a data file. In case of a centred source, the source positions were placed near the centre of the lumen contour. Non-centered catheters were positioned using the position of the guide wires, if available. Otherwise, the position was estimated based on diameter and stiffness of the catheter and geometry of the bifurcation. This estimated position of a floating catheter is subjective, but adequate because the position in the real lumen is subjected to displacement due to heart contraction [3]. To enable comparison of dose distribution, all calculated dose distributions are reported relative to the dose at 2 mm from the source axis. This is according the reference dose specification recommended by the AAPM TG-60 [9] and ESTRO [11] Again the optimal gaps width is obtained as the relative dose in the point A-H are within 50 and 200 % isodoses. Presenting dose distributions according the specific dose prescription of a particular device is beyond the scope of the paper.

## 3. Results

### *3.1. Model calculations of optimal gap widths.*

In the following sections the optimal gap widths are calculated for the idealized Y- and T-shaped tube-like model bifurcations and the 3 treatment devices.

#### *3.1.1. Calculation for a $^{90}Sr/^{90}Y$ beta source*

For the modelled Y-shape bifurcation treated with a $^{90}Sr/^{90}Y$ source the optimal gap between the 2 sources varies between 3 mm in case of a 90°angle and 8.5 mm for a 30°angle. This results in a maximal dose in point B or D of 140-220% of the prescribed dose and a minimal relative dose in point G or F of 60-90%. The mean relative dose delivered in the bifurcation, varies between 107 ± 22% and 143 ± 63 %. (Table 1a) For the T-shape bifurcation treated with the same source the optimal gap varies between 3 mm and 6.5 mm, depending on the size of the angle (90°-30°). The maximal dose is calculated in point D and varies between 150% and 190% of the prescribed dose. The minimal relative dose calculated in point G varies between 60 and 90%. The mean relative dose calculated in the bifucation varies between 114 ± 39% and 126 ± 46 (Table 1b).

#### *3.1.2. Calculation for a $^{32}P$ beta source*

Results of similar calculations for an Y-shape bifurcation treated with a $^{32}P$ source showed an optimal gap of 2 mm - 7 mm for an angle of respectively 90° and 30° (Table 2a). For the T-shape bifurcation treated with the same source the optimal gap is 3 mm - 6.5 mm depending on the size of the angle (Table 2b).

#### *3.1.3. Calculation for a $^{192}Ir$ source gamma source*

When using an $^{192}Ir$ source in a Y-shape bifurcation the optimal calculated gap is 4 mm - 8 mm for an angle of respectively 90° and 30°. (Table 3a) For the T-shape bifurcation treated with a $^{192}Ir$ source the optimal gap varies between 3.5 mm and 7 mm (Table 3b).

#### *3.1.4. Dependence of optimal gap width on bifurcation shape*

The optimal gap widths for the different source types and both basic bifurcation shapes are summarised in Figs. 3-5. The graphs clearly show that the optimal gap is dependent of both geometry and source type. It should be realised that the results are obtained for a centred source and for the same dose prescription in main vessel and side branch. Apart from a non-ideal geometry, in practice most catheters are non-centred and therefore the position in the lumen in not exactly defined. The influence of the non-ideal geometry and floating catheter on the optimal gap width is studied in a number of real bifurcations. Examples are shown in the following paragraph.

*3.2. Clinical examples of treatment planning on bifurcations*

*3.2.1. Example 1*

The first example (Fig. 6) is an inverted Y-shape bifurcation. The angle between the vessels is about 75°. The largest lumen diameter is 3.8 mm. In Fig.6A the dose distribution is shown for a $^{32}P$ source in centered catheter assuming the Guidant Galileo system was applied for irradiation. In the main vessel a 40 mm long source is inserted. This could be realized by two dwell positions of the 20 mm source. The source length in the side branch is 20 mm, that is one dwell position. The optimal gap for this bifurcation is about 3 mm, which is in accordance with Table 2a. The relative dose in points DEF is 156 ± 39 % and 79 ± 11 % in points CG (see also Fig.2a for the definition of the points DEF and CG). We also calculated the dose distribution for a 2 mm and a 4 mm gap (not shown). A 2 mm gap resulted in a more than 200 % point dose at the points DEF but the 100% isodose smoothly follows the vessel contour and point G is inside the 100% isodose. In case of a 4 mm gap the 100% isodose is close to points DEF. However point G is outside the 50% isodose. Depending on the clinical finding and the experience of cardiologist and radiation oncologist the gap will range between 2 and 4 mm.

For the same bifurcation but using a $^{90}Sr/^{90}Y$ source a non-centered catheter (Novoste Betacath device) it appeared that the optimal gap for is about 4 - 4.5 mm. Table 1a yields a 3.5 mm gap width, but this is based on model calculation for a centered source. The relative dose in points DEF is 118 ± 29 % and 95 ± 21 % in points CG. Depending on the gap width there is an overdose in point DEF or an underdose in point G.

The dose distribution for $^{192}Ir$ in a non-centered catheter is shown in Figure 6b. The source in the main vessel is 39 mm in length and 23 mm in the side branch in case of Cordis Checkmate source ribbons. The presented dose distribution is for an optimal gap of 4 mm, this is in agreement with Table 3a for a centered source. The relative dose in points DEF is 134 ± 23 % and 119 ± 18 % in points CG. Dose distributions were compared for 3.5 - 5 mm gap widths. It appeared that the degree of under- or overdosage is less critical for the $^{192}Ir$-gamma source than for the both beta sources. This is in accordance with the results of the model calculations. However, an optimal gap width exists and the most appropriate gap may be selected according to the clinical observations.

*3.2.2. Example 2*

Figure 7 shows a nearly T-shape bifurcation. The vessel lumen of the proximal part of the main vessel is about 3 mm. The initial angle is about 55° over the first 7 mm and then shows a sharp bend. After the bend the side branch is nearly parallel to the main vessel over a length of 15 mm. This complicates the dose distribution in the tissue volume between the branches. For a 40 mm long centered $^{32}P$ source in the main vessel and a 20 mm source in the side branch the optimal gap in this bifurcation is between 2.5 mm and 4.5 mm (not shown). The

optimal gap from Table 2b is 3.5 - 4 mm. The relative dose in points DEF is 231 ± 24 % and 72 ± 6 % in points CG. In case of a 40 mm non-centered $^{90}Sr/^{90}Y$ source in main vessel and side branch (shown in Fig.7), the optimal gap is between 3 mm and 4.5 mm. The optimal gap from the Table 1b is 3.5 - 4 mm. The relative dose in points DEF is 239 ± 13 % and 73 ± 8 % in points CG. As in the previous examples also the dose distribution for a 39 mm long Ir-192 non-centered source in the main vessel and a 23 mm source in the side branch was calculated. The optimal gap for the gamma source is between 3 mm and 4.5 mm, whereas the optimal gap from Table 3b is close to 3.5 mm. The relative dose in points DEF is 172 ± 7 % and 86 ± 5 % in points CG.

*3.2.3. Example 3*

The third example (Fig. 8) is at first sight an almost perfect inverted Y-shape bifurcation. The angle is about 45° and the vessel lumen of the main vessel and side branch is about 3 mm. However the proximal part of the main vessel is curved and this complicates the dose distribution in the tissue volume within the curved part of the source (points CG). Calculations were performed for 2.5 - 5 mm gaps for a centred $^{32}P$ source and 3 - 5 mm gaps for a $^{90}Sr/^{90}Y$ source in a non-centered catheter. It appeared that in this bifurcation there is no gap width that yields an acceptable dose in both points CG (dose > 50%) and points DEF (dose < 200%) at the same time. The optimal gap widths obtained from the guiding Tables 1a and 2a are 3.5 and 6 mm for $^{32}P$ and $^{90}Sr/^{90}Y$, respectively, but are not satisfactory in this case. For $^{32}P$ the relative dose in points DEF is 254 ± 50 % and 53 ± 9 % in points CG and for $^{90}Sr/^{90}Y$ the relative dose in points DEF is 247 ± 45 % and 73 ± 10 % in points CG. The best results in this example are obtained with an $^{192}Ir$ source, as shown in Fig. 7, using a 39 mm long non-centered $^{192}Ir$ source in the main vessel and a 23 mm source in the side branch. For this gamma emitter an optimal gap in this bifurcation would be about 5 mm. The optimal gap from the guide table is 6 mm. The relative dose in points DEF is 196 ± 22 % and 98 ± 10 % in points CG. In this case the gamma emitter is preferable in obtaining an acceptable dose in all critical points, but on the cost of a higher dose in the surrounding tissue compared to the beta emitters.

## 4. Discussion

*4.1 Model calculation versus clinical bifurcation.*

With the present catheter based devices for endovascular brachytherapy in coronary arteries irradiation of a bifurcation requires consecutive positioning of the source in main vessel and side branch. Intuitively it is clear that in order to avoid serious overdosage near the junction of the two source insertions some gap is needed.

Principally, the angle between main vessel and side branch determines the dose distribution in the bifurcation. In case of a sharp angle the distance between both vessel segments is small over a considerable length. In the wedge-like volume between the branches the contribution of both sources adds up, often resulting in an overdosage.

The model study in this paper shows that even in an ideal bifurcation and perfect centred position of the source in the vessel lumen the dose in the bifurcation is inhomogeneous. As demonstrated in this paper, in clinical bifurcations the optimal source positioning depends not only on the angle between both vessel segments, but also on the tortuousness of the vessel segments, the characteristics of the source and delivery catheter.

*4.2. Centred versus non-centred catheter*

The source position in the vessel lumen is influenced by the radiation delivery catheter used, e.i. centring or non-centring (floating) catheter. The actual position of both centred and non-centred catheter in the vessel lumen depends on vessel curvature and presence of residual plaque. In a centring catheter the source is positioned near the centre of the vessel lumen and there should be less longitudinal source motion during irradiation. With a non-centred catheter the source position in the vessel lumen changes with heart contractions and the longitudinal source displacement can reach a few millimetres. Heart contraction will also cause different bending of the source which may have a significant impact on dose distribution and dose maximum. All these factors cause more uncertainties for the dose calculation in a bifurcation using a non-centred than a centred catheter. The initial position is also influenced by its diameter and stiffness and by the flexibility of the source. The guiding tables are based on perfectly centred source. In the example on clinical bifurcations the validity of the table are studied. At appeared that the tables yield gap widths that usually avoid large overdosage in the wedge like volume, but on the risk of some underdosage in the opposite volume. In the presented examples the position of the non-centered catheter is based on the position of the guide wire (if available), taking into account the diameter and stiffness of the catheter. Because the dose planning is based on the 2 dimensional fluoroscopic imaging and the position of the non-centred catheter is not fixed in the lumen, we believe this approach is sufficient for the present study.

*4.3. Beta source versus $^{192}Ir$ source.*

The penetration depth of radiation is related to the type of isotope. Most sources in intracoronary brachytherapy are β-sources. β-particles have a short effective penetration depth (4-6 mm), depending on their initial energy, for higher energy particles penetration depth increases. At the present time we have the Novoste Beta-Cath™ System ($^{90}Sr/^{90}Y$, mean β-energy 2.3 MeV) and the Guidant Galileo™ ($^{32}P$, mean β-energy 1.6 MeV) available for routine clinical practice. Both β-sources were compared with $^{192}Ir$ in order to demonstrate the potential risk of

overdosage and to determine the best suitable source for irradiation of a bifurcation. The most critical dose point for overdosage (point D) is situated at 1 mm depth in the vessel wall of the bifurcation, between the two branches, point G is most sensitive for underdosage. Points A and H are expected to receive the prescribed dose at any instance. The other dose points give an impression of the dose distribution at defined points of interest.

Comparing the 3 different source types in the same inverted Y-shape bifurcation in model calculation as well as in the example clinical bifurcation (Fig. 6-8), the most homogeneous dose distribution is obtained with the Ir-192 source, due to the deep penetration the optimal gap width is less critical.

For instance, in the Y-and T-shape bifurcation (Tables 3a, 3b) with the $^{192}$Ir source the maximum dose is 170-165% of the prescribed dose, minimum dose 85%. Comparing both β-sources in a Y-shape bifurcation the dose maximum was lower using $^{90}$Sr/$^{90}$Y, with a somewhat lower minimum dose, compared to $^{32}$P. (Tables 1a, 2a). In a T-shape bifurcation the dose maximum was comparable with both β-sources, but the minimum dose was kept higher using $^{90}$Sr/$^{90}$Y. (Tables 1b, 2b)

Similar dose inhomogenities were described recently by Cygler et al.. [1] The authors used a $^{90}$Sr/$^{90}$Y source and performed 3D dose calculations with Theraplan plus for various overlaps and gaps between the source trains in mail vessel and side branch.

*4.4. Application of the gap from the guiding tables.*

The tables according to the theoretical calculations gives only an indication for the distance between the two sources, it does not take into account the bending of the sources and the source position is the vessel lumen.

The optimal gap calculations in the clinical examples show that the theoretically calculated values can be used to determine approximately the gap between both source positions. Radiation oncologist and cardiologist should decide for each individual patient the most appropriate dose distribution, taking into account the sites of under- and overdosage and the risk of restenosis at these sites of the bifurcation.

*4.5. Proposed clinical procedure and application of IC-BT doseplan*

The positioning of the sources in the main vessel and side vessel of a bifurcation should be based on angiographic data. Besides PTCA length and lumen diameters the angle of the bifurcation is the most important factor for determination of the optimal source positions in main vessel and side branch. To determine the angle of the bifurcation an angiographic image should be made with the bifurcation close to the image center and in a plane perpendicular to the central axis of the fluoroscope. In these conditions the most reliable projection of the angle between the vessels is obtained and the geometry is only slightly effected by foreshortening. The angle can be measured on the screen with appropriate QCA software or on a hard copy. The angle and characterization of

the geometry in T-shape or inverted Y-shape bifurcation serve as the entry for the pre-calculated gaps in the guide tables for a particular isotope (Table 1-3). This gap can in favorable geometries be used in conducting the treatment.

However, in less favorable geometries, e.g. heavy eccentric plaque burden or different dose specification at 2 mm from the source axis in the main vessel and side branch source positioning based on the tabulated data (gap width, maximum and minimum dose) is not possible. Then the best gap width should be established based on calculated actual dose distribution with a treatment-planning program like *IC-BT doseplan*. In case of *IC-BT doseplan* the QCA image is loaded and the vessel lumens are contoured on this QCA image (Fig.1). Next the most probable source trajectories in the vessels are drawn, taken into account which type of delivery catheter is used (e.i. centered catheter or stiffness and diameter of non-centered catheter). Note that the QCA image is only a snapshot of the geometry of the bifurcation in the maximum diastolic phase. The contouring and source position should be considered as the best guess. The gap from the appropriate table (table 1-3) now serves as start point of the proximal position of the second source insertion. Most likely the second source insertion will be in the side branch after irradiation of the main vessel. Then a number of isodoses are calculated and projected over the lumen contours. Locations with under- and overdose are inevitable. The radiation oncologist and cardiologist should decide whether these locations are incompatible with the particular clinical observations. For example, in a patient underdosage at a site where significant restenosis is seen may require a smaller gap, whereas in another patient the underdose may coincide with an area of low risk for restenosis. Based on additional clinical data the gap can be adapted until an acceptable dose distribution is achieved.

*4.5. General remarks.*

In all presented examples the optimal gap widths calculated by *IC-BT doseplan* based on the actual fluoroscopic image for a particular bifurcation and device were in agreement with the recommended gap width from the appropriate guiding tables. In some cases the maximum dose did exceed 200% (points DEF), but our aim was that the minimum dose (points EG) was never less than 50%. That is because low dose increases the risk of restenosis. The guiding table appeared to be valuable in avoiding overdosage in the presented examples. That is according the aim the tables are developed for. As a consequence the tables are insufficient to avoid underdosage and therefore isodoses based on the actual bifurcation geometry are indispensable. In that case the guiding tables provide the first guess for the gap width calculation with *IC-BT doseplan*. Consequently, the gap width is varied in the *IC-BT doseplan* input file until an acceptable dose distribution is obtained.

In the present study more detailed information from intravascular ultrasound imaging (IVUS) is not taken into account. IVUS may yield crucial information to cardiologist and radiotherapist on plaque burden, depth and asymmetry of the external elastic membrane (EEL) relative to the vessel lumen. This information may simplify the decision to accept or reject a given treatment plan. Although the guiding tables yield acceptable estimates of the optimal gap width, individual treatment planning based on actual vessel and source geometry is strongly recommended. But at the present the required software is not readily available.

**5. Conclusions**

This study demonstrates that the source positioning for irradiation of coronary bifurcations with the present commercial available catheter based devices is not unequivocal. The optimal source position clearly depends on the bifurcation geometry and characteristics of source and source catheter. Attempts to use tabulated results of theoretical calculations of optimal gap widths for various sources and idealised shape of bifurcations are insufficient for general clinical practice. However, the tables appear to be very useful for a quick estimation of the gap width for a given bifurcation angle and source type. The estimated gap width may usually prevent large overdosage, with a high risk of underdosage at unfavorable locations in the bifurcation. Iridium-192 yield the most homogeneous dose distribution in the bifurcation, at the cost of a relatively high dose outside the target volume (vessel wall). Due to the penetration depth of only several millimeters in tissue of beta particles the dose distribution around beta sources is confined to the vessel wall. This hampers a homogeneous dose distribution in a bifurcation. Treatment of bifurcations with line sources will always result in areas with serious over- and underdosage.

In clinical practice an individual treatment planning based on the actual fluoroscopic image of the bifurcation using a program such as *IC-BT doseplan* is recommended.

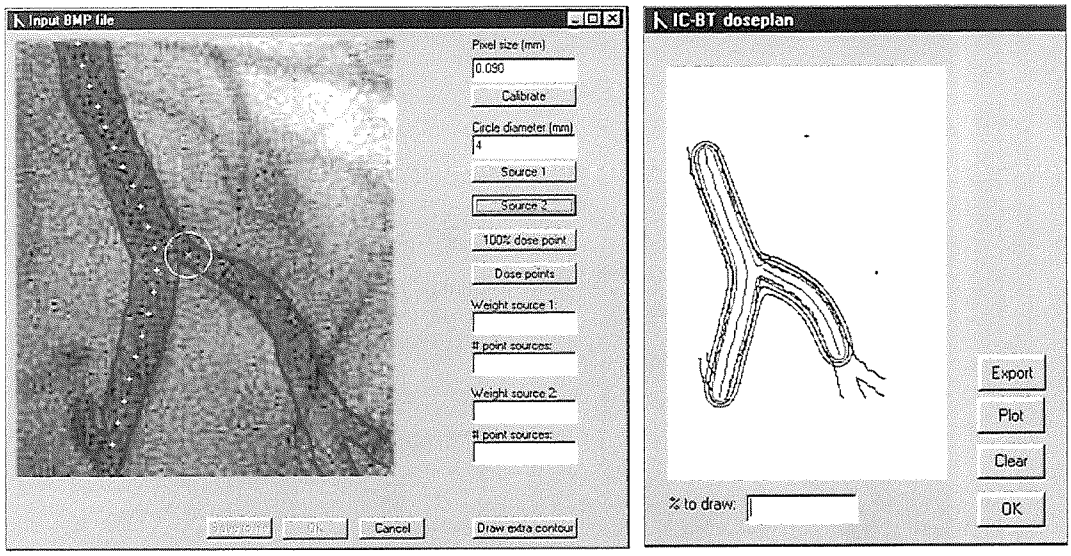


**Figure 1:** Example of the input screen (left) and output screen (right) of *IC-BT doseplan*. The pixel size is calibrated using the diameter of the guiding catheter. The source and dose point coordinates are marked on the screen with the mouse. The lumen contours drawn on the QCA image in the input screen, as well as the source position and dose point appear on the output screen with isodoses and can be send to a printer.

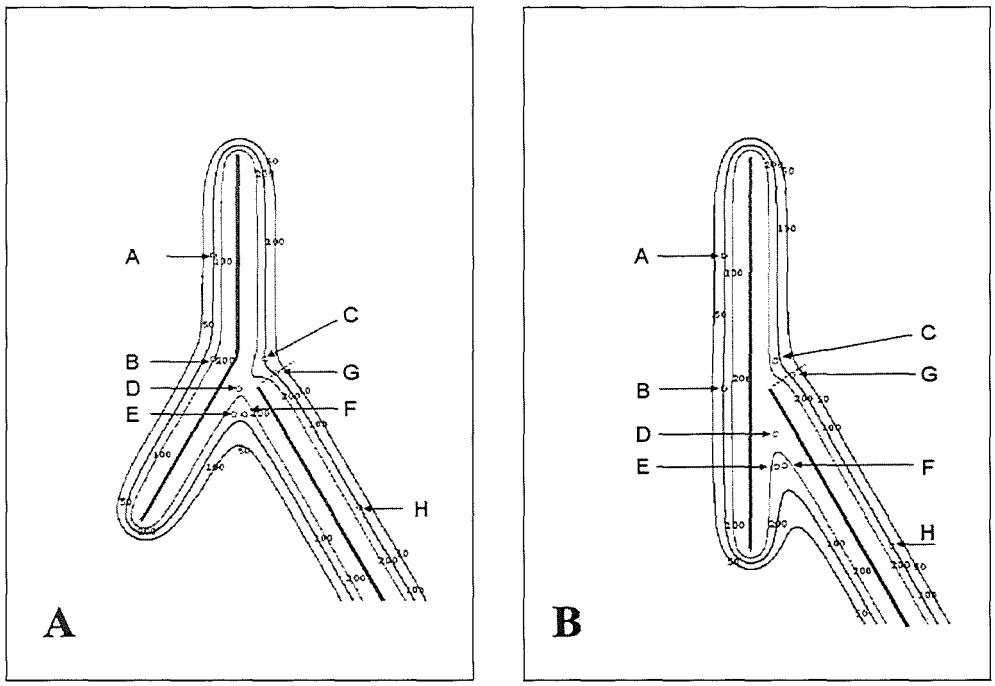


**Figure 2:** Inverted Y-shape bifurcation (left) and T-shape (right) bifurcation as used in the model calculations. The angle between the main vessel and side branch is 60 degrees in the Y-shape bifurcation and 30 degrees in the T-shape bifurcation. In all model calculations the sources were centred in the lumen. For each shape and angle of the bifurcation the dose in corresponding points A-H are calculated. These points A-H are defined in the text and are also used in comparing the dose in real bifurcations (Figs. 6-8). The shown 50, 100 and 200 isodoses are normalised to the dose in point A, which is at 2 mm from the source axis.

**Table 1a:** Optimal gap dimensions for a $^{90}Sr/^{90}Y$ beta source in inverted Y-shape bifurcation.

| Angle | Gap (mm) | Max. dose[§] (%) | Position | Min. dose[§] (%) | Position | Dose[§] ± sd (%) |
|---|---|---|---|---|---|---|
| 90° | 3 | 220 | B | 75 | F | 117 ± 52 |
| 75° | 3.5 | 180 | B | 90 | G | 116 ± 34 |
| 60° | 4.5 | 140 | B,D | 80 | G | 107 ± 22 |
| 45° | 6 | 140 | D | 75 | G | 143 ± 63 |
| 30° | 8.5 | 155 | D | 60 | G | 111 ± 34 |

[§] Dose expressed as percentage of the dose at 2 mm from the source axis.

**Table 1b:** Optimal gap dimensions for a $^{90}Sr/^{90}Y$ beta source in T-shape bifurcation.

| Angle | Gap (mm) | Max. dose[§] (%) | Position | Min. dose[§] (%) | Position | Dose[§] ± sd (%) |
|---|---|---|---|---|---|---|
| 90° | 3 | 150 | D | 90 | G | 115 ± 26 |
| 75° | 3 | 165 | D | 80 | G | 116 ± 31 |
| 60° | 3.5 | 175 | D | 75 | G | 114 ± 39 |
| 45° | 4.5 | 180 | D | 65 | G | 119 ± 40 |
| 30° | 6.5 | 190 | D | 75 | G | 126 ± 46 |

[§] Dose expressed as percentage of the dose at 2 mm from the source axis.

**Table 2a:** Optimal gap dimensions for a $^{32}P$ beta source in inverted Y-shape bifurcation.

| Angle | Gap (mm) | Max. dose[§] (%) | Position | Min. dose[§] (%) | Position | Dose[§] ± sd (%) |
|---|---|---|---|---|---|---|
| 90° | 2 | 230 | B | 80 | F | 134 ± 54 |
| 75° | 3 | 185 | B | 90 | F | 117 ± 39 |
| 60° | 3 | 180 | D | 85 | G | 124 ± 35 |
| 45° | 3.5 | 185 | D | 80 | G | 132 ± 51 |
| 30° | 7 | 185 | D | 65 | G | 136 ± 53 |

[§] Dose expressed as percentage of the dose at 2 mm from the source axis.

**Table 2b:** Optimal gap dimensions for a $^{32}P$ beta source in T-shape bifurcation.

| Angle | Gap (mm) | Max. dose[§] (%) | Position | Min. dose[§] (%) | Position | Dose[§] ± sd (%) |
|---|---|---|---|---|---|---|
| 90° | 3 | 150 | D | 80 | G | 112 ± 30 |
| 75° | 3 | 170 | D | 70 | G | 113 ± 36 |
| 60° | 3.5 | 180 | D | 70 | G | 123 ± 49 |
| 45° | 4.5 | 170 | D | 65 | G | 123 ± 54 |
| 30° | 6.5 | 190 | D | 55 | G | 132 ± 59 |

[§] Dose expressed as percentage of the dose at 2 mm from the source axis.

**Table 3a:** Optimal gap dimensions for a Ir-192 gamma source in inverted Y-shape bifurcation.

| Angle | Gap (mm) | Max. dose[§] (%) | Position | Min. dose[§] (%) | Position | Dose[§] ± sd (%) |
|---|---|---|---|---|---|---|
| 90° | 4 | 170 | B | 90 | F | 112 ± 29 |
| 75° | 4 | 150 | B | 100 | G | 116 ± 20 |
| 60° | 5 | 130 | B | 95 | G | 114 ± 16 |
| 45° | 6 | 140 | D | 90 | G | 117 ± 18 |
| 30° | 8 | 150 | D | 85 | G | 121 ± 27 |

[§] Dose expressed as percentage of the dose at 2 mm from the source axis.

**Table 3b:** Optimal gap dimensions for a Ir-192 gamma source in T-shape bifurcation.

| Angle | Gap (mm) | Max. dose[§] (%) | Position | Min. dose[§] (%) | Position | Dose[§] ± sd (%) |
|---|---|---|---|---|---|---|
| 90° | 3.5 | 135 | C | 100 | G | 121 ± 16 |
| 75° | 3.5 | 140 | D | 95 | G | 113 ± 15 |
| 60° | 3.5 | 160 | D | 95 | G | 119 ± 18 |
| 45° | 4.5 | 165 | D | 90 | G | 131 ± 30 |
| 30° | 7 | 150 | D | 85 | G | 127 ± 27 |

[§] Dose expressed as percentage of the dose at 2 mm from the source axis.

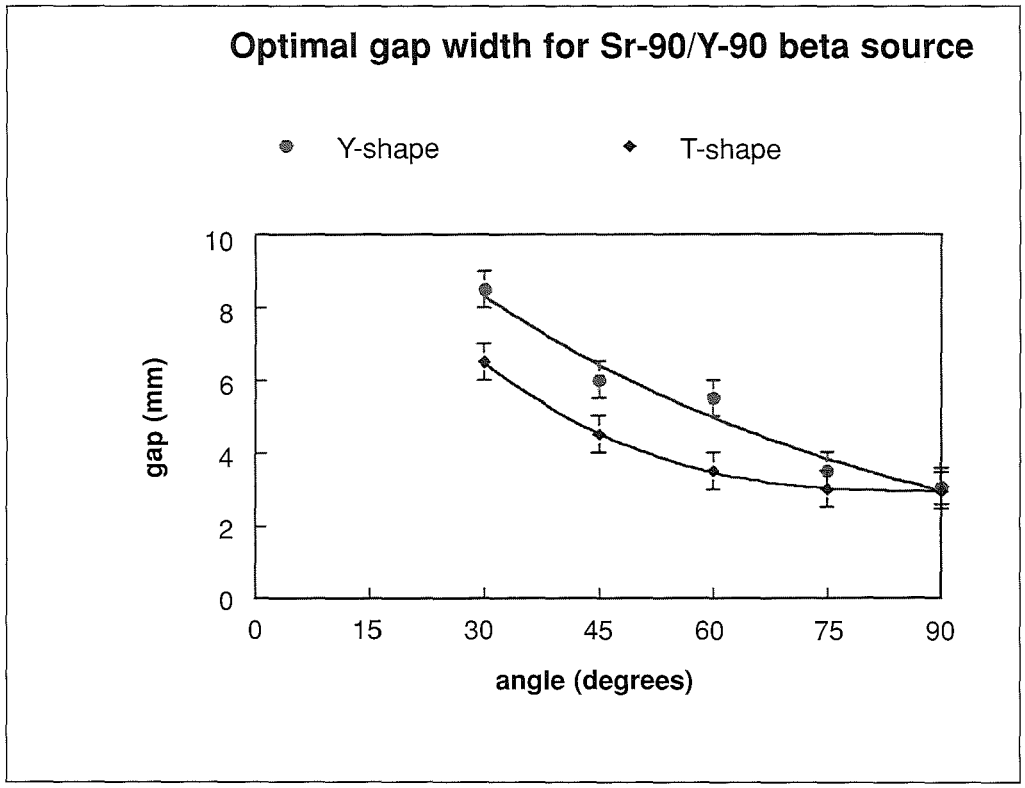


**Figure 3:** Optimal gap width for $^{90}Sr/^{90}Y$ beta source in ideal bifurcations with the sources centred in the lumen.

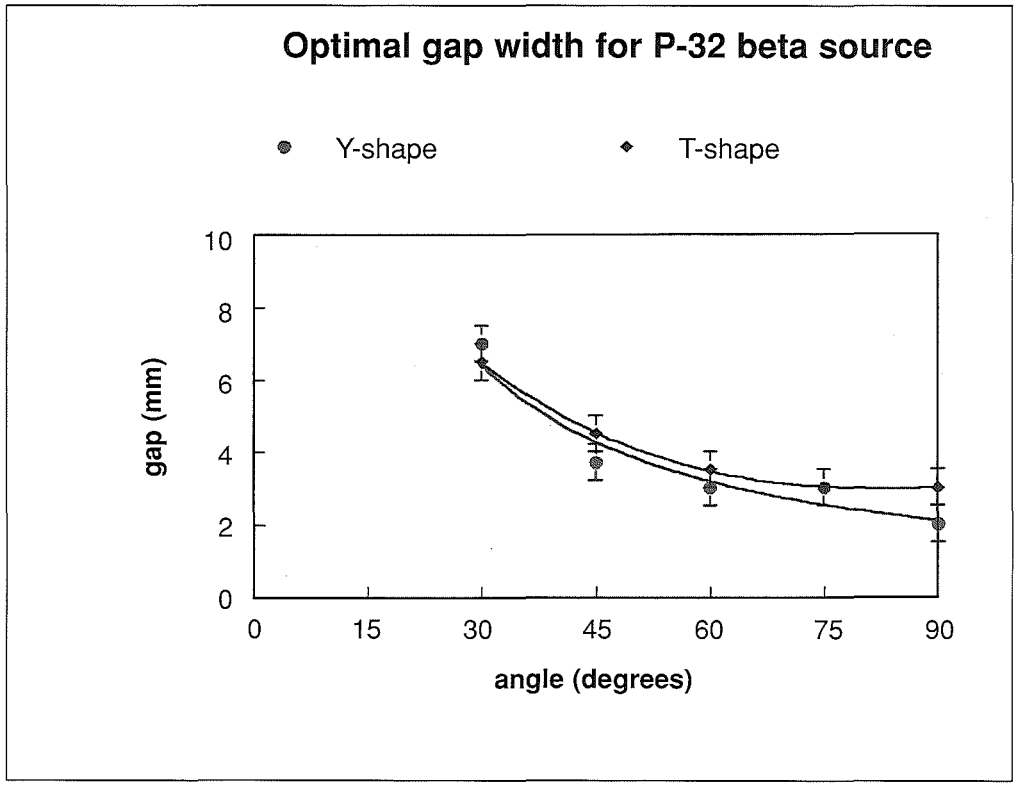


**Figure 4:** Optimal gap width for $^{32}P$ beta source in ideal bifurcations with the sources centred in the lumen.

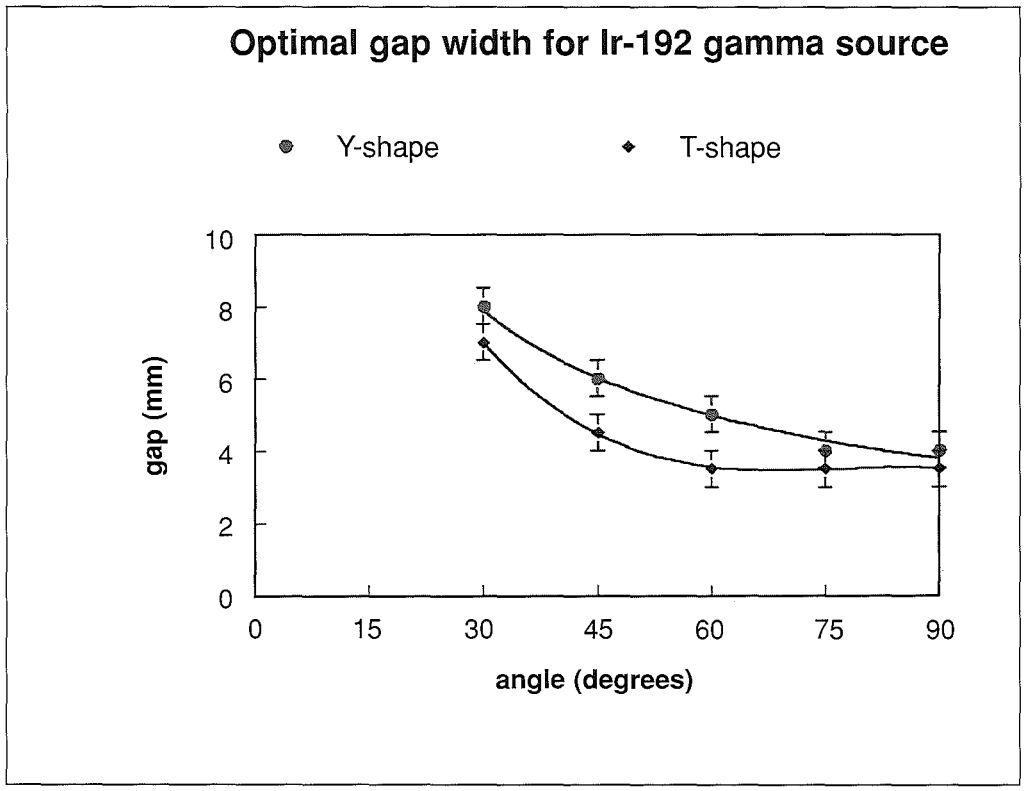


**Figure 5:** Optimal gap width for $^{192}$Ir gamma source in ideal bifurcations with the sources centred in the lumen.

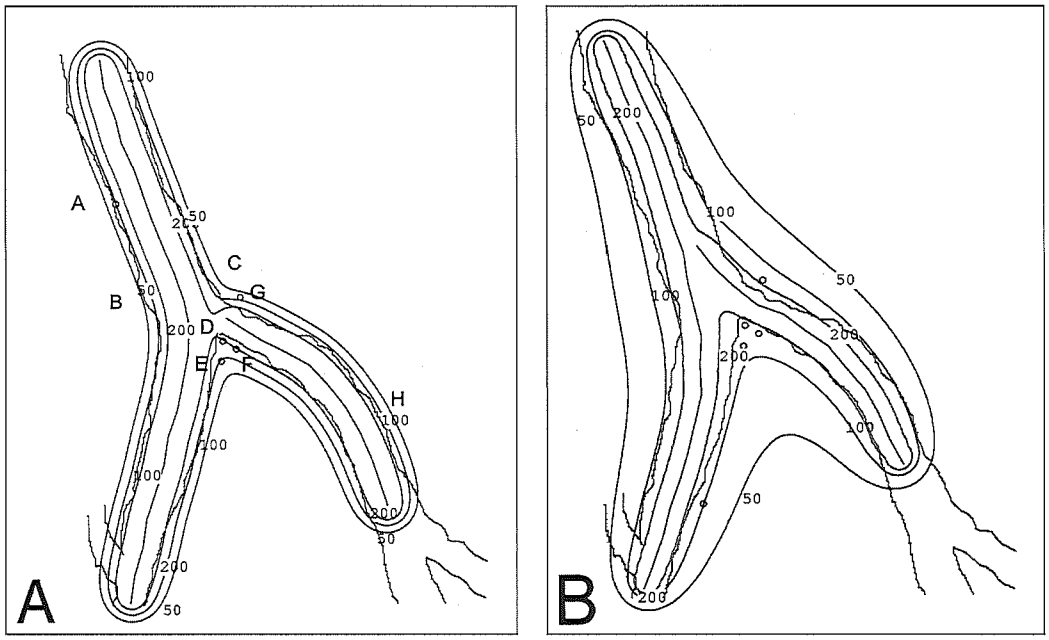


**Figure 6:** Example of an inverted Y-shape bifurcation. The angle between the vessels is about 75°. The largest lumen diameter is 3.8 mm. (A) The dose distribution of $^{32}P$ sources in centred catheters. (B) The dose distributions for $^{192}Ir$ in a non-centred catheters. The 100% isodose is at 2 mm from the source axis (see text). Due to the deep penetration of the gamma radiation compared to the beta radiation the optimal gap width is less critical for $^{192}Ir$ than for $^{32}P$.

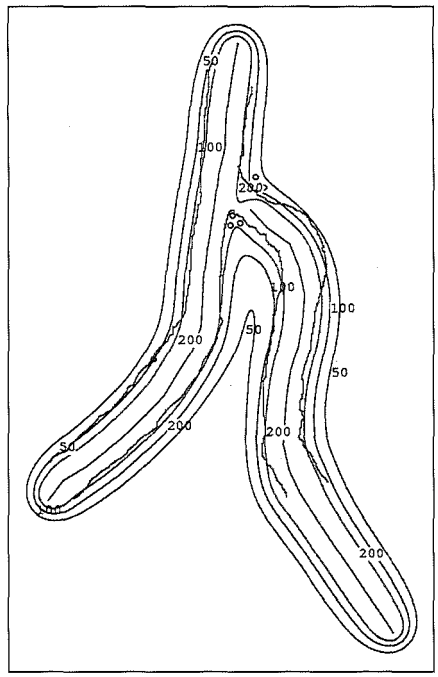


**Figure 7:** A locally T-shape bifurcation. The vessel lumen of the proximal part of the main vessel is about 3 mm. The initial angle is about 55° over the first 7 mm. Notwithstanding the complicated geometry of this bifurcation an acceptable dose distributions is achievable for all three discussed devices. From technical point of view the centred catheter is preferred, because the dose appeared highly sensitive for small displacements. The figure shows the dose distribution for a $^{90}Sr/^{90}Y$ beta source a non-centred catheter.

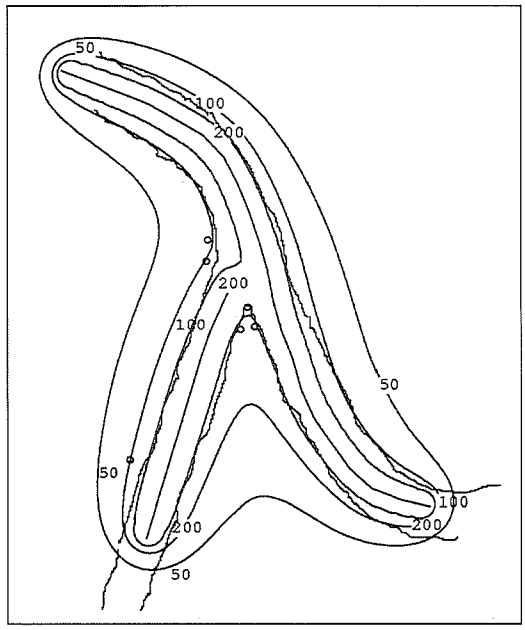


**Figure 8:** An almost perfect inverted Y-shape bifurcation. The angle is about 45° and the vessel lumen of the main vessel and side branch is about 3 mm. The proximal part of the main vessel is curved. This complicates the dose distribution in the tissue volume near the curved part of the source (points C and G). With both $^{32}P$ and $^{90}Sr/^{90}Y$ beta sources no acceptable dose distribution is achievable (not shown). Although still not ideal, the best dose distribution in this bifurcation is obtained for $^{192}Ir$.

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# PART IV

## Long term effects of radiation.

# CHAPTER 8

Late effects of ionizing radiation exposure.

V. Coen, E. Leter, P. Levendag

In: Vascular Brachytherapy: From Theory to Practice. (chapter 3, p. 27-39)
Editors: P. Tripuraneni, S. Jani, E. Minar, M. Leon
Remedica Publishing, London, January 2001.

# Late effects of ionizing radiation exposure

Veronique Coen, Edward Leter & Peter Levendag

## Classification of long-term effects

The biological effects of ionizing radiation can be classified as deterministic or stochastic. A deterministic effect will only occur above a certain dose, and both the probability and severity will increase steeply with increasing dose above this threshold. Examples of deterministic effects are erythema, cataract, and organ atrophy and fibrosis. A stochastic effect has no dose threshold; i.e. the probability increases with increasing dose, whereas the severity does not. Carcinogenesis and hereditary genetic mutations are examples of stochastic effects [1,2].

| | |
|---|---|
| Deterministic effects | Occur only above a certain dose<br>Probability and severity increase with increasing dose |
| Stochastic effects | No dose threshold<br>An 'all-or-nothing' effect |

In addition, the effects of ionizing radiation on normal tissues are commonly divided into acute and late effects. Acute effects occur hours to days after radiation exposure. Lesions are predominantly observed in rapidly renewing tissues such as skin, bone marrow, alimentary tract epithelia and germinal cells of the testis. Late side effects occur months to years after radiation exposure. Lesions are predominantly observed in slowly proliferating tissues such as the lung, kidney, heart, liver and central nervous system (CNS) [3,4].

| | Time lag after radiation exposure | Tissues affected |
|---|---|---|
| Acute effects | Hours to days | Skin, bone marrow, alimentary tract epithelia and germinal cells of the testis |
| Late effects | Months to years | Lung, kidney, heart, liver and CNS |

Most of the quantitative data concerning the effects of ionizing radiation in humans come from populations exposed to therapeutic radiation, and populations exposed to nuclear weapons, either deliberately or inadvertently. The survivors of the atomic

bomb attacks on Hiroshima and Nagasaki are perhaps the most important population studied because of the large number of subjects, the available follow-up data obtained by the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (REFR), and the fact that people of all ages and both sexes received a wide range of radiation doses [1,2].

## Deterministic effects

Details of some of the most common late deterministic effects of ionizing radiation are summarized in Table 1.

| Affected area | Observed late effects |
|---|---|
| Dermis | Atrophy of the dermis leading to contraction of the skin in the irradiated area. Late development of telangiectasia is seen as a result of progressive vascular radiation injury to the dermis (see Figure 1). |
| Gastrointestinal system | Mucosal atrophy and submucosal fibrosis, sometimes with progression to severe ulcerations, necrosis and fistulae. Late gastrointestinal effects may also be the result of persistent, very severe acute lesions such as ulcerations. |
| Liver | Late progressive fibrotic changes are seen in the liver causing dysfunction of this organ. |
| Lungs | Pneumonitis (seen at about 2–6 months post treatment) and pulmonary fibrosis (developing slowly over a period of several months to years). The latter occurs in almost 100% of patients receiving high doses of radiation, but may not be of clinical significance if the irradiated volume is small. |
| Kidney | It may take years for radiation damage to the kidney to be identified. Radiation nephropathy usually manifests as proteinuria, hypertension and impairment in urine concentration. Hypertension may develop up to 10 years after partial kidney radiation. |
| Bladder | Vascular ischemia accompanied by progressive mucosal breakdown at about 6 months to 2 years after radiotherapy. Fibrosis of the bladder wall with a reduced urine capacity may occur up to 10 years after irradiation. |
| Central nervous system | Late radiation necrosis of the brain typically occurs 3 months to several years after irradiation. Damage results in severe consequences such as paralysis. In survivors of the atomic bomb attacks on Hiroshima and Nagasaki, *in utero* exposure to ionizing radiation was shown to result in microcephaly and mental retardation. |
| Eyes | Radiation-induced cataracts of the lens were also observed in the survivors of the atomic bomb attacks on Hiroshima and Nagasaki, and in patients treated with therapeutic radiation in whom a proportion of the dose reached the eye. |
| Mouth | Xerostomia resulting from irradiation of major and minor salivary glands is a frequent complication of head and neck irradiation. |
| Thyroid | Radiation doses to the thyroid can produce hypothyroidism, which may be clinically overt or subclinical. |

**Table 1.** Deterministic effects of ionizing radiation [2,3,5].

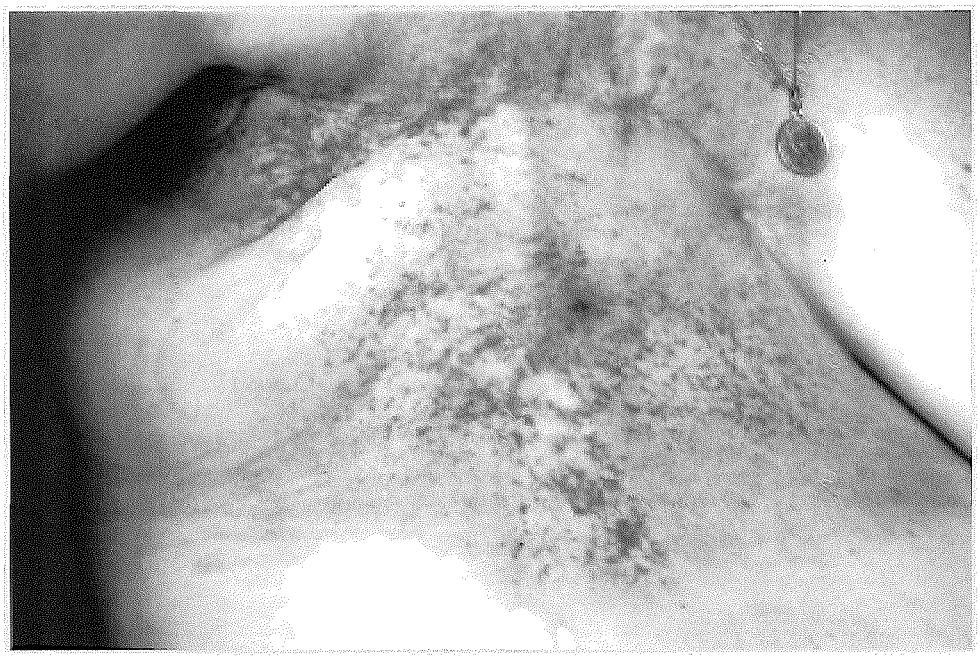

**Figure 1.** Telangiectasia after chest wall irradiation following mastectomy.

## Stochastic effects

Cancer appears to be the only stochastic somatic effect of ionizing radiation. The temporal pattern of incidence and morphology of most radiation-induced cancers cannot be distinguished from that of naturally occurring cancer; i.e. the incidence of these cancers follows the natural incidence and there is no unique radiogenic cancer. Nevertheless, radiation tends to induce only certain types of tumors in certain organs; the breast, thyroid and bone marrow appear especially sensitive to the carcinogenic effects of radiation [1,4,6].

A report by the REFR in 1996 described cancer mortality in the 1950–1990 cohort of the survivors of the atomic bomb attacks. The cohort contained 86,572 subjects. It is estimated that there were approximately 420 excess cancer deaths during 1950–1990, of which about 85 were due to leukemia and the remainder were due to solid cancers. Most of the excess cancer deaths caused by leukemia occurred in the first 10–15 years after exposure. For solid cancers, the pattern of excess risk is akin to a life-long elevation of the natural age-specific cancer risk [7]. Other disorders treated with radiation, in which an increase in the risk of cancer was observed, are listed in Table 2.

| Disorder treated | Patient population | Observed effects |
|---|---|---|
| Cervical cancer[8–10] | Women | Particular increase in cancer risk for those sites receiving large doses such as the bladder, rectum, vagina, vulva and ovary |
| Ankylosing spondylitis[11,12] | 14,000 patients, from 1935–1954, having radiotherapy administered to the spine | Significantly increased mortality due to leukemia, non-Hodgkin's lymphoma, multiple myeloma and cancers of the esophagus, colon, pancreas, lung, bones, connective and soft tissue, prostate, bladder and kidney |
| Enlarged thymus[13,14] | Children | Excess risk for both malignant and benign thyroid tumors |
| Ringworm of the scalp (tinea capitis)[15] | Caucasian children treated with X-rays during the 1940s and 50s | An excess risk for skin cancer in those areas also exposed to sunlight |
| Pulmonary tuberculosis[16,17] | Women fluoroscoped frequently in the first half of the 1900s | An excess incidence of breast cancer |
| Hodgkin's disease[18–20] | Women treated before age 30 | Markedly increased risk for breast cancer |
| Genetically transmitted repair deficiencies[21,22] | Ataxia-telangiectasia heterozygotes | Increased sensitivity to radiation-induced cancer |

**Table 2.** Stochastic effects of ionizing radiation.

In addition, miners exposed to radon in the mine atmosphere have shown a clear excess of lung cancer [23]. Hereditary effects of ionizing radiation have been epidemiologically identified in animals and plants [1]. However, so far, no significant increase in genetic disorders has been found in human populations exposed to ionizing radiation [24].

# Radiation-induced vascular lesions

Injury to vessels is one of the most common effects of therapeutic irradiation on normal tissues. Alterations in capillaries and arterioles are characteristic of delayed damage. Furthermore, many of the other delayed radiation effects, such as atrophy and fibrosis of organs can be explained by ischemia resulting from microvasculature damage. The severity of the changes that occur in vessels is often dose-dependent. The importance of the volume of normal tissue and dose-time factors needs to be stressed when considering tolerance of normal tissue [25].

Numerous publications have reported pericardial disease, diffuse myocardial fibrosis and coronary artery disease related to a dose of radiation delivered to the heart during treatment for a variety of thoracic tumors, such as Hodgkin's disease and breast cancer [26–29].

Radiation injury to the heart is most often manifested as pericarditis, although other complications such as chronic pericardial effusion and myocardial ischemia may occur. Information on radiation injuries from whole heart irradiation comes mostly from patients with Hodgkin's disease; partial volume radiation-induced heart complications are mostly from patients treated postoperatively for breast cancer [30]. The tolerance dose (TD) 5/5 (see below) of radiation is 4000 cGy for the whole heart and 6000 cGy for one-third of the organ. However, the TD 50/5 for partial and whole organ heart complications is rather speculative; doses of 7000 cGy for one-third of the heart volume, 5500 cGy for two-thirds and 5000 cGy for the whole organ are derived from sporadic information in the literature, extrapolation from TD 5/5 data and clinical experience. An inverse relationship exists between the volume of the heart that is irradiated and the tolerance dose [5].

TD 5/5 represents the dose level in cGy at which there is a 5% injury rate within 5 years
TD 50/5 represents the dose level in cGy at which there is a 50% injury rate within 5 years

## Morphology

The effects of ionizing radiation on blood vessel morphology are summarized in Table 3.

The morphology of radiation-associated coronary artery disease (CAD) is no different from that of spontaneous coronary artery disease[31]. Figure 2 shows a histologic section of the left circumflex coronary artery from a 67 year old patient, who was treated with radiotherapy for a carcinoma of the lung 7 years prior to sudden death[36].

| Vessel | Observed effects |
|---|---|
| Blood capillaries and sinusoids | These appear to be the most radiosensitive elements of the vasculature. This is related to the sensitivity of the endothelial cells[31]. As a late side effect of radiation, dilatation is commonly seen and, when superficially located, can be observed clinically as telangiectasia of skin or mucous membranes. Other lesions include asymmetry with irregularity of the wall, focal prominent endothelial cells and thrombosis. Earlier and more subtle alterations are detachment of endothelial cells from the basal lamina, thrombosis, rupture of capillary wall, loss of entire capillary segments and regrowth of lost vessels in some organs[31–34]. The most important end result of the acute damage by radiation is a reduction in the microvascular network, causing ischemia[33,35]. |
| Small arteries (≤100 μm external diameter) | These have a thin muscular wall, giving some protection from rupture. These segments may develop delayed necrosis. Common findings are subendothelial or adventitial fibrosis, hyalinization of the media (dense collagenous material) and accumulation of lipid-laden macrophages in the intima. Thrombosis may occur along with any of these changes[25,31]. |
| Medium arteries (100–500 μm) | These develop late lesions. The most common finding is intimal fibrosis, a deposition of collagen and myofibroblasts. Lipid containing macrophages (foam cells) may accumulate in the intima, sometimes causing narrowing or complete obstruction. Fibrin may be present among the foam cells and occlusive thrombosis may occur. Foam cell plaques, comparable to those seen in spontaneous atherosclerosis, in medium and small arteries are highly suggestive of radiation injury. Vasculitis may occur as a rare delayed lesion, probably focal and self-limited, and heals without therapy[25,31]. |
| Large arteries (>500 μm) | Larger arteries are less often affected than smaller vessels, perhaps because of their relatively large lumen size and thick wall, made out of relatively radioresistant cells. Lesions due to radiation can occur, such as myointimal proliferation, with or without lipid deposits, as well as mural or occlusive thrombosis and eventually rupturing of these large sized arteries[25,31]. |

**Table 3.** Effects of ionizing radiation on blood vessels.

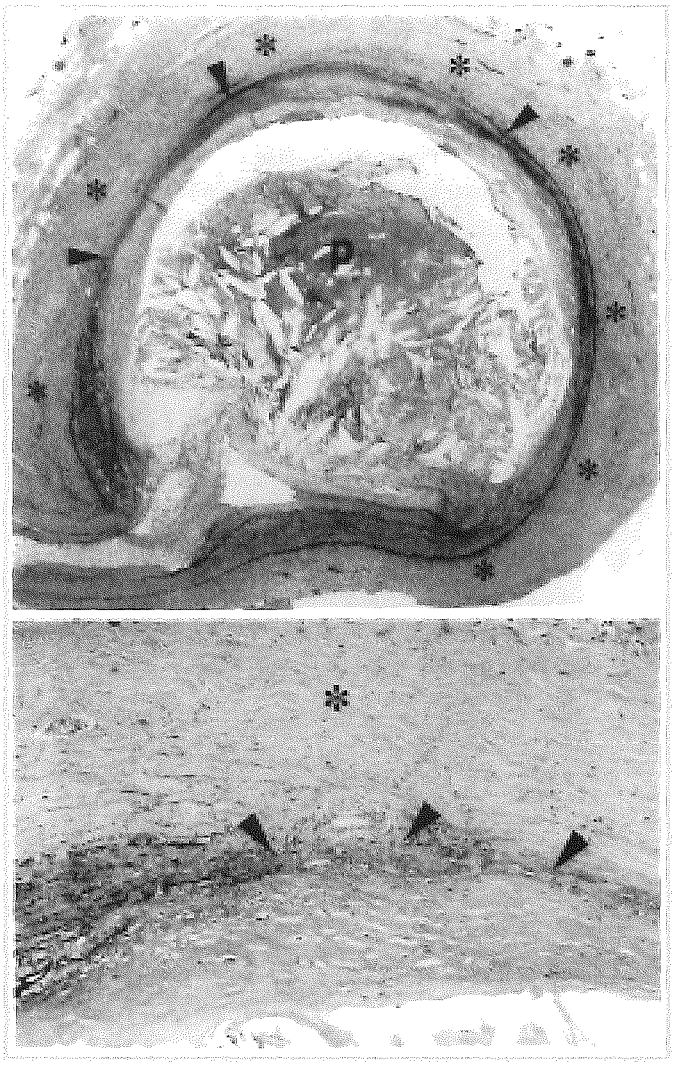

**Figure 2.** Histologic section of coronary artery 7 years after radiotherapy. **A.** Severe adventitial fibrosis (*) and focally extensive destruction of media (➤) with intimal plaque (p) causing >75% luminal narrowing, plaque consists mostly of necrotic core with cholesterol clefts. **B.** Thickened adventitia (*) with medial destruction (➤).

## Radiation therapy and coronary artery disease

A link between coronary artery disease (CAD) and radiation therapy has been noted, particularly in children and young adults of 20 years of age [28,29,37–39]. CAD appears 10–15 years after irradiation, but is affected by the usual risk factors of obesity, smoking and hypertension; it is not different in the irradiated patient. Preventive measures are desirable in reducing the incidence of CAD. The pediatric population, particularly females younger than 20 years of age, are at high risk for CAD following exposure to ionizing radiation and should be informed and encouraged to lead a healthy lifestyle. This same principle applies to young adults receiving mediastinal or mantle irradiation. Although CAD does occur, usually involving the left anterior descending artery (LAD), it is relatively uncommon and is multifactorial. Histology of the injuries shows fibrosis in the interstitium, with myocytes appearing normal, and capillary and arterial narrowing [40].

Several parameters must be considered in evaluation of radiation-induced injuries, including relative weight of the irradiation portals (and thus the amount of radiation delivered to different depths of the heart), the volume and specific areas of the heart irradiated, total and fractionated radiation dose, and the presence of other risk factors in each patient, such as age, weight, blood pressure, family history, lipoprotein levels and smoking [40]. Coronary thrombosis is relatively rare (it occurs in less than 5% of patients treated) and does not differ from spontaneous arteriosclerosis in non-irradiated patients [41].

Autopsy and patient series have documented the occurrence of CAD after radiation doses of 24 Gy and higher [42,43].

At autopsy, patients treated with anterior-weighted irradiation techniques had up to 75% narrowing of vessels, most frequently involving the proximal portion of the arteries. Media and adventitia were thickened or replaced by fibrotic tissue (diffuse or focal) and fibroblasts. Hyalinization, intimal thickening with collagen and histiocytes were also seen.

The incidence of CAD is increasing in patients with early breast cancer, particularly those with left-sided tumors treated with tangential fields including the anterior portion of the heart, and patients with Hodgkin's disease, as they become long-term survivors of their primary conditions. However, the exact incidence and extent of CAD are not clear.

There is evidence for an increased relative risk of CAD (approximately three times that of the normal control population) among survivors of Hodgkin's disease [28,37,39]. Among children, especially girls younger than 20 years, in whom the highest incidence of CAD is found, the relative risk increases to 40% [37,44]. In a retrospective study, Boivin et al. reviewed 4665 patients with Hodgkin's disease treated with

mediastinal irradiation. The average follow-up was 7 years. An excess number of deaths due to myocardial ischemia was reported, with a relative risk (RR) of 2.56 for myocardial infarction (MI). The RR for people treated at age ≥60 years was greater than for those irradiated at a younger age[28]. Hancock et al. reviewed 2232 Hodgkin's patients retrospectively, 79% of whom had received ≥40 Gy mantle field irradiation. The average follow-up was 9.5 years. Compared to a matched control population, fatal MI occurred in an unexpectedly large number of patients: 55 versus 17.3 expected for all treated patients; 35 versus 8.4 expected in patients treated by radiation alone. The overall RR for MI in patients treated by radiation alone was 3.8. This relative risk increased consistently with the latency period and was higher in patients treated by radiation at age <20 years (RR of 44)[26].

CAD is a significant side effect when (part of) the heart is included in the irradiated volume. The risk increases within the first 5 years and remains high for 10 years or more.

Because of the narrow range of doses used in radiation therapy for Hodgkin's disease it is not possible to determine whether there is a relation between dose and risk of CAD.

As a result of studies on radiation-induced pericardial and myocardial disease during the past few decades, modifications have been made to the treatment of mediastinal neoplasms. At Stanford University, after 1971, exposure of the heart to ionizing radiation was limited to 30–35 Gy (40–45 Gy prior to 1971) by use of subcarinal blocks. Also, both anterior and posterior fields were treated daily (versus only one daily) and the daily fractions were reduced from ≥2.2 to ≤1.8 Gy/day. These alterations in therapy significantly decreased the risk of pericardial disease and myocardial fibrosis, but did not alter the risk for fatal myocardial infarction; the RR was 3.7 prior to subcarinal blocking and 3.4 thereafter[26].

In 16 patients irradiated for Hodgkin's disease and evaluated after a mean follow-up of 9.3 years, a lower left ventricular performance was observed in patients subjected to irradiation of a large cardiac volume compared to those who had some portion of the cardiac volume shielded. No myocardial perfusion defects were evident in either group. Exercise tolerance testing was similar in both groups[45].

A meta-analysis of eight randomized trials showed a significant excess of late deaths among women who received postoperative radiotherapy for breast cancer, compared to those treated with surgery alone[46]. A meta-analysis some years later showed that the difference in overall mortality was no longer significant, due to the larger contribution of more recent and better designed trials[47]. Analysis of cause-specific mortality showed an excess of cardiac deaths among patients who received radiotherapy. The excess of cardiac deaths was found in patients treated using radiation techniques now judged as inappropriate. Even with the contemporary

megavoltage treatment for left-sided breast cancer, the LAD receives a substantial radiation dose, but the clinical impact is not yet confirmed.

The Danish Breast Cancer Group carried out two randomized trials in high risk breast cancer patients, comparing mastectomy and systemic treatment—chemotherapy in (pre)menopausal women and tamoxifen in postmenopausal women—with or without radiotherapy [48]. Morbidity and mortality from ischemic heart disease were not significantly altered by radiation after mastectomy. Only a small portion of the heart volume was irradiated and the dose was probably low because of the individualized radiation treatment.

This finding contrasts with results of previous studies that showed an increased risk of cardiac mortality [29,47,49–52]. Rutqvist et al. compared postoperative radiotherapy with surgery alone in breast cancer patients. They reported an excess mortality due to CAD (RR of 3.2) in patients who received high dose radiation to the heart as postoperative treatment for left-sided breast cancer [29,47].

However, two non-randomized studies showed no increased long-term risk of cardiac mortality in breast cancer patients treated with conservative surgery and radiotherapy [53,54]. These patients were treated with modern breast radiotherapy and small daily fraction sizes.

## Summary

A wide range of adverse effects have been reported as a result of long-term radiation exposure and these must be considered when embarking on a course of radiation therapy. However, if used sparingly and under the correct guidelines, the benefits of radiation therapy will far outweigh any adverse occurrences.

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# GENERAL DISCUSSION

## GENERAL DISCUSSION

### Overview of Clinical Trials

Coronary artery disease remains the major cause of death in industrialized countries. Worldwide more than one million procedures of percutaneous transluminal coronary angioplasty (PTCA) are performed each year. Despite the fact that a PTCA is successful in 95% of all cases and the complication rate being very low, restenosis remains the major drawback of succesful percutaneous coronary interventions (PCI).

Restenosis is the result of damage to intima and media during PTCA, inducing a wound healing process with hyperproliferation of cells and negative remodeling (constriction). Elastic recoil of the artery, local thrombus formation, vascular remodeling and neointimal cellular proliferation are factors contributing to a progressive narrowing of the residual lumen. [9]

Restenosis rates in short lesions are reported to be 30-50% for conventional balloon angioplasty (BA). [11,12,17] Stent implantation following PTCA minimizes the elastic recoil and vascular remodeling, but does not reduce neointimal cellular proliferation; in fact, it tends to initiate an increased proliferative response. In clinical trials stents have proven to reduce the restenosis rate significantly compared to balloon angioplasty. For example, in the STRESS and BENESTENT trials respectively a 24% and 31% reduction in restenosis rate was achieved after implantation of a single Palmaz-Schatz coronary stent for short lesions. [15,22] Nevertheless the restenosis rate remains high after stent implantation in long lesions, small vessels and diabetic patients.

Intravascular brachytherapy (VBT) has proven to be an effective mode of preventing restenosis following PCI. (Table 1-3) Several endpoints are used to evaluate the clinical trial results. Restenosis rate (RR) is an angiographic endpoint and is defined as a reduction of $\geq 50\%$ of the lumen diameter compared to the adjacent normal segments. Frequently used clinical endpoints are TLR (target lesion revascularization), TVR (target vessel revascularization) and MACE (Major Adverse Cardiac Events). TLR is the repeat revascularization (PCI or bypass surgery) of a lesion due to recurrent obstruction at the site of prior revascularization. TVR is the revascularization of a vessel which previously underwent PCI, it includes TLR and obstructive lesions requiring revascularization at other sites within the target vessel. MACE is a composite of various endpoints, including death, myocardial infarction and repeat revascularization as common components.

The Thoraxcenter in Rotterdam participated actively in several of these clinical trials. Chapter 1 reports safety and feasibility results of the first 31 patients with single de novo lesions, treated with VBT following PTCA, and

included in the BERT trial. At six months follow-up there were no serious complications. Coronary angiography showed a restenosis rate of 29%, which is still relatively high. As the goal of this trial was to assess safety and feasibility, no conclusions could be drawn according to effectiveness. In chapter 2 more than 250 patients are reviewed, which were treated with VBT, either with catheter-based systems or with radioactive stents, and included in various clinical trials. The integration of VBT in the catheterization laboratory appeared to be feasible and the different treatment techniques safe. The restenosis rates obtained in patients treated with a catheter-based technique were comparable with the published trial results: 29% in the BERT trial and 19% in the PREVENT trial. The 25 patients with recurrent in-stent restenosis, irradiated with the Beta-Cath system ($^{90}$Sr source) in compassionate use, had a restenosis rate as high as 53%, probably due to patient selection and the high rate of geographic miss (44%).

The promising results of VBT in clinical trials and the commercial availability of coronary radiation devices lead to the use of VBT in daily routine application. The RENO (REgistry NOvoste) registry reported in chapter 3 confirms that the results of randomized clinical trials can be replicated in a large cohort of unselected patients, treated with VBT in coronary arteries in 'routine clinical practice'.

Table 1: Completed randomized trials and registries for de novo lesions.

| Trial | Isotope | Number of patients | Randomi-zation | Centering balloon | Lesion length (mm) | Vessel diameter (mm) | Dose |
|---|---|---|---|---|---|---|---|
| BERT [13] | $^{90}$Sr/Y | 78 | Yes | No | < 15 | 2.3 - 3.5 | 12, 14 or 16 Gy at 2 mm radius |
| Geneva dose finding [31] | $^{90}$Y | 181 | Yes | Yes | < 15 | 2.5 - 4.0 | 9, 12, 15 or 18 Gy at 1 mm surface |

| Trial | % TLR | % restenosis | % restenosis, incl. edges |
|---|---|---|---|
| BERT | | 17 | 25 |
| Geneva dose finding | 13 ( 9 Gy)<br>7 (12 Gy)<br>7 (15 Gy)<br>7 (18 Gy) | | 29 ( 9 Gy)<br>21 (12 Gy)<br>16 (15 Gy)<br>15 (18 Gy) |

Table 2: Completed randomized trials and registries for de novo and restenotic lesions.

| Trial | Isotope | Number of patients | Randomi-zation | Centering balloon | Lesion length (mm) | Vessel diameter (mm) | Dose |
|---|---|---|---|---|---|---|---|
| Condado [6] | $^{192}$Ir | 21<br>22 lesion | No | No | | 2.5 - 3.5 | 20 / 25 Gy at 1.5 mm radius |
| SCRIPPS [25] | $^{192}$Ir | 55 | Yes | No | < 30 | 3.0 - 5.0 | IVUS based 8-30 Gy at EEM |
| Geneva Feasibility [32] | $^{90}$Y | 15 | No | Yes | < 20 | > 2.5 | 18 Gy surface |
| Bethacath [14] | $^{90}$Sr/Y | 1455 | Yes | No | < 20 | 2.7 - 4.0 | 14 / 18 Gy at 2 mm radius |
| BRIE [23] | $^{90}$Sr/Y | 149<br>175 lesion | No | No | < 20 | 2.7 - 4.0 | 14 / 18 Gy at 2 mm radius |
| PREVENT [19] | $^{32}$P | 105 | Yes | Yes | ≤ 15 | 2.4 - 3.7 | 0, 16, 20 or 24 Gy at 1 mm surface |
| RENO [30] | $^{90}$Sr/Y | 1098<br>1174 lesion | No | No | | 2.5 - 4.0 | 16.1-23 Gy + 2.3 Gy if stent |

| Trial | % TLR placebo vs VBT | % MACE placebo vs VBT | % restenosis placebo vs VBT | % restenosis, incl. edges placebo vs VBT |
|---|---|---|---|---|
| Condado | | 19 | | 27 |
| SCRIPPS | 45 vs 12 | 62 vs 19 | 36 vs 8 | 54 vs 17 |
| Geneva feasibility | 27 | 33 | | 40 |
| Bethacath | 15 vs 14 | 21 vs 19 | 34 vs 21 (BA)<br>33 vs 21 (stent) | 36 vs 31 (BA)<br>35 vs 45 (stent) |
| BRIE | 31 (TVR) | 34 | 10 | 34 |
| PREVENT | 24 vs 6 | 32 vs 26 | 39 vs 8 | 50 vs 22 |
| RENO | 16 (TVR) | 19 | | 24 |

Table 3: Completed trials and registries for in-stent restenosis.

| Trial | Isotope | Number of patients | Randomi-zation | Centering balloon | Lesion length (mm) | Vessel diameter (mm) | Dose |
|---|---|---|---|---|---|---|---|
| GAMMA I [16] | $^{192}$Ir | 252 | Yes | No | ≤ 45 | 2.75 - 4.0 | IVUS based 8-30 Gy at EEM |
| GAMMA II [27] | $^{192}$Ir | 125 | No | No | ≤ 45 | 2.75 - 4.0 | 14 Gy at 2 mm radius |
| WRIST [36] | $^{192}$Ir | 130 | Yes | No | < 47 | 3.0 - 5.0 | 15 Gy at 2.0/2.4 mm radius |
| LONG WRIST [2] | $^{192}$Ir | 211 | Yes | No | 36 - 80 | 3.0 - 5.0 | 15 Gy at 2.0/2.4 mm radius |
| BETA WRIST [34] | $^{90}$Y | 50 | No | Yes | < 47 | 2.5 - 4.0 | 20.6 Gy at 1 mm surface |
| START [18] | $^{90}$Sr/Y | 476 | Yes | No | ≤ 20 | 2.7 - 4.0 | 18.4-23 Gy at 2 mm radius |
| START 40/20 [24] | $^{90}$Sr/Y | 207 | No | No | ≤ 20 | 2.7 - 4.0 | 18.4-23 Gy at 2 mm radius |
| INHIBIT [35] | $^{32}$P | 332 | Yes | Yes | < 47 | 2.4 - 3.7 | 20 Gy at 1 mm surface |

| Trial | % TLR placebo vs VBT | % MACE placebo vs VBT | % in-stent restenosis placebo vs VBT | % restenosis, incl. edges placebo vs VBT |
|---|---|---|---|---|
| GAMMA I | 42 vs 24 | 44 vs 28 | 51 vs 22 | 55 vs 32 |
| GAMMA II | 23 | 30 | 25 | 34 |
| WRIST | 63 vs 14 | 68 vs 29 | 58 vs 19 | 60 vs 22 |
| LONG WRIST | 57 vs 30 | 59 vs 37 | 71 vs 32 | |
| BETA WRIST | 28 | 34 | 22 | 34 |
| START | 25 vs 14 | 29 vs 19 | 41 vs 14 | 45 vs 29 |
| START 40/20 | 11 | 19 | 15 | 25 |
| INHIBIT | 28 vs 10 | 34 vs 24 | 48 vs 16 | 52 vs 26 |

## Challenges in Endovascular Brachytherapy

### *Edge Effect ("candy wrapper" effect)*

Several investigators observed a difference in neointimal hyperplasia in response to VBT; an inhibition of restenosis in the middle of the treated segment and a lesser effect or worsening at the distal and proximal segments. Many factors can lead to this so called "edge effect" or "candy wrapper" effect, that is edge restenosis, which in fact arises from misalignment of the radioactive source with the injured vessel segment (geographic miss). Uncertainty in target localization is caused by the difficulty to visually estimate the proximal and distal lesion ends, mainly due to absence of anatomical landmarks. Besides, the barotrauma caused by balloon and/or stent contributes to arterial wall injury beyond their length. [5] Another factor is the longitudinal displacement of the source in the coronary vessel during the cardiac cycle, which has been observed in patients treated with a non-centered delivery catheter. [10] Also the dose falloff and penumbra effect at both ends of the source may play a role. Although controversial, some animal experiments have demonstrated that a low dose of radiation may increase the severity of neointimal proliferation [37]. This will occur most likely when the dose falloff arises in a vessel segment injured by balloon or stent.

The effect of geographic miss was demonstrated in chapter 2 in the group of 25 patients with recurrent in-stent restenosis, treated with the Beta-Cath system as a compassionate use application. The restenosis rate was 75% in the geographic miss areas compared to 33% in the non geographic miss areas.

Table 4 shows that the edge effect was demonstrated in different clinical trials; the angiographic restenosis rates in the analysis segment (source length ± 5 mm margin on both ends) was higher than in the balloon injured or stented segment.

The benefit of using longer sources and adequate margins was confirmed by comparing the results of START and START 20/40 trials. The restenosis rate of the stented segment was similar in both studies, whereas the restenosis rate in the analysis segment was markedly decreased.

IVUS analysis of 21 patients included in the BERT trial, as described in chapter 5, showed a different pattern of vessel remodeling in the irradiated segment and at both edges, resulting in a narrowing of the lumen at the edges compared to the irradiated segment.

Table 4: Edge effect in clinical trials.

| Trial | Restenosis rate (%) balloon injured / stented segment | Restenosis rate (%) analysis segment |
|---|---|---|
| START | 14 | 29 |
| START 20/40 | 15 | 25 |
| SCRIPPS | 8 | 17 |
| GAMMA I | 22 | 32 |
| GAMMA II | 25 | 34 |
| WRIST | 19 | 22 |
| BETA WRIST | 22 | 34 |
| BRIE | 10 | 34 |
| PREVENT | 8 | 22 |
| Betacath | 21 (BA)<br>21 (stent) | 31 (BA)<br>45 (stent) |

***Treatment Length***

Local failures at stent edges or near the ends of balloon angioplasty in coronary clinical trials underline the necessity of an adequate treatment margin. The length of the injury is determined by the angioplasty balloon length, taking into account some movement or sliding of the balloon. The radiation source is moving with heart contractions and therefore the uncertainty in target localization should be taken into account, as well as an additional margin for the penumbra effect of the source.

Tripuraneni et al. [28] proposed definitions of standardized terminology for treatment lengths based on gross (GTV), clinical (CTV) and planning target volume (PTV) concepts, definitions quite accepted in radiation oncology. The gross target length (GTL) is the length of the (re)stenotic lesion, which is usually determined from an angiogram or IVUS. Clinical target length (CTL) defines the length of vessel injury due to angioplasty, atherectomy, stent deployment, etc.. The planning target length (PTL) is the CTL, adding a margin for uncertainty for heart/catheter movement and uncertainty in target localization. The displacement of source and catheter relative to the vessel varies from 0.4-5.4 mm for a $^{192}$Ir source in a non-centered catheter; the recommended margin to account for this displacement is 3-5 mm. [10] The uncertainty in target localization refers to inaccuracies in the visual delineation of proximal and distal ends of the CTL and is estimated to be 2-

5 mm. The treatment length includes the PTL and an additional margin to account for the penumbra effect. The penumbra is defined as the distance from the source end to the prescribed isodose line at the distance from the source at which the dose is prescribed, it depends on the isotope.

As VBT started to be used in routine clinical practice for patients with a high risk of restenosis, there was a trend towards treating longer and more complex lesions. In chapter 6 we analysed 36 patients, included in the RENO registry. Their target length was too long for the source lengths available in our department at that time. To achieve the required radiation length manual multisegmental irradiation was performed. The goal of this analysis was to study the accuracy of manual multisegmental irradiation in coronary arteries. This technique appeared to be inaccurate, causing serious dose inhomogeneities at the junction site between the two source positions. Moreover, a perfect junction will never be possible due to movement of the radiation delivery catheter in the vessel lumen. Using longer line sources or a stepping source seems to be a more reliable and safer technique for the treatment of long lesions.

As we were also asked several times to irradiate a bifurcation, we did some theoretical calculations in different bifurcation shapes for the different sources available (chapter 7). Source positioning for irradiation of coronary bifurcations with the present commercial available catheter-based devices is not obvious. The use results of theoretical calculations is insufficient for general clinical practice. They only provide an estimation of the gap width for a given bifurcation angle and source type. Treatment of bifurcations with line sources will always result in areas with serious over- and underdosage. In clinical practice an individual treatment planning based on the actual fluoroscopic image of the bifurcation is recommended. Ideally a single stepping source with variable dwell times and an individual planning should be used, to provide a homogeneous dose to all treated vessel segments.

***Dose***

Clinical dose response data come from dose escalation studies, comparison of different studies with the same protocol entry criteria and dose variations within protocols. The Geneva dose finding study compared 4 dose levels: 9 Gy, 12 Gy, 15 Gy and 18 Gy. The angiographic restenosis rate decreased from 29% to 15% with increasing dose. In the randomized LONG WRIST trial for long in-stent restenotic lesions the radiation dose was 15 Gy. In the following registry similar lesions were treated with 18 Gy, but in half of the patients antiplatelet treatment was also prolonged. Angiographic and IVUS data showed a beneficial effect of a higher radiation dose

on preventing neointimal hyperplasia. [1] Also in the GAMMA I trial [26] the angiographic in-lesion restenosis rate showed a dose response effect in favour of the higher doses.

***Centering***

Whether centering a radioactive source in a catheter-based delivery system is necessary for optimal efficacy and safety is a matter of debate. By placing a source in the center of a circular target a circumferentially even dose distribution can be obtained, however the diseased vessel wall is often asymmetric. Centering the source in the vessel lumen can prevent high doses to the luminal surface. As the radial dose falloff is steeper for β-sources than for γ-sources, source centering seems to be a requirement for low energy β-sources, such as $^{32}P$, and for large diameter vessels. The positive data of clinical trials (SCRIPPS, WRIST, GAMMA, START) using a non-centered source in coronary arteries, treated with γ or high energy β-sources, argue that centering is not required.

***Gamma- versus Beta Radiation***

Beta-emitters have advantages over γ-sources in terms of half-life, high specific activity and dose-rate. The treatment times of β-sources are less than 5 minutes. Their major disadvantage is the rapid dose falloff, resulting in decreased dose at greater depths. This dose inhomogeneity can be improved by using a centering balloon. Gamma-sources have a superior depth dose gradient, but the irradiated volume of surrounding tissues is increased and additional radiation protection is required.

Clinical feasibility and randomized trials have been conducted with various isotopes and dose prescription methods, treating de novo lesions and in-stent restenosis. The efficacy of both γ and β-radiation to treat in-stent restenosis have been proven in large multicenter randomized trials. Currently there is no published randomized trial comparing γ and β-radiation. Recently P. Stella (EuroPCR, Paris, 2002) presented the results of the BEGUT trial, suggesting some clinical advantage for γ-radiation (TLR 12% vs 5% and MACE 10 vs 35%).

***Dose Prescription and Treatment Planning***

The prescribed dose for VBT in coronary arteries is still not well defined. In clinical trials different treatment methods and a variety of dose prescription points have been used. This makes comparison of different dose regimens very difficult. Moreover, differences in dose rate make it even more complicated; treatment times with $^{192}$Ir may be in the order of 20 minutes, whereas for a β-source it is about 5 minutes.

Most VBT treatments are prescribed by stipulating the dose to a single specified point in the artery, relative to the source or the delivery catheter. In some trials (SCRIPPS, GAMMA I) the dose prescription was more complex using intravascular ultrasound (IVUS). A dose of at least 8 Gy and not more than 30 Gy was delivered to the external elastic membrane (EEM). This wide dose range indicates the variability in position of the EEM relative to the position of the radioactive source. As described in chapters 4 and 5, IVUS was also used to analyse retrospectively the radiation doses delivered to a particular vascular structure, calculating dose volume histograms. These showed an enormous variability in doses for a defined structure in a single patient. A centered source significantly reduces the spread of dose, although the effect was greater for β than for γ-sources. [4] IVUS guided dose prescription based on dose volume histograms might be very useful. Chapters 4 and 5 also demonstrate the importance of IVUS as a tool to understand the mechanism of action of irradiation and to identify the target volume.

***Logistics and Responsibilities***

VBT is a multidisciplinary team effort that requires the cooperation of many specialities within the medical profession.

The hospital needs a license to store and use the radioactive material, also approved by the local radiation safety officer. Good communication between the departments of cardiology and radiation oncology and the cooperation of a health physicist are the cornerstones of a succesful VBT program. There is a close collaboration needed between the cardiologist and nurses on the one hand and the radiation oncologist and technicians on the other hand. Specific actions, responsibilities and competencies should be clearly determined. A separate room to prepare and store the radioactive sources is needed, access to the safe containing the sources should be controlled. Radiation safety training of the personnel is strongly recommended.

In our center the cardiologist determines the lesion and intervention length and the reference vessel diameter. He performs the angioplasty and introduces and removes the radiation delivery catheter. Cardiologist and radiation oncologist together will define CTL and PTL and the position the radiation delivery catheter (with or without dummy source). The task of the radiation oncologist and technician is to determine the source and treatment length, to prescribe the dose and calculate the treatment time and finally perform the radiation treatment. The total duration of the catheterisation procedure will be protracted by about 20-30 minutes.
The tasks of the radiation physicist are installation and commissioning of sources and devices, dosimetry and radiation safety of personnel and patients.

**Late Effects in Endovascular Brachytherapy**

***Late Thrombosis***

Late thrombosis is defined as thrombosis or occlusion of a vessel more than 30 days after treatment, it can be silent or symptomatic, often resulting in an acute myocardial infarction (MI). This complication related to VBT is reported to occur in approximately 6 to 10% of the irradiated patients. [2,14,19,34,36] From our experience in Rotterdam 6.6% late thrombosis was reported after catheter-based β-radiation. [8] Pooled retrospective data from SCRIPPS, WRIST and GAMMA I showed that symptomatic late thrombosis only increased if stenting was performed at the time of radiation. If a new stent was implanted the rate of symptomatic late thrombosis was 6.7% after radiation versus 0.7% without radiation, and without stent placement 1.2% versus 1.4%, respectively. Long-term antiplatelet therapy for at least 6 months is recommended, according to the results of the SCRIPPS III and WRIST Plus trials, in which the late thrombosis rate was significantly decreased. [29,33] During the Betacath trial the duration of antiplatelet therapy in stented patients was prolonged from 30 days to at least 60 days, which decreased the late thrombosis rate from 6.8% to 1.3%. [14]

***Other Late Sequelae***

An overview of late effects due to ionizing radiation exposure is given in chapter 8; the carcinogenic effect and a review of the literature of radiation induced coronary artery disease. The potential development of late side

effects, such as radiation induced malignancies is probably negligible. VBT is dealing with very small volumes and thight dose distributions; the whole body radiation exposure is very low.

Irradiation of arteries increases the incidence of atherosclerosis. Evidence for this is an increased relative risk of ischemic heart disease among long-term survivors of radiation therapy for Hodgkin's disease and breast cancer, appearing 10-15 years after treatment. [3,7,20] The relevance of these observations for the application of VBT following angioplasty in coronary arteries is uncertain. Radiation induced atherosclerosis may develop more quickly in patients who already have atheromatous degeneration than in younger patients. On the other hand the length of coronary arteries and the volume of surrounding tissues treated with external beam irradiation is much larger than in VBT. The risk-benefit analysis should take into account the long-term risk of radiation induced ischemic heart disease over the short-term risk of restenosis following angioplasty. Moreover, the age of the vast majority of patients undergoing PTCA is above 60 years.

Long term follow-up of patients treated with endovascular brachytherapy is mandatory to assess long term effects of this new treatment modality.

**Future Perspectives**

The prevention of restenosis is still subject of research. At present there is still incomplete understanding of the target cells for radiation, inadequate knowledge of the dose required to prevent restenosis and the maximum dose that can be given with an acceptable level of complications. It is important to improve on the information about the doses delivered in the different tissues of the vessel wall. Increased use of IVUS prior to treatment and calculation of dose volume histograms will allow the correlation of clinical results with detailed information about delivered doses.

A limiting factor in VBT are the available source lengths, especially for β-sources. Long radiation treatment lengths can be achieved by using a multisegmental irradiation with the available line souces or using sources of different lengths. All these sources should be stored in the department, which is expensive and causes a lot of radioactive waste. The main disadvantage of long sources is that dwell time and radiation dose cannot be adapted along the source length for variations in vessel diameter. A stepping source has three main advantages. All lesions can be treated with a single source, eliminating the need to handle and store different sources. The irradiation length can be adapted to the injured length, avoiding tight or excessive safety margins. The dwell times can be optimized to improve the conformality of the dose distribution and target geometry, avoiding areas

with over- or underdosing. A computerized stepping source allows for accurate source movements. This technique would be particularly important in case of long lesions and bifurcations in preventing serious over- and underdosage. Stepping source devices with a source shorter than 5 mm are not yet available for coronary application. However, recently Schaart et al. [21] reported on a novel intravascular beta source designed for application as a stepping source.

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# SUMMARY

## SUMMARY

Coronary artery disease remains the major cause of death in industrialized countries, with more than one million procedures of percutaneous transluminal coronary angioplasty (PTCA) performed worldwide each year. Restenosis, however, remains the major limiting factor of percutaneous coronary interventions (PCI). Even after stent implantation the restenosis rate remains as high as 20-30%. The use of drugs or atherectomy techniques did not reduce the resenosis rate considerably. Intravascular brachytherapy (VBT) has proven to be an effective mode of preventing restenosis following PCI. The efficacy of vascular brachytherapy to prevent restenosis in de novo and (in-stent) restenotic lesions has been demonstrated in the various trials, summarized in introduction and general discussion. Nevertheless, VBT has technical limitations. In this regard, the occurrence of edge effect and late thrombosis have tempered the initial enthusiasm to some degree. Also, whether β or γ-emitters should be used and the utility of a centering device is still a matter of debate.

**Chapter 1** demonstrates safety and feasibility of VBT with a $^{90}Sr$ source following PTCA in 31 patients with single de novo lesions treated in Rotterdam and included in the BERT trial. At six months follow-up no serious complications occurred, but the restenosis rate obtained was relatively high (29%).

**Chapter 2** describes the integration of VBT with different treatment techniques in the catheterization laboratory as feasible and safe. In more than 250 patients, entered in various trials, different restenosis rates and TLR rates were obtained, depending on technique and lesion type. Problems, such as edge restenosis and late thrombotic occlusion have been studied and identified as limiting factors of this technique.

In **chapter 3** data, derived from a large cohort of unselected patients, treated with VBT in coronary arteries in many centers in Europe (RENO registry), confirm that the excellent results of randomized clinical trials can be replicated in 'routine clinical practice'. However, results can probably be improved by using more generous margins at the edges and the optimal radiation dose is still subject for further investigation.

**Chapter 4**: Intravascular ultrasound (IVUS) in coronary arteries appears to be an indispensable tool for understanding the mechanisms of action of radiotherapy in the prevention of restenosis and to identify the target volume. The dose absorbed in different arterial structures could be evaluated in more detail, since the target volume to irradiate is still controversial. Calculation of dose volume histograms of a specific structure might be useful for dose prescription and dosimetry.

**Chapter 5**: IVUS was used as an imaging technique to understand the mechanisms of action of brachytherapy. A difference in pattern of remodeling was observed in coronary segments treated with β-radiation following

angioplasty. In the irradiated segments, the increase of EEM volume appears to be the major contributor to the luminal volume at follow-up. Conversely, at both edges an increase in plaque volume was seen without a change in EEM volume, resulting in a decrease of the luminal volume.

**Chapter 6**: In 36 patients with long lesions, included in the RENO registry, adequate irradiation length required manual multisegmental irradiation. The inaccuracy of this technique in coronary arteries was shown, with significant dose inhomogeneities at the junction site between the two source positions. A perfect junction will not be possible due to movement of the radiation delivery catheter in the vessel lumen. The use of longer line sources or, even better, a stepping source seems to be a more reliable and safer technique for treatment of long lesions.

**Chapter 7**: This chapter analyses in more detail the problem of junction between intravascular sources, as mentioned in chapter 6. To determine the source positions for irradiation of coronary bifurcations with the available catheter-based devices, the use of theoretical calculations is insufficient. They only provide an estimation of the gap width for a given bifurcation angle and source type. Treatment of bifurcations with line sources will always result in areas with serious over- and underdosage. Individual treatment planning based on the actual fluoroscopic image of the bifurcation is recommended. Ideally a single stepping source with variable dwell times and an individual planning should be used, to provide a homogeneous dose to all treated vessel segments.

**Chapter 8** considers the most common late side effects of radiation in different organs including its carcinogenic effect. The literature of radiation induced coronary artery disease is reviewed. Changes in blood vessel morphology, induced by ionizing radiation are described. However, it is not clear if long term effects of radiation of normal arteries in cancer patients will be comparable to those in atherosclerotic arteries of patients undergoing balloon angioplasty. The potential induction of secondary tumors appears to be extremely small, since in VBT one is dealing with very small volumes and tight dose distributions. Long term follow-up of patients treated with endovascular brachytherapy is mandatory to assess long term effects of this new treatment modality.

Finally, the development of new technologies has not stopped. Nowadays, drug-eluting stents are one of the most promising techniques to prevent restenosis in interventional cardiology. The first significant reduction of in-stent restenosis was demonstrated for a stent coated with an antimitotic agent (rapamycin), the sirolimus-coated stent. Trials using paclitaxel-coated stents also showed promising results and many other clinical trials are in progress. As the logistics of this technology is less complicated, it is in fact a strong competitor for brachytherapy in the cathlab, at least if the excellent results will be confirmed and last over time.

# SAMENVATTING

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Atherosclerose van coronaire arteriën is de belangrijkste doodsoorzaak in geïndustrialiseerde landen. Jaarlijks worden wereldwijd meer dan één miljoen percutane transluminale coronaire angioplastieken (PTCA) verricht. Het frequent voorkomen van restenosering blijft echter de voornaamste beperkende factor van percutane coronaire interventies (PCI); zelfs na plaatsing van een stent blijft de kans op restenosering 20-30%. De toepassing van medicamenteuze behandelingen of atherectomie technieken heeft de frequentie van restenosering niet significant verlaagd. Intravasculaire brachytherapie (VBT) blijkt een efficiënt middel te zijn om restenosering na PCI gedeeltelijk te voorkomen. De effectiviteit van VBT inzake preventie van restenosering na PTCA van de novo laesies en (in-stent) restenosen werd aangetoond in diverse gerandomiseerde studies. Deze behandeling kent echter ook technische beperkingen. Zo hebben het optreden van restenosering aan de randen van het behandelde gebied, het zogenaamde "edge effect", en het optreden van late thrombose het oorspronkelijk enthousiasme enigszins getemperd. Ook vormen het gebruik van $\beta$ of $\gamma$-bronnen en het nut van een centrerende catheter nog steeds punten van discussie.

In **hoofdstuk 1** wordt de uitvoerbaarheid en veiligheid aangetoond van VBT met een $^{90}Sr$ bron na PTCA bij 31 patiënten met enkelvoudige de novo laesies, behandeld in Rotterdam en geïncludeerd in de BERT studie. Na 6 maanden follow-up waren er geen ernstige complicaties, maar het aantal restenoseringen was relatief hoog (29%).

**Hoofdstuk 2** beschrijft dat de integratie van VBT met verschillende bestralingstechnieken in het cathlab uitvoerbaar en veilig is. Bij meer dan 250 patiënten, geïncludeerd in diverse studies, werden verschillende percentages restenosering en revascularisatie bereikt, afhankelijk van de behandelingstechniek en het type laesie. Problemen, zoals het "edge effect" en het optreden van late thrombose werden bestudeerd en worden gezien als beperkende factoren van VBT.

In **hoofdstuk 3** worden de resultaten beschreven van een grote groep niet geselecteerde patiënten, die behandeld werden met VBT in coronaire arteriën in verschillende centra in Europa. Deze registratie (RENO) studie bevestigt dat de goede resultaten van VBT, verkregen in gerandomiseerde klinische studies, reproduceerbaar zijn in de dagelijkse klinische praktijk. Wellicht kunnen de resultaten verder verbeterd worden door het gedilateerde gebied aan de randen met een ruimere marge te bestralen. Ook de optimale dosis straling is nog steeds onderwerp voor verder onderzoek.

**Hoofdstuk 4**: Intravasculaire echografie (IVUS) van coronaire vaten is een belangrijk instrument in het onderzoek naar de werkingsmechanismen van radiotherapie inzake preventie van restenosering en draagt bij tot de identificatie van het doelvolume. De dosis bestraling geabsorbeerd in de verschillende wandlagen van de coronaire arteriën zou op deze manier geëvalueerd kunnen worden; er wordt nog steeds onderzoek gedaan naar het exacte doelvolume voor de bestraling. De berekening van dosis volume histogrammen van een specifieke structuur in de vaatwand kunnen nuttig zijn voor dosis voorschrift en dosimetrie.

**Hoofdstuk 5**: IVUS werd gebruikt als afbeeldingstechniek om de werkingsmechanismen van brachytherapie te bestuderen. Verschillende reacties werden gezien in de verschillende segmenten van het bloedvat na angioplastiek en behandeling met een β-bron. In de bestraalde segmenten bleek de toename van het lumen van het bloedvat vooral te wijten aan een toename van het volume van de lamina elastica externa. Ter plaatse van beide uiteinden daarentegen, was er een toename van de plaque zonder verandering van de lamina elastica externa, resulterend uiteindelijk in een afname van het lumen.

**Hoofdstuk 6**: Bij 36 patiënten met lange laesies, geïncludeerd in de RENO registratie, was de lengte van het behandelde traject in de coronairen te lang voor de bronlengtes beschikbaar op de afdeling. Om het volledige traject adequaat te kunnen bestralen werden verschillende segmenten achtereenvolgens bestraald door de bron manueel te verplaatsen. De resultaten van dit onderzoek wijzen uit dat deze techniek niet erg accuraat is; zo ontstaat er een zeer inhomogene dosisverdeling in het aansluitingsgebied van de twee bronposities. Daarenboven zal een perfecte aansluiting nooit mogelijk zijn door de beweging van de bestralingscatheter in het bloedvat ten gevolge van de hartcontracties. Het gebruik van langere lijnbronnen of een stappende bron lijkt een meer betrouwbare en veiligere techniek te zijn voor de bestraling van lange laesies.

**Hoofdstuk 7**: Dit hoofdstuk is een nadere uitwerking van de aansluitingsproblematiek van intravasculaire bronnen zoals reeds in hoofdstuk 6 genoemd. Het bepalen van de bronposities voor bestraling van bifurcaties in coronaire vaten op basis van theoretische berekeningen voldoet niet echt. Ze geeft slechts een schatting van de afstand tussen de twee bronposities voor een gegeven bifurcatiehoek en brontype. Bestraling van bifurcaties met lijnbronnen zal dus altijd resulteren in gebieden met ernstige over-en onderdosering. In de klinische praktijk wordt een individuele planning op basis van afbeeldingen van de bifurcatie geadviseerd. Met een korte stappende bron, waarvan de bestralingstijd voor elke bronpositie kan worden aangepast, en een individuele planning zou een meer homogene dosisverdeling verkregen kunnen worden over de verschillende vaatsegmenten.

**Hoofdstuk 8** beschrijft de meest voorkomende late bijwerkingen van ionizerende stralen op diverse organen en het carcinogene effect. Morfologische veranderingen van bloedvaten ten gevolge van bestraling worden

beschreven, gevolgd door een literatuuroverzicht van coronairlijden na radiotherpie. Het is niet duidelijk of lange termijn effecten van bestraling op normale arteriën bij kankerpatiënten vergelijkbaar zijn met die van atherosclerotische vaten van patiënten behandeld met angioplastiek. De kans op inductie van secundaire tumoren na VBT is erg klein; we hebben immers te maken hebben met kleine bestralingsvolumes en een sterk dosisverval. Langdurige follow-up van patiënten behandeld met VBT is essentieel om de lange termijn effecten van deze nieuwe behandelingsmodaliteit te evalueren.

Tot slot, de ontwikkeling van nieuwe technologieën is vanzelfsprekend doorgegaan. Heden ten dage zijn "drug-eluting stents" een van de meest belovende technieken om restenosering te voorkomen in interventionele cardiologie. De eerste significante reductie van in-stent restenose werd aangetoond na plaatsing van een stent met een mitose remmend middel (rapamycin), de "sirolimus coated stent". Studies met "paclitaxel coated stents" tonen eveneens veelbelovende resultaten en meerdere klinische studies zijn in gang gezet. Aangezien de logistiek van deze technologie minder ingewikkeld is, valt te verwachten dat de"drug-eluting stents" de brachytherapie uit het cathlab zullen verdrijven, indien de goede resultaten worden bevestigd en duurzaam blijken te zijn.

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# CURRICULUM VITAE

## CURRICULUM VITAE

Véronique Coen werd geboren op 28 december 1965 te Vilvoorde (België). In juni 1983 behaalde zij het getuigschrift Hoger Algemeen Secundair Onderwijs / Wiskunde aan het Koninklijk Atheneum te Zaventem (België). Na haar studie Geneeskunde aan de Vrije Unversiteit te Brussel (België) verkreeg zij op 29 juni 1990 het getuigschrift van Doctor in de Genees-, Heel- en Verloskunde. Aansluitend startte zij met de opleiding tot radiotherapeut op de afdeling Radiotherapie van het Academisch Ziekenhuis - Vrije Universiteit te Brussel. Om meer ervaring te krijgen in de brachytherapie werkte zij van oktober 1994 tot juni 1995 op de afdeling Radiotherapie/Brachytherapie van het Institut Gustave Roussy te Villejuif (Frankrijk). Na enkele maanden activiteit op de afdeling Radiotherapie van het AZ-VUB te Brussel, werd zij werkzaam als staflid op de afdeling Radiotherapie van het Academisch Ziekenhuis Rotterdam / Dr. Daniel den Hoed Kliniek (maart 1996 - december 2001). Sinds 1 januari 2002 werkt ze als radiotherapeut-oncoloog in het Zeeuws Radio-Therapeutisch Instituut te Vlissingen.

# DANKWOORD

## DANKWOORD

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