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Two decades after coronary radiation therapy: A single center longitudinal clinical study

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Abstract

Objectives: The aim of this study was to evaluate the very long-term clinical outcome after radioactive stent (RS) implantation and intracoronary β radiation brachytherapy (IRBT).

Background: Radioactive stents (RS) and intracoronary β radiation brachytherapy (IRBT) were introduced to prevent restenosis after percutaneous coronary intervention (PCI). Both techniques were associated with a higher incidence of major adverse cardiac events (MACE) in the short and intermediate-term follow up as compared to conventional PCI.

Methods: One hundred and thirty-three patients received radioactive stents (³²P) and 301 patients were treated with IRBT adjunctive to PCI. These groups were propensity matched to respectively 266 and 602 control patients who were treated with routine PCI during the same inclusion period. Endpoints were all-cause mortality and MACE, defined as all-cause death, any myocardial infarction or any revascularization.

Results: Median follow-up duration was 17 years. All-cause mortality rates were similar in all groups. Adjusted hazard ratios for MACE and mortality in the RS cohort were 1.55 (95% CI 1.20–2.00) and 0.92 (95% CI 0.63–1.34), respectively. Adjusted hazard ratios for MACE and all-cause mortality in the IRBT cohort were 1.41 (95% CI 1.18–1.67) and 0.95 (95% CI 0.74–1.21), respectively. The difference in MACE rates was predominantly driven by coronary revascularizations in both groups, with a higher MI rate in the IRBT group as well.

Conclusions: Coronary radiation therapy was associated with early increased MACE rates, but the difference in MACE rates decreased beyond 2 years, resulting in a comparable long-term clinical outcome. Importantly, no excess in mortality was observed.

KEYWORDS

brachytherapy, coronary artery disease, percutaneous coronary intervention (PCI), restenosis

Abbreviations: BMS, bare metal stent; CHD, coronary heart disease; DES, drug eluting stents; IRBT, intracoronary radiation brachytherapy; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RS, radioactive stents; TLR, target lesion revascularization; TVR, target vessel revascularization.

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1 | INTRODUCTION

Despite widespread use of percutaneous coronary intervention (PCI), even today restenosis remains a limitation of PCI, and it was even more so in the past.¹⁻⁴ Restenosis after stent implantation is thought to be the result of neointimal proliferation, while restenosis after coronary angioplasty and atherectomy is mainly caused by vessel wall remodeling.⁵⁻⁷ Over the past decades, multiple solutions have been suggested to prevent the occurrence of restenosis. Around the year 2000, intracoronary radiation therapy, also referred to as coronary brachytherapy, was introduced as a potential solution to restenosis using several isotopes with different radiation particles. The underlying rationale was that radiation is a potent inhibitor of cellular proliferation. Rather disappointing short- and mid-term clinical results together with a high demand on logistical and radiation safety aspects on one hand and the promising early results of drug eluting stents that were introduced soon after and, which were much easier to handle in the catheterization laboratory on the other hand, led to a rapid decline of intracoronary brachytherapy which was, at that time, then widely perceived as "treatment failure."⁸⁻¹¹ This failure was mainly caused by the occurrence of restenosis at the extremities of the irradiated coronary segment, a phenomenon described in the past as "edge effect," typically caused by "geographic miss."

Geographic miss refers to an anatomical mismatch between the coronary segment that has been injured by dilation and/or implantation balloons and the segment that has received full-dose irradiation. Injured coronary segments, receiving low-dose radiation due to sub-optimal position of the radiation source have been demonstrated to cause restenosis, typically at the edges of the irradiated lesions.¹²⁻¹⁴

However, there is paucity of data when it comes to the long run after coronary radiation therapy. The aim of this study is to evaluate the long-term (17 years) clinical outcome after radioactive stent implantation (³²P β-emitting radioactive stents [RS]) and intracoronary β radiation brachytherapy (IRBT) in comparison to matched control groups.

2 | MATERIALS AND METHODS

2.1 | Patient population

Our study was an observational, longitudinal, matched (propensity score 1:2) single-center study of 434 radiation therapy patients and 868 control patients. Between November 1997 and July 2000, 133 patients received one or two radioactive stents and between April 1997 and December 2002, 301 patients were treated with intracoronary β radiation brachytherapy adjunctive to PCI at the Erasmus University Medical Center in Rotterdam, the Netherlands.^{15,16} The patients in the radioactive stent group were part of five different studies, previously reported. Briefly, the IRIS 1 study was a safety and feasibility study and IRIS 2 was a European dose finding study.^{8,17} The cold end, the hot end and the square-shouldered balloons were studied with dedicated RS and balloons to overcome the problem of edge stent restenosis observed with this therapeutic modality.^{18,19}

To evaluate radiation therapy related outcomes, each of the two radiation groups was compared with control patients who were treated with standard routine PCI during the same inclusion period. In the same time span, a total of 5,224 patients were treated with bare metal stents, balloon angioplasty or atherectomy in our institution. For selecting a representative control group, propensity score methodology was used to match the 133 radioactive stent patients with 266 control patients and the 301 IRBT patients with 602 control patients.

Informed, written consent was retrieved for all radiation therapy patients. For the patients in the control group, approval was retrieved from the Medical Ethical Committee (METC-2013-262).

PCI, radiation therapy and concomitant medication were described in detail previously.¹⁰⁻¹² Antiplatelet therapy after RS implantation consisted of either aspirin 80 mg daily indefinitely and ticlopidine 250 mg BID or clopidogrel 75 mg daily for one to 6 months according to the study, while all BMS (bare metal stent) patients received aspirin 80 mg daily and ticlopidine 250 mg BID or clopidogrel 75 mg daily for 1 month.

2.2 | Techniques/methods

In short, the coronary artery can be exposed to radiation by means of radioactive stents or catheter-based systems. Several isotopes with different radiation particles can be used during radiation therapy. This study will focus on the ³²P β-emitting radioactive stents (RS) and intracoronary β radiation brachytherapy (IRBT).²⁰ In the original IRBT studies, both the centered (Guidant) as noncentered (Novoste) devices were used.

2.3 | Quantitative coronary angiography

Coronary angiography was performed after intracoronary administration of nitrates. The off-line analysis of at least two orthogonal projections was performed by means of the CAAS II (Cardiovascular Angiographical Analysis System) (Pie Medical B.V., Maastricht, The Netherlands).^{8,17} Edge restenosis was defined as >50% diameter stenosis at follow-up, located within 5 mm proximal and/or distal to the stent. Target vessel stenosis was defined as >50% diameter stenosis at follow-up, located on any segment of the treated vessel.

2.4 | Follow-up

In 2015, survival status of all patients was retrieved from the Municipal Civil Registry. Questionnaires were sent to all living patients focusing on the occurrence of major adverse cardiac events (MACE). In case of events reported, events were retrieved from medical records in the hospitals. Two cardiologists adjudicated these events by using a predefined classification form. In all RS studies, follow-up angiography was performed at 6 months and 1 year as mandated by the protocol;

a follow-up angiography in RS patients with a target lesion revascularization at 6 months was not performed again at 1 year. In the IRBT patients, control angiography was performed at 6 or 8 months, depending on the study. In the control group, no routine angiographic follow-up was performed.

2.5 | Study endpoints and definitions

Endpoints were: all-cause mortality and the patient oriented composite endpoint of major adverse cardiac events (MACE) which included all-cause mortality, any myocardial infarction (MI) and any repeat revascularization.

Repeat revascularization was defined as any PCI or CABG during follow-up. Target lesion revascularization (TLR) was defined as any surgical or percutaneous reintervention due to restenosis within the stent or in the 5 mm proximal or distal persistent segments (edge restenosis). Target vessel revascularization was defined as any reintervention driven by lesions located in the treated vessel. Total occlusion was defined as stent occlusion documented by coronary angiography.

2.6 | Statistical analysis

Propensity score methodology was used to identify comparable patients who were treated with standard routine PCI. The propensity score was initially proposed by Rosenbaum and Rubin and has been used in prior observational studies to help adjust for treatment selection bias.²¹ First, a propensity score for each patient was constructed, providing an estimate of the propensity toward belonging to one treatment group versus the other. This was done by using a multivariable logistic regression model with the type of intervention (standard routine treatment coded as 0, IRBT as 1) as the dependent variable. The following variables were entered into the model as independent variables: age, gender, diabetes mellitus, hypertension, smoking, prior MI, prior CABG, prior PCI, multivessel disease, impaired left ventricular function (ejection fraction <40%), and clinical presentation. Second, each IRBT patient was matched with two control patients with identical propensity score by four decimals.¹⁶ The baseline characteristics of the cohort before matching were as follows; mean age 59 years, 73% male, 25% history of PCI, 10% diabetes mellitus, 27% hypertension, and 26% smoking.

Categorical variables (presented as counts and percentages) were compared between groups using the chi-square test or Fisher's exact test and continuous variables (presented as their mean \pm SD) were compared using the Student's *t* test. Survival and event-free survival rates were estimated by Kaplan–Meier curves and differences between groups were assessed with the use of the log-rank test. Univariate and multivariate Cox regression analyses were performed to assess the associations between RS/IRBT and mortality or MACE and to investigate an effect of a learning curve. Furthermore, multivariate Cox regression and Kaplan–Meier curves were used for a landmark

analysis to investigate the association between RS/IRBT and MACE beyond 2 years of follow-up. The following variables were entered into the model: radiation therapy treatment (RS or IRBT), age, indication for PCI, gender, prior MI, prior PCI, prior CABG, extent of vessel disease, left ventricular ejection fraction, smoking, hypertension, and diabetes mellitus. Hazard ratios (HR) are presented with their 95% confidence intervals (CI). Statistical significance of all tests was defined at the $p < .05$ level. The SPSS statistical software package (version 21.0 for Windows, SPSS Inc. Chicago, IL) was used for the analysis.

3 | RESULTS

3.1 | Baseline characteristics

Mean age of the RS patients and IRBT patients was 59 years. In the RS group, 26% were female, compared to 29% in the IRBT group (Table 1). Baseline characteristics of treatment and control groups were comparable, although IRBT patients more often had a history of previous PCI (IRBT 52% versus control 41%, $p < .01$) and were more often treated for restenosis (IRBT 41% versus control 26%, $p < .001$). Median follow-up time was 17 years. Complete follow-up regarding overall survival was achieved in 97% and the response rate of the questionnaires was 84%. The missing information on overall survival was caused by migration of patients.

3.2 | Radioactive stents

The cumulative survival at 5, 10, 15, and 17 years in the RS group was 92%, 84%, 73%, and 60%, respectively and 91%, 80%, 68%, and 65%, respectively in the control group (Log rank $p = .45$) (Figure 1). After adjustment, the hazard ratio for RS associated all-cause mortality was 0.92, 95% CI 0.63–1.34 (Table 2).

The cumulative MACE-free survival at 1, 5, 10, 15, and 17 years in the RS group was 68%, 53%, 42%, 27%, and 20%, respectively and 84%, 72%, 54%, 40%, and 36%, respectively in the control group (Log rank $p = .0013$) (Figure 1). Radioactive stents were associated with a higher MACE rate at 17 years (adjusted HR 1.55, 95% CI 1.20–2.00). Hazard ratios concerning TVR and MI are shown in Table 2.

3.3 | Intracoronary β radiation brachytherapy

The cumulative survival at 5, 10, 15, and 17 years in the IRBT group was 90%, 80%, 69%, and 64%, respectively and 92%, 80%, 65%, and 58%, respectively in the control group (Figure 2). The difference in mortality was not significant (Log rank $p = .34$). After adjustment, the hazard ratio for IRBT associated all-cause mortality was 0.95, 95% CI 0.74–1.21 (Table 2).

The cumulative MACE-free survival at 1, 5, 10, 15, and 17 years in the IRBT group was 70%, 47%, 34%, 25%, and 24%, respectively

TABLE 1 Baseline characteristics

| | RS group (n = 133) | Propensity matched control group (n = 266) | p-value | IRBT group (n = 301) | Propensity matched control group (n = 602) | p-value |
|----------------------------------|--------------------|--|---------|----------------------|--|---------|
| Sociodemographic characteristics | | | | | | |
| Age | 58.6 (±10.8) | 59.1 (±10.8) | .66 | 59.1 (±10.3) | 59.4 (±11.0) | .53 |
| Female gender (%) | 35 (26.3) | 68 (25.6) | .87 | 86 (28.6) | 161 (26.7) | .56 |
| Risk factors | | | | | | |
| Diabetes mellitus (%) | 13 (9.8) | 32 (12) | .50 | 46 (16) | 78 (13) | .33 |
| Hypertension (%) | 47 (35.3) | 101 (38) | .61 | 94 (31.2) | 180 (29.9) | .67 |
| Smoking (%) | 32 (24.1) | 58 (21.8) | .61 | 57 (18.9) | 129 (21.4) | .40 |
| Cardiac history | | | | | | |
| Previous MI (%) | 60 (45.1) | 110 (41.4) | .47 | 101 (33.6) | 204 (33.9) | .87 |
| Previous PCI (%) | 18 (13.5) | 47 (17.7) | .29 | 156 (51.8) | 247 (41.0) | <.01 |
| Previous CABG (%) | 4 (3) | 11 (4.1) | .59 | 53 (17.6) | 95 (15.8) | .52 |
| Extent of vessel disease | | | | | | |
| | | | .29 | | | .66 |
| 1 | 95 (71.4%) | 197 (74.1%) | | 173 (57.5%) | 349 (58.0%) | |
| 2 | 32 (24.1%) | 51 (19.2%) | | 78 (25.9%) | 156 (25.9%) | |
| 3 | 5 (4.5%) | 18 (6.8%) | | 50 (16.6%) | 97 (16.1%) | |
| Indication for PCI | | | | | | |
| | | | .67 | | | .8 |
| Unstable angina | 58 (43.6) | 122 (45.9) | | 92 (30.6) | 195 (32.4) | |
| Stable angina | 75 (56.4) | 144 (54.1) | | 207 (68.8) | 407 (67.6) | |
| Ejection fraction | | | | | | |
| | | | .22 | | | .36 |
| Normal (>50%) | 112/127 (88.2%) | 215/232 (92.7%) | | 239/292 (81.8%) | 448/486 (92.2%) | |
| Moderate (35–50%) | 14/127 (11.0%) | 14/232 (6.0%) | | 44/292 (15.1%) | 32/486 (6.6%) | |
| Poor (<35%) | 1/127 (0.8%) | 3/232 (1.3%) | | 9/292 (3.1%) | 6/486 (1.2%) | |
| Vessels treated | | | | | | |
| | | | .67 | | | .1 |
| Left anterior descending | 60 (45.1%) | 124 (46.6%) | | 116 (38.5%) | 242 (40.2%) | |
| Right coronary artery | 45 (33.8%) | 79 (29.7%) | | 106 (35.2%) | 167 (27.7%) | |
| Left circumflex | 28 (21.1%) | 63 (23.7%) | | 52 (17.3%) | 144 (23.9%) | |
| Left main | - | - | | 4 (1.3%) | 9 (1.5%) | |
| Saphenous vein graft | - | - | | 20 (6.6%) | 30 (4.9%) | |

Abbreviations: CABG, coronary artery bypass graft; IRBT, intracoronary radiation brachytherapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; RS, radioactive stents.

and 79%, 67%, 52%, 37%, and 30%, respectively in the control group (Log rank $p < .001$) (Figure 2). After adjustment, IRBT was associated with a higher MACE rate in comparison to the control group, HR 1.41, 95% CI 1.18–1.67 (Table 2). Whereas in the RS cohort MACE rates were mainly driven by coronary revascularizations, MACE rates in the IRBT cohort were driven by a higher revascularization rate as well as a higher MI rate (adjusted HR 1.54, 95% CI 1.09–2.19). Hazard ratios concerning the other endpoints are shown in Table 2.

When studying the Kaplan–Meier curve for the MACE-free survival of the IRBT cohort, three phases can be distinguished (Figure 2). First of all there is an early sharp decrease in the IRBT group, where

after the curves run parallel until 10 years of follow-up. After 10 years, the curves seem to converge. In phase 1 (0–2 years), MACE in the IRBT group ($n = 122$) and control group ($n = 157$) was predominantly driven by revascularizations (79% and 78%, respectively), followed by MI (16% and 9%, respectively) and mortality (5% and 12%, respectively). In phase 2 (2–8 years), MACE in the IRBT group ($n = 66$) was mainly driven by revascularizations (64%), followed by MI (18%) and mortality (18%), while in the control group MACE ($n = 97$) was driven by revascularizations (44%) and mortality (43%), followed MI (12%). In phase 3 (8–17 years), MACE in the IRBT group ($n = 39$) was driven by mortality (46%) and revascularizations (41%), followed

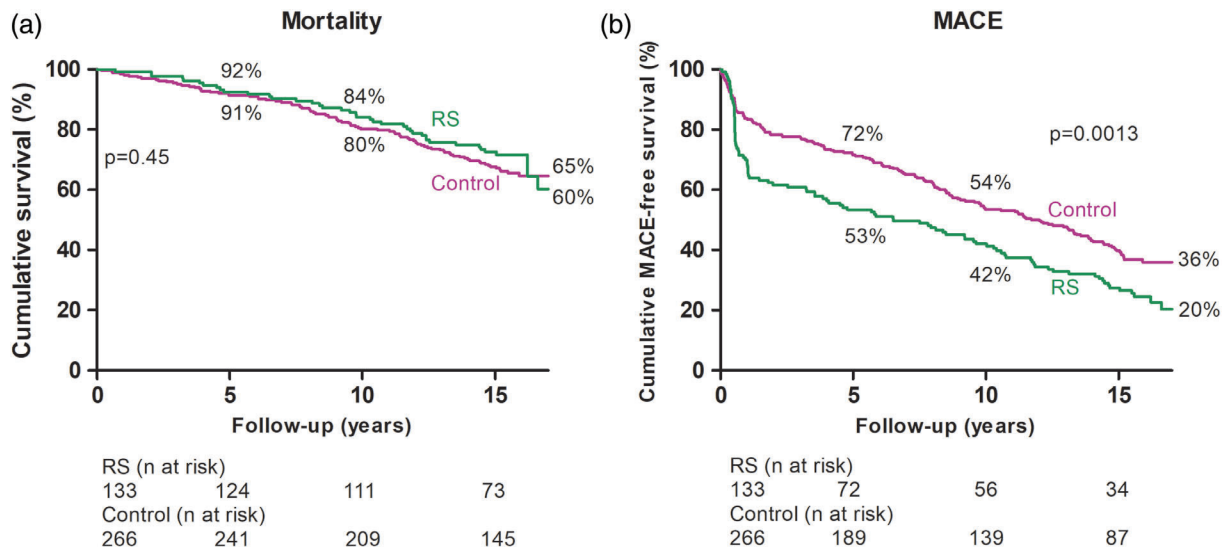


FIGURE 1 Kaplan–Meier survival curves for the radioactive stents (RS) versus control for all-cause mortality and major adverse cardiac events (MACE) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Hazard ratios radioactive stents cohort and intracoronary beta radiation brachytherapy cohort

| Event | RS cohort | | IRBT cohort | |
|----------------------|------------------------|-----------------------------------|------------------------|-----------------------------------|
| | Unadjusted HR (95% CI) | Adjusted HR ^a (95% CI) | Unadjusted HR (95% CI) | Adjusted HR ^a (95% CI) |
| Death from any cause | 0.86 (0.59–1.24) | 0.92 (0.63–1.34) | 0.88 (0.69–1.12) | 0.95 (0.74–1.21) |
| MACE | 1.49 (1.16–1.91) | 1.55 (1.20–2.00) | 1.48 (1.26–1.75) | 1.41 (1.18–1.67) |
| TVR | 1.78 (1.31–2.41) | 1.92 (1.40–2.62) | 1.87 (1.54–2.28) | 1.73 (1.42–2.12) |
| MI | 1.32 (0.75–2.33) | 1.39 (0.78–2.50) | 1.58 (1.12–2.21) | 1.54 (1.09–2.19) |
| Death or MI | 1.03 (0.75–1.41) | 1.08 (0.78–1.49) | 1.01 (0.82–1.24) | 1.07 (0.86–1.32) |

Abbreviations: IRBT, intracoronary beta radiation brachytherapy; MACE, major cardiac events; MI, myocardial infarction; RS, radioactive stents; TVR, target vessel revascularization.

^aThe following variables were entered into the model: age, gender, prior MI, prior PCI, prior CABG, extent of vessel disease, left ventricular ejection fraction, indication for PCI, smoking, hypertension and diabetes mellitus.

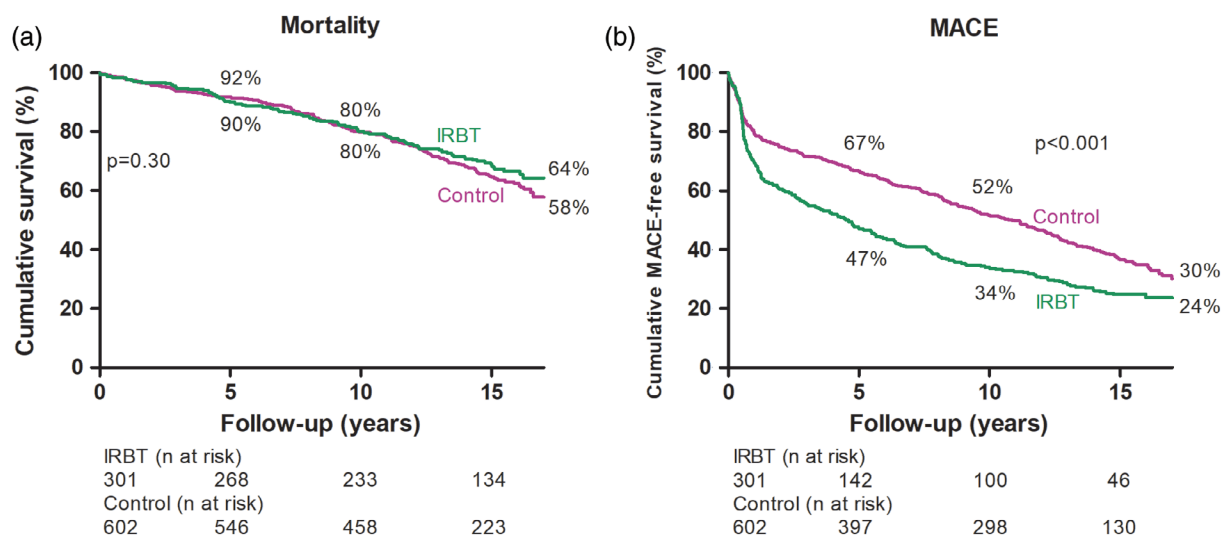


FIGURE 2 Kaplan–Meier survival curves for intracoronary beta radiation brachytherapy (IRBT) versus control for all-cause mortality and major adverse cardiac events (MACE) [Color figure can be viewed at wileyonlinelibrary.com]

by MI (13%), while in the control group MACE ($n = 131$) was mainly driven by mortality (57%), followed by revascularizations (26%) and MI (17%). Revascularizations in the IRBT patients were predominantly classified as TLR.

3.4 | Landmark analyses beyond 2 years

Additional landmark analyses were performed to explore the difference in MACE rates between radiation therapy and control groups beyond 2 years of follow-up. In the RS cohort, there were no differences in MACE-free survival (Figure 3, Log rank $p = .22$, adjusted HR 1.23, 95% CI 0.87–1.75).

In the IRBT group, the differences remained significant but were less pronounced (Figure 3, Log rank $p = .013$, adjusted HR 1.35, 95% CI 1.064–1.72).

3.5 | Angiographic characteristics during target lesion revascularizations

To investigate the impact of edge restenosis on the revascularization rate of radiation therapy patients, angiography images from our center were analyzed. Of the 133 RS patients, 56 (42%) underwent at least one TLR in our center (either surgical or percutaneous), resulting in a total of 73 analyzed TLR's. Within the first year after RS implantation, edge restenosis was responsible for an intervention in 20% ($n = 27$) of the patients and for 29 lesions (71% of all lesions within the first year). During the complete follow-up period, edge restenosis was responsible for an intervention in 29% ($n = 38$) of the patients and for 43 lesions (59%).

Of the 171 IRBT patients, 77 underwent at least one TLR in our center, resulting in a total of 107 analyzed TLR's. Within the first year

after IRBT, edge restenosis was responsible for an intervention in 5% ($n = 9$) of the patients and for 10 lesions (25%). During the complete follow-up period, edge restenosis was responsible for an intervention in 14% ($n = 24$) of the patients and for 26 lesions (24%). Total occlusion occurred in 34 of the 107 TLR's (32%).

3.6 | Effect of a learning curve

Two analyses were performed to investigate an effect of the learning curve during the IRBT period. First, the five-year period of IRBT treatment was divided into two periods by using January first 2000 as cut-off point. Cox proportional hazards analyses with occurrence of MACE as outcome resulted in a univariate HR of 0.91 (95% CI 0.69–1.19) and a multivariate HR of 0.84 (95% CI 0.62–1.13). Second, the last 2 years of IRBT treatment were tested against the first 2 years. This resulted in a univariate HR of 1.0 (95% CI 0.72–1.39) and a multivariate HR of 0.84 (0.57–1.12).

4 | DISCUSSION

This study evaluated the very late (17 years) clinical outcome of both radioactive stents and intracoronary β radiation brachytherapy as compared with matched control groups treated with routine PCI during the same time period in our center. The main findings were (a) in the very long-term, there were no survival differences between the treatment group and controls, (b) the excess in MACE as reported previously in the treatment group at 6 months and 12 months is not persistent: beyond the second year, the difference in MACE rates decreased, and (c) interestingly, the event rates in the IRBT group started to decrease in comparison to the control group after 10 years, resulting in a comparable clinical outcome in the very long-term.

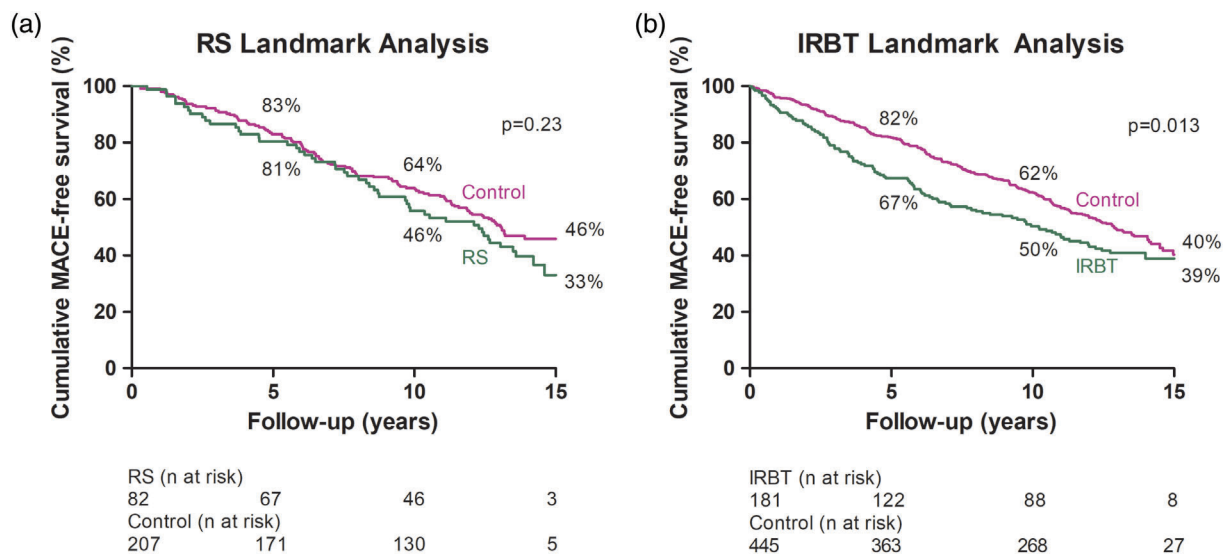


FIGURE 3 Landmark analyses for radioactive stents (RS) and intracoronary beta radiation brachytherapy (IRBT) versus control for major adverse cardiac events (MACE) [Color figure can be viewed at wileyonlinelibrary.com]

4.1 | Radioactive stents versus intracoronary β radiation brachytherapy

Radioactive stents were implanted in one quarter of our radiation therapy group, while the remaining patients underwent IRBT. Interestingly, in both groups the same patterns were observed with respect to all-cause mortality and MACE. The landmark analyses showed that the first 2 years of follow-up account for a significant part of the observed difference in MACE rates. In fact, beyond 2 years, there no longer were differences between RS and control patients. Furthermore, in the IRBT cohort, the differences in MACE rates decreased after moving the baseline to 2 years after treatment.

In both treatment groups, MACE was predominantly driven by TLR within the first 2 years after treatment. Our angiographic analysis showed that approximately 30% of the RS patients and 15% of the IRBT patients had a TLR because of the edge effect. In the IRBT patients, stent thrombosis was responsible for 32% of the TLR's.

In the IRBT cohort, MACE rates were also driven by a higher MI rate. However, the important question is whether the higher MI rate is a true phenomenon or the result of information bias. Events were initially reported through questionnaires where after medical records were obtained to confirm self-reported events. Between-group differences in this self-reporting may have accounted for a part of the observed differences.

4.2 | Intracoronary radiation therapy—persistent failure?

When studying the Kaplan–Meier curve for MACE-free survival of the IRBT cohort (Figure 2), there is a sharp decrease in the IRBT group during the first 2 years of follow-up. Eventually, the difference in MACE rates decreased over time. These data with most radiation failure occurring within the first two years, might suggest rather the aftermath of technical shortcomings in the baseline procedure (with geographical miss) than a deleterious effect of radiation itself. This is important, as in the past both, potentially beneficial radiation effects such as hormesis and potentially adverse radiation effects such as media fibrosis of the epi- and endocardial vessels have been described. Fortunately, there was no MACE excess at the long-term outcome.^{22,23} Additional analyses showed no effect of a learning curve.

It is not clear why this effect seems to be more pronounced in the IRBT group as compared to the RS group. A possible explanation could be the different vascular response to short (IRBT) versus prolonged (RS) after loading as observed in the past. Radioactive stents have been associated with inward vessel remodeling, whereas IRBT was associated with outward vessel remodeling with an increase in plaque and total vessel volume at 6 months.^{24,25} However, there are no data elucidating the relevance of these effects in the very long run.

4.3 | Role of coronary radiation therapy in daily clinical practice—cure for restenosis?

To the best of our knowledge, this is the first study presenting the results of both radioactive stents and intracoronary β radiation therapy after more than 10 years of follow-up. Because of the poor short- and intermediate-term results of radioactive stents, they have been discarded as an option in the treatment of coronary artery disease. However, there are some highly specialized centers where catheter based brachytherapy is still being performed. RS have never been tested against drug eluting stents (DES) in a clinical trial, but IRBT has been tested.

The SISR trial compared sirolimus-eluting stents (SES) to vascular brachytherapy for in-stent restenosis within bare metal stents. After 3 years of follow-up, SES were associated with a better TLR- and TVR-free survival.²⁶ The TAXUS V ISR trial randomized patients between a paclitaxel-eluting stent (PES) and vascular brachytherapy as treatment for bare metal stent restenosis.²⁷ At 2 year follow-up, the PES subgroup suffered less from clinical restenosis and therefore MACE and TVF appeared to be in favor of PES. The paclitaxel- and sirolimus-eluting stents that were used in the previously mentioned trials are early-generation DES. Use of these stents has drastically decreased since the availability of new-generation DES. Recent guidelines by the European Society of Cardiology state that new-generation DES are recommended over BMS in non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS).²⁸ Furthermore, their guidelines suggest that new-generation DES are more effective and potentially safer than BMS during primary PCI in patients presenting with ST-segment-elevation myocardial infarction (STEMI).²⁹ New-generation DES have drastically reduced the incidence of restenosis since the BMS era, but they still suffer from a restenosis rate of approximately 10–15%.¹ Therefore, the focus should be on preventing restenosis of the new-generation DES.

There are a number of possible treatment options such as restenting with a DES, angioplasty with (drug-coated) balloons and coronary surgery. Although each patient requires a tailored approach based on the location and extent of restenotic tissue, the presence of additional lesions and comorbidity, restenting with DES or the use of drug coated balloons, which are currently not available in the United States, seem to be among the best choices.^{30–32}

4.4 | Limitations

Some limitations need to be acknowledged. First, the study was not randomized, which is generally preferred when comparing treatments. Because of the study design, potential validity issues need to be addressed. First of all, confounding might have biased the results. By using propensity scores, both groups were evenly matched with regard to the patient characteristics, except for previous PCI and restenosis, which were more prevalent in the IRBT group. Furthermore, multivariable analyses were performed to adjust for possible confounders. However, residual confounding might still have

influenced the results. Second, patients from both the radioactive stent- as well as the IRBT cohort were part of different trials with variability in terms of the applied technology and medication. At last, the coronary radiation patients were part of different studies whose protocols mandated angiographic control after 6 and/or 12 months. Thus, information bias has affected the short- and intermediate-term results and therefore caution is urged when reviewing the early results.

5 | CONCLUSION

Coronary radiation therapy was associated with a relatively high failure rate within the first year. However, the difference in MACE rates decreased beyond 2 years, resulting in a comparable long-term clinical outcome. Importantly, no excess in mortality was observed.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

- Cassese S, Byrne RA, Tada T, et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart*. 2014;100(2):153-159.
- Gruentzig AR, King SB 3rd, Schlumpf M, Siegenthaler W. Long-term follow-up after percutaneous transluminal coronary angioplasty. The early Zurich experience. *N Engl J Med*. 1987;316(18):1127-1132.
- Holmes DR Jr, Vlietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol*. 1984;53(12):77C-81C.
- Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. *J Am Coll Cardiol*. 1988;12(3):616-623.
- Hoffmann R, Mintz GS, Dussallant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation*. 1996;94(6):1247-1254.
- Kimura T, Kaburagi S, Tamura T, et al. Remodeling of human coronary arteries undergoing coronary angioplasty or atherectomy. *Circulation*. 1997;96(2):475-483.
- Mintz GS, Popma JJ, Pichard AD, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation*. 1996;94(1):35-43.
- Wardeh AJ, Knook AH, Kay IP, et al. Clinical and angiographical follow-up after implantation of a 6–12 μ Ci radioactive stent in patients with coronary artery disease. *Eur Heart J*. 2001;22(8):669-675.
- Sianos G, Hoye A, Saia F, et al. Long term outcome after intracoronary beta radiation therapy. *Heart*. 2005;91(7):942-947.
- King SB 3rd, Williams DO, Chougule P, et al. Endovascular beta-radiation to reduce restenosis after coronary balloon angioplasty: results of the beta energy restenosis trial (BERT). *Circulation*. 1998;97(20):2025-2030.
- Serruys PW, Sianos G, van der Giessen W, et al. Intracoronary beta-radiation to reduce restenosis after balloon angioplasty and stenting: the beta radiation in Europe (BRIE) study. *Eur Heart J*. 2002;23(17):1351-1359.
- Sabate M, Costa MA, Kozuma K, et al. Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy. *Circulation*. 2000;101(21):2467-2471.
- Sianos G, Kay IP, Costa MA, et al. Geographical miss during catheter-based intracoronary beta-radiation: incidence and implications in the BRIE study. *Beta-radiation in Europe*. *J Am Coll Cardiol*. 2001;38(2):415-420.
- Albiero R, Adamian M, Kobayashi N, et al. Short- and intermediate-term results of (32)P radioactive beta-emitting stent implantation in patients with coronary artery disease: the Milan dose-response study. *Circulation*. 2000;101(1):18-26.
- Sianos G, Papafaklis MI, van Domburg R, et al. Eight-year clinical outcome after radioactive stent implantation: a treatment failure without irreversible long-term clinical sequelae. *EuroIntervention*. 2011;6(6):681-686.
- Cheng JW, Onuma Y, Eindhoven J, et al. Late outcome after intracoronary beta radiation brachytherapy: a matched-propensity controlled ten-year follow-up study. *EuroIntervention*. 2011;6(6):695-702.
- Wardeh AJ, Kay IP, Sabate M, et al. Beta-particle-emitting radioactive stent implantation. A safety and feasibility study. *Circulation*. 1999;100(16):1684-1689.
- Wardeh AJ, Albiero R, Kay IP, et al. Angiographical follow-up after radioactive "cold ends" stent implantation: a multicenter trial. *Circulation*. 2002;105(5):550-553.
- Kay IP, Wardeh AJ, Kozuma K, et al. The pattern of restenosis and vascular remodelling after cold-end radioactive stent implantation. *Eur Heart J*. 2001;22(15):1311-1317.
- Regar E, Van der Giessen WJ, Vos J, De Feyter PJ, Smits P, Serruys PW. Coronary brachytherapy. In: Marco J, Serruys PW, Biamino G, Fajadet J, de Feyter PJ, Morice MC, eds. *The Paris course on revascularization*. Paris: Europa edition; 2002.
- Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55.
- Basavaraju SR, Easterly CE. Pathophysiological effects of radiation on atherosclerosis development and progression, and the incidence of cardiovascular complications. *Med Phys*. 2002;29(10):2391-2403.
- Scott BR. Radiation-hormesis phenotypes, the related mechanisms and implications for disease prevention and therapy. *J Cell Commun Signal*. 2014;8(4):341-352.
- Kay IP, Sabate M, Costa MA, et al. Positive geometric vascular remodeling is seen after catheter-based radiation followed by conventional stent implantation but not after radioactive stent implantation. *Circulation*. 2000;102(12):1434-1439.
- Sabate M, Serruys PW, van der Giessen WJ, et al. Geometric vascular remodeling after balloon angioplasty and beta-radiation therapy: a three-dimensional intravascular ultrasound study. *Circulation*. 1999;100(11):1182-1188.
- Holmes DR Jr, Teirstein PS, Satler L, et al. 3-Year follow-up of the SISR (Sirolimus-eluting stents versus vascular brachytherapy for in-stent restenosis) trial. *JACC Cardiovasc Interv*. 2008;1(4):439-448.
- Ellis SG, O'Shaughnessy CD, Martin SL, et al. Two-year clinical outcomes after paclitaxel-eluting stent or brachytherapy treatment for bare metal stent restenosis: the TAXUS V ISR trial. *Eur Heart J*. 2008;29(13):1625-1634.
- Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Rev Esp Cardiol (Engl Ed)*. 2015;68(12):1125.
- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *Rev Esp Cardiol (Engl Ed)*. 2015;68(2):144.
- Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol*. 2014;63(24):2659-2673.

31. Giacoppo D, Gargiulo G, Aruta P, Capranzano P, Tamburino C, Capodanno D. Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients. *BMJ*. 2015; 351:h5392.
32. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet*. 2015;386(9994):655-664.

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