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Intracoronary β-radiation to reduce restenosis after balloon angioplasty and stenting

The Beta Radiation In Europe (BRIE) study

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Aims The BRIE trial is a registry evaluating the safety and performance of ^{90}Sr delivered locally (Beta-Cath TM system of Novoste) to de-novo and restenotic lesions in patients with up to two discrete lesions in different vessels.

Methods and Results In total, 149 patients (175 lesions) were enrolled; 62 treated with balloons and 113 with stents. The restenosis rate, the minimal luminal diameter and the late loss were determined in three regions of interest: (a) in a subsegment of 5 mm containing the original minimal luminal diameter pre-intervention termed target segment; (b) the irradiated segment, 28 mm in length, and (c) the entire analysed segment, 42 mm in length, termed the vessel segment. Binary restenosis was 9·9% for the target segment, 28·9% for the irradiated segment, and 33·6% for the vessel segment. These angiographic results include 5·3% total occlusions. Excluding total occlusions binary restenosis was 4·9%, 25% and 29·9%, respectively. At 1 year the incidence of major adverse cardiac events placed in a hierarchical ranking were: death 2%, myocardial infarction 10·1%, CABG 2%, and target vessel revascularization 20·1%. The event-free survival rate was 65·8%. Non-appropriate coverage of the injured segment by the radioactive source termed geographical miss affected 67·9% of the vessels, and increased edge restenosis significantly (16·3% vs 4·3%, $P=0·004$). It accounted for 40% of the treatment failures.

Conclusion The results of this registry reflect the learning process of the practitioner. The full therapeutic potential of this new technology is reflected by the restenosis rate at the site of the target segment. It can only be unravelled once the incidence of late vessel occlusion and geographical miss has been eliminated by the prolonged use of thienopyridine, the appropriate training of the operator applying this new treatment for restenosis prevention, and the use of longer sources.

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Introduction

Following coronary balloon angioplasty, restenosis of the dilated segment occurs in 30% to 50% of patients and results from elastic recoil, neointima formation, and negative remodelling[1–4]. The advent of coronary stenting reduced restenosis to 15% in certain type of lesions[5,6], but introduced the even more difficult to treat in-stent restenosis[7]. Radiation has been shown to be effective in the management of other benign proliferative conditions, such as keloids, heterotopic bone formation, pterygia, and Grave's opthalmopathy[8–11]. Endovascular radiation has been evaluated in animal balloon and stent restenosis models and was shown to reduce neointima formation in a dose- related manner both

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with gamma and beta emitters[12–15]. Clinical feasibility studies and randomized trials with beta and gamma emitters have been proven to be effective in reducing restenosis after balloon angioplasty, and recurrent in-stent restenosis[16–21]. Recent intravascular ultrasound studies have documented the favourable mechanisms of positive remodelling and inhibition of plaque formation[22,23] resulting in lumen enlargement after radiotherapy of de-novo lesions. In contrast the development of re-narrowing at the edges of the irradiated segment — related to vascular injury non-effectively irradiated[24–26] — the late total occlusions[27,28], the delayed healing[29], the increased thrombogenicity[30], and the persistent dissections[31,32] are limiting the effectiveness of this treatment. The purpose of the BRIE study was to introduce in a registry mode this new technology in Europe while awaiting the results of a large randomized trial (Beta-Cath trial), using the same source, in the U.S.A.

Methods

Objectives

The primary clinical end-point was freedom from major adverse cardiac events including death, CABG, myocardial infarction (defined as increase in the level of creatine kinase or MB isoenzymes to more than twice the upper limit of normal), and target vessel revascularization assessed at 1 year. The major adverse cardiac events were adjudicated by an independent clinical event committee. The angiographic end-point was restenosis (diameter stenosis >50%), by quantitative coronary angiography, at 6 months. Secondary angiographic end-points were minimal luminal diameter and late loss.

Patient selection

Between July 1998 and June 1999, 149 patients were enrolled in the study. Major inclusion criteria were: (1) objective evidence of ischaemia on exercise testing, (2) lesions located in vessels >2·7 mm and <4·0 mm in diameter, (3) patients with up to two discrete de-novo or restenotic lesions in different native coronary arteries who were eligible to undergo elective balloon (<24 mm) angioplasty or provisional stent (<22 mm) placement. Major exclusion criteria were (1) patients with unstable angina or acute myocardial infarction, (2) patients with in-stent restenosis, (3) bifurcation lesions and total occlusions.

The Institutional Review Boards or Ethics Committees and the Radiation Safety Committees of the participating institutions approved the protocol of the study. Written informed consent was obtained from all patients. The study was conducted at nine clinical sites listed in the appendix.

Table 1 Patients and procedural characteristics

Age (range)	60 (35–85) years
Males	111/149 (74·4%)
Diabetes	21/149 (14·1%)
Hypertension	54/149 (36·2%)
Prior MI	51/149 (34,3%)
Prior CABG	8/149 (5·4%)
LAD	65/175 (37·1%)
CFX	38/175 (21·7%)
RCA	72/175 (41·2%)
De-novo lesions	165/175 (94·3%)
Restenotic lesions	10/175 (5·7%)
Balloon angioplasty	62/175 (35·6%)
Rescue stenting	13/175 (7·4%)
Provisional stenting	100/175 (57%)

MI=myocardial infarction; CABG=coronary artery bypass graft operation; LAD=lleft anterior descending; LCX=left circumflex; RCA=right coronary artery.

Procedure

Overall, 123 patients underwent single-vessel angioplasty and 26 patients double-vessel angioplasty. In total, 175 vessels were treated. In the single-vessel group 48 vessels were treated with balloon angioplasty and 75 with stenting (64 provisional and 11 rescue). In the double-vessel group, 14 vessels were treated with balloon angioplasty and 38 with stenting (36 provisional and two rescue). Overall, 62 vessels were treated with balloon angioplasty alone. In 42 of these, radiation was the last intervention whereas additional balloon angioplasty was necessary after radiation in the remaining 20 (32·2%). In 113 vessels, stents were implanted (100 provisional and 13 rescue). All the stents but four (109/113, 96·4%) were placed after radiation. In these four cases, stenting was necessary before radiotherapy due to threatened vessel occlusion after the initial balloon angioplasty. Overall, post-radiation intervention was performed in 73·7% (129/175) of the vessels treated. Baseline patients and procedural characteristics are presented in Table 1.

Balloon angioplasty and stent implantation was carried out according to investigator's standard practice, with all patients receiving heparin and aspirin before the procedure. By-protocol stenting was not discouraged. The angiographic criteria for stent placement were residual stenosis >30%, flow-limiting dissection or threatened vessel occlusion. After successful dilatation, the balloon catheter was removed, with the guidewire left in place. The radiation delivery catheter was then inserted over the guidewire and advanced so that the two marker bands encompassed the angioplasty site with a margin of 3 mm, as specified in the protocol. Once satisfactory positioning of the catheter was confirmed under fluoroscopy, the transfer device was connected to the delivery catheter, the gate of the transfer device was opened, and the source train was hydraulically delivered down the catheter. During the procedure, minimal pressure and fluid flow were required to maintain the source train at the distal end of the source lumen. After

radiation therapy, the source train was returned to the transfer device by reversal of the switching system, which enabled injected fluid to push the train back into the transfer device. Further intervention was carried out when necessary and after achievement of a satisfactory result the procedure was concluded with filming of the final result after administration of intracoronary nitrates.

Post-procedural antiplatelet treatment

By protocol, the recommendation of antiplatelet treatment was 2 to 4 weeks. Due to the high incidence of angiographic vessel occlusion observed in the initial period of recruitment before 1999, prolongation of antiplatelet treatment for at least 8 weeks and up to 6 months was recommended after 1999.

Radiation delivery system

The device has been described elsewhere[20,33]. In summary, it consists of three components: (1) the transfer device which stores the radiation source train and allows its positioning within the catheter; (2) the delivery catheter, which is a 5 Fr multilumen non-centred catheter which uses saline to send and return the radiation source train; and (3) the radiation source train which consists of 12 independent cylindrical seeds which contain the radioisotope $^{90}Sr/^{90}Y$ source bounded by two gold radiopaque markers (30 mm in length). The longitudinal distance of the 'full' prescribed dose (100% isodose) coverage, measured by radiochromic films, is about 26 mm[34] constituting the effective irradiation length.

Dosimetry

The prescribed dose was 14–18 Gy, at 2 mm from the centreline of the source axis, based on the reference diameter, by on-line quantitative coronary angiography, which measured <3·35 mm or >3·35 mm, respectively. Overall, 57·5% of the patients received 14 Gy and 42·5% 18 Gy. The dwelling time was on average 3·12 ± 0·43 min (mean ± SD).

Angiographic analysis

Quantitative coronary angiography was performed off-line by an independent Core-lab (Cardialysis, Rotterdam, Netherlands). All angiograms were evaluated after intracoronary administration of nitrates. The analysis was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). Calibration of the system was based on the dimensions of the catheters empty of contrast medium[35]. This method of analysis has been previously validated[36,37].

A new methodological approach, recently reported[38], was used in order to define accurately the effect of brachytherapy on the treated coronary arteries. In each analysed coronary artery the following segments were determined: The vessel segment was defined as the segment bordered by two side branches, which encompassed the original lesion, the angioplasty balloon and the radiation source. The irradiated segment was defined as the segment encompassed by the two gold markers of the radiation source train. The target segment was defined as the 5 mm subsegment containing the pre-procedural minimal luminal diameter. In each of the above subsegments minimal luminal diameter, reference diameter, late loss, and restenosis-defined as diameter stenosis >50% at follow-up was determined. The segment encompassed by the most proximal and distal markers of the angioplasty balloon-defined the injured segment. The effective irradiated segment was the segment that received the full-prescribed dose and corresponded to the vessel segment covered by the 26 mm long central part of the radioactive source train. These segments are illustrated in Fig. 1.

Geographical miss

Geographical miss was defined for those cases where the entire length of the injured segment was not fully covered by the radioactive source. To determine whether the edges of the effective irradiated segment were injured, we retrospectively analysed (blinded to the presence or absence of restenosis and its location at follow-up) all the baseline (intervention plus radiation) angiograms. The following steps were followed: during the procedure all the interventions (balloons or stents) deflated at the site of injury and the radioactive source in place were filmed during contrast medium injection in identical angiographic projections. This approach allowed us to define the location of the various subsegments (effective irradiated segment, injured segment, edges) in relation to side branches and the correct matching of the intervention and radiation angiograms in the off-line analysis. The ECG recording was also displayed on screen, allowing the selection of still frames in the same part of the cardiac cycle. Multiple angiographic loops and ECG matched still frames could be displayed simultaneously, side-by-side, on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). By identifying the relationship between the effective irradiated segment and its edges relative to the injured segment we determined the geographical miss edges[26]. Computer-defined subsegmental analysis (mean subsegment length was 5·0 ± 0·3 mm) was also performed. In each subsegment percentage diameter stenosis was also automatically calculated. This allowed the determination of restenosis location in relation to the edges of the effective irradiated segment.

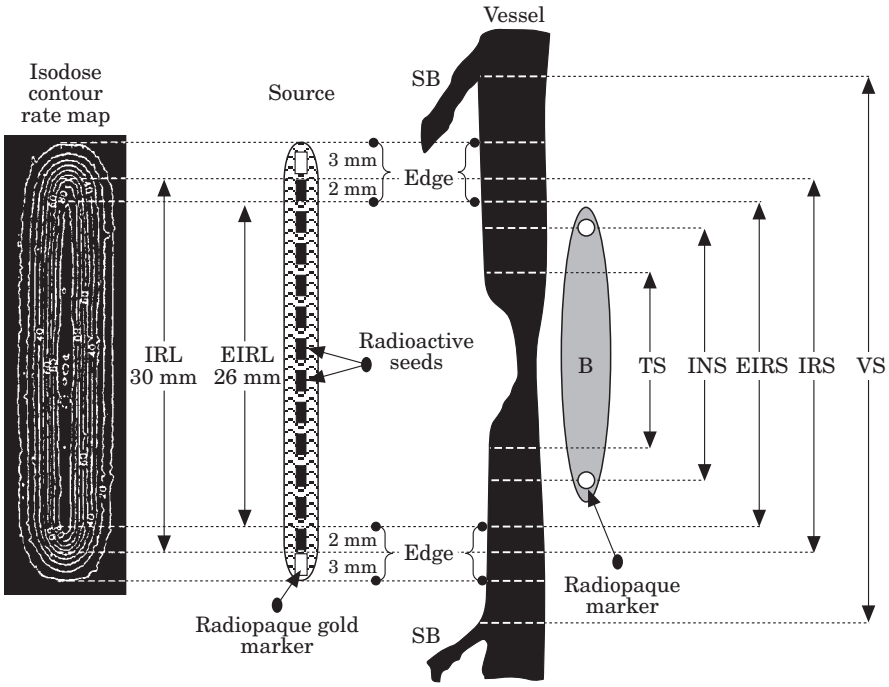

Figure 1 **Left side: Isodose rate contour map and radiation source train. Isodose rate contour map at a depth or 1·89 mm (10 mGy . s^{-1} contour intervals) as described by NIST (The National Institute of Standard and Technology). This depth (1·89 mm) illustrates an isodose model resembling the radius of the coronary artery wall. The longitudinal dose fall-off may be extrapolated from this graphic. The central part of the source train (26 mm) radiates approximately the full dose (100% isodose) constituting the EIRL. Right side: A diagram of an irradiated coronary artery and the anatomical and dose-based subsegment definition. B=balloon; EIRS=effective irradiated segment; INS=injured segment; IRS=irradiated segment; SB=side branch; TS=target segment; VS=vessel segment; IRL=irradiation length, EIRL=effective irradiation length.**

Statistical analysis

Patient survival curves were constructed according to the Kaplan–Meier method. Continuous parameters are presented as mean values and standard deviations, discontinuous parameters are presented as percentages. Continuous parameters are compared using Student's t-test, where binary parameters are compared using Fisher's Exact-test. The statistical significance of all tests was defined at the $P<0·05$ level.

Results

Major adverse cardiac events

In-hospital major adverse cardiac events

Three patients developed Q myocardial infarction after the procedure. In two patients Q myocardial infarction was due to total occlusion of the treated vessel (one occlusive dissection and one thrombotic occlusion) related to radiotherapy. In the third case the Q myocardial infarction was due to the occlusion of a side branch.

There were three patients with non-Q myocardial infarction; one from occlusion of a side branch after additional balloon dilatation following radiation, another with distal embolization of the treated vessel, and the third related to transient vessel occlusion, due to type F dissection following radiation, that required three stents to restore flow.

Major adverse cardiac events up to 1 year

The major adverse cardiac events up to 1 year follow-up are presented in Tables 2 and 3. The event-free survival curve up to 1 year is presented in Fig. 2. The incidence of major adverse cardiac events in the balloon group was 40% and in the stent group 30·9%. There was no difference between the two groups ($P=0·3$).

Angiographic results at 6 months

Twenty asymptomatic patients refused follow-up angiogram, leaving 129 patients with 152 lesions for angiographic analysis. The quantitative coronary analysis angiographic results are presented in Table 4.

Table 2 Major adverse cardiac events at 1 year — hierarchical ranking scale

	Up to 31 days		Up to 6 months		Up to 365 days	
	n	%	n	%	n	%
Death	0	0·0	3	2·0	3	2·0
MI	7	4·7	14	9·4	15	10·1
Q MI	3	2·0	8	5·4	8	5·4
Non-Q MI	4	2·7	6	4·0	7	4·7
CABG	0	0·0	2	1·3	3	2·0
TVR	0	0·0	23	15·4	30	20·1
No MACE	142	95·3	107	71·8	98	65·8

Hierarchical ranking scale considers only the worst event; i.e. if a patient required repeat angioplasty and later coronary artery bypass grafting the ranking scale would reflect only the worst event. MI=myocardial infarction; CABG=coronary artery bypass graft operation; TVR=target vessel revascularization; MACE=major adverse cardiac events.

Table 3 Major adverse cardiac events at 1 year — total count of events

	Up to 31 days		Up to 6 months		Up to 365 days	
	n	%	n	%	n	%
Death	0	0·0	3	2·0	3	2·0
MI	7	4·7	17	11·4	19	12·8
Q MI	3	2·0	10	6·7	11	7·4
Non-Q MI	4	2·7	7	4·7	8	5·4
CABG	0	0·0	4	2·7·3	5	3·4
TVR	0	0·0	33	22·1	46	30·9

All events reflects the total count of events i.e. if a patient required repeat angioplasty an later coronary artery bypass grafting the total count would reflect both events and not just the worst occurred. MI=myocardial infarction; CABG=coronary artery bypass graft operation; TVR=target vessel revascularization; MACE=major adverse cardiac events.

The average vessel size was $3{\cdot}06 \pm 0{\cdot}5$ mm, the minimal luminal diameter $1{\cdot}01 \pm 0{\cdot}31$ mm, the lesion length $11 \pm 3{\cdot}9$ mm. The restenosis rate in the target segment was always significantly lower compared with the restenosis rate in the irradiated segment and the vessel segment in all groups of patients including or excluding the total occlusions ($P<0{\cdot}001$). This association was less strong for the balloon group, including (7% vs 21·1%, $P=0{\cdot}06$) or excluding (5·4% vs 19·6%, $P=0{\cdot}04$) the total occlusions. There was no difference in the restenosis rate between the irradiated segment and the vessel segment in all groups of patients (P=ns). The late loss between target segment, irradiated segment, vessel segment was comparable in all group of patients (P=ns).

There was no difference in the restenosis rate and the late loss in the vessel subsegments (target segment, irradiated segment, vessel segment) when comparing the groups with and without the total occlusions (P=ns).

Significantly lower late loss was observed in the balloon group compared with the stent group including (target segment: $-0{\cdot}03$ mm vs 0·44 mm, $P<0{\cdot}001$, irradiated segment: 0·14 mm vs 0·43 mm, $P=0{\cdot}004$, vessel segment: 0·12 mm vs 0·37 mm, $P=0{\cdot}009$) (Fig. 3) or excluding the total occlusions (target segment: $-0{\cdot}07$ mm vs 0·33 mm, $P<0{\cdot}001$; irradiated segment: 0·11 mm vs 0·33 mm, $P=0{\cdot}004$; vessel segment: 0·08 mm vs 0·28 mm, $P=0{\cdot}009$) but there was no difference in the restenosis rate (P=ns).

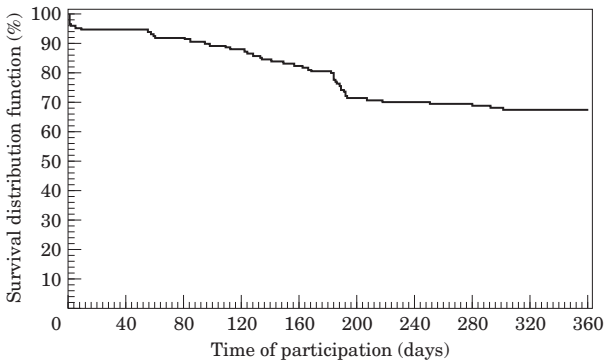

Figure 2 **Event-free survival curve up to 1 year. This curve consists of three distinct segments. Up to 6 months a relapse is clearly visible followed by a sharp decrease related to the angiographic control as mandated by the protocol. From 6 months up to 1 year the curve remains reasonably stable.**

Late vessel occlusions

In 5·3% (8/152) of the treated vessels a total occlusion was documented at the follow-up angiogram. In five of them (four stents and one balloon) the patients were asymptomatic (silent total occlusion). The other three (all stents) presented with an acute coronary syndrome (two with Q myocardial infarction and one with non-Q myocardial infarction) 94, 59 and 80 days after the index procedure and were revascularized successfully. The incidence of vessel occlusion was 10·5% (six out of 57, all stents) in the initial period of recruitment, before 1999, when the recommendation for the duration of the antiplatelet therapy was 2 to 4 weeks. It dropped to 2·1% (two out of 95, one balloon and one stent) ($P=0{\cdot}02$) after 1999 with the prolongation of the antiplatelet treatment for at least 8 weeks and up to 6 months.

One patient in the balloon group with a patent vessel without restenosis at 6 months presented with unstable angina 279 days after radiation. A late thrombotic occlusion of the irradiated vessel was documented at the angiogram. The patient was revascularized successfully.

Geographical miss and treatment failure

Geographical miss could not be determined in 25·1% (44/175) of the treated vessels due to inadequate filming. The geographical miss was observed in 67·9% (89/131) of the interpretable vessels and in 41·2% (108/262) of the edges of the effective irradiated segment and resulted in

Table 4 Angiographic results

	TS (5 mm)		IRS (28 mm)		VS (42 mm)	
	Post	F/UP	Post	F/UP	Post	F/UP
All patients with total occlusions (n=152 lesions)						
MLD mm	2·54	2·28	2·08	1·75	1·93	1·65
Reference diameter mm	2·86	2·68	2·84	2·61	2·81	2·59
Late loss mm	0·26		0·33		0·28	
Restenosis rate %	9·9		28·9		33·6	
All patients without total occlusions (n=144 lesions)						
MLD mm	2·58	2·41	2·08	1·84	1·93	1·73
Reference diameter mm	2·89	2·83	2·87	2·76	2·84	2·74
Late loss mm	0·17		0·24		0·20	
Restenosis rate %	4·9		25·0		29·9	
Balloon group with total occlusions (n=57 lesions)						
MLD mm	2·20	2·23	1·97	1·83	1·88	1·76
Reference diameter mm	2·55	2·65	2·71	2·66	2·73	2·66
Late loss mm	−0·03		0·14		0·12	
Restenosis rate %	7·0		21·1		24·6	
Balloon group without total occlusions (n=56 lesions)						
MLD mm	2·20	2·27	1·97	1·86	1·87	1·79
Reference diameter mm	2·55	2·70	2·70	2·71	2·72	2·71
Late loss mm	−0·07		0·11		0·08	
Restenosis rate %	5·4		19·6		23·2	
Stent group with total occlusions (n=95 lesions)						
MLD mm	2·77	2·33	2·13	1·70	1·94	1·57
Reference diameter mm	3·05	2·70	2·93	2·59	2·86	2·55
Late loss mm	0·44		0·43		0·37	
Restenosis rate %	11·7		33·7		38·9	
Stent group without total occlusions (n=88 lesions)						
MLD mm	2·82	2·49	2·16	1·83	1·97	1·69
Reference diameter mm	3·10	2·91	2·98	2·80	2·92	2·75
Late loss mm	0·33		0·33		0·28	
Restenosis rate %	4·6		28·4		34·1	

MLD=minimal luminal diameter; TS=target segment; IRS=irradiated segment, VS=vessel segment.

a 16·3% incidence of edge restenosis, while the restenosis at the edges without geographical miss was only 4·3% (P=0·004)[26]. Out of the 44 vessels with restenosis at the irradiated segment, in 24 restenosis was located at the edges and in 18 it was related to geographical miss. This inadequate treatment was responsible for 40% (18/44) of the treatment failures. In 20 vessels the restenosis was located in the effective irradiated segment and they represent the true treatment failures.

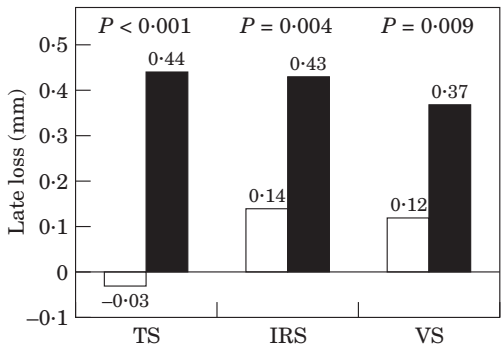

Figure 3 **Difference in the late loss in the target segment (TS), the irradiated segment (IRS) and the vessel segment (VS) between patients treated with balloon angioplasty (□) and stent implantation (■).**

Discussion

Endovascular radiotherapy has emerged as a promising treatment for reducing restenosis. Investigations using animal models of restenosis demonstrate a dramatic inhibition of neointima formation after balloon and stent injury both after intravascular gamma and beta-radiation[12–15]. Following these encouraging results, human feasibility studies both with beta[39] and gamma[16] emitters showed that intracoronary brachytherapy is feasible and safe. In two randomized trials intracoronary gamma radiation showed a significant reduction in angiographic and clinical assessment of restenosis in patients undergoing coronary intervention for restenotic lesions after balloon angioplasty treated with stent[19] and in-stent restenosis[17].

Beta sources with more limited penetration may have inherent safety advantages over gamma sources, but conversely less efficacy in preventing restenosis, particularly in stented arteries[40]. King *et al.*[20] in a non-controlled feasibility trial using $^{90}Sr/^{90}Y$ demonstrated a

low late lumen loss and late loss index compared with historical controls in patients with de novo lesions treated with balloon angioplasty followed by radiation with a non-centred source. Using the ^{32}P as a beta-emitter reduced the restenosis rate and improved clinical outcome, as reported in a small randomized trial[21]. Recently beta radiation was proved to be as effective as gamma in reducing in-stent restenosis in a non-randomized trial[18].

Evidence of treatment efficiency

The angiographic end-points in the current study suggest effective inhibition of restenosis (9·9%) within the target segment in patients receiving radiotherapy compared with historical cohorts[5,6] treated with balloon angioplasty or stents. Excluding the late total occlusions, which have a different pathophysiology from that of the restenotic process, binary restenosis in the same segment is as low as 4·9%. This result is comparable with the 3·9% restenosis observed in the balloon group that received 18 Gy in the Dose Finding study[41]. The target segment represents the subsegment in which inappropriate radiation is technically excluded since this corresponds to the treatment target and is always appropriately covered by the radiation source and thus receives the prescribed dose. The restenosis rate in this segment reflects the full therapeutic potential of this treatment. Late lumen loss in this segment was also substantially lower compared with historical trials with similar angiographic and demographic characteristics[5,6]. Most importantly, in patients treated with balloon angioplasty alone, a negative late loss is observed in the target segment with enlargement of the vessel lumen at follow-up. A similar result was reported in the balloon group that received 18Gy in the Dose Finding study. The vessel expansion in the target segment resulted in comparable minimal luminal diameters between the balloon and the stent group at the 6 months follow-up angiogram (2·23 mm and 2·31 mm, respectively) and no difference in the restenosis rate (7% and 11·7%, respectively, $P=0·41$). This confirms previous observations made with intravascular ultrasound[22] indicating positive remodelling with enlargement of the total lumen and vessel volume 6 months after intracoronary beta radiation in vessels treated with balloon angioplasty. Radiotherapy is the first therapeutic modality achieving such a beneficial effect.

Edge restenosis and treatment failures

Edges restenosis, the so-called 'edge effect', observed both after radioactive stent implantation[25] and catheter-based radiotherapy[24] limits considerably the positive results observed at the site of the target segment, increasing binary restenosis from 9·9% to 28·9% at the irradiated segment. Careful retrospective analysis of all the procedural films revealed the aetiology of this failure. The combination of low dose radiation with injury, the so-called geographical miss, was responsible for 75% (18/24) of the edge failures or 40% (18/44) of the restenosis observed in the irradiated segment. Our ignorance of the microscopic extent of the perivascular injury (up to 10 mm away from the macroscopic injury)[42], of the proliferative effect of low dose radiation on the injured tissue[43,44], and the actual length of the effective radiation source account for this phenomenon. Beta radiation due to low penetration in the tissue results in acute fall-off of the dose delivered at the edges of the sources in the axial direction. This in an inherent property of all beta sources. For the current source this fall-off area was 2 mm on each side of the source. as measured with radiochromic film[34] limiting the effective radiation length to 26 mm, as opposed to the 30 mm distance between the gold markers which were used as guides for proper positioning of the source. For achieving a sufficient margin of effectively irradiated vessel at the edges of the injured segment a balloon to source ratio of one to two is advised. The use of longer sources up to 60 mm in length, which are now available, will allow treatment of lesions up to 30 mm.

In 73·8% of the vessels treated post-radiation intervention was performed. This was responsible for 53% of the incidence of geographical miss[26]. To avoid this complication, radiation therapy should be planned as the last intervention.

All the edge restenotic lesions were new non pre-existing lesions. In seven vessels the minimal luminal diameter was located outside the irradiated segment but inside the analysed vessel segment increasing binary restenosis from 28·9% (irradiated segment) to 33·6% (vessel segment). These were pre-existing lesions (five vessels), unmasked after the treatment of the target segment, or progression of the disease (two vessels) non-related to brachytherapy, which has proved to be safe in non-injured vessels both with beta[34] and gamma[45] emitters.

The edge restenosis phenomenon and the positive vascular remodelling observed after brachytherapy increased the incidence of relocation of minimal luminal diameter compared to the standard treatments[38]. This, in conjunction with the increment in the mean length of the analysed vessel segment, 42 mm in our study compared to the 28 mm in the Benestent I trial[5], made the interpretation of the results in brachytherapy trials more complex and any direct comparison with historical trials unfair. New methodological approaches in the quantitative coronary analysis, such as the one used in the present study with reports of the angiographic parameters for the stenotic, the irradiated and the total analysed segment will improve our understanding of the results of brachytherapy.

In 20 patients the restenosis was located in the effective irradiated segment representing the true failures of the treatment. Dose inhomogeneity, since our system is not centred or inappropriate dose, are possible explanations for these failures.

Clinical thrombosis and late angiographic occlusion

Eight patients (5·3%) presented with late total occlusion. Seven of the patients had a stent implanted during the index procedure and one was treated with balloon angioplasty alone. The incidence of occlusion in the stent group was 7·3% and in the balloon group 1·7% ($P=0·1$). An incidence of 9·1%[28] for in-stent restenotic lesions and 6·6%[27] for non-restenotic lesions has been recently reported with higher prevalence in patients treated with stent implantation. Various causes such as delayed healing[29], persistent dissections[31,32], late stent malaposition[46], and increased radiation induced thrombogenicity[30] have been hypothesized to be the reasons. In our study a significant decrement in the incidence of vessel occlusion was observed with the prolongation of the antiplatelet treatment up to 6 months (10·5% vs 2·1%, $P=0·02$). Reduction in the incidence of the total occlusion and the late thrombosis was recently reported with the use of clopidogrel for 6 months in combination with aspirin after intracoronary γ-radiation for the treatment of in-stent restenosis[47]. Further randomized trials are necessary to evaluate the efficacy and the duration of antiplatelet treatment for the prevention of late vessel occlusion after intracoronary radiation therapy.

Recently drug eluting stents have been introduced for the prevention of restenosis. Preliminary results indicate that restenosis may be completely abolished by the sirolimus drug-eluting stents[48], and if confirmed could have a drastic impact on the use of brachytherapy for de novo lesions.

Study limitations

This in not a placebo-controlled study and the number of patients included is limited. Further randomized placebo-controlled studies are warranted to validate the efficacy of ^{90}Sr radiotherapy for prevention of restenosis.

Conclusions

The results of this registry reflect the learning process of the practitioner. The full therapeutic potential of the brachytherapy with strontium 90, potentially reflected by the restenosis rate in the target segment, can only be unravelled once the incidence of the late vessel occlusion and geographical miss has been eliminated. Probably this report will herald some of the results of the large randomized trial undertaken in the U.S.A. using the same source (Beta-Cath trial).

Appendix

The participating centres and investigators of the BRIE group are listed along with the number of included patients in parenthesis.

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UZ Virga Jesse Ziekenhuis, Hasselt, Belgium (20): E. Benit, MD, M. Brosens, MD.
Clinique St. Jean, Brussels, Belgium (18): M. Vandormael, MD, R. Burette, MD, S. Latinis, RN.
Academisch Ziekenhuis Rotterdam Dijkzigt, Thoraxcenter, Rotterdam, The Netherlands (11): P. W. Serruys, MD, PhD, V. L. M. A. Coen, MD, P. Levendag, MD.
Klinik Weisser Hirsch, Dresden, Germany (10): R. Dörr, MD, Th. Herrmann, MD.
Clinique Universitaire de Saint-Luc, Brussels, Belgium (5): N. Debbas, MD, P. Scalliet, MD.
Internistische Klinik, Munich, Germany (4): S. Silber, MD, R. von Rotkay, MD, I. Krischke, MD.
Data co-ordinating centre: Lincoln, Paris, France (D. de Segonzac, J. Paget, S. Crethien).
Angiographic core-laboratory and data analysis: Cardialysis, Rotterdam, The Netherlands (C. Disco, MSc, M-a. Morel, BSc, C. v.d. Wiel).
Monitoring: Lincoln, Paris, France (D. de Segonzac).
Angiographic committee: P. W. Serruys, MD, PhD, P. Urban, MD, R. Bonan, MD.
Clinical Events Committee: C. Lefeuvre, MD, M-L. Lachurie, MD, R. Bonan, MD.

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