Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 40, No. 7, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)02108-3

Interventional Cardiology

Geographical Miss During Intracoronary Irradiation: Impact on Restenosis and Determination of Required Safety Margin Length

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OBJECTIVES The goal of this study was to evaluate the incidence and effects of underdosage of injured segments during intracoronary irradiation and to define the minimal length of safety margin required to avoid mismatched source placement.

BACKGROUND Underdosage of injured segments due to misplacement of active source has been suggested as the underlying mechanism for the occurrence of edge restenosis.

METHODS Baseline angiograms of 112 vessels in 109 patients with in-stent restenosis undergoing coronary reintervention followed by intracoronary irradiation (^{192}Ir: Checkmate, Cordis, Miami, Florida; ^{32}P: Gallileo, Guidant, Houston, Texas; ^{90}Sr/Y: Beta-Cath, Novoste, Norcross, Georgia) were analyzed. The distances between the outermost injury and outermost end of "reference isodose length" (RIL), defined as a segment with ≥90% of reference dose at 1 mm vessel wall depth, were measured. "Safety margin" was defined as the distance between the outermost injury and outermost end of the RIL, "geographical miss" (GM) as a complete injured segment not being covered by the RIL, and "restenosis" as the percent diameter stenosis >50%.

RESULTS Baseline angiographic analysis was performed for 224 edges in 112 vessels. Geographical miss was found in 46 (20.6%) edges. The incidence of target lesion restenosis within the 78 vessels with available follow-up was 43.3% for patients with GM versus 14.9% for patients with no GM ($p = 0.005$). Analysis of various injured segments exposed highest restenosis rates in injured segments with negligible irradiation (27.8%) in comparison with injured segments with dose fall-off (16.7%) or injured segments with full-dose irradiation (7.7%) ($p = 0.006$). Receiver operating curve analysis revealed a safety margin of 10 mm required per vessel (i.e., 5-mm safety margin/edge) to achieve 95% specificity of GM.

CONCLUSIONS Geographical miss is associated with a higher incidence of restenosis at the corresponding edges. Restenosis was more pronounced in injured segments with negligible irradiation than in injured segments at the dose fall-off zones. We recommend a safety margin of 10 mm per vessel to minimize GM. (J Am Coll Cardiol 2002;40:1225–31) © 2002 by the American College of Cardiology Foundation

Intracoronary irradiation with both beta and gamma sources has previously been demonstrated to confer clinical benefit in the treatment of in-stent restenosis (ISR) (1–3). However, intracoronary radiation therapy is still limited by the occurrence of edge restenosis (4). Geographical miss (GM) (i.e., irradiation underdosage within injured segments due to mismatched placement of the active source) has been suggested as the underlying mechanism (5,6). Besides other factors such as mechanical difficulties in source placement, GM may result from inadequate determination of the active source length. Appropriate safety margins in the evaluation of the active source length might reduce the incidence of GM; however, required safety margin lengths have not been defined.

Recent studies have analyzed the effect of GM on angiographic outcome at follow-up (7,8) and have suggested GM as a potential factor for the occurrence of edge restenosis. However, the precise mechanism involved in edge restenosis is yet unknown, and so far, both neointimal proliferation (9) and absence of positive remodeling (10) have been implicated. Moreover, it is unclear if the higher restenosis rate in the dose fall-off zone is caused by an underdosage or absence of irradiation, similar to conventional intervention, or rather by a stimulatory effect of the combination of low-dose irradiation with mechanical injury.

In this study we aimed to determine the incidence of GM in patients with in-stent lesions undergoing beta or gamma radiation treatment, to evaluate its impact on restenosis in the dose fall-off zones in comparison with zones of negligible irradiation and to define the minimal length of safety margin required to minimize GM.

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Manuscript received March 5, 2002; revised manuscript received April 24, 2002, accepted May 31, 2002.

JACC Vol. 40, No. 7, 2002
October 2, 2002:1225–31

Abbreviations and Acronyms

%DS	= percent diameter stenosis
GM	= geographical miss
ISR	= in-stent restenosis
MLD	= minimal lumen diameter
RIL	= reference isodose length
ROC	= receiver operating curve
START	= Stents and Radiation Therapy registry

METHODS

Patient population. Clinical, interventional, and baseline angiographic data of 117 vessels undergoing coronary reintervention of ISR with subsequent intracoronary irradiation between September 1999 and July 2001 at the Department of Cardiology, University of Vienna, were prospectively selected and analyzed. Follow-up angiographic analysis of 78 vessels with available follow-up before November 2001 was performed. Ethics approval and written informed consent according to the institutional guidelines for cardiac catheterization and intracoronary irradiation were available for all patients.

Coronary angiography and intervention. All patients underwent routine biplane coronary angiography using the Judkins technique. Before angiography 0.1 to 0.2 mg intracoronary nitroglycerine was administered to achieve maximal vasodilation. Baseline angiograms were recorded in at least two projections on CD-ROM. Interventional treatment of ISR included percutaneous transluminal balloon angioplasty in 54 vessels (69.2%) and additional stent deployment in 24 vessels (30.8%). All balloon inflations and stent deployments were recorded.

According to the decision of the interventionist, intracoronary irradiation was performed using one of three available systems (^{192}Ir: Checkmate, Cordis, Miami, Florida; ^{32}P: Gallileo, Guidant, Houston, Texas; ^{90}Sr/Y: BetaCath, Novoste, Norcross, Georgia). Dosimetry was performed based on the reference diameter as determined by intravascular ultrasound. Patients receiving ^{192}Ir treatment were irradiated with 13.5 Gy at 1 mm vessel depth, patients receiving ^{32}P treatment with 20 Gy, and patients receiving ^{90}Sr/Y with 13.5 Gy at 1 mm vessel depth. After the procedure patients were given aspirin (100 mg) for at least one year and clopidogrel (75 mg) for at least six months. Follow-up angiography was performed on a routine basis after 6.9 ± 2.3 months and was available for 78 vessels until November 2001.

Definitions. *Injury:* intervention length. *Reference isodose length (RIL):* segment receiving >90% of reference dose at 1 mm vessel wall depth. *Safety margin:* distance between outermost injury and outermost end of RIL. *Edge of irradiation (dose fall-off segment):* segment with 10% to 90% of reference dose at 1 mm vessel wall depth. The length of this segment was assumed 4.5, 2.0, and 2.5 mm proximal and distal to the end of the active source for ^{192}Ir, ^{32}P, and ^{90}Sr/Y treatment, respectively (11) (Fig. 1). *Segment of negligible irradiation:* segment with <10% of reference dose at 1mm vessel wall depth. This was taken as segment outside the 4.5, 2.0, and 2.5 mm dose fall-off zone after the end of the active source for ^{192}Ir, ^{32}P, and ^{90}Sr/Y application, respectively (11). *No geographical miss:* complete injured segment covered by RIL. *Geographical miss:* complete injured segment not covered by RIL. *Target lesion:* segment affected by injury and/or irradiation.

Assumptions. Only the ^{32}P system is capable of centering the catheter within the vessel. However, in this analysis we assumed all three sources to be centered in the lumen. Further, based on experimental data, we assumed the vessel diameter to have no significant impact on the length of the dose fall-off zone and, consequently, on the RIL (11).

Angiographic analysis. A computer-assisted quantitative coronary arteriographic edge-detection algorithm (ACOMPC, Siemens, Erlangen, Germany) was used for cineangiographic analysis. Both baseline and follow-up angiographic analyses were performed in identical angiographic projections by two experienced observers. Consen-

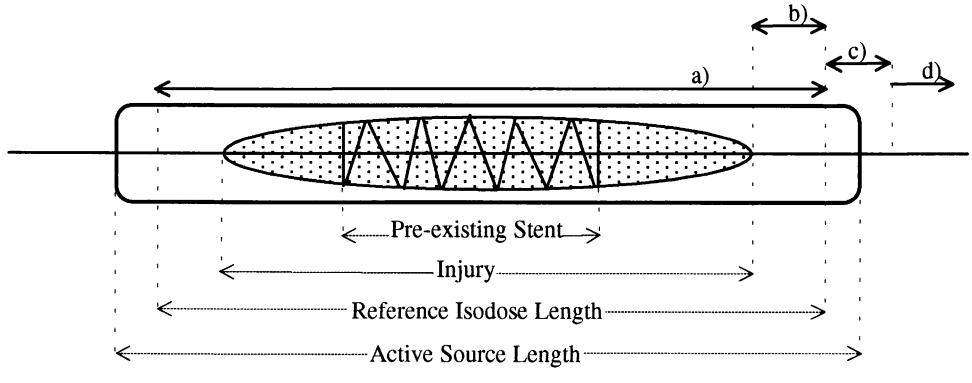

Figure 1. Segmental distribution of radiation dose. **(a)** Segment of full-dose irradiation with >90% of reference dose at 1-mm vessel depth (= reference isodose length [RIL]). **(b)** Segment between end of injury and end of RIL receiving full-dose radiation with >90% of reference dose at 1-mm vessel depth (= safety margin). **(c)** Segment of dose fall-off with 10% to 90% of reference dose at 1-mm vessel depth (= edge of irradiation). This segment was assumed 4.5, 2.0, and 2.5 mm proximal and distal to the end of the active source for ^{192}Ir, ^{32}P, and ^{90}Sr/Y application, respectively (11). **(d)** Segment of negligible irradiation with <10% of reference dose at 1 mm vessel depth.

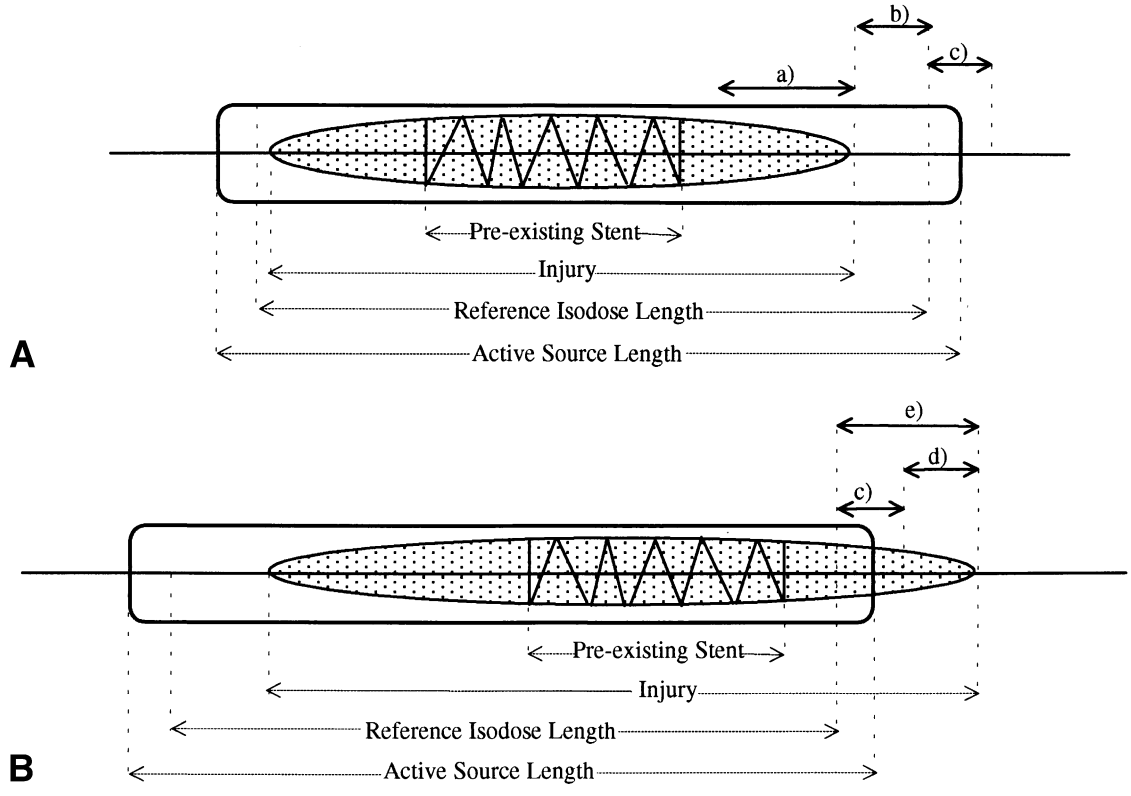

Figure 2. Analyzed segments in patients with no geographical miss (GM) **(A)** and GM **(B). (a)** Injured segment with full-dose radiation. For comparison with the median length of injured segments without full-dose irradiation in patients with GM **(segment e in Fig. 2B)**, this segment was equally set to 4 mm. **(b)** Distance between end of injury and end of reference isodose length (full dose irradiation zone). **(c)** Edge of irradiation (dose fall-off zone). **(d)** Distance between end of dose fall-off zone and outermost injury (negligible irradiation zone). **(e)** Length of GM.

sus between the two observers was reached in all cases. Baseline and follow-up analyses were performed for proximal and distal edges.

Baseline analysis. Outermost proximal and outermost distal injuries were determined from end-diastolic frames analyzing all film sequences with inflated balloons and inflated stents in identical angiographic projections. The length between the outermost injury and the outermost end of the active source was calculated by subtracting the distance between the pre-existing stent-ending and the outermost end of injury from the distance between the pre-existing stent-ending and the outermost end of the active source. Based on experimental data, end of RIL at each edge was assumed to be 4.5, 2.0, and 2.5 mm shorter than the active source length for patients receiving ^{192}Ir, ^{32}P, and ^{90}Sr/Y treatment, respectively (11). The safety margin per edge was calculated as the difference between outermost end of injury and outermost end of RIL (Fig. 1). Because the pre-existing stent was used as a reference to evaluate the safety margin, failure to locate its exact position excluded the corresponding edge from further analysis.

Follow-up analysis. Follow-up angiographic analysis included the assessment of minimal lumen diameter (MLD) and percent diameter stenosis (%DS). Restenosis was defined as %DS $>$ 50% and was assessed at the edges of irradiation, within the sites of the pre-existing stents, in non-injured irradiated segments in patients without GM, and injured nonirradiated segments in patients with GM (Figs. 2A and 2B). Further, because the median length of all GMs of the 224 edges with baseline analysis was 4 mm, MLD and %DS were equally assessed at the outermost 4 mm injured segments in patients with no GM (segments of full-dose irradiation) (Fig. 2A), at the injured edges of irradiation in patients with GM (segments of dose fall-off), and at injured segments between end of dose fall-off zone and outermost end of injury in patients with GM (segments of negligible irradiation) (Fig. 2B). It should be noted that the criteria of restenosis may be fulfilled in more than one subsegment in the same vessel. Analysis was performed at end-diastolic frames in order to minimize the variation caused by cardiac motion and to maximize the contrast filling of the coronary vessels.

Statistics. Data are expressed as frequencies or percentages for discrete variables and means ± SD for continuous variables. Comparisons between groups were made using the chi-square test for categorical variables and the Student *t* test for continuous variables. Statistical significance was considered present if $p < 0.05$.

Sensitivity, specificity, and the cut-off value of safety margin length as predictor of GM was established on the basis of receiver operating characteristic (ROC) curves. Receiver operating curve analysis was performed after ex-

Table 1. Incidence of GM Using the Different Radiation Sources

	Total Population (n = 224 Edges)		
	^{192}Ir (n = 48)	^{32}P (n = 74)	^{90}Sr/Y (n = 102)
No GM (n = 178 edges)	35 (72.9%) (15 p/20 d)	64 (86.5%) (32 p/32 d)	79 (77.5%) (41 p/38 d)
GM (n = 46 edges)	13 (27.1%) (9 p/4 d)	10 (13.5%) (5 p/5 d)	23 (22.5%) (10 p/13 d)
	Population With Available FUP (n = 153 Edges)		
	^{192}Ir (n = 30)	^{32}P (n = 60)	^{90}Sr/Y (n = 63)
No GM (n = 117 edges)	20 (66.6%) (8 p/12 d)	51 (85.0%) (26 p/25 d)	46 (73.0%) (25 p/21 d)
GM (n = 36 edges)	10 (33.3%) (3 d/7 p)	9 (15.0%) (5 D/4 p)	17 (27.0%) (9 d/8 p)

d = distal edge; FUP = follow-up; GM = geographical miss; p = proximal edge.

cluding all patients with GM resulting from mechanical resistance while advancing the catheter.

RESULTS

Baseline data of total patient cohort. Baseline angiographic analysis was performed for 117 vessels. Five vessels could not be evaluated owing to poor quality of the angiogram. Thus, final baseline analysis was available for 224 edges in a total of 112 vessels in 109 patients. Of these 112 vessels, 24 (21.5%) were treated with ^{192}Ir, 37 (33.0%) with ^{32}P, and 51 (45.5%) with ^{90}Sr/Y.

Geographical miss occurred at 46 of 224 (20.5%) edges in 42 of 112 (37.5%) vessels. Reasons for GM were additional dilations owing to unsatisfactory angiographic results after irradiation in 17 edges (37.0%), mechanical difficulties while advancing the catheter in eight edges (17.4%), and unintended mismatching between outermost injury and radiation source in 21 edges (45.6%).

Detailed analysis of the incidence of GM with regard to the different radiation sources is presented in Table 1. The occurrence of GM was equally distributed among the three radiation sources as well as between the proximal (24 of 112) and distal (22 of 112) edges. In edges with GM, mean length of inadequate source coverage was 5.7 ± 5.7 mm (median length, 4.2 mm). Mean safety margin within the 178 edges without GM was 7.5 ± 5.2 mm (median length, 6.0 mm).

Figure 3 shows the sensitivity/specificity for each safety margin length per vessel. Receiver operating curve analysis revealed a cut-off value of 7.8-mm safety margin per vessel (i.e., 3.9 mm for each edge) for the prediction of GM with a sensitivity and specificity of 83.7%. The area under the ROC curve is 0.92 (Fig. 4). In order to achieve 95% specificity (true negative rate of GM), a safety margin length of 10 mm is required per vessel (i.e., 5-mm safety margin for each edge) (Fig. 3).

Baseline data of patients with available follow-up. Angiographic follow-up was available for 78 vessels in 77 patients (^{192}Ir: 17 vessels; ^{90}Sr/Y: 33 vessels; ^{32}P: 28 vessels) with a mean follow-up period of 6.9 ± 2.3 months. Follow-up analysis could not be performed in three distal edges, because of total vessel occlusion proximal to the corresponding edge. Thus, a total of 153 edges—78 proximal edges and 75 distal edges—were included in the follow-up analysis.

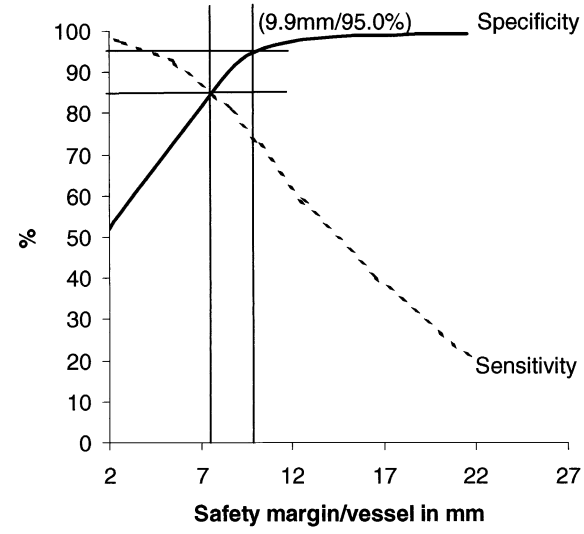

Figure 3. Sensitivity and specificity curves for prediction of geographical miss in relation to various safety margins per vessel. Determination of the cut-off point with equal sensitivity and specificity (7.8 mm; 83.7% sensitivity/specificity). In order to achieve 95% specificity, a safety margin of 9.9 mm is required per vessel.

In patients with available follow-up, GM occurred at 36 of 153 (23.5%) edges in 32 of 78 (41.0%) vessels. Mean length of inadequate source coverage in edges with GM was 4.5 ± 4.3 mm. Mean safety margin within the 117 edges without GM was 7.2 ± 5.0 mm.

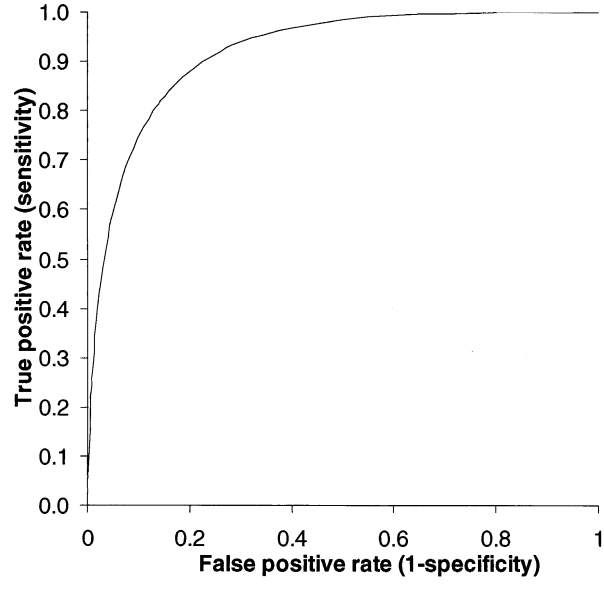

Figure 4. Receiver operating characteristic curve demonstrating the performance of different safety margins for prediction of geographical miss. Area under the curve: 0.92.

Table 2. Incidence of Restenosis Within Different Analyzed Segments at Follow-Up

	No-GM (n = 117)	GM (n = 36)	p Value
(A) Dose fall-off	5 (4.3%)	6 (16.7%)	0.01
(B) Outside target lesion	8 (6.8%)	0	NS
(C) Noninjured irradiated	5 (4.3%)	NA	—
(D) Injured nonirradiated	NA	10 (27.8%)	—

Analysis comprised the following segments: (A) dose fall-off zones in patients with and without GM; (B) segments outside the target lesion in patients with and without GM; (C) segments between outermost injury and outermost RIL in patients without GM; (D) segments of negligible irradiation in patients with GM.

GM = geographical miss; NA = not applicable; RIL = reference isodose length.

Follow-up data. VESSEL ANALYSIS. Target vessel restenosis was 30.8% in patients with available angiographic follow-up and tended to be higher in patients with GM (GM vs. no GM: 43.3% vs. 23.0%, p = 0.05). The incidence of restenosis within the entire length of the target lesion was 25.7%, with a pronounced increase in the presence of GM (GM vs. no GM: 43.3% vs. 14.9%, p = 0.005). Regarding ISR within the site of the pre-existing stent, we found no higher incidence in patients with GM (GM vs. no GM: 13.3% vs. 6.2%, p = NS). Accordingly, the %DS within the site of the former lesion was similar in both groups (GM vs. no GM: 21.1 ± 27.7% vs. 15.4 ± 18.9%, p = NS).

EDGE ANALYSIS. The rate of restenosis at the edges of irradiation was significantly higher in patients with GM than in patients with no GM (GM vs. no GM: 16.7% vs. 4.3%, p = 0.01) (Table 2). However, merely 5.6% exhibited restenosis at the injured edges of irradiation only, without extension into the zones of negligible irradiation, whereas 27.8% were found to have restenosis in injured segments of negligible irradiation (p = 0.01).

Table 3 compares angiographic follow-up data between injured segments with negligible irradiation, injured segments with dose fall-off, and injured segments with full-dose irradiation, demonstrating highest restenosis rates in injured segments of negligible irradiation.

DISCUSSION

In this study we evaluated the incidence of GM during intracoronary irradiation as an adjuvant treatment of ISR and analyzed its impact on re-restenosis in different segments of the treated vessel. We found higher restenosis rates at the edges of irradiation in patients with GM than in patients with no GM, as well as increased restenosis rates in injured segments with negligible irradiation compared with injured segments of dose fall-off. Based on our data, we developed a safety margin recommendation to minimize the occurrence of GM.

Incidence of GM. Retrospective analysis of large-scale trials has recently increased the general awareness of GM during intracoronary irradiation as a potential predictor of long-term restenosis (7,8). While Sianos et al. (7) describe an incidence of 41.2% GM during beta irradiation in de novo lesions, Kim et al. (8) report 34% GM during gamma irradiation of in-stent lesions. Mismatched placement of the radiation source may be explained by mechanical difficulties due to complex vessel anatomy, technical limitations such as short source lengths, lack of international definitions regarding the parameters for the assessment of safety margin length, and the presence of a learning curve in the initial era of intracoronary irradiation. Initially, the length of the irradiation segment was kept short in order to avoid irradiation of noninjured segments, thus increasing the risk of GM. Hesitance in application of tandem treatment, because of unknown consequences of overlapping irradiation, may also have increased the incidence of GM. Today, international recommendations for endovascular irradiation may be used in treatment planning to determine the application dose (12); however, definite safety margin lengths in order to avoid GM have not been reported, and recommendations given by the industry are not based on clinical data. Applied to our definition of safety margin, the industrial recommendations may be interpreted as a 2-mm margin at each edge for the ^{32}P-system and 2.5 mm at each edge for the ^{90}Sr/Y system (no definite recommendations available for the ^{192}Ir system). Our analysis revealed that a 10-mm safety margin length per vessel is required to avoid GM in >95% of all cases. The 10-mm safety margin recommendation is also supported by data from the Stents and Radiation Therapy (START) 40 registry, where the incidence of GM was found to be lowered with the use of a longer source wire of 40 mm (GM: 7%) when compared with GM of the placebo arm of the START trial with a shorter source wire of 30 mm (GM: 34%) (13). In fact, if we had always used a safety margin ≥10 mm in all vessels in our patient cohort, GM would theoretically have occurred in only three vessels (2.7%). We point out from this analysis the importance of

Table 3. Angiographic Results at Follow-Up Comparing Various Injured Segments

	(A) Segment of Full-Dose Irradiation (n = 117)	(B) Segment of Dose Fall-Off (n = 36)	(C) Segment of Negligible Irradiation (n = 36)	p Value
Restenosis	9 (7.7%)	6 (16.7%)	10 (27.8%)	0.006
%DS	21.1 ± 19.7	28.7 ± 16.5	38.7 ± 23.4	0.001
MLD	2.0 ± 0.7	1.8 ± 0.6	1.4 ± 0.7	0.003

(A) = segments of full dose irradiation in patients with no GM; (B) = segments of dose fall-off at edges of irradiation in patients with GM; (C) = segments of negligible irradiation between end of dose fall-off zone and outermost injury in patients with GM; GM = geographical miss; MLD = minimal lumen diameter; %DS = percent diameter stenosis.

determining the active source length adequately, and we suggest that a safety margin of at least 10 mm per vessel (i.e., 5 mm per edge) be added to the injury length when determining the RIL.

Impact on restenosis. Patients with ISR have an increased incidence of neointimal hyperplasia after re-dilation, and re-restenosis rates of up to 50% have been reported (14–16). Catheter-based intracoronary irradiation as an adjunct treatment was able to reduce the incidence of re-restenosis to 20% to 30% (1,2). However, uncertainties remain regarding the occurrence of intima hyperplasia at the edges of irradiation. The phenomenon of candy-wrapper restenosis has been previously described in the dose fall-off zones of the beta-emitting radioactive stents (17). Furthermore, recent studies have suggested catheter-based low-dose irradiation at edges of the active source in combination with the presence of injury to be responsible for the recurrence of edge restenosis (7,8). However, both of these studies concentrated their analysis on the edges of irradiation only and did not include segments of GM with negligible irradiation.

Similar to these studies, our analysis also confirms a higher incidence of restenosis (16.7%) in the dose fall-off zones at the edges of the active source in the presence of injury. However, only 5.6% of all patients with GM exhibited the restenotic lesion at the site of the dose fall-off zone only, without extension into segments of negligible irradiation. In contrast, 27.8% of all patients with GM experienced restenosis in injured segments of negligible irradiation, and, in fact, the restenosis rates in these segments were comparable with those after conventional balloon dilations without intracoronary irradiation (18,19). Furthermore, direct comparison of injured segments with negligible irradiation, injured segments with dose fall-off, and injured segments receiving full-dose radiation revealed the highest restenosis rates in segments with negligible irradiation and only moderately increased restenosis rates in segments of dose fall-off. So far, it is unknown if the higher restenosis rates in the dose fall-off zone are caused by an underdosage or missing irradiation similar to conventional intervention, or rather by a stimulatory effect of the combination of low-dose irradiation with mechanical injury. Whereas candy-wrapper restenosis appears to be the result of neointimal hyperplasia in the ^{32}P-emitting stents (20), both neointimal proliferation (9) and the absence of positive remodeling (10) have been suggested as possible explanations for restenosis at the edges of irradiation in catheter-based intracoronary irradiation. Nevertheless, our findings show that restenosis rates at the injured dose fall-off zones are still lower than those in injured segments with negligible irradiation. In fact, in cases with no GM, there is no significant difference between restenosis rates among the non-injured zones of dose fall-off (4.3%) and the non-injured zones of negligible irradiation (6.8%). In contrast, in patients with GM, significant associations are found between dose application and the recurrence of restenosis (16.7% restenosis in injured zones of dose fall-off vs. 27.8% restenosis in injured zones of negligible irradiation).

Clinical implications. The present study demonstrates that target lesion restenosis rates are markedly increased from 15% to 43% in cases with GM during intracoronary irradiation of ISR. Thus, even without GM, radiation therapy cannot entirely eliminate intimal hyperplasia occurring in in-stent lesions (9,21); however, appropriate irradiation of the entire injured segment can drastically reduce the incidence of target lesion restenosis. Based on our data, we recommend that a 10-mm safety margin per vessel (i.e., 5 mm per edge) be added to the injury length when determining the RIL in order to minimize GM in daily routine use.

Study limitations. This study included patients undergoing either beta (^{90}Sr/Y, ^{32}P) or gamma (^{192}Ir) irradiation treatment, applying various radiation doses using three different radiation sources. However, different radiation sources with different dose applications best represent the use of intracoronary irradiation in the clinical routine as an adjunct treatment of ISR.

Injury was considered present in cases of balloon inflations as recorded during angiography. However, injury may have also been caused by guide wires, radiation catheters, or balloon inflations mistakenly not recorded. Even the removal of uninflated balloons may have caused vessel irritation.

Safety margin recommendations are based on retrospective data of our patient cohort. However, the analysis included all consecutive irradiated in-stent lesions between September 1999 and July 2001. Prospective validation of our safety margin recommendation will be required to assess its effect on the occurrence of GM and on long-term clinical outcome. Further, the application of a 10-mm safety margin will not necessarily prevent GM resulting from mechanical difficulties in placement of the active source; however, technical improvements such as the development of smaller-sized radiation catheters will reduce this problem.

Conclusions. Geographic miss during intracoronary irradiation is strongly associated with the development of restenosis at the corresponding edges. This restenosis process is more pronounced in injured segments receiving negligible irradiation than at the dose fall-off zones. We recommend the inclusion of a safety margin of 10 mm per vessel (i.e., 5 mm per edge) for the determination of the RIL in order to minimize the occurrence of GM in clinical applications.

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