The purpose of intracoronary brachytherapy is to reduce the incidence of lesion recurrence (restenosis) after percutaneous coronary intervention. Its rationale is based on the concept that restenosis is a process of benign tissue proliferation and that locally applied radiation can prevent or attenuate the magnitude of this response. After encouraging results from animal models, \textsuperscript{1,2} small observational and randomized clinical trials were initiated to demonstrate the feasibility and safety of this unique application of radiation. \textsuperscript{3-5} Positive findings led to larger randomized trials that demonstrated a powerful treatment effect. \textsuperscript{6,7} In patients presenting with restenosis within a previously implanted stent, the likelihood of repeat restenosis was reduced by \(-50\%\). Results of brachytherapy administered to patients undergoing balloon angioplasty alone or at the time of stent implantation have been inconsistent. At this time, brachytherapy is considered to be a standard treatment alternative for selected patients with in-stent restenosis, and it is performed as a component of routine practice in interventional cardiology.

Several questions remain unanswered, however, about intracoronary brachytherapy. In particular, does this treatment delay or prevent restenosis? Can it stimulate atherosclerosis elsewhere in the coronary circulation? Does it create the potential for spontaneous coronary rupture or thrombosis? Are there any untoward extra-coronary effects, such as myocardial or pericardial fibrosis?

In this issue of \textit{Circulation}, Grise and colleagues \textsuperscript{8} provide information to help answer these questions. They report the 5-year clinical outcomes of 55 patients enrolled in the first randomized trial comparing \(^{199}\)Ir to a nonradioactive control. Each patient in this trial had restenosis within a previously implanted stent or had a stent placed as therapy for restenosis. Many patients had recurrent in-stent restenosis.

In this trial, the 5-year rate of recurrent restenosis among irradiated patients was only 48\% of that in the placebo controls. When individual patients were analyzed, however, delayed recurrence was observed in some that received brachytherapy. Thus, of the 6 treated patients who experienced recurrent restenosis during the 5 years, 2 occurred after 3 years. It is interesting to note that delayed recurrent restenosis was not observed among placebo patients, suggesting this phenomenon was unique to brachytherapy. Certainly, the very small sample size of this trial limits our ability to be conclusive when interpreting its results. Nevertheless, it appears that efficacy of brachytherapy was sustained over the period of 5 years. There was some attrition of effectiveness, and we can expect that, for certain patients, recurrent restenosis will be delayed rather than prevented.

Are there harmful effects of brachytherapy that occur late after treatment? To this point, stent thrombosis has been the only major adverse clinical consequence of brachytherapy. In the absence of brachytherapy, stent thrombosis typically occurs soon after the procedure, and almost always within 1 month. In the setting of brachytherapy, stent thrombosis may be more common, and its temporal pattern is different, with episodes occurring between 1 and 15 months. \textsuperscript{9} This propensity for late stent thrombosis has been attributed to excessive inhibition of neointima formation, resulting in continued intravascular exposure of the bare metal stent. Notably, in the study by Grise et al, stent thrombosis was not observed during late follow-up. Furthermore, the incidence of myocardial infarction, a possible clinical manifestation of stent thrombosis, actually occurred less often among irradiated patients.

Involvement of cardiac structures remote from the lesion targeted for radiation has been another concern. Patients who receive radiation for malignancy may experience accelerated coronary atherosclerosis, myocardial fibrosis, or constrictive pericarditis. In this 5-year follow-up report, some patients underwent revascularization procedures for coronary disease at sites remote from their initial stent site. The prevalence of repeat revascularization procedures was greater among control patients. Furthermore, there was no excess mortality or heart failure noted within the brachytherapy group. These findings suggest that the effects of intracoronary brachytherapy were limited to the coronary artery targeted for treatment.

In placing the observations of this report in perspective, certain qualifications are noteworthy. As mentioned, the trial’s sample size was small and limits our ability to interpret its results conclusively. For example, absence of late stent thrombosis among the 26 patients receiving brachytherapy does not exclude the possibility that this adverse event might occur after the procedure. Similarly, we should not consider as precise the rates of recurrent restenosis or the proportion of restenotic events that occurred at a delayed time. Furthermore, the investigation was performed at a single site and only \(\gamma\) radiation was used. One could question the generalizability this study’s findings if \(\beta\) radiation was used, or if the...
procedure was performed by different, less experienced operators. Nevertheless, the conclusion that a profound treatment effect was detected at 5 years remains valid and is an important contribution to our understanding of this technology.

What is the role for brachytherapy in interventional cardiology today? Many consider that brachytherapy should be offered routinely to patients with in-stent restenosis, particularly those with patterns associated with very high recurrence rates. Observational and small randomized trials have suggested a positive treatment effect when used with balloon angioplasty alone or with initial stent implantation. Confirmation of these findings is lacking.

Many patients who are candidates for this technology do not receive it, despite its favorable efficacy/safety profile. Excessive prolongation of procedure duration is one concern. Also, brachytherapy is encumbered by the need for the simultaneous presence of a radiation oncologist, radiation physicist, and interventional cardiologist to perform the procedure. Often, 1 or more of these professionals is not immediately available. Because many patients with restenosis experience unstable symptoms, treatment delays are clinically unacceptable. Delegating some of the radiation oncologist’s responsibilities to the physicist or the interventionalist may help resolve this dilemma.

The emergence of stents that elute drugs capable of inhibiting neointimal hyperplasia and clinical restenosis poses an enormous threat to intracoronary brachytherapy. Advances in stent design and the refinement of deployment techniques have substantially reduced the rates of stent restenosis. Further reductions of angiographic restenosis rates to <5% have been reported with stents that elute the antiproliferative agent sirolimus. Although stent thrombosis has been observed among patients receiving stents coated with certain antiproliferative drugs, the incidence of this adverse event may be low with some agents, and well within a clinically acceptable range. Should further evaluations of drug-eluting stents confirm the very favorable initial results, the need for any other technology to treat in-stent restenosis will be minimal.

Technologies that enter the discipline of interventional cardiology may experience several types of lifespans. One common example occurs with the initial development of an innovative approach motivated by a legitimate clinical need. With great zeal, safety and feasibility trials are initiated and rapidly followed by randomized controlled trials. Favorable results lead to widespread adoption and, consequently, the elimination of the earlier technology. Despite confirmation of initial findings by long-term results, the new technology dies. The terminal event is not a shortcoming of the technology, but rather the emergence of a yet newer predator. Certainly the course of directional atherectomy represented such a lifespan. It is quite likely that we are now witnessing a similar lifespan for intracoronary brachytherapy.

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References

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