

Brachytherapy: here today, gone tomorrow?

M R Thomas

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By the late 1990s intracoronary brachytherapy had become the gold standard therapy for the treatment of in-stent restenosis (ISR) in bare metal stents. Despite this, the “uptake” of this treatment by the interventional community worldwide, and certainly in the UK, was low. In 2005, drug eluting stents (DES) have entered the interventional armamentarium. The potential for DES to lower the primary incidence of ISR dramatically, and their potential use to treat ISR, challenges the very existence of intracoronary brachytherapy.

INTRACORONARY BRACHYTHERAPY: THE EARLY YEARS

The efficacy of intracoronary brachytherapy for the treatment of de novo coronary disease and ISR was proven in animals^{1 2} and subsequently in a number of human registries,³ single centre^{4 5} and multicentre randomised trials^{6 7} for both β and γ radiation. Setting up a brachytherapy programme was, however, complex because of the need for cardiologists to gain therapeutic radiation licenses in association with medical oncologists and medical physicists. This process led to a reputation that the procedure itself was “difficult and complex” and certainly limited the uptake of the technique among the interventional community, despite the compelling clinical data.

During the same period companies who were developing brachytherapy devices were keen to quickly establish its use in the treatment of de novo coronary disease. Registries and randomised trials were started at an early stage (perhaps too early) in the development of the technique. The pivotal trial in this area—the Beta Cath system trial—was probably performed at a time when many of the lessons of brachytherapy were still being learned (presentation by Richard Kuntz at the 2001 meeting of the American College of Cardiology). The trial randomised 1500 patients to β radiation or placebo following balloon angioplasty or provisional stenting in the treatment of de novo coronary disease. All of the pitfalls of brachytherapy were seen in this trial including geographic miss (where a segment of coronary artery is injured but not irradiated), the edge effect (where a segment of coronary artery is injured and receives a low dose of radiation resulting in an increased neointima and potentially the “candy-wrapper” effect), and late late stent thrombosis. Late treatment site (> 30 days) stent thrombosis was seen in 6.8% of brachytherapy patients compared to 0% of placebo patients until the antiplatelet regimens were extended to > 60 days. Prolongation of the antiplatelet regimen led to an equalisation of the stent thrombosis/late occlusion rate to 1.3% in each group. This solution to the late stent thrombosis problem was confirmed in the START (stents and radiation therapy) trial (a similar randomised β radiation trial, this time in the treatment of ISR) where again the occlusion rates in brachytherapy and placebo patients were similar.⁷ The concept that the combination of stenting or re-stenting and brachytherapy is not a good one because of a variety of adverse clinical events is established.⁸ In the Beta Cath trial, because only a 30 mm short source train was

available, geographic miss was seen in over 80% of the cases. The combination of these factors in the Beta Cath trial led to a 44.9% angiographic restenosis rate in stented patients receiving brachytherapy compared to a 35.3% in similar patients receiving placebo. This was the “death knell” for the use of brachytherapy in de novo coronary lesions. This may have been an opportunity missed. A smaller carefully performed trial on de novo disease hinted at potentially spectacular results. This trial started a little later when the technique was more developed. In the Schneider dose ranging trial a dose of 18 Gy of β radiation in combination with balloon angioplasty (with no stents) led to an in-segment restenosis rate of only 4%.⁹ Interestingly this is lower than many of the current results for DES in similar lesions which we are seeing today; with 8.9% in-segment restenosis in the SIRIUS trial and 5.5–8.6% in the TAXUS II trial.^{10 11}

INTRACORONARY BRACHYTHERAPY: AN ESTABLISHED TECHNIQUE

By the year 2000 brachytherapy had become an established technique, the devices had CE marks, and this technique was generally felt to be the gold standard treatment for ISR. The Registry Novoste (RENO) prospectively collected data in over 1000 patients receiving brachytherapy in routine clinical practice throughout Europe and the Middle East.¹² The aim of the registry was to monitor the results of brachytherapy in a “real world” environment. The data indicated that the learning curve was complete with a 96% technical success rate, only one third of patients received a new stent, a “pullback” to ensure all injured segments were irradiated was used in 16.3%, the 60 mm source train was in development, and geographic miss was seen in only 6.1% of cases. In addition WRIST (Washington radiation for in-stent restenosis trial)¹² had indicated the need for 12 months of antiplatelet treatment to minimise late stent thrombosis.¹³ In those patients being treated for ISR ($n = 878$) the major adverse cardiac events (MACE) rate at 6–12 months was 17.7%, made up of 1.9% death, 2.6% myocardial infarction, and 16.3% target vessel revascularisation. This compares very favourably with the rates seen in the brachytherapy arms of the randomised trials (18–29%) and is clearly better than the placebo results in the same trials (25–68%).

However, a combination of deliberate limitation of licensed centres (at least in the UK), plus a reluctance of physicians to undertake the time consuming licensing procedures, limited the access of this form of treatment to patients. Many patients continued to be treated by other methods for which there were no data to suggest that these modalities were any better than balloon angioplasty (including cutting balloon¹⁴ and re-stenting¹⁵). Drug eluting stents then appeared on the horizon and many clinicians started to assume there was no need to provide a brachytherapy service or indeed to establish

Abbreviations: DES, drug eluting stents; ISR, in-stent restenosis; MACE, major adverse cardiac events; RENO, Registry Novoste; START, stents and radiation therapy; WRIST, Washington radiation for in-stent restenosis trial

referral lines to other centres providing this service. This was based on the extremely low restenosis rate seen in the early trials, including the zero restenosis rate seen in the RAVEL trial.¹⁶ Many operators also assumed that DES would be an efficacious and easy treatment of ISR in a bare metal stent. Until recently optimism by the interventional community for the use of DES in treating ISR had not been born out in interventional trials.^{17, 18} The data thus far suggests that DES will be a good treatment for "simple" ISR but complex patients do less well. In a complex group of patients treated in Rotterdam, four of 16 patients had an angiographic or clinical event by nine months.¹⁸ Most recently Franz-Josef Neumann presented the final results of the TROPICAL study (TCT, Washington 2004). This was a registry of 162 patients with relatively straight forward single vessel ISR treated with the Cypher DES. The results were very impressive, with an in-lesion late loss of 0.08 mm and a restenosis rate of 9.7%, resulting in a very low TLR rate of 2.5%. This registry may well signal the end for brachytherapy in "simple" ISR.

The results of DES deployment in non-simple lesions has led to a clear indication that the problem of restenosis is not solved.^{10, 19, 20} The SIRIUS trial indicated that in diabetics with long lesions (> 15 mm) in small vessels (< 2.5 mm), the angiographic restenosis rate is 23.7%.¹⁰ The RESEARCH registry from Rotterdam has indicated a 10.7% restenosis rate when 2.25 mm sirolimus stents are used.¹⁹ Colombo *et al*²⁰ have reported an angiographic restenosis rate of 25.7% and stent thrombosis rate of 3.5% when sirolimus eluting stents are implanted in coronary bifurcation lesions. The way in which ISR in a DES will be treated is far from clear.

PATTERNS OF RESTENOSIS FOLLOWING DES FAILURE

In-stent restenosis following deployment of DES will be a small but significant clinical problem. The same clinical scenario following bare metal stenting proved to be extremely difficult to treat and led to the "birth" of intracoronary brachytherapy. It appears clear that the ease with which this new disease is treatable will now decide the fate of brachytherapy.

The trials of DES use to date have indicated that restenosis following DES placement is predominantly focal in nature and therefore may be easy to treat. In the SIRIUS trial ISR was focal in 87% of the DES patients and only 42.2% of the control patients.¹⁰ Potentially, patients with focal ISR following a DES may be treated by balloon angioplasty alone. However there will remain a small group of patients who experience diffuse ISR in a DES.

Diabetics will be most at risk of ISR following DES. The current epidemic of obesity will lead to an increasing number of diabetic patients requiring interventional treatment for obstructive coronary disease. A total of 44 913 angioplasty procedures were performed in the UK in 2002. In the recent past there has been an annual growth rate of 15–20% in the UK. If one assumes the following:

- a continued growth rate of 20% per annum
- an increase of diabetes to 25% of our population
- angiographic ISR will occur in 15% of diabetics and will be diffuse in nature in 3%

then by 2006 there will be the need to treat 600 patients with diffuse ISR following DES placement in diabetics alone. As a percentage of the total angioplasty workload this will be small, but for these individuals it is clearly a problem that needs to be solved. This will be the next major challenge for the future and potentially is the "lifeline" for brachytherapy because the potential solutions appear to lie between further DES placement, surgery, or brachytherapy. Data suggest that

the benefits of brachytherapy for ISR in bare metal stents are similar in diabetic and non-diabetic patients.^{21, 22}

There has been some concern over the use of brachytherapy following DES but one may take the view that if the vessel remains capable of a biological response (as proven by the presence of neointima after DES) then the use of brachytherapy carries no more "risk" than after its use in bare metal ISR.

BRACHYTHERAPY: THE FUTURE?

The role and very existence of brachytherapy in the future is far from clear. It may be that there will be a role in the treatment of diffuse ISR following DES but data for this type of therapy remain limited. At our own institution we have performed this type of treatment in six cases. Maximum follow up to date is one year and no clinical events have been seen. A number of registries are ongoing to monitor the results of this form of treatment. Certainly this will be a niche role carried out in a very limited number of centres in any given country. Investment of any centre in a "new" brachytherapy programme would seem unwarranted. Currently only two systems are in general use (Novoste and Guidant, both β radiation systems) and the development of these systems will be limited by the companies because of the low numbers being performed. The support of the companies for this type of technology may be a factor in the sustainability of brachytherapy in the future.

CONCLUSION

Brachytherapy is backed by an impressive literature demonstrating its efficacy in the treatment of diffuse ISR following the placement of a bare metal stent. Centres performing the technique are now well established and experienced in safely delivering radiation therapy. Until a solution is found for the treatment of diffuse ISR following the placement of a DES, it would be premature to abandon this technology and therefore it is unlikely that brachytherapy will be "gone tomorrow".

ADDENDUM

In March 2005 brachytherapy centres were informed that the Novoste device was being withdrawn by the company. It is clear from this stance that the demand for brachytherapy procedures does not make economic sense to the industry. Therefore the decision has been made for the interventional community; interestingly not by "us" but by industry based on the economics of supporting this niche procedure. Brachytherapy really has gone.

Correspondence to: Dr MR Thomas, Department of Cardiology, King's College Hospital, London SE5 9RS, UK; mttw@aol.com

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