**Review Article**

**Intracoronary radiation therapy**

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**Introduction**

Over the past 15 years, despite a great deal of effort in assessing a variety of approaches, restenosis reduction has remained the most problematic complication of percutaneous transluminal coronary angioplasty (PTCA)[1–3]. Initial attempts focused on assessing systemic drugs including anticoagulant and antiplatelet agents[4–6], calcium antagonists[7,8] and lipid-lowering agents[9–11]. Subsequently, agents that were shown to significantly reduce neointima formation in animal models, including angiotensin-converting enzyme inhibitors, low molecular weight heparin, HMG-CoA reductase inhibitors, ketanserin and angiopeptin, were tested but were not found to be successful in restenosis reduction in clinical trials[9,12–17]. The introduction of interventional techniques such as directional atherectomy[18–20] rotational atherectomy [21] and laser angioplasty[22] on their own or as part of facilitated angioplasty[23] or transcatheter device synergy [24] have not generally reduced the frequency of restenosis[25–28]. Stent implantation initially appeared promising with rates of around 20%–30% in so-called ‘ideal’ lesions[29,30], but with improvement of stent technology, the indications for stenting have broadened. Meanwhile the restenosis rate has remained significant[31–33] with the rate ranging from 15%–50% at 6 months depending on the lesion morphology and other factors. In addition, the use of stents has led to the growing problem of in-stent restenosis. More recently, however, the concept and technique of applying ionizing radiation to the arterial wall during the percutaneous coronary intervention procedure has emerged and gained considerable momentum[34–36] including entry into clinical trials[37–40].

Since intracoronary radiation therapy is a relatively new and emerging field in interventional cardiology, there is a need to share and disseminate information about the technique. This review presents some of the basic concepts involved in using this strategy, examines some of the important animal experimental data, and goes on to review the evidence of efficacy and safety from the clinical trials.

**The rationale for intracoronary radiation therapy**

Restenosis after PTCA results from a narrowing of the vessel lumen due to a variable combination of neointima formation (from increased cellular proliferation, migration and net accumulation of extracellular matrix components) and reduction in the vessel cross-sectional area (a process called negative vascular remodelling) usually with the return of ischaemic symptoms[41–47]. Restenosis within stents is due to intimal hyperplasia as the stent largely prevents acute elastic recoil and virtually abolishes negative remodelling[48,49].

Radiotherapy, originally designed to kill relatively fast growing tumour cells, or at least, prevent them from replicating[50], is also used to treat benign but problematic hyperplastic conditions including post-surgical keloids[51–53], heterotopic bone formation[54,55] and recurrent pterygium[56,57]. In addition, in-vitro studies have shown that radiation can inhibit serum-stimulated growth of arterial smooth muscle cells and fibroblasts, and decrease collagen synthesis by fibroblasts[58–61]. Intuitively, therefore, given the known effects of ionization radiation on inhibiting cellular hyperplasia and the potential for inhibiting matrix deposition, as well as the current knowledge of the biology of restenosis, there appears to be a firm rationale for the idea of delivering ionizing radiation to the sites of coronary angioplasty and stenting to prevent restenosis.

**Ionizing radiation**

Ionizing radiation is radiation of sufficient energy to disrupt chemical bonds. Historically, ionizing radiation...
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has been classified as electromagnetic (X-rays or gamma rays) or particulate (beta particles or electrons/protons/neutrons/alpha particles, etc). In this review we will focus on a variety of radiation sources that emit either beta particles or gamma rays.

Radiation sources contain radioisotopes which are characterized by their activity (frequency of disintegration), half-life (the time it takes to decay to one-half of the original activity) and the type(s) and energy of their emissions. Some radioisotopes occur naturally; others can be produced by (1) fission of heavy metals into fission products including radioisotopes which can be chemically separated and concentrated and (2) particle bombardment of non-radioactive materials. Table 1 shows the method of production of some of the radioisotopes that have been used in vascular brachytherapy.

The dose of radiation absorbed by a medium is defined as the amount of energy in Joules (J) absorbed per unit mass (kg) of medium. 1 Gray (Gy) is defined as 1 J / kg. The Gy is an S.I. unit and has replaced the older term Rad; 1 Gy = 100 Rad. It is possible (using the ‘Monte Carlo method’) to predict the dose distribution in a tissue through knowledge of the radiation source and the probabilities of the various interactions of radiation with matter[62–64].

Isotopes and delivery systems used in intracoronary radiation therapy

Both gamma and beta emitters have been utilized in clinical trials of intracoronary radiation therapy. Initial experimentation in endovascular brachytherapy in animals utilized $^{192}$Ir (a gamma source) since it is widely available and had been extensively used for the treatment of cancer. The long dwell times and radiation safety concerns associated with $^{192}$Ir led to the development of a number of beta sources. Presently, the only gamma emitter used in animal and human trials of intracoronary radiation therapy is $^{192}$Ir. A large number of beta emitters are being, or have been, assessed in animal studies ($^{90}$Sr/$^{99}$Y seeds, $^{90}$Y wires, $^{186}$Re liquid, $^{186}$Re liquid or wires, $^{32}$P liquid, wires/stents and coated balloons, $^{133}$Xe gas, and $^{198}$Ru/Rh wires) with others ($^{90}$Sr/$^{99}$Y seeds, $^{90}$Y wires, $^{188}$Re liquid, $^{32}$P wire) progressing on to clinical trials. The radiation delivery systems for intracoronary radiation therapy can be thought of as being either catheter-based (with a temporary application of the radiation source from a catheter within the coronary artery), or stent-based (with the radiation source being permanently implanted in the vessel). The sources for the catheter-based systems include: (1) fixed length wires; (2) seed trains, which may be of various lengths; and (3) balloons filled with either liquid (e.g. liquid-$^{188}$Re, $^{188}$Re), gas ($^{133}$Xe), or with a solid material internally lining the balloon ($^{32}$P). As the source is deployed from its shielded container it radiates along the catheter length, with associated exposure to the operator and the patient’s tissue. This exposure is transient and inconsequential in the case of hand-delivered wire sources or seed trains, but is more substantial for radioactive-liquid-filled balloons since the isotope is present in the shaft of the catheter for the entire treatment.

The radiation source in catheter-based systems is generally delivered within a closed lumen, preventing the radiation source from coming into direct contact with the patient’s blood. Some catheter-based systems allow the source to be centred within the lumen by inflation of a balloon during treatment[73]. Both segmented and helical balloons are used for this purpose.

The length of time required to deliver the desired dose to the artery is dictated by the source, its activity, and the distance between the source and the target. Because the delivery systems used to position the source within the coronary arterial segment may temporarily occlude the artery, fractionation of the dose by intermittent withdrawal of the catheter or balloon deflation may be necessary. Non-occluding catheter systems or perfusion catheters may extend the dwell time by preventing ischaemia. In general, a high activity source is desirable to minimize the treatment time.

Another novel concept of delivering radiation to the vessel wall via the endovascular route is the use of ‘soft X-rays’ or Grenz rays[74]. These X-rays are of a longer wavelength and thus less penetrating than conventionally used radiotherapy settings. The low penetrating
<table>
<thead>
<tr>
<th>Isotope</th>
<th>Emission</th>
<th>Max energy</th>
<th>Half-life</th>
<th>Method of production</th>
<th>Length (mm)</th>
<th>Diameter (mm)</th>
<th>Radiation delivery system</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{192}$Ir</td>
<td>$\gamma, \beta$</td>
<td>0.37 MeV</td>
<td>73.8 days</td>
<td>Neutron bombardment</td>
<td>3.0</td>
<td>0.5</td>
<td>Seeds in nylon ribbon delivered by hand or afterloader, Fixed wire via balloon</td>
</tr>
<tr>
<td>$^{90}$Sr/$^{90}$Y</td>
<td>$\beta$</td>
<td>2.3 MeV</td>
<td>29.2 years</td>
<td>Fission product</td>
<td>2.5</td>
<td>0.6</td>
<td>Multiple seeds hydraulically</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>$\beta$</td>
<td>2.3 MeV</td>
<td>64.1 h</td>
<td>Neutron bombardment</td>
<td>29.0</td>
<td>0.34</td>
<td>Fixed wire via balloon by afterloader</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>$\beta$</td>
<td>1.71 MeV</td>
<td>14.3 days</td>
<td>Neutron bombardment</td>
<td>27.0</td>
<td>0.4</td>
<td>Fixed wire via balloon by afterloader</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>$\beta, \gamma$</td>
<td>2.12 MeV</td>
<td>17 h</td>
<td>Elution from parent</td>
<td>Balloon</td>
<td>Balloon</td>
<td>Liquid filled balloon</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>$\beta$</td>
<td>1.08 MeV</td>
<td>90 h</td>
<td>Neutron bombardment</td>
<td>Balloon</td>
<td>Balloon</td>
<td>Liquid filled balloon</td>
</tr>
<tr>
<td>$^{133}$Xe</td>
<td>$\beta, \gamma$, X-ray</td>
<td>360, 81, 32 keV</td>
<td>5-3 days</td>
<td>Reactor product from $^{131}$Xe</td>
<td>Balloon</td>
<td>Balloon</td>
<td>Gas filled balloon</td>
</tr>
</tbody>
</table>
power of this type of radiation has lent itself to the
treatment of superficially-sited conditions e.g. kel-
oids\[75,76\] and would similarly make it appealing for
endovascular use. The use of soft X-rays from an
endovascular miniature X-ray generator would have
potential advantages over beta- or gamma isotopes.
These would include the avoidance of isotope storage
and disposal, no risk of isotope loss either in the patient
or with external spillage, and also no need for oversight
by nuclear regulatory authorities.

**Basic dosimetry considerations for
temporary-dwelling radiation sources**

Since the exact cellular target(s) for vascular brachy-
therapy to prevent restenosis is presently unknown, the
current strategy is to deliver enough radiation to the
entire vessel wall at the balloon–injured site without
exceeding tissue tolerance. Animal data suggest that
doses of 8–40 Gy satisfy this biological window. Mini-
mizing the coronary-dwell time of the source and keep-
ing the source as small as possible has precluded the use
of certain lower-energy gamma emitters $^{125}$I and $^{103}$Pd
that would otherwise be attractive sources for this
application. The only gamma source with a high enough
dose rate for intracoronary radiation therapy is $^{192}$Ir.
This is in contrast to beta sources, which are numerous,
as shown in Table 1.

The calculations of dose distributions for beta and
gamma line-sources are outside the scope of this review
article. Suffice to say that while the dose distribution for
gamma line-sources had been well characterized for
distances of centimeters to meters, there existed little
reliable measured or calculated data for distances of
0–10 mm. The American Association of Physicians in
Medicine (AAPM) convened a Task Group (TG43) to
to examine these issues. They have developed standards for
measuring and calculating the dose rate at short dis-
tances (<10 mm) for both gamma and beta source
trains\[77,78\]. GafChromic film (Nuclear Associates, NY)
has become a standard tool for measuring dose at
short distances because of its linear dose response
characteristics and high resolution\[79\].

Beta-particles have a finite range in tissues that is
proportional to their energy. As a consequence, shield-
ing and safety are more straightforward than with
gamma radiation. $^{90}$Sr, $^{90}$Y and $^{32}$P are pure beta
emitters whereas $^{188}$Re and $^{186}$Re also have significant
fractions of medium-energy gamma emissions. The cal-
culations of dose from beta emitters have been recently
described\[80\]. Figure 1 compares the radial dose distribu-
tion for $^{192}$Ir and $^{89}$Sr$^{90}$Y, in which the dose has been
normalized to 21 Gy at a radial distance of 2 mm. Two
points are of interest: (a) at distances less than 2 mm, the
use of beta sources results in a higher dose to the vessel
luminal surface compared to gamma; however, this dif-
ference is less than 15% approximately, (b) compared to
beta emissions, gamma irradiation results in a signif-
cant amount of dose delivered at distances of a few centi-
meters from the source e.g. within the myocardium.
Heterogeneous doses are delivered to the arterial wall
from any point source used for endovascular irradiation
with a gradient from the luminal surface outwards. This
heterogeneity may be increased if the source is not
centred within the vessel lumen. As a result, attempts to
improve dose homogeneity with centring devices have
been developed. However, even with a centred source,
dose heterogeneity to the arterial wall will result from
irregularity of wall thickness (due, for instance, to an
eccentric atheromatous plaque) or from an angulated
segment of artery. Radioactive liquid or gas-filled bal-
loon catheters have a potential advantage over non-
centred radioactive wires and seeds, in that they may
provide a more uniform dose to the vessel wall. $^{188}$Re,
$^{186}$Re, $^{125}$P and $^{90}$Y can be prepared in a liquid form to

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Figure 1  Dose–depth Plot Comparing $g$ ($^{192}$Ir) with $b$ ($^{89}$Sr$^{90}$Y) GafChromic
film — 21 Gy at 2 mm. ■=iridium; ▲=strontium.
have concentrations from 50–250 mCi · ml⁻¹, to deliver doses of approximately 4 Gy · min⁻¹. However the (as yet) theoretical benefit of more desirable dose distribution needs to be balanced against the potential problem of leaks and spills of radioactive liquid, and ischaemia due to vessel occlusion. There is a possible, but low, risk of balloon rupture or other component failure when the systems are pressurized (usually around 4 atmospheres). This makes a liquid form of ³²P and ⁹⁰Sr undesirable as they are bone-seeking and would result in significant bone marrow toxicity. Liquid Rhenium-filled balloons are a safer alternative. We have found that when liquid ¹⁸⁶Re is directly injected into the coronary arteries, most of it is rapidly excreted via the kidneys and this excretion is enhanced by fluid loading. The solid source ³²P balloon catheter shares the potential advantages of the liquid filled balloons in terms of less dose heterogeneity but has the added advantage of less potential for radioactive leak. The positive clinical experiences with non-centred or partially centred devices bring into question whether active centring devices will produce any further benefit.

Radioactive stents

Since Fischell et al. first proposed that radioactive stents might be useful in decreasing restenosis, a number of animal studies have been performed with promising results, which led to rapid progression to clinical trials. Stents can be made radioactive by (a) bombarding the metallic stent with subatomic particles (e.g. deuterons or protons) to render all the elements of the metal radioactive, (b) ion implantation of the stent with radioisotopes e.g. ³²P, or (c) chemical methods that incorporate the radioactive material into metallic stents. Neutron bombardment of stainless steel stents produces mainly beta particles but also lower doses of gamma and X-radiation from the plethora of isotopes generated from the stent metal alloy (i.e., ⁵⁵Fe, ⁵⁵Co, ⁵⁶Co, ⁵¹Cr, ⁵²Mn, and ⁵⁷Ni). Stents made with this technique might be problematic for permanent implantation as some of the isotopes created have very long half-lives. Consequently, ion implantation and neutron bombardment techniques to produce ³²P-stents have been more widely accepted. Fischell and colleagues described the properties of a radioactive wire incorporating ³²P that inhibited smooth muscle cell proliferation in vitro.

Several additional issues regarding radioactive stents deserve clarification. Since the stent is permanently deployed the total dose delivered to the artery depends on the activity of the source, the half-life of the isotope and the length and design of the stent. The activity of radioactive stents needs to be low (e.g. <35 μCi) and the half-life of the isotope limited to allow delivery of an appropriate dose of radiation in a relatively short time frame. The short half-life of ³²P (14.3 days), while desirable from a biological point of view, limits the shelf life of the stent. This contrasts with temporary catheter-based sources, where a long half-life and high activity are desirable. ¹⁹²Ir-wire source typically has an activity around 300 mCi and a half-life of 73.8 days, ⁹⁰Sr/Y has an activity of 40 mCi and a half-life of 29.2 years making shelf-life irrelevant. The effects on the blood pool of permanent radioactive implants in the coronary artery are also unknown. The dose delivered to the arterial wall from radioactive stents is even more heterogeneous and complex than with a catheter based system.

Endovascular irradiation in animal studies

An examination of animal studies is important as it provides insight into changes that occur within the vessel wall after endocoronary irradiation at the angioplasty site. Even before the advent of angioplasty, Friedman and colleagues demonstrated that endovascular irradiation with ¹⁹²Ir performed in rabbit aorta prior to high-cholesterol feeding prevented the formation of hyperplastic atherosclerotic intimal lesions. It is interesting to note the authors’ comment back in 1964, ‘Neither the present study nor . . . indicate that ¹⁹²Ir . . . will ever find a place in the armamentarium against clinical atherosclerosis’.

More recently, a number of investigators have used both externally delivered X-irradiation as well as various catheter- and stent-based endovascular approaches with diverse isotopes, to determine whether such systems might affect cellular proliferation and neointima formation after angioplasty and stenting in animal models of restenosis. The design of many of these studies was roughly similar: angioplasty or stenting was performed in a pair of arteries, and radiation was delivered to one of these either immediately before or afterwards (in some cases up to 6 days afterwards). At a later date, tissue was harvested for histomorphometric and/or immunocyto-chemical analyses to determine any differences in the healing responses to the vascular intervensional procedures. The results using external irradiation have been mixed at low and intermediate doses (4–15 Gy), but higher doses (21 Gy) have shown inhibition of neointima formation at 30 days. However, external beam irradiation applied to the heart in these experiments was associated with significant myocardial inflammation and fibrosis. On the other hand, numerous studies using ionizing radiation from various isotopes delivered by an endoluminal approach have consistently demonstrated remarkable suppression of neointima formation with little or no histological myocardial changes.

Animal studies on endovascular gamma radiation using removable sources

Wiederman et al. at Columbia (New York), were the first to report the effects of endovascular gamma
irradiation (\(^{192}\text{Ir}\)) in coronary arteries\(^{[105]}\). Using the pig coronary overstretch balloon-injury model, they demonstrated that a dose of 20 Gy delivered at a radial depth of 1.5 mm just before arterial injury resulted in a significant reduction in neointima formation at 30 days. The same group demonstrated persistence of this effect in arteries harvested at 6 months\(^{[106]}\). Subsequently, Waksman et al. at Emory (Atlanta) confirmed the short-term (with 3-5, 7 and 14 Gy) and long-term beneficial effect (with 7 and 14 Gy) of gamma irradiation in inhibiting neointima formation in balloon-injured pig coronary arteries. Interestingly, radiation delivered 2 days post balloon injury had a greater effect in reducing neointima formation compared to radiation at the time of balloon injury\(^{[107]}\). Also, a dose–response relationship was demonstrated and this was subsequently corroborated by Weinberger et al.\(^{[108]}\).

Using a high dose rate source and mechanical afterloader system to deliver the source to the coronary arteries (in contrast to the above cited experiments which used manual delivery of lower-activity gamma sources), Mazur et al. at Baylor (Houston), found that 10–25 Gy of \(^{192}\text{Ir}\) gamma energy at 1.5 mm inhibited the 4-week post-injury loss of lumen diameter and suppressed intimal thickening in the balloon-injured left circumflex and stented left anterior descending coronary arteries, but had no effect on the stented right coronary artery\(^{[109]}\). In another study evaluating endovascular gamma irradiation as an adjunct to stenting, Waksman et al. demonstrated that a high-activity \(^{192}\text{Ir}\) wire delivering 14 Gy to pig left anterior and left circumflex coronary arteries resulted in a significant reduction in neointimal area in the irradiated stented arteries compared with stented controls\(^{[110]}\).

**Endovascular beta radiation animal studies using removable irradiation sources**

Verin et al. in Geneva reported in February 1995 the first results on high-dose-rate beta endovascular irradiation (\(^{80}\text{Y}\); on a wire with use of a centring balloon) in atherosclerotic rabbit carotid and iliac arteries. Doses of 6, 12 and 18 Gy to the luminal surface resulted in a significant decrease in BrdU-labelling of smooth muscle cells in the vessel wall at the injured site. However, a significant reduction in neointima formation at 6 weeks was observed only in the group receiving 18 Gy\(^{[111,112]}\). The beneficial effects of beta irradiation in balloon-injured coronary arteries were confirmed by the Emory group using a \(^{90}\text{Sr}\)/\(^{89}\text{Y}\) source in the form of a train of radioactive seeds which were delivered hydraulically via a 5F non-centred radiation catheter at doses of 7, 14, 28 and 56 Gy at 2 mm from the source centre\(^{[113]}\). In addition, neointima area corrected for medial fracture length was shown to be inversely proportional to the radiation dose. This study also documented for the first time an effect of endovascular irradiation on chronic vessel constriction or shrinkage (so-called ‘negative remodelling’). Analysis of variance documented a treatment effect of radiation to increase the area within the external elastic lamina (vessel area), which was significantly larger in the 28 Gy group compared to controls. The Emory group also demonstrated the efficacy of beta endovascular irradiation in stented pig coronary arteries\(^{[110]}\), and this was corroborated by Makkar et al. using the \(^{188}\text{Re}\)-filled balloon\(^{[114]}\).

Balloon catheters can be made radioactive by inflating the balloon with a radioactive liquid or gas. Balloons filled with liquid beta irradiation sources have been evaluated by a number of investigators in pig coronary arteries. The group from Baylor found that the \(^{32}\text{P}\)-liquid-filled balloons delivering a dose of 30 Gy decreased percent area stenosis, although interestingly the relatively high dose of 20 Gy did not\(^{[115]}\). However a \(^{32}\text{P}\)-liquid source is not an attractive one for vascular brachytherapy since this isotope is bone-seeking and could have significant bone-marrow toxicity in the event of balloon rupture. Liquid rhenium, a safer alternative, has been evaluated. Robinson et al. used liquid \(^{186}\text{Re}\) (250 mCi·mL\(^{-1}\)) to demonstrate a dose–response relationship (0–30 Gy) in reducing neointima formation after balloon injury in pigs\(^{[116]}\). Gield et al.\(^{[117]}\), Raizner et al.\(^{[118]}\) and Eigler et al.\(^{[119]}\) evaluated another isotope of Rhenium (\(^{188}\text{Re}\)) which can be produced from an on-site generator. Neointima formation was reduced at 30 days when between 16–30 Gy was delivered 0.5 mm radial to the balloon surface. One concern about the use of liquid-filled balloons is the edge stenosis effect observed, possibly due to a rapid dose fall-off at the balloon ends\(^{[119]}\). The \(^{133}\text{Xe}\)-gas-filled balloon system has been evaluated by Waksman and co-workers. They demonstrated that 2.5 cc of the gas (with an activity of 300 mCi) injected to fill the balloon, resulted in 15 Gy at 0.25 mm from the balloon surface, which produced a significant reduction of intimal area compared to control at 2 weeks. The dwell-time was short at 2.0 ± 0.2 min\(^{[120]}\).

Apart from the study by Verin et al.\(^{[112]}\), a number of groups have investigated the use of beta irradiation sources in the form of a wire. Raizner and co-workers evaluated the effect of beta irradiation using \(^{32}\text{P}\) in the form of a 30 mm \(^{32}\text{P}\)-wire source delivered with an automatic afterloader to the centring balloon. Lower doses of 6-5, 12 or 19 Gy to the adventitia were ineffective, whilst higher doses of 25–63 Gy (using a 27 mm \(^{32}\text{P}\)-wire) were effective in reducing neointima formation\(^{[115]}\). Mild dilatations of the vessels were observed with fibrin deposition in the media and adventitia. The 27 mm \(^{32}\text{P}\)-source-wire was also seen to be effective in reducing neointima formation in stented pig coronary arteries at doses of 25–45 Gy to the adventitia. The effectiveness of \(^{188}\text{Re}/^{186}\text{Re}\) in the form of a wire-coiled system (1 mm in diameter and 30 mm in length) was assessed by Waksman et al. The dose of 15 Gy delivered to 2 mm into the arterial wall resulted in a significant reduction in neointima formation at 2 weeks\(^{[123,124]}\).
Radioactive stents in animals

Hehrlein et al. initially studied implantation of stainless steel stents made radioactive by particle bombardment in a cyclotron[87]. These devices produced mainly beta particle radiation but also lower doses of gamma and X-radiation from the plethora of isotopes generated from the stent metal alloy. The stents (17–5–35 μCi) were highly effective at inhibiting neointima formation in rabbit iliac arteries, with delayed re-endothelialization observed at higher doses. Since this type of stent might be problematic for permanent implantation, as some of the isotopes created have very long half-lives, the same group of researchers investigated the effects on neointima formation in rabbit iliac arteries of stents that had undergone an ion implantation process with 32P[88]. In that study, at the 4-week time point, there was marked inhibition of neointima formation with either the 4 or 13 μCi activity stents. However, by 12 weeks, beneficial effects of the 4 μCi stents were lost and only the higher dose (13 μCi) stents had a significant effect in reducing neointima formation. Cellularity of the neointima was markedly reduced in irradiated groups at 4 and 12 weeks. Re-endothelialization, as determined by von Willebrand factor immuno-staining, showed only partial recovery at 4 weeks but this progressed to complete coverage at the 12 week observation period.

A similar technique was independently developed and tested by Fischell and colleagues: titanium stent wires underwent ion implantation with 31P and was subjected to slow neutron bombardment to produce wires containing 32P with activities of 0.019–0.060 μCi. These wires effectively inhibited smooth muscle cells proliferation in vitro[85]. Subsequently, the stent (0–140 μCi) was found at 28 days to inhibit neointima formation by 37% in pig iliac arteries without delaying re-endothelialization and in pig coronary arteries at various levels (0.15, 0.5, 1.0, 3.0, 6.0, 14.0 and 23.0 μCi) of radioactivity. Curiously, in the latter study, it was found that low-activity (0.15–0.5 μCi) and high-activity (3.0–23.0 μCi) stents inhibited neointima formation compared to control non-radioactive stents, but those of the intermediate activity (1.0 μCi) had nearly twice as much neointima. The authors speculated that either delayed endothelialization or a stochastic effect on extracellular matrix production might be responsible for this puzzling finding.

The effect of low dose radioactive stents (0.6 μCi) on neointima formation in pig coronary arteries was also evaluated by Rivard et al. using intravascular ultrasound[125]. In keeping with the results of Fischell et al., low dose irradiation significantly inhibited neointima formation in the short term, in this case at 3 months. The longer-term effect of implanting 32P-stents on inhibiting neointima formation appears to be more problematic. As mentioned above[88], 4 μCi stents demonstrated benefit at 4 weeks, but the benefit was lost at 12 weeks (unlike 13 μCi stents). Farb et al.[126] also evaluated the effects of 32P stents in rabbit iliac arteries at 3 months. Using the BX stent (6 and 24 μCi), they found that the neointima was reduced, but scanning electron microscopy demonstrated endothelialization to be incomplete even at this relatively late time point. Carter et al.[127] examined the effects at the late time point of 6 months using 32P stents across a range of activities (0–12 μCi) in the porcine double injury model. Stents with activities <1 μCi, showed no significant reduction in neointima formation at 6 months. This contrasts with the short-term results in the three previously mentioned studies that also used low activity 32P-stents[123–125]. The lack of efficacy at 6 months seems likely, therefore, to be due to delayed neointimal growth between 1–6 months, which in theory could have been due to inadequate cumulative dose (8 Gy) or dose rate (1.5 cGy h⁻¹) with these low activity stents in this particular model. At 6 months stents at the higher activities (3–12 μCi) demonstrated a positive linear dose-dependent increase in neointima formation with atherosclerotic changes consistent with radiation induced arteriopathy[128]. This is perhaps not surprising since the cumulative near-field (0.1 mm from the stent surface) dose for a 3 μCi 32P-stent is in excess of 100 Gy. Studies with 1-year follow up using a radioactive stent producing a combination of beta and gamma irradiation with an initial activity of 17.5 μCi, demonstrated almost total inhibition of neointima formation in a rabbit model[87].

Effect of endovascular irradiation on phenotypic cellular changes

Studies on the expression of cell-specific markers in control and irradiated balloon-injured arteries revealed that the endothelial cell-specific marker von Willebrand factor (factor VIII-related antigen) can be detected in per-iluminal cells at 2 weeks in control and irradiated arteries[129]. It appears, however, that irradiation results in an inability of neointimal cells to acquire smooth-muscle specific α-actin even by 6 months after angioplasty, whereas controls gain this characteristic by 4 weeks[129]. This may have important implications for the long-term consequences of vasomotor function and thrombogenicity as well as arterial structure.

Effects of endovascular irradiation on vasomotor function

Using in vivo intravascular ultrasound imaging in pig coronary arteries, Wiedermann and co-workers found a loss of vasodilation to both nitroglycerin and the endothelium-dependent dilator acetylcholine acutely after irradiation with 20 Gy[130]. However, at 32 days they observed restoration of acetylcholine-mediated (endothelium dependent) vasodilation but paradoxically, persistent loss of response to nitroglycerin.
Effects on endothelialization, platelet recruitment and thrombosis in animal studies

Using scanning electron microscopy we found that coronary arteries injured by balloon catheter without irradiation, completely re-endothelialize by 2 weeks in juvenile pigs. We also observed from scanning electron microscopy that vessel segments treated with 14 Gy showed complete recovery of the luminal surface with a confluent layer of cells with endothelial-like morphology at 2 weeks.[13]. However, at 28 and 56 Gy arteries displayed a lack of endothelial recovery and unresolved intramural haemorrhage[129]. The neointima consisted almost solely of mural thrombus without evidence of organization or mesenchymal cell ingrowth in juvenile domestic pigs. A later study in adult Yucatan miniature pigs by Salame et al. also at Emory, found that coronary arteries irradiated at 15 or 30 Gy at 2 mm from the 90Sr/Y source had areas within the injured segment that had not been fully re-endothelialized by 1 month. There was also an associated significant increase in platelet recruitment at the angioplasty site compared to balloon injured non-irradiated controls even at 1 month post injury.[131]. Thrombus deposition was also assessed by Vodovotz et al. using semi-quantitative histology.[132] They found that higher doses of endocoronary irradiation was associated with an increase in the number of thrombi observed, although interestingly the size of the thrombi were smaller. Raizner et al. presented data on 6-month follow-up after endocoronary irradiation in pigs, showing that higher doses of endocoronary irradiation were associated with late deaths in pigs, which were felt to be related to thrombotic events[133]. We also observed similar findings in the adult Yucatan miniature pig when 21 and 28 Gy were delivered. Vessels in which radioactive stents have been implanted also display delayed re-endothelialization. Using scanning electron microscopy, Farb et al.[126] found the endothelium still to be incomplete in rabbit iliac arteries after implantation of BX stents (6 and 24 μCi) at the relatively late time point of 3 months. Taylor et al.[134] found that 32P stents (3–5-6 0 μCi) as well as (6–5–14-4 μCi) implanted in coronary arteries resulted in delayed healing with persistent fibrin in the neointima and incomplete re-endothelialization in vessels with the higher dose stents, suggesting that the delay in re-endothelialization was dose dependent. Taken together these findings imply there may be a need for more prolonged systemic antiplatelet therapy for patients undergoing coronary irradiation.

Clinical studies on endovascular coronary brachytherapy using gamma irradiation

As in the case of angioplasty itself as well as endovascular stenting, endovascular irradiation was first attempted clinically in peripheral rather than coronary arteries. The first reference to endovascular irradiation as used specifically to inhibit restenosis appeared in 1994 from Liermann et al. in Germany[135]. Although this initial clinical study when reported was very small (n=4), it demonstrated the feasibility of using endovascular gamma irradiation (192Ir) to deliver a dose of 12 Gy after percutaneous intervention in peripheral arteries. Importantly it also demonstrated promise with good long-term patency. This, coupled with the promising results of subsequent animal studies encouraged interventional cardiologists to initiate pilot studies with endocoronary irradiation.

The first clinical feasibility trial on endovascular brachytherapy in human coronary arteries was conducted in Venezuela by Condado et al.[137]. This was an open-label study in 21 patients in which 22 lesions (17 de novo, 19 AHA Type B and a mean reference vessel diameter of 2.96 ± 0.49 mm) were prescribed gamma radiation from a 30 mm 192Ir-line source which was inserted by hand into a 4F monorail close-end lumen catheter. The reference lumen diameter was estimated by the operator during the procedure and the radiation dose calculations were performed at that time to deliver 20–25 Gy at a distance of 1.5 mm from the centre of the source. However, based on the luminal diameters determined by the core laboratory, the actual calculated doses ranged between 19 and 55 Gy at the luminal surface. Subacute thrombosis occurred in two patients by the 30-day follow-up and a pseudoaneurysm was observed in one patient at 60 days at the treated site. The first angiographic follow-up (mean 8 months) demonstrated a binary restenosis rate of 28% with a late loss index of 0.19 with favourable remodelling in 10 (45%) arteries. Arterial dilation or vessel irregularities were observed in an additional three arteries, all of which received a calculated dose greater than 25 Gy and in some cases as high as 92 Gy.

The 3-year follow up of these patients[136] demonstrated that the binary restenosis, which was 28% at 6 months, was 23·8% at 2 and 3 years due to regression of stenosis in one lesion. The late loss was 0.29 mm, with a late loss index of 0·25. There were four aneurysms noted, with one aneurysm that had increased in size between 3 months and 2 years (from 27 mm2 to 46 mm2), but did not show a further increase at 3 years. Clinically, one patient had a non-target lesion myocardial infarction. Target lesion total occlusions developed in three lesions (two early and one at 2 years).

These results raise at least two issues. Firstly, the rate of subacute thrombosis was ~10% and it is possible that the subsequent total occlusion that occurred late was also due to thrombus given the low late loss in arteries that were not totally occluded. Secondly, the incidence of aneurysms was around 20%. Both the thrombosis as well as the pseudoaneurysms may have been the result of the relatively high doses to some arteries. This would be in keeping with what we have observed histologically in pig coronaries exposed to...
high doses of endovascular irradiation — i.e. a delay in re-endothelialization, the presence of unresolved thrombus at the balloon injury site and the development of aneurysmal dilatation — and it may emphasize the importance of appropriate radiation dosimetry in vascular brachytherapy.

The SCRIPPS trial\(^{139}\) was the first randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of coronary brachytherapy in reducing restenosis. Lesions chosen (length <30 mm) were either in-stent restenotic lesions or restenotic lesions in which a stent was to be implanted. Vessels were coronary arteries or saphenous vein grafts, 3.0–5.0 mm in diameter. Patients (n=55) were randomized to receive either a 0.930 inch ribbon containing a sealed \(^{192}\)Ir source, or a ribbon containing placebo seeds. The intended dose was to be 8 Gy at the leading edge of the media (based on intravascular ultrasound measurements) as long as the maximum dose was less than 30 Gy. The gamma radiation source was of low activity to allow it to be hand-delivered. Consequently, the dwell-time of the radiation source in the coronary artery was relatively long, with a mean of 36 ± 7 min. The angiographic restenosis rate at 6 months was 53.6% in the control vs 16.7% in the irradiated group; an almost 70% relative reduction, \(P<0.02\). Although at first sight the angiographic restenosis rate in the treated group appears similar to the rate seen in the STRESS-II and BENESTENT trials\(^{29,30}\), it has to be borne in mind that these lesions were all restenotic ones and most were in-stent restenosis. The composite event-free survival rate (death, myocardial infarct, CABG or stent thrombosis within 30 days) was 5% in the treated group vs 52% in the placebo group. At the 2-year follow-up\(^{137}\), the clinical benefits of the treated group were maintained with a target lesion revascularization of 15.4% vs 44.8% for the placebo group (\(P<0.01\)). Unlike the Venezuelan series, patients in the SCRIPPS trial did not experience total occlusions or aneurysms. This may be a reflection of the more careful dosing in the latter trial. In addition, the stents may have prevented aneurysm formation. Although the number of patients was small, subgroup analyses revealed a dramatic benefit in diabetic patients\(^{138}\).

WРИST (Washington Radiation for In-stent Restenosis Trial)\(^{139}\), a randomized placebo-controlled single-centre double-blind trial in 130 patients with in-stent restenosis has been reported. Native coronary arteries (n=100) and saphenous vein graft(s) (n=30) were randomized to receive placebo or hand delivered non-centred gamma irradiation (\(^{192}\)Ir) source wire at a dose of 15 Gy in vessels 2–4 mm in diameter and with lesions <47 mm in length. Primary end-points were MACE (major adverse cardiac event) and binary restenosis at 6 months. The mean dwell time was 22.3 ± 2.1 min. The restenosis rate was 19% in the irradiated arm compared to 58% for the placebo arm, whereas target lesion revascularization was 14% and 63%, respectively, \(P<0.001\). MACE at 6 months was 29% in the irradiated group vs 68% in the placebo arm, \(P<0.001\).

GAMMA-1 is the first completed multicentre double-blind randomized trial to evaluate endovascular gamma irradiation in coronary arteries\(^{139b}\). Patients (n=252) had in-stent restenosis in native coronary arteries (2.75–4.0 mm in diameter) and a lesion length <45 mm. The coronary dwell time was approximately 20 min. The frequency of the primary composite end-point of death, myocardial infarction (Q wave and non-Q wave) and target lesion revascularization at 9 months was 43.8% in the placebo arm compared to 28.2% in the radiation arm, \(P=0.012\). Angiographic follow-up at 6 months, completed on 86% of the patients, demonstrated that intracoronary radiation therapy was associated with a reduction of restenosis in-stent (51% vs 22%, RR=58%) and in-lesion (57% vs 32%, RR=43%).

**Ongoing clinical trial using endocoronary gamma irradiation**

The ongoing clinical trials using gamma irradiation are shown in Table 2. ARREST (Angiorad Radiation for Restenosis Trial) and ARTISTIC (Angiorad Radiation Therapy for In-Stent Restenosis Intra-Coronary trial) both use the Angiorad radiation system. Preliminary data on the first 26 patients from the latter trial\(^{140}\) showed that the minimum and maximum dose delivered to the vessel wall was 10 and 45 Gy, respectively, and the mean dwell time was 10.3 ± 2.1 min. Clinical restenosis at 6 months was 425 (16%) whereas MACE at 9 months was 11-5% (death 2/26 and CABG 1/26) with PTCA to target lesion revascularization 1/26 and PTCA to non-target lesion revascularization 1/26. The European GRANITE study (described in Table 2) importantly will be looking at angiographic restenosis at the relatively long time point of 3 years.

The influence of lesion length on restenosis rate after balloon angioplasty appears controversial\(^{141–143}\), whereas the relationship between stent length and restenosis rate is more consistent. LONG-WРИST is designed to assess the effectiveness of the \(^{192}\)Ir wire in stent restenotic lesions 45–80 mm in length.

Small vessels are less attractive for percutaneous coronary intervention since they typically have relatively high restenosis rates\(^{144}\). However, subgroup analysis of the SCRIPPS trial suggested that smaller vessels might derive benefit from radiation in lowering the restenosis rate\(^{138}\). The SMART (Small Artery Radiation Therapy) study will be evaluating the safety and efficacy of \(^{192}\)Ir, with provisional stenting in vessels less than 2.75 mm in diameter. The primary end-point is MACE at 6 months and 2 years and binary restenosis at 6 months.

Another difficult condition to treat is restenotic saphenous vein graft lesions, which, apart from the periprocedural thrombotic occlusive risks, is the relatively high rate of restenosis. WRIST-SVG trial (see Table 2) will examine the effects of gamma irradiation on MACE and binary restenosis at 6 months.
<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>$^{192}$Ir dose</th>
<th>Radiation system</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condado et al.</td>
<td>Phase I, open-label, n=21</td>
<td>20–25 Gy (actual 19–55 Gy)</td>
<td>30 mm Ir wire, hand-delivered 0.014–0.018 inch wire, non-centred (Angiorad)</td>
<td>Started in July 1994, ended in 1997, 3-year follow-up — 1999</td>
</tr>
<tr>
<td>SCRIPPS</td>
<td>Single centre, double blind, randomized, n=55, restenosis+stenting</td>
<td>8–30 Gy to media by IVUS</td>
<td>0.03 inch nylon ribbon with seeds, hand delivered, non-centred</td>
<td>Started in March 1995, ended 1997, 3-year results 1999</td>
</tr>
<tr>
<td>WRIST</td>
<td>Single centre, randomized, double blind, n=100, in-stent restenosis, 47 mm length</td>
<td>15 Gy at 2 mm for vessels 3–4 mm</td>
<td>0.03 inch nylon ribbon with seeds (Best Medical), hand delivered, non-centred, 5 F close-ended (Medtronic)</td>
<td>Started in February 1997 Presented AHA 1998</td>
</tr>
<tr>
<td>GAMMA-1</td>
<td>Multicentre, randomized, double blind, n=252, in-stent restenosis, 2.75–4.0 mm</td>
<td>8–30 Gy to adventitia; IVUS-guided in vessels 2.75–4.0 mm</td>
<td>As for WRIST but 4 F catheter (Cordis)</td>
<td>Started in December 1997. Completed July 1998. Published January 2001</td>
</tr>
<tr>
<td>ARREST</td>
<td>Multicentre, double blind, n=800, restenosis; post PTCA or in-stent, 20 mm in length</td>
<td>12 Gy to 2 mm, vessel 2.5–5 mm</td>
<td>Angiorad system: 30 mm Ir 0.014 inch wire, balloon centring, 3.2 F closed-end lumen catheter, manual delivery</td>
<td>Started in Spring 1998, ongoing</td>
</tr>
<tr>
<td>ARTISTIC</td>
<td>In-stent restenosis, native artery, lesion &lt;2 mm, n=290</td>
<td>12–18 Gy to 2 mm from source, vessels &gt;2.5 mm</td>
<td>Angiorad system</td>
<td>Feasibility phase completed, ongoing</td>
</tr>
<tr>
<td>GRANITE</td>
<td>Multicentre, European uncontrolled, n=100, 2.75–4.0 mm vessels</td>
<td>Low dose $\gamma$</td>
<td>Seeds in nylon ribbons 23, 39, 55 mm in length Cordis</td>
<td>Ongoing</td>
</tr>
<tr>
<td>SMARTS</td>
<td>Multicentre, double blind, placebo controlled non randomized, 2.0–2.75 mm, n=180</td>
<td>12 Gy to 2 mm from vessel wall</td>
<td>Angiorad system, as above</td>
<td>Started autumn of 1998, ongoing</td>
</tr>
<tr>
<td>WRIST-SVG</td>
<td>Multicentre, randomized double blind, n=120, saphenous vein graft, 45 mm in length</td>
<td>15 Gy to 2.4 mm for vessels, 3.4–4.0 mm, in stent restenosis</td>
<td>As for WRIST</td>
<td>Ongoing</td>
</tr>
<tr>
<td>WRIST-LONG</td>
<td>Single centre, randomized, double blind, n=120, 36–80 mm, in-stent restenosis</td>
<td>15 Gy to 2.0 mm for vessels 3.0–4.0 mm</td>
<td>As for WRIST</td>
<td>Started January 1998, results expected soon</td>
</tr>
<tr>
<td>GAMMA-2</td>
<td>n=125</td>
<td>14 Gy at 2 mm</td>
<td>As for WRIST but 4 F catheter (Cordis)</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Clinical endocoronary irradiation trials using beta irradiation

The first endocoronary beta radiation clinical study was conducted in Geneva [30]. This study was small (n=15), open-label and lesions were either de novo (n=11) or restenotic (n=4) including one in-stent restenosis in coronary arteries (lesion length <20 mm and reference segments >2.5 mm). A dose of 18 Gy was administered to the vessel luminal surface via a 90Y beta emitting line-source delivered through a closed-end mono-rail catheter which was guided into the artery over a conventional 0.014 inch guidewire and centred in the artery by a 30 mm segmented balloon. The mean catheter dwell time was approximately 6.5 min, with dose fractionation being necessary in four vessels because of ischaemia. Angiographic restenosis occurred in six patients (40%), and target lesion revascularization was performed in four (27%). There were no aneurysms or angiographically detectable thrombi observed at 6 month follow-up. Whilst the results did not show a benefit in restenosis, it demonstrated the feasibility and safety of using beta irradiation in coronary arteries. It is possible that the lack of beneficial effect was due to an inadequate dose delivered to the deeper layers of the vessel wall with the adventitia receiving <4 Gy.

The Beta Energy Restenosis Trial (BERT) was the first FDA approved trial of irradiation for restenosis and was designed as a feasibility study to evaluate the safety and efficacy of endocoronary beta irradiation using the Beta-cath system (Novoste, GA) at doses of 12, 14 and 16 Gy at 2 mm from source centre in single ‘de novo’ lesions less than 15 mm long in vessels with an angiographical 2.5–3.5 mm reference diameter. Efficacy was determined in terms of clinical (in-hospital MACE) and angiographical (binary restenosis at 6 months) endpoints [40]. The initial portion of the study was carried out at Emory and Brown Universities. The source was a train of 90Sr/Y seeds delivered hydraulically down the 5 F semi-centred catheter system. Dwell time to deliver the dose was around 2.5–4 min. Radiation measurements at the patient’s chest and operator position were extremely low, 2.1 mRem and 0.3 mRem·h⁻¹ respectively. Angiographic follow-up at 6 months demonstrated a late loss of 0.05 mm, a late loss index of only 4% with a lower-than-expected restenosis rate of 15%. In an expanded phase involving the Montreal Heart Institute and the Thoraxcenter in Rotterdam, 78 patients had angioplasty followed by irradiation. There was 17% restenosis at the lesion (13/78) with a late loss of 0.08 mm. New lesions were identified outside the radiation zone in the balloon injury area in six patients (7.7%). Target lesion or revascularization in this series was 14.1%.

The BETA-WRIST trial was an open-label study evaluating the safety and efficacy of beta irradiation using 90Y (Schneider) in 50 patients with in-stent restenosis. The control group comprised of the placebo group of the WRIST trial. The vessel sizes were 2.5–4.0 mm with lesion lengths being <50 mm. The mean dwell time was 183 ± 56 s in the treated arm. The primary end-points are both clinical (MACE at 6 months and 2 years) and angiographic (binary restenosis and late loss at 6 months). Preliminary results indicated that restenosis at 6 months was 16% compared to 66% in the control group. MACE at 6 months was 33% compared to 72% in the control arm.

The European Dose Finding trial [148] evaluated the 90Y-wire delivering 9, 12, 15 or 18 Gy at 1 mm into the vessel wall following successful angioplasty and, in 28% of cases, coronary stents. The recently published data showed that beta-radiation resulted in a significant dose-dependent decrease in the rate of restenosis after angioplasty (without stenting), with only a 4% restenosis rate in the 18 Gy treatment group. The MACE-free rate at 6 months was 86%.

PREVENT (Proliferation REduction with Vascular ENergy Trial) [149] is a small randomized study in 105 patients using a 32P-wire (see Table 3). Restenosis target lesion revascularization in the irradiated arteries was 6% whereas it was 24% in the placebo group. Late loss index was only 5% in the treated arm compared to 51% for the placebo arm, P=0.0001. The INHIBIT trial is also evaluating a 32P line source. Primary end-points will be MACE at 6 months and angiographic binary restenosis.

Ongoing clinical trial using endocoronary beta irradiation

BETA CATH is the largest multicentre placebo controlled trial assessing intracoronary radiation therapy (90Sr/Y source) for restenosis prevention in 1400 patients after PTCA or stenting (see Table 3). Clinical end-points will be MACE (death, myocardial infarction, target lesion revascularization) at 8 months, 1 and 2 years. In addition, angiography at 8 months will be performed to assess binary restenosis. Over 1200 patients have been enrolled already and the results were expected in the autumn of 1999. BRIE (Beta Radiation In Europe) is a European trial in 180 patients also using the Novoste Beta-Cath system (see Table 3) following angioplasty or provisional stenting. End-points are angiographic restenosis and MACE at 1 and 12 months. Interim results in 90 patients were encouraging with a restenosis rate of the initial obstructed segment of 8% in the PTCA group and 16% in the stent group. Another trial using the Novoste system is the START trial (STents And Radiation Therapy). Primary end-points are target lesion revascularization and MACE at 6 months and 2 years as well as binary restenosis at 8 months. An intravascular ultrasound substudy will be performed on 100 patients.

Liquid 188Rh-filled balloons was evaluated in a small Australian pilot study following conventional percutaneous coronary intervention for 28 lesions with in-stent restenosis. Preliminary reports on the angiographic follow-up demonstrated a lower-than-expected rate of restenosis with only one vessel having restenosis in the irradiated segment and four vessels having restenosis at

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<th>Status</th>
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<tr>
<td>The GENEVA study: Verin et al.</td>
<td>Phase I, de novo or restenotic, 15 patients</td>
<td>$^{90}$Y, 18 Gy to balloon surface</td>
<td>Manual delivery of 29-mm titanium-coated Yttrium wire (0.014 inch diameter). Centred with 30 mm balloon</td>
<td>Started in June 1995, ended in November 1995, published in March 1997</td>
</tr>
<tr>
<td>BERT King et al.</td>
<td>Phase I, 23 patients, de novo lesions</td>
<td>$^{90}$Sr/Y, 12, 14, 16 Gy to 2 mm from source</td>
<td>Novoste beta-cath system 12 radioactive seeds delivered in a closed-end catheter by hand generated hydraulic pressure. Non-balloon centred</td>
<td>Started in January 1996, ended in October 1996, Emory arm published in May 1998</td>
</tr>
<tr>
<td>BERT Canadian Bonan et al.</td>
<td>Phase I, 30 patients</td>
<td>$^{90}$Sr/Y, 12, 14, 16 Gy to 2 mm from source</td>
<td>Novoste Betacath system as above</td>
<td>Started February 1997. Presented at AHA 1997</td>
</tr>
<tr>
<td>BERT European Serruys</td>
<td>Open label, n=30</td>
<td>$^{90}$Sr/Y, 12, 14, 16 Gy to 2 mm from source</td>
<td>Novoste Betacath system as above</td>
<td>Presented</td>
</tr>
<tr>
<td>The European Dose Finding Study Group Verin et al.</td>
<td>Multicentre, randomized, dose finding, n=181, de novo, native</td>
<td>$^{90}$Y, 9, 12, 15, 18 Gy at 1 mm</td>
<td>Schneider System. Automatic afterloading of 0.014 inch 29 mm titanium-coated Yttrium coil. Centred with 30 mm segmented balloon</td>
<td>Started in September 1997. Published January 2001</td>
</tr>
<tr>
<td>BETA-CATH Kuntz et al.</td>
<td>Phase III, multicentre, randomized, n=1400 after PTCA and stenting</td>
<td>$^{90}$Sr/Y, 14, 18 Gy to 2 mm from source</td>
<td>Novoste Betacath System as above</td>
<td>Started July 1997. Over 1400 patients randomized</td>
</tr>
<tr>
<td>CURE Weinberger et al.</td>
<td>Phase I, single centre, open labelled, 2-75-4-0 mm</td>
<td>$^{188}$Re, 20 Gy to balloon surface</td>
<td>Perfusion balloon (Lifestream®) which is filled with liquid $^{188}$Re from generator (Oakwood)</td>
<td>Started October 1997. Pending</td>
</tr>
<tr>
<td>PREVENT Raizner et al.</td>
<td>Phase I, open label, multicentre, n=84, de novo or restenotic lesions, length 12-22 mm</td>
<td>$^{32}$P, placebo, 28, 35 or 45 Gy to 1 mm from wire</td>
<td>Guidant $^{32}$P-wire system. Wire (0.018 inch) delivered by afterloader through radiation catheter which is centred by a helical balloon</td>
<td>Started in November 1997. Phase 1 completed in May 1998</td>
</tr>
<tr>
<td>BETA WRIST Waksman et al.</td>
<td>Phase I, single centre registry, in-stent restenosis, 2-5-4 mm in diameter, &lt;47 mm length</td>
<td>$^{90}$Y, 20 Gy at 1-2 mm</td>
<td>Schneider System. Automatic afterloading of 0.014 inch 29 mm titanium-coated Yttrium coil. Centred with 30 mm balloon</td>
<td>Completed in June 1998. Publication awaited</td>
</tr>
<tr>
<td>BRIE Serruys et al.</td>
<td>Multicentre European study, de novo or restenotic, n=180 PTCA or stenting</td>
<td>$^{90}$Sr/Y, 14, 18 Gy at 2 mm from source</td>
<td>Novoste Betacath system as above</td>
<td>160 patients enrolled as of August 1999</td>
</tr>
<tr>
<td>INHIBIT Waksman et al.</td>
<td>Phase III, n=320, randomized, multicentre, double blind, in-stent restenosis</td>
<td>$^{32}$P, 20 Gy at 1 mm</td>
<td>26 mm $^{32}$P source line, nucleotron afterloader, helical centring balloon</td>
<td>Started in June 1998. Pending</td>
</tr>
<tr>
<td>STARTS Waksman et al.</td>
<td>Phase III, n=390, in-stent restenosis &lt;30 mm</td>
<td>$^{90}$Sr/Y, 18-20 Gy at 2 mm</td>
<td>Novoste BetaCath system</td>
<td>Started in September 1998. Enrolment completed, results pending</td>
</tr>
<tr>
<td>MARS-I De Scheerder et al.</td>
<td>2 centres, open label, de novo lesions, n=60</td>
<td>$^{188}$Re, 20 Gy to 0.5 mm into vessel wall</td>
<td>Mallinckrodt, liquid filled balloon system</td>
<td>Started in December 1998. Pending</td>
</tr>
</tbody>
</table>
the irradiation border zone\textsuperscript{146}. CURE (Columbia University RhÉnium) and MARS-1 (Mallinckrodt Angioplasty Radiation Study) will also be evaluating the efficacy and safety of the liquid-filled Rhenium balloons.

**Clinical trials on radiation stents**

IRIS-1A (Isostent for Restenosis Intervention Study) was a phase I non-randomized trial designed to evaluate the safety of implanting low activity (0–5–1 µCi, mean 0–69 µCi) 15 mm Palmaz–Schatz \( ^{32} \)P-stents in 32 patients with de novo or restenotic native coronary artery lesions\textsuperscript{147}. There were no cases of subacute stent thrombosis, target lesion revascularization or MACE at the primary end-point of 30 days. The binary restenosis rate was, however, 31% at 6 months. Of note, however, seven vessels were <2.5 mm. This trial was extended (IRIS-1B) to evaluate the slightly higher dose of 0–7–1–5 µCi (mean 1–14 µCi) in 25 additional patients and a similar result was obtained with no stent thrombosis at 30 days and a 32% binary restenosis rate at 6 months\textsuperscript{148}. The Heidelberg Moderate-Activity \( ^{32} \)P-Stent trial\textsuperscript{149} evaluated a dose of 1–5–3–0 µCi (mean 2.2 µCi) in 11 patients with restenosis using intravascular ultrasound guided stent deployment. Clinically driven TVR was 4/11 (36%) at 6 months. Of particular interest, the restenosis was observed to occur at the articulation point of this stent and to a lesser extent at the proximal and distal edges\textsuperscript{149}. These early radioactive stent trials used the Palmaz–Schatz stent with its central articulation, a potential dose drop off zone, which could have accounted for the number of angiographic failures observed in that region. European trials on a second generation radioactive stent, the \( ^{32} \)P-Isostent BX\textsuperscript{50}, stent; resulted in a 43%–50% binary restenosis due to increase in restenosis at the stent edges, the so-called ‘candy wrapper’ effect\textsuperscript{150,151}. A dose escalation study (up to 20 µCi) conducted in Milan demonstrated that in-stent neointimal hyperplasia was reduced in a dose related manner while intra-lesion restenosis was 39%–55% due to late loss proximal and distal to the stent edges\textsuperscript{152}.

The cause of the adverse changes in the reference segments is presently unknown. It may be that this edge effect is no different from those reported for the margins of non-radioactive stents\textsuperscript{153}. This may suggest that the restenosis at the uncovered stent edges results from vessel injury by the stent balloon or indeed from balloon dilation(s) during the procedure. The combination of balloon trauma beyond the stent edge coupled with no stent coverage plus an insufficient radiation dose in these areas might therefore account for the edge effect. Indeed the edge effect has also been observed for both beta and gamma afterloading systems.

**Safety aspects of removable endocoronary radiation devices**

The requirement for high-activity sources for endovascular irradiation necessitates safety protocols when temporary-dwelling radiation-emitting isotopes are used. This is more relevant for gamma rays especially when (in order to keep the dwell time to a minimum) high dose rates are used. In these situations, the dose would be high enough to be of significance for a distance of several meters around the gamma source in the treatment position. The standard lead apron which is able to attenuate a fluoroscopic beam by more than 90%, provides essentially little protection for the high-energy \( ^{192} \)Ir gamma rays. Long distances or very thick lead shields and short exposure times are the only effective protective measures for high dose rate gamma radiation. In contrast, a pure beta radiation source outside the patient is effectively shielded by the source container and a cylindrical Perspex glass covering the radiation catheter, whereas when the source is within the patient, the radiation is shielded by the patient’s tissues, resulting in little or no radiation exposure to staff. Automatic afterloaders have been used to provide an extra degree of radiation safety by delivering the source to the patient without the operator being physically near to the source. Table 5 shows the doses of radiation that operators have been exposed to in some of the early studies and compares these doses to some of the common other uses of radiation in medicine.

**Possible long-term sequelae of vascular irradiation**

Decades of experience with external irradiation and to a much lesser extent with interstitial brachytherapy for the treatment of malignancies give some insight into the effects of irradiation on different parts of the vascular tree\textsuperscript{154,156}. It is now generally accepted that coronary atherosclerosis (with essentially the same morphology as spontaneous coronary atheroma) is increased in cohorts receiving external thoracic irradiation for lymphomas especially Hodgkin’s disease. It is therefore possible that coronary arteries treated for restenosis with endocoronary irradiation may have further atheromatous development in the long term.

In addition, although thrombosis tends to occur early after vascular damage due to incident irradiation, late thrombotic occlusions in arteries that have been exposed to ionizing radiation has been known for a long time\textsuperscript{157}. The profound effects of intracoronary radiation on re-endothelialization and thrombosis have already been described in this review article in the section on animal studies. In the clinical intracoronary radiation therapy trials the incidence of ‘late late’ thrombosis is now becoming an important issue. Indeed, the incidence of ‘late late’ thrombosis in the sum total of patients in the intracoronary radiation therapy trials at the Washington Heart Center have been approximately 9%, of which approximately 40% present with myocardial infarctions and 30% as unstable angina. The figures were higher for stented patients compared to PTCA (Waksman R, presented at the European Society of Cardiology, Barcelona, 1999).
Aneurysmal dilation is also well described with higher doses of irradiation\textsuperscript{129}. Indeed in the initial human intracoronary radiation therapy trial\textsuperscript{37,136} four aneurysms were observed with one showing progression between 3 months and 2 years. Certainly in the pig model, we have observed significantly more dilation in arteries treated with 30 Gy compared to 15 Gy or controls.

**Oncogenesis**

The ability for irradiation to induce oncogenesis is well known\textsuperscript{158-160}. The risk of oncogenesis caused by endovascular irradiation will, in theory, depend on the volume and types of tissue that have been subjected to the incident radiation as well as the radiation dose. In the case of beta endocoronary irradiation, the coronary vessel will be exposed and in theory malignancies could arise from endothelial cells, smooth muscle cells, fibroblasts or mesothelial cells. With more penetrating gamma irradiation, tissues further away from the treatment target site could potentially be affected, including the pericardium, the myocardium, mediastinal lymph nodes, the lungs and the breasts. The Swedish Cancer Registry\textsuperscript{161,162} showed that the incidence of sarcomas is 0.02% per annum in patients who had undergone local irradiation for carcinoma of the breast, with one third of these being angiosarcomas. If one assumes that the amount of tissue exposed to irradiation when endocoronary irradiation is used is approximately 1/1000, that when external irradiation is used to prevent recurrence of breast carcinoma, the risk of sarcomas after endocoronary irradiation would be in the order of 0.00002% per year\textsuperscript{163}. To the best of our knowledge, coronary artery angiosarcomas have not been reported in patients receiving local irradiation for either breast carcinoma or thoracic lymphoma. This might suggest that the coronary artery is not particularly susceptible to malignant transformation.

**Conclusion**

Arguably, the application of ionizing radiation to prevent restenosis in atherosclerotic lesions treated with

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**Table 4 Clinical trials with radioactive stents in coronary arteries**

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Isotope/dose/stent</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS 1A Fischell et al.</td>
<td>Multicentre, open label, phase I, n=32, de novo or restenotic lesions</td>
<td>(^{32})P, 0.5–1.0 μCi, Palmaz-Schatz 15 mm stent</td>
<td>Started in January 1997, published</td>
</tr>
<tr>
<td>IRIS 1B Moses et al.</td>
<td>Extension of IRIS 1A, multicentre, open label, n=25</td>
<td>(^{32})P, 0.7–1.5 μCi, Palmaz-Schatz 15 mm stent</td>
<td>Published in 1998</td>
</tr>
<tr>
<td>Hehrlein et al.</td>
<td>Dose response study, single centre</td>
<td>(^{32})P, 1.5–3.0 μCi, Palmaz-Schatz 15 mm stent</td>
<td>Started in June 1997, ended in December 1997</td>
</tr>
<tr>
<td>MILAN BX-1 Colombo et al.</td>
<td>Dose response study, single centre, n=32 lesions</td>
<td>(^{32})P, 3–6 μCi, 15 mm BX stent 0.75 to 20 μCi, Palmaz-Schatz 15 mm stent and 15 mm BX stent</td>
<td>Started in December 1997, presented at AHA 1998</td>
</tr>
<tr>
<td>Serruys et al.</td>
<td>Dose response study</td>
<td>(^{32})P, 6 and 20 μCi, BX 15 stent</td>
<td>Presented at Cardiovascular radiation Therapy III, 1999</td>
</tr>
</tbody>
</table>

**Table 5 Radiation doses in coronary brachytherapy**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Radiation dose</th>
<th>Bedside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray radiograph</td>
<td>20–100 mRem</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cardiac catheterization and angioplasty</td>
<td>Fluoroscopy = 2000–4000 mRem . min(^{-1})</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Coronary angiogram procedure (mean ± SD)</td>
<td>0.024 ± 0.002 mRem . h(^{-1})</td>
<td></td>
</tr>
<tr>
<td>Coronary angioplasty procedure (mean ± SD)</td>
<td>15.4 ± 1.4 mRem . h(^{-1})</td>
<td></td>
</tr>
<tr>
<td>Coronary brachytherapy</td>
<td>Chest wall</td>
<td>8–30 Gy</td>
</tr>
<tr>
<td>(\gamma) based — SCRIPPS</td>
<td>—</td>
<td>13.2 ± 1.9 mRem . h(^{-1})</td>
</tr>
<tr>
<td>(\beta) based — ARTISTIC</td>
<td>2800 mRem/h</td>
<td>145 mRem . h(^{-1})</td>
</tr>
<tr>
<td>(\beta) based — BERT</td>
<td>2.1 mRem</td>
<td>0.3 mRem/12 min treatment</td>
</tr>
<tr>
<td>(\beta) based — PREVENT</td>
<td>12–16 Gy</td>
<td></td>
</tr>
<tr>
<td>Total body irradiation for bone marrow transplantation</td>
<td>30 Gy to mantle field (~3 000 000 mRem)</td>
<td>0.3 mRem/12 min treatment</td>
</tr>
<tr>
<td></td>
<td>12–14 Gy to whole body except lungs (~1 300 000 mRem)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
balloon angioplasty and stenting has been the most innovative recent development in interventional cardiology, with a virtual explosion of research activity in this field. Using a variety of radiation sources and delivery systems in animal models of restenosis, investigators have found some of the most profound effects in reduction of neointimal proliferation in the short term when injured vessels are irradiated. The isotopes and radiation doses that demonstrated efficacy in reducing neointima formation in animal studies have been applied to clinical feasibility studies. The early human trials demonstrate feasibility and appear to show some promise. However, it should be stressed the data come from a relatively small number of patients. Nevertheless, of particular interest is the late gain that is observed between 24 h and 6 months post procedure, a finding not previously reported from the revascularization device trials. More recently, a number of randomized multicentre trials have been initiated and the results are eagerly awaited. However, more work still needs to be done on the short- and long-term vascular biological effects of brachytherapy. Amongst these, the effects on local alterations in thrombotic potential and vasoreactivity needs clarification. Last but certainly not least, if this form of therapy proves efficacious in the large randomized clinical trials, its cost effectiveness will then need to be established.

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