

Guidelines for Intravascular Brachytherapy

These guidelines have been prepared by the Radiation Safety Program and Radiation Advisory Committee following wide consultation with interested persons and organisations. The guidelines are to be used in conjunction with the licensing requirements of the Victorian Radiation Safety Regulations to ensure that intravascular brachytherapy is carried out only by appropriately trained persons taking account of relevant radiation protection issues

Introduction

These notes have been prepared on behalf of the Victorian Radiation Advisory Committee (RAC) as a guide to organisations planning projects involving intravascular brachytherapy (IVBT).

The Victorian *Radiation Act 2005* and the *Radiation Regulations 2007* control all uses of ionizing radiation in Victoria, and include a system requiring the licensing of users of radiation equipment and radioactive sources, and the licensing of radiation practices involving irradiating apparatus, sealed radioactive sources and radioactive material.

IVBT is still in its infancy. While randomised studies demonstrate benefit, that is reduced rates of re-stenosis, the spectrum of late effects from the variety of sources types, dosimetric points and delivery systems has not become clear. Hence, at this time, the procedure is best considered to be experimental and should only be performed as part of a research project in institutions with licence to perform experiments on humans with radiation under the surveillance of an appropriate ethics committee and with the approval of the RAC. Bearing this in mind, this document is not intended to be definitive. It has been prepared as a guide for those groups planning an IVBT project.

The objective is to maximise both the safe and optimum delivery of radiation therapy in this context whilst providing an objective

framework for this promising procedure to develop during its investigational phase.

Background

It has been estimated that approximately 5,000 angioplasties per year are carried out in Australia. Of these about 30-40% will restenose in the succeeding 12 months requiring repeat interventions, causing stress to both the patient and the national health budget.

Restenosis, defined as narrowing of the vascular lumen by $\geq 50\%$, is a benign proliferative disorder and radiation therapy has been successful in treating other such disorders.

Over the past ten years, both animal and human studies have been carried out to investigate the role radiation may play in the inhibition of restenosis.

Animal Studies

The results to date have been quite varied with a range of different doses and prescription points to different parts of the vessel wall having been used.

The number of animals used in the studies has been small and the follow-up studies

have been short, ranging from between one to six months.

Both beta (β) and gamma (γ) emitting sources have been used in the form of wires, seeds, stents and liquids.

Delivered doses have ranged between 3.5 and 54 Gray (Gy) given as single fractions.

Even though there are distinct differences in methodology, it is clear that radiotherapy does reduce neo-intimal hyperplasia (NIH) keeping the vascular lumen patent in the irradiated animals. However the data, in particular that relating to toxicity and efficacy, need to be interpreted with caution when extrapolating to humans

Human Studies

To date, upwards of 30 human studies are in progress, aimed at prevention of coronary artery restenosis. A limited number of peripheral artery studies have commenced.

External beam radiotherapy, endovascular catheter based irradiation and radioactive stents are all under investigation.

Catheter based endovascular techniques have been the most popular, following some mixed results from the other two modalities.

Both beta and gamma sources are being used.

Beta sources, due to the small range of penetration, have the attraction of significantly reduced radiation risk to the Brachytherapy team and limited irradiation of non-target tissues. Manual loading devices and absence of shielding reduce costs of purchase and shielding requirements. The major disadvantage is steep decline of dose with distance from the source (dose gradient), making accurate source placement critical and dosimetry less certain.

High output gamma sources present potential radiation hazards to the operating team with increased dose to local non-target organs. To reduce exposure risk to operators, safe use requires employment of automatic computer controlled afterloading devices, shielding and distance. The main advantage is the availability of high specific activity sources that can be readily manufactured in an appropriate form, for example ^{192}Ir .

Some Selected Results

Condado *et al* (1997)¹ conducted the first human trial using an ^{192}Ir non-centered wire source in 21 patients (22 lesions) with de novo or restenotic coronary artery lesions. The prescribed doses were 20 and 25 Gy at a distance of 1.5 mm from the source. The doses were administered immediately post Percutaneous Translumen Coronary Angioplasty (PTCA). It was calculated that that up to 92 Gy (single fraction) was delivered to sections of vessels treated, due to non-centering and lumen eccentricity problems.

At 3 years follow up, 19% of treated vessels had developed pseudoaneurysms. A restenosis rate of 28.6% was achieved which may reflect under-dosing to certain areas of the adventitia.

Costa *et al* (1999)² reported the phenomenon of sudden, late coronary artery thrombotic events following PTCA and IVBT with β source. 108 patients were treated with either ^{90}Sr or ^{32}P and 91 of these patients had minimum 2 months follow-up. Six of the 91 (6.6%) patients presented with sudden late thrombotic events 2-15 months after PTCA with and without stenting. Five of these patients experienced acute myocardial infarction (AMI). The range of doses delivered 2 mm from the source utilising a non-centered catheter system was 12-35 Gy with 5 of the 6 patients receiving a dose of 12-18 Gy. The authors suggest that the late thrombotic events maybe a result of the beta radiation treatment suggesting that the healing process after dissection could have been impaired by the radiation treatment. The authors further state that they are unable to determine if the late thrombosis is a generic complication of IVBT or restricted to the use of β radiation sources only.

Subacute thrombosis (within 30 days) has been reported previously, but late thrombosis is relatively uncommon. Colombo *et al* (1995)³ reported late thrombosis in only 0.6% of patients after stenting alone.

Waksman (1999)⁴ looked for this phenomenon in other completed studies after 6 months with angiographic follow-up, and found that, of the published series, 4-10% of patients had late total occlusions despite anticoagulant therapy. He reasoned the occlusions were likely to be

radiation-induced thromboses as have been seen in animal studies.

The potential causes of thrombosis include delayed re-endothelialisation, unhealed dissection or fibrin deposition and platelet recruitment.

Recent Gamma Studies

In the first randomised human clinical trial, Teirstein *et al* (1997)⁵ demonstrated a safe and relatively effective method of irradiating restenotic coronary arteries. Using ¹⁹²Ir seeds immediately post PTCA with and without stenting, a dose of greater than 8 Gy and less than 30 Gy was administered to the leading edge of the media under intravascular ultrasound (IVUS) control in 26 of 55 randomised patients. At 6 months, angiographic follow up revealed a 17% restenosis rate in irradiated patients compared with 54% in the control group. This represented a 66% reduction in restenosis.

At two years, the target lesion revascularisation (TLR) rate in irradiated patients was 15.4% vs. 48.2% in controls. For target lesion restenosis, acute myocardial infarction or death combined the rates were 23.1% vs. 51.7%.

Notably, between the 1 and 2 year follow-up an increase in TLR rate from 11.5% to 15.4% occurred, possibly representing a lack of durability due to under-dosing of the adventitia.

The recently completed, randomised Washington Radiation for In-Stent Restenosis trial (WRIST)⁶ using ¹⁹²Ir gamma seeds to treat 65 patients (65 controls) with focal (<4.7cm) in-stent restenotic lesions, has also shown efficacy. A dose of 15 Gy prescribed at 2 mm from the source was administered. At 6 month clinical and angiographic follow-up, there was a significant (67%) reduction in restenosis rate (19% vs. 58%). Other significant end points included:

- TLR rate 13.8% vs. 63.7%; and
- Either TLR, AMI or death combined 29.2% vs. 67.7%.

However, at the time of writing, follow-up is still too short to assess fully, the long-term efficacy and toxicity profiles of these gamma trials.

Recent Beta Studies

In a pilot study, Verin (1997)⁷ found no significant impact on restenosis rates after clinical and angiographic assessment at six month follow-up. Of 15 patients studied, 5 had major clinical events, 4 required TLR and 6 had developed restenosis. An endoluminally centred pure metallic ⁹⁰Y source was used to deliver 18 Gy to the luminal surface immediately after PTCA. No aneurysm was detected angiographically.

During the feasibility phase of the PREVENT⁸ trial conducted by Raizner to demonstrate the safety aspects of a ³²P system, low rates of late loss in the irradiated group was observed (4.8% cf. 51.3%) with significant reduction in TLR (4% cf. 18%). Three dose levels were used, the prescribed doses from the 27 mm length ³²P source being 16, 20 and 24 Gray at 1 mm from the source.

The authors noted that owing to an increase in edge effects, the TLR rates were similar in the treated vessels (24% cf. control 29%). A sub-analysis of patients with in-stent restenosis treated with ³²P, demonstrated lower rates of recurrences - 20% cf. 67% (matched control group from the WRIST study).

The CURE (Columbia University Radiation Energy)⁹ trial was the first clinical trial assessing feasibility of a radioisotope liquid-filled balloon system. This used ¹⁸⁸Re with a prescription dose of 13 Gray to the vessel wall surface. The trial included 30 patients who had balloon angioplasty and 30 patients undergoing intracoronary stenting. TLR was reported in 5/30 patients treated (17%).

Summary

These studies demonstrate an improved outcome as measured by restenosis, AMI or death but late complication rates are not yet reported, hence the overall benefit cannot yet be assessed.

The large variation in dosimetry requires ongoing assessment and the optimal doses to the appropriate vascular structures are yet to be determined. There are practical and theoretical advantages associated with the employment of gamma radiation based delivery systems but they are associated with greater technical requirements for safe use.

Hence this procedure must, at present, be regarded as investigational.

Table 1. Summary of gamma and beta results.

Research Group	Source & Dose	Outcomes
Condado ¹ <i>et al.</i> 21 Patients	¹⁹² Ir (γ) - 20 to 25 Gray @ 2 mm from the source	Restenosis rate 28.6% @ 3 years. (Possibly due to underdosing)
Costa <i>et al.</i> ² 91 patients	⁹⁰ Sr or ³² P (β) - 12 –18 Gray @ 2 mm from source	Late thrombotic events in 6.6% @ 2-15 months after irradiation
Teirstein ⁵ 26 randomised patients	¹⁹² Ir (γ) - >8 and <30 Gray to leading edge of the media	66% reduction in restenosis @ 6 months Increase in TLR for 11.5-15.4% @ 1- 2 years (possibly due to underdosing of the adventia)
Waksman <i>et al</i> (WRIST) ⁶ 65 randomised patients	¹⁹² Ir (γ) 20 to 25 Gray @ 2 mm from the source	67% reduction in restenosis
Verin <i>et al</i> ⁷ Pilot study	⁹⁰ Y (β) 18 Gray to luminal surface	No significant impact on restenosis
Raizner <i>et al</i> (PREVENT) ⁸ 80 randomised patients	³² P (β) - 16, 20 or 24 Gray @ 1 mm from source	Lower late loss and target revascularisation (TLR) in the irradiated group.
Weinberger (CURE) ⁹ 30 patients post-PTCA and 30 before stenting	¹⁸⁸ Re (β) liquid filled balloon- 13 Gray to the vessel wall	Reported TLR of 17%.

Dose Inhomogeneity

Dose inhomogeneity is a fundamental determinant of both efficacy and adverse toxicity following irradiation to prevent restenosis.

Delivering a homogenous dose to the target region including adventitia and vessel wall is the optimum aim. It is however technically difficult, as the typical lesion is rarely concentric. Even a catheter-centering device cannot eliminate dose inhomogeneity across the vessel wall during IVBT because of inverse square law effects where a lesion is eccentric.

Dose exceeding tissue tolerance is associated with an increased probability of complications, that is thrombosis, aneurysmal dilation and rupture. Under-dosing can lead to treatment failure.

In clinical trials, inhomogeneity is advanced as the most likely reason for less than

optimal improvement in TLR rates, where insufficient radiation dose was delivered. Better patency rates may be associated with unacceptable toxicity at the other end of the scale.

Dose inhomogeneity can be minimised by the use of external beam radiotherapy. This ensures an homogenous dose across the vessel wall and to the perivascular tissue. However, if used alone, an excessive volume of healthy tissue is treated, unnecessarily, to a cytostatic dose, which may increase the possibility of late normal tissue toxicity.

The specific problem of dose inhomogeneity using beta sources, due to the more rapid dose fall-off, has been noted in some studies.

Dose Prescription

At present it is generally assumed that modified smooth muscle cells and neo-intimal cells as well as adventitial

fibroblasts, contribute to restenosis as a result of re-population of scar tissue resulting from tear injury.

Since the position of the target tissue itself is not clearly identified, the distance from the centre of the vessel for adequate dose prescription is still controversial.

Utilising reports of the American Brachytherapy Society (ABS)¹⁰ and the American Association of Physicists in Medicine (AAPM)¹¹, the Radiation Advisory Committee recommends the following:

- For a catheter based systems:
 - The depth of dose prescription used for reporting purposes should be at a radial distance of 2 mm from the centre of the source.
 - For gamma emitters, the source strength should be specified as an air kerma dose.
 - For beta emitters, the source strength should be specified as a dose rate in water at a reference distance of 2 mm.
 - Dose uniformity should be better than $\pm 10\%$ at a radius of 2 mm along the source axis. The region of uniformity should be determined in the centered two thirds range of the treated length of at least 3 cm along the catheter axis.
- For brachytherapy of peripheral vessels, the dose specification should be at 2 mm plus the average lumen diameter.
- The source strength should be determined with calibration traceable to a national standard.
- The prescription dose, the dose prescription point, lesion length, target length, treatment length, average and minimal lumen diameter should all be reported.
- For radioactive stents, the dose prescription point should be at 0.5 mm radial distance from the surface of the stent in the midplane. This should be based on the stent diameter, nominal and deployed, the length, type, brand and model of the stent, radionuclide and radioactivity.
- For radioactive stents, the relative doses at 0.5 mm radial distance from the

surface of the stent in the mid-plane and over a time period of three half-lives of the radionuclide should also be reported.

Reported Doses

The prescription doses reported from clinical trials have been variable, depending on the prescription point adopted, for example

- In the Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) trial with ¹⁹²Ir gamma sources, Teirstein⁵ prescribed 8 Gy to the farthest media point.
- In the WRIST trial, Waksman⁶ prescribed a nominal dose of 14 Gy at 2 mm from the source.
- Weinberger (Columbia, 1996)¹² prescribed 20 Gy at 1.5 mm from the centre.
- Condado (Venezuela)¹³ prescribed 20-25 Gy at 1.5 mm from the centre. The corresponding doses at 2 mm from the centre of the catheter were 13, 15.5, 13.5 and 14.8 - 18.5 Gy respectively. The minimum dose at the maximum distance to the leading edge of the media was between 7 and 8 Gy although whether this minimum is adequate is not yet confirmed.

To date, it has been generally accepted that the maximum dose, to the closest distance at the leading edge of the media, should be restricted to 30-35 Gy.

Based on the results of the current trials, it appears that a prescription dose of approximately 20 Gy at 2 mm from the source centre may be appropriate to reduce the rate of restenosis.

Centering

There is controversy regarding centering the catheter in the artery. The radial dose gradient from source axis can be very steep, due to the non-centric nature of arteries, inverse square law effects coupled with absorption in the intervening tissues.

For medium energy beta sources, for example ³²P, there is a decrease of almost 50% of dose for every 0.5 mm distance from the source.

For gamma sources, for example ¹⁹²Ir, there is a dose gradient fall-off of approximately 30% per 0.5 mm. increase in distance Thus small differences in the source to media

distance can result in quite high variations in delivered doses.

Asymmetric placement of a catheter will result in asymmetry of dose across the vessel wall tissues. Clearly a source positioned closer to one side of the wall will give a much higher dose to that part compared with the opposite area. It is also possible that due to the irregular stenotic growth the lumen itself may not be in the centre of the artery.

The SCRIPPS trial used non-centred ^{192}Ir sources. While this demonstrated benefit of IVBT in preventing restenosis, the subgroup with larger arteries had a restenosis rate of about 38% compared with 6% in the group with smaller arteries.

Similarly, IVBT using non-centering catheters has not proven as effective in the more curved right coronary artery when compared with the more straight left anterior descending coronary artery.

In summary, for small vessel brachytherapy, it has not been established that radiation source centering devices improve the rate of re-stenosis, especially for gamma radiation treatment. For larger arteries treated with either beta or gamma sources, the need for centering is considered advantageous, as it increases the probability that a uniform dose distribution is obtained.

Edge Effects

While the initial trials of intra-vascular brachytherapy (IVBT) have been encouraging, with increasing follow-up periods, physicians are being faced with a newly observed problem following stenting and radiation treatment. This phenomenon being observed is narrowing or restenosis at both ends of the stent. This type of restenosis has been named as 'edge effect' or the 'candy wrapper effect'. While it remains uncertain as to why an increased growth of tissue has been observed at the edges of the stent, it has been postulated that a lower dose of radiation combined with the physical injury associated with stenting or angioplasty may actually promote cellular proliferation beyond the treated region of the vessel. The higher dose in the central region of the stent may restrict the growth of new tissue as expected.

Based on current theory, to ensure that the incidence of edge effects is reduced, the complete area of the stented region,

including the junction between the end of the stent and artery, should be exposed to a uniform dose of radiation.

As previously discussed, the dose rate fall-off from beta sources is greater, compared with gamma sources. Therefore, when using beta sources, extreme care should be observed to ensure a uniform dose is delivered over the region of the stented area. Typically, the dose rate at the extreme ends of a beta emitting source is less than the dose rate in the central region of source.

For gamma sources, the dose rates tails off rather than dropping sharply, therefore the probability of a 'geographical miss' or underdosing of the ends of the target are less likely. However, the users of the gamma systems should be aware of the importance of adequate margin and once again, aim to ensure a uniform dose to the entire target including distal and proximal injury sites.

Radiation Sources for Intravascular Brachytherapy.

The physical characteristics of radiation sources currently being trialled or proposed are listed in Table 2.

Presently:

- radioactive stents use ^{32}P and ^{48}V ;
- catheter based system use ^{32}P , ^{90}Sr - ^{90}Y , or ^{192}Ir ; and
- liquid filled balloon systems use ^{106}Rh , ^{188}Re , ^{125}I or ^{103}Pd .

Some other radionuclides with higher energy beta emissions are also being investigated.

The utility of these different sources depends upon several factors:

- Dose gradient (depth dose) around the source.

Availability of the source in dimensions suitable for introduction into the catheter or artery.

- Availability of the source at appropriate activities to keep the treatment time to a few minutes.
- A half-life sufficiently long for acceptable and economic periods of use; and
- Radiation safety in the handling and management of the source.

Table 2: Summary of potentially useful radionuclides

Radio-nuclide	Emission	Maximum Energy E_{max} (keV)	Average Energy E_{avg} (keV)	Half Life	Comments
^{32}P	beta	1710	693	14.28d	Easy to shield, but dose penetration limited.
^{90}Y	beta	2282	934	2.67d	Identical to Sr/Y-90, but worse than gamma.
$^{90}Sr/^{90}Y$	beta	2282	565	28.5y	Better dose than P-32, but worse than gamma.
^{106}Rh	beta	923	307	2.17h	Short half-life, not as energetic as ^{32}P .
^{188}Re	beta	2120	765	16.98h	Similar dose to Y-90. used for liquid balloons.
^{192}Ir	gamma		379	74.2d	Best dose distribution, hard to shield.
^{48}V	positron	696	144	15.98d	Possible use for radioactive stent.
^{125}I	X-ray	35	28	60.14d	Good dose, easy to shield, needs high activity.
^{103}Pd	X-ray	21	21	19d	Good dose, easy to shield, needs high activity.

These factors are discussed in more detail below:

Dose gradient

Since the distance of interest in IVBT is only a few millimetres from the source, the effect of distance is highly significant and will be enhanced by attenuation in the tissue around the source.

There can be a large difference between the dose at intima and that at adventitia.

Figure 1 indicates the dose distribution for a number of different radionuclides versus radial distance from the source. The dose has been normalised to 1.0 at a radial treatment distance of 2.0 mm.

For all of the sources presented in figure 1, the radiation dose rapidly falls off with radial distance from the prescription point. Beta emitting nuclides show the greater dose gradients (fall-off) compared with gamma nuclides.

If the target tissues are confined to the lumen wall, then radiation dose penetration

from a beta emitting nuclide maybe the preferred option since the majority of the dose will be confined to the area of interest.

If the target is deeper in the media or adventitia, then a gamma emitting nuclide maybe a better option since the dose distribution does not fall off at the same rate as compared with a beta emitting nuclide.

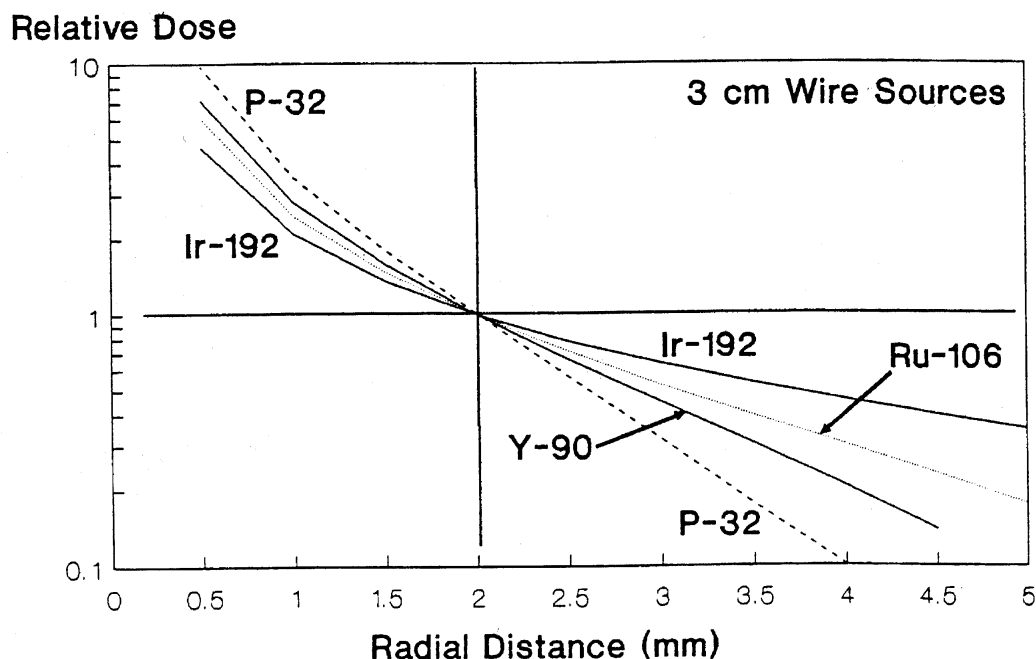
Dose uniformity to the arterial wall depends on source centering and the cylindrical nature of the artery. Because of the greater fall-off and high dose rates exhibited by beta emitting nuclides it maybe important to use centering devices.

It should also be noted that the observed restenosis rates have been higher in clinical trials for the subset with larger arteries treated with beta radiation. This would suggest that beta sources can be used effectively only in smaller arteries.

Another approach to overcome the uniformity problem is to inflate balloon catheters with radioactive liquids (Re-188).

Figure 1

(from Handbook of Vascular Brachytherapy 2nd Edition Waksman & Serruys Martin Dunitz Ltd London 2000)



Suitability of Sources

Given the site of treatment and the potential blocking of the artery during treatment (other than with spiral balloon catheters), IVBT irradiation times need to be kept as short as possible. It is desirable therefore to use radionuclides of high activity. Due to the small size of the lumen, the dimensions of the source also have to be small, necessitating the use of very high specific activity sources. In addition the radionuclide has to be available in a form suitable for introduction into and removal from the treatment catheters.

The system also has to have enough tensile strength and flexibility to negotiate the tortuous path required of it.

Half-life

Ideally the radionuclide used should have a long half-life that allows the treatment time to remain constant over a reasonable period of time. A long-lived radionuclide will not require frequent re-calibration or replacement, reducing the overall cost of the treatment.

For example, ³²P sources with a $t_{1/2}$ (half-life) = 14 days, have to be replaced every two to three weeks.

In contrast, a ⁹⁰Sr source, need not be replaced for at least 15 years.

Radiation Safety

All personnel involved in the procedure must have appropriate training in the safe handling of radiation sources. All members of the team must wear individual radiation monitors, Thermoluminescent Dosimeters (TLD) or similar, at all times during brachytherapy procedures.

If the source drive mechanism is not operated by remote control, the person introducing and withdrawing the source should wear both whole body and extremity monitors.

Radiation exposure levels should be monitored at the locations occupied by participating personnel.

Shielding requirements should be determined only by appropriately trained radiation safety personnel. This to ensure that radiation exposures are consistent with the 'As Low As Reasonably Achievable' (ALARA) principle.

The following effective personal dose limits should not be exceeded:

(a) 20 Sv per year, averaged over five consecutive years for occupational exposure.

(b) 1 mSv per year for members of the public

On completion of the treatment the area must be monitored to ensure that source is back in the storage and not in the patient or in the transit system.

Emergency procedures should be planned, posted and practised for each facility. The physical, biochemical and radiological nature of the radionuclide and delivery system will determine the accident control measures to be adopted.

All personnel need to be familiar with the emergency procedures, and be required to participate in emergency drills.

Quality Assurance

An extensive Quality Assurance (QA) program is essential if patient and operator safety is to be achieved and maintained. The specific QA program to be adopted will depend largely on the type of system to be used.

The following should be included in the QA assurance program:

- Documented physical details of the radioactive source being used;
- Details of the safe storage of the radioactive source and guidelines indicating which personnel should have access to the source;
- Protocols for the safe transport of the radioactive source from the storage facility to the treatment room;
- Physical integrity checks of the sealed source device prior to its use;
- For remote after-loading devices this should include:
 - Room safety interlocks;
 - Lights and alarm functions;
 - Console functions;
 - Visual inspection of all source guides;
 - Source positioning accuracy;

- Timer function; and
- Calibration of the source activity.

- Methodology to verify source activity using in-house measuring equipment;
- Protocols to be followed in the advent of any unexpected emergencies, for example: source breakage's, spills, loss of source either in the patient or treatment room, cardiac arrest while the source is within the patient and emergency surgery;
- Verification of the prescribed dose prior to treatment;
- Verification of both the correct patient and radioactive source to be used for the treatment;
- Monitoring of radiation dose rates around the treatment room;
- Monitoring the treatment room post exposure, to ensure that the source has been successfully returned to the storage rig and that there is no radioactive contamination if liquid sources have been used;
- A safety program for fluoroscopic procedures;
- Provision of education to all staff involved with the treatment;
- Comprehensive record keeping, and
- Advice to patients of appropriate safety and follow-up issues for permanent radioactive stent implants.

The Team

The study personnel required to perform IVBT will depend on the technique employed. At the time of writing the techniques used in Australia include:

- Automatic remote controlled afterloading systems using ^{192}Ir (traditionally used in Radiation Oncology);
- Automatically controlled after loading systems using ^{32}P ;
- Manual after loading systems using ^{90}Sr ; and

- Manual after loading systems using liquid ^{188}Re .

Intravascular Brachytherapy (IVBT) is a highly skilled, high precision procedure requiring the expertise of a multi-disciplinary team that can ensure that the correct dose is delivered to the right location with a minimal radiation hazard to both the operators and patient.

Ideally, the team should include individuals with the expertise to be able to:

- Determine the radiation dose required;
- Position the catheter correctly to ensure the dose is delivered at the correct location; and
- Operate the after-loading device or any other specialised equipment associated with the radioactive source.

The team must ensure that the patient and all personnel involved with the procedure are not exposed to any unnecessary radiation.

A Cardiologist, Vascular Physician or Interventional Radiologist should perform a majority of the non-dosimetric tasks with the assistance of an experienced radiotherapy team.

The radiotherapy team is responsible for operation of the radiation source device and the radiation safety matters related to the use of that source.

Determination of Dose

In most situations, the prescribed dose will have been predetermined by the research protocol in use in conjunction with a radiation oncology team.

If, as the encouraging findings from early studies suggest will happen, IVBT becomes a routinely and widely practiced procedure, then the dose being delivered will need to be prescribed and calculated for each individual irradiation as is the current standard practice for all brachytherapy procedures carried out in the State of Victoria.

Typically, the calculation and delivery of dose for oncologic brachytherapy procedures have been carried out using the expertise located within the confines of radiotherapy

departments. It is, therefore recommended that this expertise also be utilised for IVBT.

The factors involved in calculation should be determined by a team consisting of a Radiation Oncologist, Radiation Therapist and a Physicist experienced in the field of radiotherapy. The dose should be delivered and documented by the same team.

In Victoria the Radiation Oncologist will be the only team member licensed to prescribe radiation therapy doses.

Team Roles

The potential team members and their recommended roles are outlined below.

(1) Cardiologist, Vascular Surgeon or Interventional Radiologist

The delivery of dose should only proceed once the patient has been assessed as being a suitable candidate and the specialist physicians are satisfied that the patient has the potential to benefit from the radiation exposure involved.

The lumen diameter post-intervention has to be determined prior to and post-exposure. Accurate determination of the lumen diameter is needed to ensure that the precise treatment distance is calculated.

This group will have responsibility for:

- Assessing patient eligibility and acquiring informed consent;
- Performing the required fluoroscopic and PTCA or stent procedures according to the standard practice for the investigation site;
- Determining the lumen diameter post-intervention;
- Introducing and placing the treatment applicator;
- Removing the applicator following treatment; and
- Monitoring the status of the patient during and after the procedure.

(2) Radiation Oncologist

The Radiation Oncologist will have responsibility for:

- Prescribing the treatment and reviewing the treatment plan;

- Being available for any other considerations involved with the delivery of the prescribed dose;
- Assessing and informing the patient of potential issues arising from delivery of the planned dose as part of the procedure;
- Assessing the individual patient risks from radiation exposure (that is any history of previous radiotherapy) and considering radiobiological effects; and
- Applying or supervising the actual delivery of treatment.

The Radiation Oncologist will introduce and remove the treatment applicator for manually after-loaded procedures.

(3) Physicist and Radiation Therapist

The Physicist and Radiation Therapist will have the role and responsibility for:

- Conducting quality assurance (QA) checks on the source delivery unit and source wire if applicable;
- Determining the treatment plan based on the source and activity proposed for use;
- Reviewing the computed treatment plan prior to the initiation of treatment; and
- Applying the treatment under supervision of the treating physicians.

(4) Radiation Safety Officer

The tasks of the Radiation Safety Officer *for example shielding, distance, monitoring QA, education, ALARA principles application*, could be performed by either an additional appropriately qualified and experienced physicist or a physicist qualified in the field of radiotherapy, for example the physicist involved in the treatment plan for the procedure.

Summary

Listed above is the recommended basic framework of 'The Ideal Team' for Intravascular Brachytherapy. It is provided as a guide and if other individuals possess the necessary skills and experience required to perform some of these procedures or functions, they should be considered by the appropriate authority.

Licensing Requirements

Whilst intravascular brachytherapy remains an experimental procedure, IVBT projects must comply with the requirements of the Victorian *Radiation Act 2005*.

In summary, the steps required are as follows:

- Approval for research projects involving radiation exposure of volunteers must be obtained from the Department of Human Services by direct application to the Radiation Safety Program, after approval has been obtained from the Ethics Committee of the Institution proposing the project.
- Research applications are reviewed by the Radiation Safety Program prior to referral to the Radiation Advisory Committee for their consideration.
- As IVBT is currently considered an area of active research, details of all involved personnel, their professional background, qualifications and experience should be included with the research proposal. The roles of each of these individuals should be clearly defined in the proposal and if their professional background, qualifications or experience differ from the recommendations listed above, then a clear justification to why these personnel are part of the research team should accompany the research proposal.
- Applications also need to include:
 - The study protocol.
 - Estimates of the radiation doses expected to be delivered to the patient,
 - The patient information and consent sheet; and
 - A copy of the lay summary provided to the Institutional Ethics Committee.

A copy of the Radiation Safety Program Information Bulletin setting out the full procedure for obtaining approval for research involving radiation exposure of human volunteers is attached to this bulletin.

Reporting

The potential benefits of intravascular brachytherapy are attracting considerable interest at both national and international levels. Accordingly, the Radiation Advisory Committee believes it is important to keep the procedure under active, multi-disciplinary review, particularly from a radiation safety perspective which subsumes the heuristic principle, that is benefit demonstrably exceeds harm in the application of radiation in the treatment of human beings.

Whilst IVBT retains experimental procedure status, the Radiation Advisory Committee intends to review and, where appropriate, revise this document and its recommendations at regular intervals, until such time that the procedure meets criteria satisfying first level scientific evidence of overall benefit for this mode of therapy.

Researchers in the field are requested to keep the RAC advised of:

- Professional acceptance of the procedure.
- Information on delayed biological effects; and
- Unexpected incidents or complications involving the procedure.

It should be noted that it is a mandatory requirement to report any radiological accidents and incidents to the Radiation Safety Program of the Department of Human Services.

Further Information

Further information can be obtained from the:

Radiation Safety Program
Department of Human Services
GPO Box 4057
Melbourne Victoria 3001

Phone: 1300 767 469
Fax: 1300 769 274
email: radiation.safety@dhs.vic.gov.au

References

1. Condado *et al*: Long term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty (PTCA) and intracoronary angioplasty (PTCA) in humans. *Circulation* 1997; 96: 727-732.
2. Costa *et al*: Late coronary occlusion after intracoronary brachytherapy. *Circulation* 1999; 100.
3. Colombo *et al*: Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound (IVUS); *Circulation* 1995: 91 1676-1688.
4. Waksman R. Late thrombosis after radiation-Sitting on a time bomb (Ed) *Circulation* 1999; 100: 780-782.
5. Teirstein *et al*: Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997; 336: 1697-1703.
6. Waksman *et al*: Intracoronary radiation therapy for patients with in-stent restenosis: 6-month follow-up of a randomized clinical study. *Circulation* 1998; 98: 17,1-651:3421.
7. Verin *et al*: Feasibility of intracoronary β -irradiation to reduce restenosis after balloon angioplasty: a clinical pilot study. *Circulation* 1997; 95: 1183-1144.
8. Raizner *et al*: The PREVENT trial, a feasibility study of intracoronary brachytherapy in the prevention of restenosis: An interim report. *Circulation* 1998; 98: 1-651 (abstract).
9. Weinberger J.: Clinical experience with the liquid-filled balloon: The CURE Study, *Advances in Cardiovascular Radiation Therapy III*, Washington DC Feb 17-19,1999.
10. Subir Nag *et al*: The American Brachytherapy Society Perspective on Intravascular Brachytherapy. *Cardiovascular Radiation Medicine*, 1999; 1:1; 8-19.
11. Nath R. *et al*. Intravascular brachytherapy physics: report of AAPM Radiation Therapy Committee Task Group No. 60 Medical Physics, 1999, 26(2), 119-152.
12. Weinberger J. *et al*: Intracoronary irradiation: dose response for the prevention of restenosis in swine. *Int. J. Radiat. Oncol., Biol., Phys*, 1996; 26, 767-775.
13. Condado JA., *et al*: Percutaneous transluminal coronary angioplasty (PTCA) and intracoronary radiation therapy (ICRT): a possible new modality for the treatment of coronary restenosis-a preliminary report of the first 10 patients treated with intracoronary radiation therapy. *J. Am. College Cardiol.*, 1995; 288A, 0 (special issue).