Basic Rules of Dosimetry in Endovascular Brachytherapy

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Endovascular brachytherapy after percutaneous coronary intervention (PCI), is becoming a standard approach for the treatment and prevention of restenosis. A variety of technical approaches are currently available to deliver ionizing irradiation to the vascular target. Basically two kinds of radioactive isotopes are available that emit gamma radiation (photons) or beta radiation (electrons). The pitfalls and solutions for the optimization of dosimetry are discussed. As might be expected, the inhomogeneous dose distribution across the target volume results in recurrence by underdosage or in complications because of overdosage. Moreover, uniformization of the target definition and reporting of the dose distribution in endovascular brachytherapy is a prerequisite for comparison between the results of the various clinical trials and is absolutely necessary to improve the therapeutic efficacy of this new approach in the prevention of restenosis after coronary angioplasty with or without stenting.
(J Interven Cardiol 2000;13:425–430)

Introduction

Cardiovascular disease is one of the leading causes of death in developed countries. It is characterized by a vascular stenosis process that is multifactorial in its origin. Andreas Grüntzig[1] introduced the technique of percutaneous transluminal coronary angioplasty (PTCA) in 1977 to complement the only available revascularization technique at that time, the coronary bypass. However, the long-term vascular efficacy of PTCA is reduced by the occurrence of restenosis in the dilated segment.[2–6] This vascular restenosis is known to be due to several mechanisms: elastic recoil of the artery immediately post-PTCA, negative vascular remodeling, thrombus formation at the site of the injured vessel, excessive healing with neointimal proliferation, and matrix deposition resulting in a hypertrophic scar.[7–10] A variety of therapeutic approaches to prevent restenosis after revascularization have been tested. One of these approaches is the use of stents that are designed to reduce the elastic recoil and the negative remodeling, but obviously the use of stents does not influence the neointimal cellular proliferation and matrix synthesis.[10–12] Moreover, it has been shown in experimental animal models and in the clinical setting that this healing process is even stimulated by the use of stents resulting in persisting restenosis rates in about 30% of the cases.[2,5,6,10,13–17] Until recently published trials,[18,19] none of the pharmaceutical approaches tested resulted in the same reduction in the rate of vascular stenosis as the one observed after endovascular brachytherapy, especially for in-stent restenosis. The use of ionizing irradiation for benign diseases is not a new concept.[20] It is currently well known that radiotherapy is able to block benign proliferative disorders like keloid formation. The restenosis can also be considered, at least in part, as an uncontrolled proliferative process and as such it can be potentially inhibited by ionizing irradiation.

To deliver the radiation dose to the target vessel, sealed sources (solid or liquid) have been developed and are considered as the preferred treatment approach, although some research teams are working on the use of external irradiation to prevent restenosis, especially in peripheral artery diseases[21–23] or on the use

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of "soft" X rays endoluminally. Two kinds of isotopes are available for the sealed sources: gamma and beta emitters. The ideal source to be used in endovascular brachytherapy should be a source with a high specific activity, a long half-life, and yielding a dose distribution as uniform as possible over a distance of 2–3 mm. Some of the problems related to the definition of target volume, to dose prescription, and the published trials concerning endovascular brachytherapy are discussed in this article.

Dosimetric Requirements and Choice of the Isotope

The dosimetric requirements for intraluminal treatment are listed in Table 1. None of the sources available for endovascular brachytherapy completely meet all the requirements. Iridium (^{192}Ir) sources (photons) have the disadvantage of a high "integral dose" because of the higher penetration in the surrounding normal tissues. The use of isotopes like ^{192}Ir present radiation safety problems for the patient (whole body dose) and attending staff, and most catheterization laboratories are not equipped for these high activity sources (around 10 Curie = Ci). Beta sources such as strontium (^{90}Sr) and yttrium (^{90}Y) have the advantage of reducing the integral dose to the normal tissues of the patient and do not represent a radiation safety problem for the attending catheterization laboratory staff. These beta sources with modest activities (150–300 mCi) are able to provide high dose rates (short dwell times), and do not require supplementary radiation safety procedures other than those already available in any catheterization laboratory. However, the dose falloff in the tissue is much steeper compared to gamma radiation, resulting in a higher dose inhomogeneity between the endoluminal surface and the adventitial surface, especially for pure beta emitters. This inhomogeneity can have long-term deleterious effects because at these high doses of irradiation close to the source, definitive radiation damage may occur at the endovascular surface, predisposing to thrombus formation. Beta emitters such as ^{90}Y and phosphorus (^{32}P) have the practical disadvantage of a short half-life (64 hours and 14.3 days, respectively) compared to the gamma emitter ^{192}Ir (74 days). However, the ^{90}Sr/^{90}Y beta source is an interesting alternative as a beta-emitting isotope because it has a half-life of 28 years.

Table 1. The Dosimetric Requirements for Intraluminal Treatment

1. The single fraction acute dose should be 15–20 Gy applied to a length of 2–3 cm of arterial wall, approximately 2–5 mm in diameter and 0.5-mm thick.
2. The high dose volume should be tightly confined to the region of angioplasty with a minimum dose to normal vessels and myocardium.
3. The dose rate should be > 5 Gy/min to keep treatment times < 5 minutes to reduce the risk of thrombosis other cardiac complications.
4. The radioactive source should have physical properties suitable for endovascular applications through angioplasty catheters (dimensions, stiffness, flexibility).

Modified from H.I. Amols, J. Weinberger in *Vascular Brachytherapy*, R. Waksman, ed. *the Netherlands*; IR Crocker & RF Mould. Pub. Nucletron B. V., 1996.

International Commission on Radiation Units and Measurements Report 58 and Vascular Brachytherapy

The International Commission on Radiation Units and Measurements (ICRU) has developed "internationally accepted recommendations regarding quantities and units of radiation and radioactivity, procedures suitable for measurement and application of these quantities, and physical data needed in the application of these procedures, the use of which tends to assure uniformity in reporting." According to these recommendations collected in ICRU Report 58, a distinction has to be made between "temporary" and "permanent" implants. It is obvious that in the case of vascular brachytherapy we are dealing with temporary implants because the source is removed after the dose delivery, an exception being the radioactive implantable stents. For the clarity of the subsequent discussion, only the dosimetry problems related to sealed sources and not the radioactive stents are discussed.

The total time of the "implantation" (= dwell time) in temporary implants depends on the number of sources, their strength, and pattern of implantation. In vascular brachytherapy, we are dealing with a source pattern, which is a "single plane" implant, in which improvement of the dose distribution is possible through modulation of the dwell time. The activity of the source should be expressed in Reference Air Kerma rate (KERMA = Kinetic Energy Released in Material) (unit = mGy.h^{-1} at one meter), but in general

and in most of the papers related to endovascular brachytherapy, the activity of the source is reported as the number of disintegrations per time unit expressed in Curie (1 Ci = $3.7.10^{10}$ disintegrations per second). The official unit, however, should be the Becquerel (1 Bq = $2.703.10^{-11}$ Ci), and in theory the Ci has not been used since 1985.

As it is the case for external radiotherapy in oncology, the ICRU has defined volumes to be used for "interstitial" therapy. By analogy *gross tumor volume* (GTV) could be replaced by *vascular stenosis volume* (VSV), which can be further subdivided in different volumes as proposed by Carlier et al. The *clinical target volume* (CTV) should be the tissue volume containing the VSV and the volume injured by the angioplasty procedure and stenting. The *planning target volume* (PTV) is the volume to be irradiated to make sure that the CTV receives a therapeutic dose, and therefore, it contains a safety margin dependent on the isodose distribution characteristic for the source train used. Finally, the *treated volume* (TV) is the volume receiving a minimum target dose that is deemed necessary to achieve the treatment goal.

The volume definitions proposed by the ICRU should be used as these definitions are universally accepted and are also used in radiation oncology. The problem of definition of the target and the prescription and reporting of the dose in endovascular brachytherapy is fundamentally the same as the one encountered in radiation-oncology and, therefore, the same rules should be applied. The aim of the treatment team is to apply a dose distribution as uniform as possible to a "volume at risk" to develop restenosis after PTCA with or without stenting. This should be a three-dimensional approach and not a "vascular segment" seen on angiography that is only a reductive two-dimensional approach. A lot of attention is dedicated to correct longitudinal coverage of the CTV, as it has been shown that vessel wall injury, concomitantly to low dose irradiation results in an increase of stenosis at the edge.[24–27]

In most of the papers published on the subject of endovascular brachytherapy, there is no homogeneous way of defining the target volumes and no uniform way of dose prescription and reporting. It must be emphasized that this is important for the analysis and especially the comparison of the success rate and complication rate between different clinical trials in which often various irradiation techniques have been used. For the success rate, we are basically interested in whether the target volume received an adequate dose and if there is no "edge effect" (due to the isodose configuration at both extremities of the source train) or "geographical miss" (due to insufficient covering of the volume to be treated).[24–27] For the complication rate, it is going to be important to correlate irradiated volume of healthy tissues surrounding the target vessel to risk of complications as beta and gamma radiation yield a complete different integral dose.

The Dose Distribution and Dose Volume Histogram Concept

Accurate dosimetry requires the introduction of parameters allowing a good evaluation of the geometry of the target. This implies not only a knowledge of the configuration of the target in its longitudinal direction (i.e., the total length of the injured vessel as seen on angiography),[25,26] but also its radial distribution along this longitudinal axis (i.e., the depth of the target at any segment of the vessel).[28,29] The Rotterdam group[30] proposed using constant step pullback intravascular ultrasound (IVUS) controlled by the electrocardiographic trigger algorithm to avoid alteration of the ultrasonographic imaging by the movement of the heart. This technique allows the description of the cumulative dose-volume frequency distribution (known as the *dose volume histogram* [DVH]) over three specific volumes: (1) the luminal surface volume with a thickness of 0.1 mm, (2) the adventitial volume (at 0.05 mm from the external elastic lamina [EEL]), and (3) the plaque + media volume located between the other two volumes.[28,29] The IVUS technique allows automated identification of the lumen-intima and the media-adventitia boundaries. A three-dimensional reconstruction of the above defined volumes is possible over the total length of the vessel segment to be irradiated, which in theory at least allows a calculation of the cumulative dose-volume frequency distribution on these predefined volumes. This DVH approach potentially offers the opportunity for a unique and universally applicable definition of volumes of interest (VOI) and a uniform way of reporting dose distribution in published data (Table 2). Another refinement of dose prescription and reporting with this IVUS-based approach is the possibility of defining D_{v90}Adv (the minimal dose absorbed by 90% of the adventitial volume).[31]

One of the assumptions made with this IVUS approach is that the catheter of the ultrasound is in ex-

Table 2. Dose Specifications in the Randomized Trials for In-Stent Restenosis

START	$^{90}Sr/^{90}Y$	< 20 mm In-stent restenosis	16 or 20 Gy at 2 mm depending on vessel ϕ
WRIST	^{192}Ir	< 47 mm In-stent restenosis	15 Gy at 2 mm (ϕ = 2–4 mm) 15 Gy at 2.4 mm (ϕ > 4 mm)
GAMM-I	^{192}Ir	< 45 mm In-stent restenosis	8 Gy to target farthest from source but < 30 Gy closets to source
SCRIPPS-II	^{192}Ir	< 30 mm In-stent restenosis	8 Gy to target farthest from source but < 30 Gy closets to source

actly the same position as the catheter containing the source train, which is not necessarily the case. Other limitations of this IVUS technique are the image artifacts due to cyclic changes in coronary dimensions and movement of the IVUS catheter in the arterial lumen.[32] Finally, the DVH cannot be used alone to evaluate the quality of the treatment and should be used in conjunction with a two-dimensional dose display to obtain information on the spatiality of the dose distribution.[33] However, the strength of this approach based on DVH is that it allows screening of different treatment techniques, comparison, and real-time optimization of dose prescription. This leads potentially to inverse treatment planning, that is, automatic generation of a treatment plan based on the dosimetric intent, a technique which is largely implemented in external radiotherapy in oncology.[34]

It is currently known that the matched peripheral dose (MPD) concept, as used for the first time in interstitial brachytherapy in prostate cancer by Anderson,[35] through a dimension averaging procedure (considering the volume to be an ellipsoid) and introduced de facto in vascular brachytherapy and the minimal dose at the periphery of the target are suboptimal ways of estimating the quality of the dosimetry. This approach does not offer any estimation of the dose inhomogeneity within the target volume. Real-time dosimetry based on ultrasound imaging is certainly going to be possible in the near future and will allow a quantitative volumetric dosimetry analysis in the context of vascular brachytherapy.[34] This is the first step to optimizing treatment as, in theory, different techniques (centered vs noncentered) and different isotopes (gamma versus beta) could potentially be compared to obtain the best therapeutic index.[28,29,31]

Conclusion

Optimal endovascular irradiation (i.e., maximizing the response rate while keeping the complication rate as low as possible) will require a more refined way of defining target volume and dose prescription than the one used in the published trials. Proponents of the simple approach (i.e., prescribing the dose at a fixed distance from the source) will argue that in the previously published randomized clinical trials (WRIST, GAMMA I, SCRIPPS, and START trials) there is a statistically and clinically significant decrease in the in-stent restenosis rate even if no special effort was made for a unique and universally accepted definition of the target volume, and even if there are major differences in dose prescription and reporting. However, one should be aware that in radiation therapy there is always a therapeutic window, and therefore, special efforts should be made to apply standardized rules for target volume definition, dose prescription, and reporting to allow intercomparison between different technical approaches. That is the price to pay for the increase of therapeutic efficacy and the reduction of long-term complications. We are all aware that the inhomogeneous dose distribution is inherent to the brachytherapy technique, but the extent of the dose inhomogeneity should be kept as small as possible to reduce the risk of late complications.[36,37] Methods such as image acquisition through constant step pullback of the IVUS controlled by the electrocardiogram (ECG) trigger algorithm with automatic real-time target delineation and three-dimensional reconstruction combined to computerized dosimetry is certainly one of the ways to make progress in successful endovascular brachytherapy for the prevention of stenosis.

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