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Activity characterization of pure-β-emitting brachytherapy sources

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Abstract

A generalized approach for characterizing the activity content of sealed β-emitting sources has been developed, and was employed to establish National Institute of Standards and Technology based activity standardizations for three different types of intravascular brachytherapy sources. Initial ionization current measurements on the sources prior to destructive assays led to the establishment of calibration factors that can be used for subsequent non-destructive measurements of similar sources. Activity characterizations are needed to unequivocally relate theoretic absorbed-dose modeling results to dosimetric measurements, as well as to establish production and quality controls by the source manufacturers, and to satisfy the requirements of various governmental regulatory authorities. Published by Elsevier Science Ltd.

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1. Introduction

The use of radionuclides in medicine was initiated at the very beginning of the last century, within just a few years of the discovery of radioactivity (cf. Grigg, 1965; Mould, 1995). The word *brachytherapy*, derived from the ancient Greek words for short distance or close (*brachy*) and treatment (*therapy*), is generally used to describe the use of radionuclides in the treatment of cancer and benign diseases. Perhaps the most well-known and common example is the implantation of radioactive seeds into a cancerous prostate. An older, but synonymous, term which is still in use within Europe, is *endocurietherapy*.

This paper: (i) focuses on one of the more rapidly growing and advancing areas of brachytherapy, viz., the use of intravascular sources for the prevention of restenosis following angioplasty; (ii) reviews the need for activity characterizations of such sealed sources; and (iii) generalizes the standardization procedures that have been used by the National Institute of Standards and Technology (NIST) over the past four years for these activity characterizations, with particular emphasis on those for pure β emitters that require destructive radioassays.

2. Intravascular brachytherapy

Coronary artery disease (CAD), a principal form of heart disease due to the atherosclerotic narrowing (or stenosis) of the heart's arteries, is one of the leading causes of both morbidity and mortality in the western world (AHA, 1999). Advanced CAD cases are most frequently treated, invasively, by percutaneous transluminal coronary angioplasty (PTCA) procedures, commonly called "balloon angioplasties", that are used to widen the coronary arteries. Unfortunately, restenosis—or a re-narrowing of a stenosed artery that has been opened by PTCA—occurs in nearly half of all patients within six months of treatment (Kotzerke et al., 2000). Restenosis and its treatment have recently become quite well known because of the world-wide press coverage of the US Vice President's ailments (Altman, 2001). Extensive research is currently under-

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way to investigate ways to prevent restenosis, including the use of both β- and γ-emitting sources, in a variety of configurations and dose-delivery systems (Coursey et al., 1998; Kotzerke et al., 2000).

The clinical and economic repercussions will be profound if the radiation-induced prophylactic reduction in the rate of occurrence of restenosis with brachytherapy sources becomes successful. In 1999 alone, about 650,000 PTCA procedures were performed in the US and another 500,000 were done abroad (AHA, 1999). Considering the high rate of restenosis and that restenosis often requires one or more revascularization procedures (either PTCA at an average cost of $20,000 USD or by the even more expensive bypass graft surgery), it has been estimated that the annual cost of restenosis treatments in the US is more than $3 billion USD (Novoste, 2000).

3. Need for activity characterizations

The importance of activity standardizations is illustrated by its central role in the schematic of Fig. 1, which is one version of the oft-replicated Coursey triangle that is used to show the symbiotic relationships amongst dose rate measurements $\mathrm{d}D/\mathrm{d}t$, dose rate modeling calculations $(\mathrm{d}D/\mathrm{d}t)A^{-1}$ and activity measurements A. Collé (1999) previously discussed, from several perspectives and in greater detail, this need for standardizations as well as the driving forces for accurate determinations of the activity content of brachytherapy sources. As noted, "primary" activity standardizations serve two essential purposes: firstly, to unequivocally relate theoretic absorbed-dose modeling results to dosimetric measurements of the spatial distributions; and secondly, to establish transfer standards or calibration factors for "secondary" measurement methods. With respect to the former, uniform and consistently determined dose profiles are critical for evaluating the efficacy of the radiation treatments with the sources, for comparisons of treatments that may use a variety of radionuclides and different dose-delivery configurations, and for the meaningful interpretation of results from various preclinical studies and clinical trials. The latter purpose satisfies the measurement needs of users who must know and/or assign activity values to the sources and those of manufacturers who must establish production and quality controls. One must also recognize that some substantial part of the motivation to have activity characterizations of brachytherapy sources is to satisfy the requirements of various governmental regulatory authorities that are concerned with radiation protection or the use of medical devices.

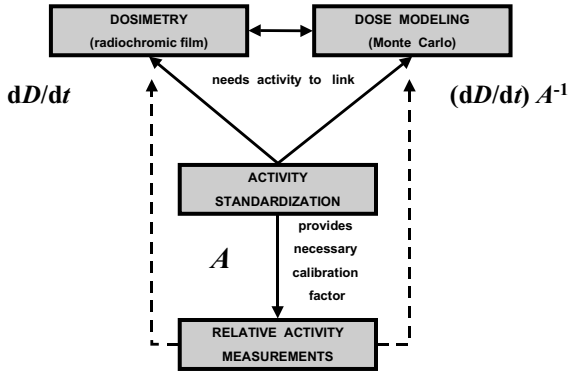

Fig. 1. Illustration of the central role of the activity standardization in providing the necessary link for relating dose measurements and calculations and to establish calibration factors for routine activity measurements.

4. NIST standardizations of intravascular brachytherapy sources

It is possible, of course, to standardize some brachytherapy sources by non-destructive means. These can include sources that consist of liquid- or gas-filled catheters and whose assays require quantitative collections of the activity contained in the catheters, or those utilizing γ-emitting nuclides having well-known branching ratios (like ^{192}Ir which is widely used in interstitial brachytherapy) that can be measured spectrometrically with efficiency-calibrated detectors. In contradistinction, sealed sources of nuclides that decay by pure β emission require that they initially be assayed by destructive radiochemical methods. Firstly, these sources do not exhibit any distinctive radiative signatures (e.g., monoenergetic γ rays) that could be easily measured and related to the contained activity; and secondly, measurements of the scattered and energy-degraded β spectra or the internally generated photonic emissions (e.g., bremsstrahlung or X-rays) emerging from the encapsulated source cannot be usefully related to the activity.

Fig. 2 summarizes the activity standardizations of various intravascular brachytherapy sources that have been performed at NIST since 1996. They fall into three general categories of sources, each of which requires very different radioanalytical treatments. The first kind, encompassing the last four columns of the figure, is for those in which the radioactive source material is readily available in a liquid or gaseous form. Zimmerman and Pipes (2000) and Zimmerman et al. (1999, 2002) have described some of these standardizations. The second kind is for solid sources that must be assayed by destructive means, but yet have compositions that are amenable to complete dissolution. An example of this

Manufacturer/ Collaborator	Guidant	Novoste	Isostent	Radiance	Cedars-Sinai Medical Center	Mallinckrodt	Washington Hospital Center	Interventional Technologies
Nuclide (half-life)	^{32}P (14 d)	^{90}Sr -^{90}Y (29 a, 64 h)	^{32}P (14 d)	^{32}P (14 d)	^{188}Re (18 h)	^{186}Re (89 h)	^{133}Xe (5 d)	^{99m}Tc (6 h)
Source configuration	Encapsulated seed in long wire	Encapsulated seed for catheter train	Stent	"Hot wall" balloon catheter	Liquid-filled balloon catheter	Liquid-filled balloon catheter	Gas-filled balloon catheter	Liquid-filled perfusion catheter
Source composition	Inert polymeric material	Refractory "ceramic" matrix	Ion-implanted stainless steel	Thin film/inert matrix	^{188}Re-MAG3 solution in saline solution	Proprietary ^{188}Re-labeled compound in saline solution	^{133}Xe gas in CO_2 carrier	Liposome-encapsulated ^{99m}Tc or Ceretec® in saline
Encapsulation	TiNi jacket	Stainless steel	N/A	Double-walled polyethylene balloon	Balloon wall	Balloon wall	Balloon Wall	N/A

Fig. 2. Activity calibrations of intravascular brachytherapy sources performed by NIST: 1996–2000.

kind of source is the ^{32}P-ion-implanted stainless-steel stent (column 3) whose standardization has been reported by Cessna (2002). The third category, which is the present focus, is also for solid sources that require destructive assays, but whose compositions preclude complete digestions. The physiochemical digestion methods used to assay these sources leave behind some debris that requires an independent residual activity determination.

NIST-based activity standardizations have been established for three different types of sources in this third category. They include: (i) a TiNi-encapsulated ^{32}P seed having a highly inert polymeric core (Collé, 1999); (ii) a stainless-steel-jacketed ^{90}Sr–^{90}Y source with a highly refractory, ceramic-like matrix (Collé, 2000); and (iii) a "hot wall" balloon catheter source that consists of a thin film of ^{32}P enveloped between the polyethylene balloon walls (Collé, 2001). They are the proprietary products, respectively, of Guidant Vascular Intervention, Inc. (Houston, TX), Novoste Corp. (Norcross, GA), and Radiance Medical Systems, Inc. (Irvine, CA). The specific digestion and standardization procedures, including detailed schematic outlines, used for each of these have been published (Collé, 1999, 2000, 2001), and have used one of two general approaches. Although generalizations are possible, it is important to realize that the destructive assays, in each case, were performed by unique radiochemical digestion procedures that were specifically designed for each source type, followed by liquid scintillation (LS) spectrometry of the resulting solutions. In the first approach, employed for the Guidant TiNi seeds and the Radiance "hot-wall" balloons, the procedure relied upon opening or destroying the source structure and then performing successive extractions on the debris until there was a sufficiently low level of activity in the debris that could be independently assayed. In the second approach, used for the ceramic-like Novoste sources, the fraction of remaining unextracted activity in the source matrix was determined by ionization current measurements before and after the chemical extractions. In both approaches, the extractions involved very quantitative solution transfers and collections, gravimetrically based dilutions, and assays of gravimetrically determined aliquants of the resulting master solutions. The LS spectrometry with ^{3}H standard efficiency tracing was based on well-established procedures, which are somewhat routine for this laboratory (cf. Collé and Zimmerman (1997) and references therein). The assays for the ^{32}P sources utilized a previously developed technique for resolving the always-present ^{33}P impurity (Collé, 1997). Novel methods (which incorporated the use of LS vials to perform all the chemistry in, and the use of miniature "chemistry kits") were devised to account for any residual activities in the digested sources and on any of the apparatus used for the assays.

Fig. 3 contains a generalized overview of the approach used to provide these activity standardizations. An important part of this work is to use the "primary" standardization to establish a calibration factor for a secondary, non-destructive measurement method (e.g., relative ionization current measurements with a re-entrant chamber). Typically, we establish an in-house calibration for NIST chamber "A", which is a unique,

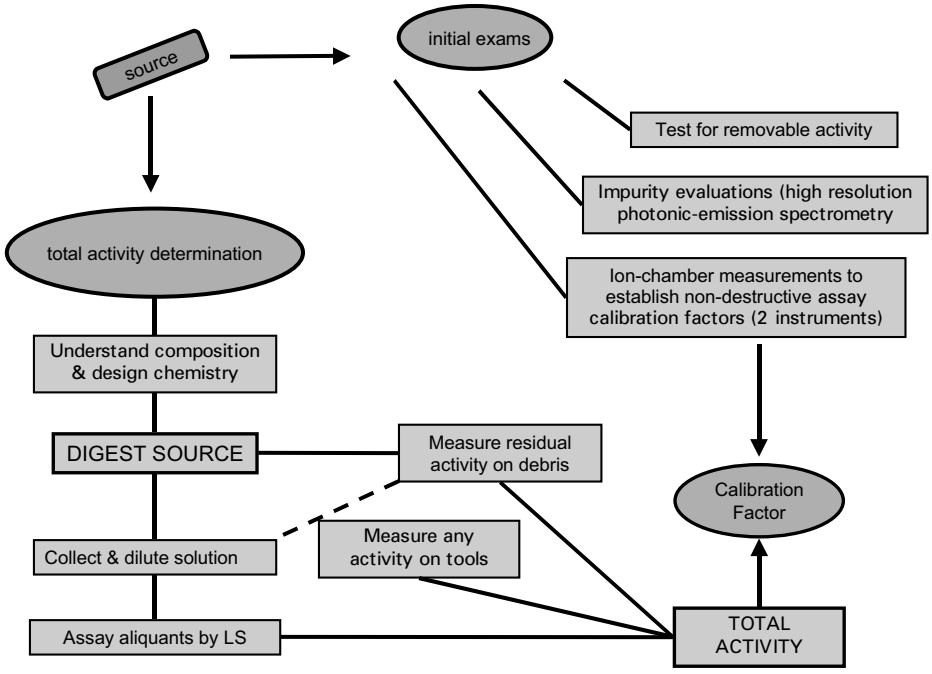

Fig. 3. Overview of the generic procedure used to standardize brachytherapy sources.

argon-filled, pressurized (2 MPa) re-entrant ionization chamber. Such an established secondary calibration can then be used to provide the source manufacturers with additional certified measurements (for continuing quality assurance purposes) without performing the much more expensive and labor-intensive destructive assays. Often, calibration factors for commercial (radionuclide or "dose" calibrator type) instruments in specific geometries are also established (cf. Collé et al., 1999; Coursey et al., 1998; Mitch et al., 2000; Zimmerman and Pipes, 2000; Zimmerman et al., 1999, 2002).

Once source manufacturers have received the results of an NIST-based primary standardization, we encourage them to occasionally submit additional sources for calibration. We also encourage them to submit the sources with reported activities (based on their own determinations) that can be directly compared to NIST values. This serves as a kind of informal proficiency test that can be used to demonstrate continuing measurement assurance.

5. Some findings

Space limitations imposed on this paper prohibit giving more than a few examples of some results of these NIST activity standardizations.

The NIST Radioactivity Group's primary standardization for the Guidant ^{32}P seeds was transferred to both the NIST Dosimetry Group and to Guidant. Soares (2001) recently reported that ionization chamber measurement intercomparisons between Guidant and NIST Dosimetry on seeds manufactured by Guidant over nearly 4 yr exhibited a continuing agreement of well within $\pm 2\%$.

Over the course of a few years of experience with these different types of β-emitting sources, we have found that initial ionization current measurements should be performed with at least two different instruments or at least measured in two different configurations with one instrument. This approach of establishing two separate calibration factors for each type of source can be used to provide a degree of quality assurance for subsequent non-destructive calibrations that are performed (Collé, 2001). The results given in Fig. 4 for two batches of Novoste seeds (Batch A was an early prototype) illustrate how the relative responses of two sets of measurements can be used to insure that the source compositions have not changed (compared to sources used for the original standardization), or that they have indeed changed and cannot therefore be calibrated with the extant calibration factors. In the absence of such a confirmation, it would be possible to assign incorrect certified activities for the submitted sources on the basis of an invalid calibration factor. This type of evaluation to insure consistency between batches of sources is now routinely used before we perform any non-destructive calibration for manufacturers.

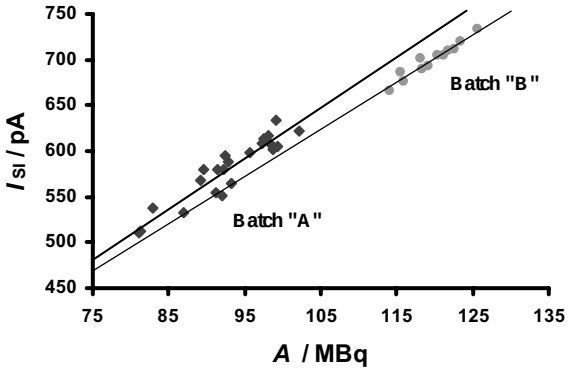

Fig. 4. Comparison of two ionization chamber responses for two dissimilar batches of ^{90}Sr–^{90}Y brachytherapy sources. The data were decay corrected to a common reference time. The ionization currents I_{SI} (in units of pA) on the ordinate were obtained with a commercial Standard Imaging, Inc. (Middleton, WI) "HDR-1000 Plus" chamber; while the assigned activities A (in units of MBq), for the abscissa, were based on relative ionization current measurements using NIST chamber "A" and the originally established calibration factor (Collé, 2000) for the Novoste seeds.

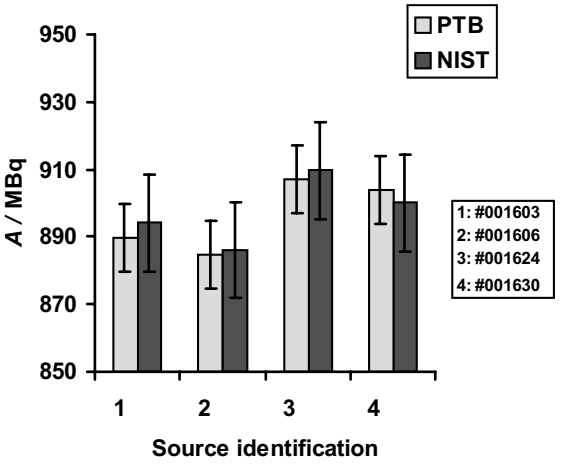

Fig. 5. Comparison of activity determinations made by PTB and NIST on four Radiance ^{32}P "hot all" angioplasty-balloon catheter sources. The data were decay corrected to a common reference time. The NIST results were obtained from relative ionization current measurements with chamber "A" and the originally established calibration factor (Collé, 2001) for the balloon sources, while the results from PTB (2000) were based on destructive radionuclidic assays. The uncertainty bar shown on each reported value corresponds to a ± 2 standard uncertainty interval.

The primary standardization provided for the Radiance "hot-wall" balloon sources was not only transferred to Radiance, but also to secondary calibration laboratories like the Radiation Calibration Laboratory at the University of Wisconsin. In addition, four sources that had been secondarily calibrated at NIST by ionization chamber measurements were sent by Radiance to the Physikalisch-Technische Bundesanstalt (PTB) in Braunschweig, Germany for independent destructive analyses (PTB, 2000). The method used by Günther (2002) consisted of a combustion-tube digestion, followed by a chemical leaching, and collection of the solution for assay by LS spectrometry. A comparison of the NIST and PTB results is shown in Fig. 5. The excellent agreement between these sister laboratories using two very different digestion methods is indeed gratifying.

At the present time, US regulatory authorities have become so very impressed with our successes in providing brachytherapy source manufacturers with these activity characterizations that they have begun to expect and require manufacturers to obtain the necessary primary activity standardizations as a condition for approval as medical devices.

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