AAPM recommendations on dose prescription and reporting methods for permanent interstitial brachytherapy for prostate cancer: Report of Task Group 137

Ravinder Nath[a)]
Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut 06510

William S. Bice
International Medical Physics, San Antonio, Texas 78259

Wayne M. Butler
Schiffler Cancer Center, Wheeling Hospital, Wheeling, West Virginia 26003

Zhe Chen
Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut 06510

Ali S. Meigooni
Department of Radiation Medicine, North Shore University Hospital-Long Island Jewish Health System, Manhasset, New York 11030

Vrinda Narayana
Department of Radiation Oncology, Providence Cancer Center, Southfield, Michigan 48075

Mark J. Rivard
Department of Radiation Oncology, Tufts University School of Medicine, Boston, Massachusetts 02111

Yan Yu
Department of Radiation Oncology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania 19107

(Received 20 July 2009; revised 22 September 2009; accepted for publication 22 September 2009; published 20 October 2009)

During the past decade, permanent radioactive source implantation of the prostate has become the standard of care for selected prostate cancer patients, and the techniques for implantation have evolved in many different forms. Although most implants use ^{125}I or ^{103}Pd sources, clinical use of ^{131}Cs sources has also recently been introduced. These sources produce different dose distributions and irradiate the tumors at different dose rates. Ultrasound was used originally to guide the planning and implantation of sources in the tumor. More recently, CT and/or MR are used routinely in many clinics for dose evaluation and planning. Several investigators reported that the tumor volumes and target volumes delineated from ultrasound, CT, and MR can vary substantially because of the inherent differences in these imaging modalities. It has also been reported that these volumes depend critically on the time of imaging after the implant. Many clinics, in particular those using intraoperative implantation, perform imaging only on the day of the implant. Because the effects of edema caused by surgical trauma can vary from one patient to another and resolve at different rates, the timing of imaging for dosimetry evaluation can have a profound effect on the dose reported (to have been delivered), i.e., for the same implant (same dose delivered), CT at different timing can yield different doses reported. Also, many different loading patterns and margins around the tumor volumes have been used, and these may lead to variations in the dose delivered. In this report, the current literature on these issues is reviewed, and the impact of these issues on the radiobiological response is estimated. The radiobiological models for the biological equivalent dose (BED) are reviewed. Starting with the BED model for acute single doses, the models for fractionated doses, continuous low-dose-rate irradiation, and both homogeneous and inhomogeneous dose distributions, as well as tumor cure probability models, are reviewed. Based on these developments in literature, the AAPM recommends guidelines for dose prescription from a physics perspective for routine patient treatment, clinical trials, and for treatment planning software developers. The authors continue to follow the current recommendations on using D_{90} and V_{100} as the primary quantities, with more specific guidelines on the use of the imaging modalities and the timing of the imaging. The AAPM recommends that the postimplant evaluation should be performed at the optimum time for specific radionuclides. In addition, they encourage the use of a radiobiological

model with a specific set of parameters to facilitate relative comparisons of treatment plans reported by different institutions using different loading patterns or radionuclides. © *2009 American Association of Physicists in Medicine*. [DOI: 10.1118/1.3246613]

Key words: prostate, brachytherapy, prescription, reporting

TABLE OF CONTENTS

I. INTRODUCTION

Permanent interstitial brachytherapy using low-energy photon emitters, such as ^{125}I and ^{103}Pd, has become the method of choice for treatment of early-stage organ-localized prostate cancer. Since its introduction about 50 years ago, a number of methods have been used for describing the dosimetry of these implants. In the early clinical implementation of this method before soft-tissue imaging was available, it was common to report the prescription parameters that described the dose distribution in relation to the implanted seeds rather than to the underlying anatomy. These methods included concepts such as the "natural dose-volume histogram (DVH)," "matched peripheral dose," etc. One common approach was to use the highest dose rate with a continuous isodose surface that encloses the implanted volume.[1] Recently, it has become a common practice to image soft tissues of interest using ultrasound, CT and/or MRI to define the various clinical volumes such as gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV).[2] However, these volumes can be considerably different depending on the imaging modality, the time of imaging, and the margins used. Different margins are chosen in different directions, and their sizes are also different in various clinics; sometimes there are differences among the physicians in the same clinic. With the widespread use of image-guided dosimetry, there is now a need for developing a consensus methodology for dose prescription and reporting for prostate implants. This report from the AAPM Task Group 137 (TG-137) has been reviewed and approved by the AAPM Therapy Physics Committee. The full report containing extensive background on prostate brachytherapy physics and rationale for the included recommendations is available on the AAPM website http://www.aapm.org/pubs/reports/.

II. IMPACT OF IMAGING MODALITY ON DOSE REPORTING

The AAPM TG-64 and the American Brachytherapy Society (ABS) as well as European groups recommend the use of CT to evaluate the implant. Dosimetric parameters D_i and V_i that are used to score an implant are dependent on accurate identification of source position, dose calculation, and target delineation. Most inconsistencies in dose reporting are a result of disparity in target delineation. Various imaging modalities can be used to evaluate an implant. Plane films provide source positions but lack soft-tissue contrast. The ultrasound images provide prostate definition but cannot offer unambiguous seed positions. The use of CT to evaluate the implant is currently the standard of care. CT images of the pelvis provide excellent source definition within the limits of axial slice spacing and partial-volume artifact, and exhibit reasonable soft-tissue contrast. However, they are not as reliable as MR images for prostate or normal-tissue delineation. MR imaging requires multiple scans for optimal viewing of the soft tissue and sources.

Imaging plays a crucial role in dose reporting for prostate implant. The dose indices used for evaluating an implant are dependent on target and normal structure delineation, which is highly variable. With the intent of providing consistent and

reproducible dosimetric information without increasing healthcare costs the following guidelines are suggested.

(1) Axial CT (2–3 mm) contiguous images should be used for postimplant evaluation. Although drawing the prostate is easier with 5 mm slices because of better contrast, the seed locations are more precisely located using smaller slice thicknesses, as demonstrated by the European group Brachytherapy Physics Quality Assurance System (BRAPHYQS) in a study using the Kiel phantom.[3–5]
(2) The prostate should be contoured being mindful of the difficulties that are encountered at the prostate base and apex.
(3) The outer rectum should be contoured 1 cm superior and inferior to the prostate on CT. The volume of the rectum receiving greater than 100% of the prescription dose should be recorded. The rectum should not be distended when scanned.
(4) The rectal wall on CT can be approximated by a 0.5 cm contraction of the outer rectal surface.
(5) A Foley catheter should be used during day 0 imaging, and the urethra should be contoured on all slices within the prostate. For postimplant dose evaluation, a Foley catheter is optional.
(6) The penile-bulb dose can be used as a surrogate for dose to erectile tissues.

It is recommended that the guidelines below be followed when MR imaging is available. Generally speaking, contours of the normal structures and tumor volumes are better identified with MR, whereas seed locations are more precisely located by CT. It is ideal that CT and MR images be obtained on the same day and be fused using appropriate software.

(1) Axial, coronal, and sagittal, T2-weighted (3 mm) contiguous images should be obtained immediately before or immediately after the CT. The prostate should be contoured on MR using the information from axial, coronal, and sagittal scans.
(2) Axial CT (2–3 mm) contiguous images should be used to determine the source positions for postimplant evaluation.
(3) The outer and inner rectum should be contoured on the axial MR 1 cm above and below the prostate. The volume of the rectum receiving greater than 100% of the prescription dose should be recorded. The rectum should not be distended when scanned (i.e., do not use a rectal coil).
(4) The bladder should be contoured on the axial MR.
(5) The axial and sagittal MR should be used to contour the urethra.
(6) Other normal tissues responsible for erectile function should be contoured on MR.
(7) MR and CT datasets should be registered only in the area immediately surrounding the prostate and not the entire pelvic region.
(8) The dose distribution for the CT-determined seed positions should be displayed on an axial MR dataset.

III. EFFECT OF IMAGING TIMING ON DOSE REPORTING

A number of studies have shown that the postsurgical edema and its resolution can alter the dose delivered by an implant.[6–9] The dynamics of edema resolution and the decay of radioactivity can lead to large changes in the dose delivered if this effect is not taken into account. The magnitude of this effect further depends on the timing of imaging after the implant for the purpose of dose evaluation and dose reporting.

Despite many reported studies and the theoretical considerations discussed earlier, there is currently no single postimplant dosimetry time that is followed consistently by every institution. The postimplant dosimetry time adopted by different clinics varied significantly, from immediately after the procedure to several hours or weeks after the procedure. Even within the same institution, a locally established dosimetry time was not always followed consistently for a variety of reasons.[10,11] For ^{125}I implants, the traditional postimplant dosimetry time of about 1 month following the procedure was established without explicit consideration of edema and has been used by most clinics. It is very close to the calculated nominal optimal time that results in minimization of dosimetry error due to a lack of edema consideration in dose calculations.[12,13] This postimplant time was also used by some clinics for ^{103}Pd implants before the effects of edema were actively investigated.[14] However, because of the differences in radioactive decay half-life, the nominal optimal times for ^{103}Pd and the newly introduced ^{131}Cs sources are significantly different from that for ^{125}I implants.[12,13,15]

It is also important to note that the existing dose response reported by Stock *et al.*[16] for ^{125}I implants was based on CT dosimetry (D_{90}) performed at 1 month postimplant.[1] The dose-response relationship for D_{90} reported by Potters *et al.*[11] for ^{125}I and ^{103}Pd implants was also based on CT postimplant dosimetry performed at average 21 days (11–45 days) after the procedure. Given our current understanding of prostate edema and its expected impact on dosimetry, there is a need to establish a consistent dosimetry time in order to minimize artificial fluctuations in the reported dosimetry indices. Such a dosimetry time should also be consistent with the established dose-response studies until a new dose response based on dosimetry quality indicators calculated at other times or with the full consideration of edema is established. In the meantime, new data that provide information relevant to prostate edema should also be reported to allow eventual correlation of the treatment response with the true dosimetry received by each implant.

In light of these considerations, the following data should be included in reporting prostate brachytherapy dosimetry.

(1) *Preimplant prostate volume.* Preimplant prostate volume is known for almost all implants. It does not require additional effort unless a preferred imaging modality is specified.
(2) *Implant-day dosimetry.* Implant-day dosimetry based on TRUS imaging and the actual or derived source locations is readily available for clinics currently performing

real-time dynamic dosimetry. For those clinics that do not perform real-time dosimetry, dosimetry based on CT or MRI images acquired at 2–4 h after the procedure is recommended. This has the clinical advantage of aiding future improvements by closing the learning curve early while memory of the details is still fresh. In the case of an obvious overdose to critical structures such as rectum, urethra, or erectile bodies, the physician can prepare a plan of prophylactic management of expected symptoms. The implant-day volume at the completion of the procedure is also relatively easy to obtain with TRUS.

(3) *Postimplant dosimetry at the nominal optimal dosimetry time for respective radionuclides.* Because of the existing dose-response data, the postimplant dosimetry for ^{125}I implants should be performed at 1 month (± 1 week) after the procedure. For ^{103}Pd and ^{131}Cs, postimplant dosimetry should be performed at their respective nominal optimal times, 16 ± 4 and 10 ± 2 days, respectively.

IV. COMMON TREATMENT PLANNING APPROACHES FOR PROSTATE IMPLANTS

The initial seed-placement approach when transperineal, ultrasound-guided prostate implants began in Seattle in 1985 was to distribute a relatively large number of low-strength seeds evenly throughout the prostate.[17] The uniform seed-loading approach assumed the photon energy was sufficiently low that cumulative dose at large distance would be negligible. Even though the photons from radionuclides used in permanent prostate implants are attenuated with distance more rapidly than the inverse-square dependence indicates, the cumulative effects are not negligible when clinically relevant distances separate the sources. In any prostate volume filled with sources spaced at lattice points forming a 1 cm cubic grid, the central dose will be much higher than the peripheral dose because of such cumulative effects. In the early Seattle implants, central prostate and urethral doses frequently exceeded 300% of the minimum prescribed peripheral dose. Within 2 years after the start of their program, unacceptably high urinary morbidity led them to abandon uniform loading in favor of a modified version. Nevertheless, the principles of their uniform-loading approach form the basis for most manually planned implants today.

At the opposite extreme from uniform loading is peripheral loading, which, as the name suggests, places sources only at the edge of the target volume. Although this approach is appropriate for small prostates or in patients with a large defect from a transurethral resection of the prostate where the epithelial surface of the defect must be spared, peripheral loading in typical prostate implants places the patient at risk of underdosing the prostate centrally in exchange for very high-dose gradients close to the rectum. Wallner used this approach in his pioneering work at Memorial Sloan Kettering that also helped define dose thresholds for high-grade morbidity.[18]

Standardization of certain planning parameters would assist in understanding differences in outcomes and morbidity as well as differences in postoperative dosimetry. Users are encouraged to use the following definitions and procedures for planning and postimplant evaluations, which were proposed by the PROBATE group of GEC ESTRO.[19] A brief summary of these PROBATE recommendations is presented below, and the reader is referred to the original document by Salembier *et al.* for details.[19] We acknowledge that parts of the following recommendations in this section were based on this protocol.

IV.A. GTV

The gross tumor volume corresponds to the gross palpable, visible, or clinically demonstrable location and extent of the malignant growth. Given the TNM definition for prostate cancer, GTV can only be defined for tumor stages larger than T1c. Whenever possible, the GTV should be contoured on the preimplantation ultrasound-acquired images. Where necessary, correlation with endorectal coil magnetic resonance and spectroscopy should be used.

IV.B. CTV

The clinical target volume is the volume that contains the GTV and includes subclinical malignant disease at a certain probability level. Delineation of the CTV is based on the probability of subclinical malignant cells present outside the GTV. It is well documented in surgical literature that prostate cancer is in the majority of cases a "whole gland" disease. Even in a very early stage, prostate cancer presents as a multifocal disease—both lobes can contain microscopic disease. Given this specific behavior, at least the whole prostate gland has to be considered as "target" and included in the CTV. The extent of subclinical extraprostatic extension of early prostate cancer needs further study, but is generally less than 3 mm in most studies. The clinical target volume for preimplant dosimetry should be the prostate gland with a margin. For T1–T2 prostate cancer, the CTV corresponds to the visible contour of the prostate with a three-dimensional (3D) volume expansion of 3 mm. This three-dimensional expansion can be constrained to the anterior rectal wall (posterior direction) and the bladder neck (cranial direction).

IV.C. PTV

The PTV surrounds the CTV with a margin to compensate for the uncertainties in treatment delivery. The PTV is a geometric concept, introduced for treatment planning. A margin must be added to the CTV either to compensate for the expected physiological movements and variations in size, shape, and position of the CTV during therapy (internal margin) or for uncertainties (inaccuracies and lack of reproducibility) in the patient setup during irradiation, which may be random or systematic. The CTV to PTV margin can be minimized in brachytherapy because there are no significant opportunities for setup error. Using online *in vivo* 3D dosimetry and fluoroscopy in addition to sonography to eliminate seed-placement errors, there is no need for an expansion from the

CTV to define the PTV, i.e., PTV=CTV. However, this approach is debatable for permanent implants.

IV.D. Organs at risk (OARs)

Three different organs at risk can be defined in the preimplantation setting for prostate treatment:

(a) Prostatic urethra: A common practice to obtain visualization of the urethra is to use a urinary catheter. This should be a small-gauge catheter, French gauge 10, to avoid distension of the urethra. The surface of the catheter can be used to define the urethral surface from the prostatic base to apex. However, in practice, the urethra is not a circular structure, and an alternative that might give a more accurate anatomical picture is to instill aerated gel into the urethra prior to obtaining the ultrasound images.
(b) Rectum: Using transrectal ultrasound, the anterior rectal wall can be visualized, but may introduce artifacts due to displacement and distension. Many brachytherapists simply outline the outer wall, and this should be regarded as the minimum requirement; others define outer and inner walls. In terms of the critical cells in the rectum for late damage, the latter is probably more correct.
(c) Penile bulb and/or neurovascular bundles: Currently this remains investigational.

IV.E. Prescription doses for prostate cancer

Prescription dose is the intended dose to the 100% isodose. Commonly used prescription doses for monotherapy are 145 and 125 Gy for ^{125}I and ^{103}Pd, respectively.[20,21] The values for ^{131}Cs remain investigational; 100–125 Gy have been used or suggested by some.[22–24] It should be pointed out that these values are nominal values. The effectiveness of a nominal prescription dose for individual patients can vary, depending on the radiobiological characteristics of the patient's cancer cells and on other factors such as the presence of procedure-induced edema. The dose prescribed to individual patients is primarily a clinical decision and ideally should be established through clinical trials and confirmed by treatment-outcome analysis. Recently, a group of experienced brachytherapists in the publication by Bice *et al.*[25] recommended 115 Gy for ^{131}Cs monotherapy implants and noted the increase in the original recommended prescription dose (from 100 to 115 Gy) following revision of the dose-rate constant.

IV.F. Planning criteria for target volumes and organs at risk

For the CTV, the following conditions correlate with a good preimplantation dosimetry:

- The V_{100} (the percentage of the CTV that receives at least the prescribed dose) must be at least 95% ($V_{100} > 95\%$ of CTV). Therefore, the D_{90} (the dose that covers 90% volume of the CTV) will be larger than the prescription dose ($D_{90} > 100\%$ of prescription dose).
- The V_{150} (the percentage of the CTV that receives at least 150% of the prescription dose) should be equal to or less than 50% ($V_{150} \leq 50\%$ of CTV).

For the organs at risk, the following conditions correlate with acceptable levels of toxicity:

(a) Rectum: Primary parameter: $D_{2\ cc} <$ reference prescription dose. Secondary parameter: $D_{0.1\ cc}(D_{max}) < 150\%$ of the reference prescription dose.
(b) Prostatic urethra: Primary parameter: $D_{10} < 150\%$ of reference prescription dose. Secondary parameter: $D_{30} < 130\%$ of the reference prescription dose.
(c) Penile bulb and neurovascular bundles: Investigational at present, no parameters can be reliably defined.

IV.G. Postimplant dose reporting

The postimplant analysis should include the outline of the target volumes as described below for evaluation of the two- and three-dimensional dose distributions. In addition, it is recommended to construct the DVH for this target volume and to document the dose levels that cover 100% and 90% of the target volume for postimplant evaluation, i.e., D_{100} and D_{90}, and the fractional volume receiving 200%, 150%, 100%, and 90% of the prescribed dose, i.e., V_{200}, V_{150}, V_{100}, and V_{90}. All implants should undergo postimplant evaluation including intraoperative implants. This should be based on imaging at optimum times after implantation, at which time effects of prostate edema are minimal. Optimal imaging should include MRI, but if not available, CT alone is adequate. Seed evaluation and localization is a critical step in postimplant dosimetry. There is a small risk of seed loss or seed migration. Depending on the implantation technique and on the type of seeds used (loose seeds versus stranded seeds), migration rates between 1% and 15% have been described anecdotally. If migration rates of 15% or more are observed, the implant technique should be changed to the one associated with lower migration rates. For postimplant purposes, the exact number and position of seeds in the target area must be determined.

For postimplant, it is almost always impossible to define a GTV on the radiological images due to interference from the seeds. Two different CTV definitions have been proposed by PROBATE:

(a) CTV-P=CTV for prostate, the postimplant contour of the prostatic gland defined by the capsule on radiological examination.
(b) CTV-PM=CTV for prostate plus margin, the postimplant contour of the prostatic gland defined by the capsule with a three-dimensional uniform expansion of 3 mm.

For postimplant, the only OAR that can be defined reliably both on CT and MRI is the rectum. For contouring purposes, using CT only the outer rectal wall can be reliably defined; using MR the outer and inner walls of the rectum

over the whole region of interest can be indicated. The lower rectum is poorly defined on CT and best shown with MRI. Image-fusion techniques should therefore be of value. However, there is no consistent definition of the rectal volume to be outlined. Therefore, PROBATE recommended constructing the DVH for the volume, in cm^3, of the outer rectal wall.

Furthermore, Salembier *et al.*[19] recommended localizing the prostatic urethra and documenting the urethra dose in terms of the urethral V_{100}, V_{150}, D_{50}, and D_{10}. Urethra visualization at the recommended imaging time rather than immediately postimplantation can involve additional catheterization and might not be possible or worth performing. It is hoped that a more convenient contrast-enhancing technique will become available in the near future. Correlation with, or formal fusion of, TRUS images with those obtained by CT or MR imaging may be the optimal noninvasive technique for localization of the urethra on the postimplant scan. Institutional policy should be described if urinary parameters are published.

Defining the penile bulb and neurovascular bundles is only possible with accuracy on MRI and may be performed if available. As set by PROBATE, dose parameters in the postimplant setting are as follows:

Target volumes: D_{90}, V_{100}, and V_{150} are primary parameters and should always be reported for both CTV-P and CTV-PM. The secondary parameters V_{200}, V_{150}, V_{90}, D_{100}, and biological equivalent dose (BED) may also be reported, although their value in relation to outcome is not proven and should be a focus for further research.

Organs at risk: $D_{2\ cc}$ for the rectum and D_{10} for the urethra are the primary parameters. Secondary parameters, $D_{0.1\ cc}$ and V_{100} for rectum and $D_{0.1\ cc}$, D_{30}, and D_5 for urethra may also be reported. For organs at risk, volume parameters should be expressed in absolute values (cm^3). No parameters can be given at present regarding penile bulb and neurovascular bundles. Further investigation and evaluation is needed.

This section has presented a comparison between the recommendations by the PROBATE group from GEC-ESTRO (Salembier *et al.*[19]) with the present recommendations. As shown in this section, the differences between the two recommendations are related to the selection of the CTV margin, the dose to rectal-wall volume versus dose to rectum volume, and the timing of the postimplant imaging procedure. Further research and analysis of patient data should be encouraged to clarify the clinical importance of these variations.

V. INTRAOPERATIVE PROSTATE PLANNING AND ITS IMPACT ON DOSE REPORTING

Recent advances in technology allow real-time treatment planning and dose calculations during the implantation procedure. This offers the opportunity to improve the quality of implants by appropriate modifications in the seed implants and replanning during the procedure itself. This technology of intraoperative treatment planning raises unique challenges and opportunities for dose reporting in prostate implants. With treatment planning in the OR; the patient and TRUS probe are not moved during the time between the volume study and seed-insertion procedure. This procedure can be performed in three different forms:

- Intraoperative preplanning: Creation of a plan in the OR just before the implant procedure, with immediate execution of the plan.
- Interactive planning: Stepwise refinement of the treatment plan using computerized dose calculations derived from image-based needle-position feedback.
- Dynamic dose calculation: Constant updating of calculations of dose distribution using continuous deposited-seed-position feedback.

V.A. Intraoperative preplanning

Some institutions with generous inventory of seeds do not require the conventional preplanning visit (a few days or weeks prior to the implant) to obtain prostate volume and subsequent number and strength of seeds to order from a CT scan or ultrasound. TRUS is performed in the OR, and the images are imported in real time into the treatment planning system (TPS). The target volume, rectum, and urethra are contoured on the TPS either manually or automatically, and a treatment plan is generated. The prostate is implanted according to the plan. Intraoperative preplanning has some advantages over the conventional two-step preplanned method. It avoids the need for two separate TRUS procedures and for reproducing patient positioning, and the setup is obviated. However, intraoperative preplanning does not account for intraoperative changes in prostate geometry or deviations of needle position from the preplan.[26,27]

V.B. Interactive planning

In this approach, the process of seed ordering, image acquisition, target definition, and organ contouring is similar to the intraoperative preplanning method. An optimized treatment plan is then performed, the DVH is generated, and the plan is examined. If necessary, seeds can be added or deleted manually, and the new isodose distributions and DVH displays are regenerated. The needles are inserted as per plan. In interactive planning, it is critical that the dose calculation is updated based on the estimated seed positions derived from the actual (imaged) needle positions. The needles are repositioned, or subsequent needle positions are altered in the plan, if there are adverse dosimetric consequences. The dose calculation is then updated based on the actual needle location. The interval at which the dose distribution is recalculated is operator dependent.

Interactive planning represents an improvement over intraoperative preplanning, potentially allowing for a shortening of the learning curve for inexperienced brachytherapists, and the technical outcome of the procedure would be less operator dependent. However, in interactive planning the calculated dose distribution is based on the implanted needle position, and hence interactive planning might not account for seed movement after deposition. This is most probably

true and is the conclusion of a recent paper in which a comparison of the results from two different centers (one with experience and one without) using the same equipment was presented.[28]

V.C. Dynamic dose calculation

In comparison to interactive planning, dynamic dose calculation requires the following additional components. The essential feature is that the deposited-seed positions are captured in real time such as via an image-guided robotic brachytherapy device, and the optimization is based on deposited-seed location (rather than needle location). The dose distribution is updated dynamically based on the actual positions as the seeds are deposited. The motion of the prostate during placement, as well as changes in the prostate size and shape due to intraoperative edema, are accounted for. Obviously, dynamic dose calculation entails a paradigm shift in dose prescription and specification in that an intended prescription dose is adaptively "painted" to a changing 3D target volume. This process of dose painting can result in multiple alterations of a previously accepted isodose distribution and total implanted activity until the end of the procedure when a satisfactory dose distribution is achieved.

At this time, dynamic dose calculation is not available for permanent prostate brachytherapy because it is difficult to image individual seeds on TRUS. Dynamic dose calculation is feasible for high-dose-rate (HDR) prostate brachytherapy because it requires imaging the needles, not the individual seeds, with TRUS. However, dynamic dose calculation has been used for HDR prostate brachytherapy, and some of its components could be adapted for permanent prostate dynamic dose calculation and may become available by the time this report is published.[29,30]

The technique of robotic assistance in prostate brachytherapy has attracted much research interest recently.[31] Several robotic-system designs have been proposed, including adaptation of an industrial robot, adaptation of a research robot, and robots specially designed for seed implantation.[32,33] It has been shown that the potentially larger implantation space made available by eliminating the restriction to a fixed-grid spacing can be used to advantage in dynamic-dose-calculation planning to counter deleterious effects of intraoperative edema if a periphery-to-center sequence of seed deposition by single needles is followed.[34] These robotic-assisted approaches open up many new issues regarding dose specification and delivery of the prescribed dose in a dynamic setting. The AAPM Science Council has recently approved the formation of the Robotic Brachytherapy working group to examine the role of robots for prostate implants.

V.D. Recommendations on intraoperative planning and evaluation

Intraoperative planning and dose evaluation offer the potential for enhancing the quality of implants and a more accurate determination of the dose distributions at the time of the implant. However, postimplant dosimetry (on the optimum day for imaging with respect to edema resolution) should be performed also in order to take into account the effects of edema and seed migration.

VI. SECTOR ANALYSIS OF POSTIMPLANT DOSIMETRY

VI.A. Sector analysis

Any spatial information with regard to the dose distribution within the structure is lost in the creation of the DVH. From the DVH, one can see that there are high- and low-dose regions within the structure but not where they are. For brachytherapy, in which the dose can change dramatically over a few millimeters distance, spatial dose information may be very useful: Are the low-dose areas in the regions where cancer is expected, or are high-dose areas located where the higher dose levels might cause complications? There is a trade-off then between retaining spatial information of 3D dose distribution and having the DVH as an analytical tool.

In prostate brachytherapy this dilemma has been partly resolved by dividing the prostate into sectors or quadrants. Bice *et al.*[35] used this technique to compare compiled data from 58 patients performed by a single implant team operating at two different institutions: one that used loose seeds and spacers in needles and the other at which a Mick applicator was employed to implant the sources. The authors divided the gland into 12 sectors by first dividing the gland into three in the cranial-caudal direction—base, midgland, and apex. Then, each was further subdivided on each transverse slice into anterior, posterior, left, and right sectors. Each of the 12 sectors had its own DVH. The implant team discovered that their delivery with the Mick applicator did not provide the same degree of coverage as they were able to achieve with loose seeds in needles. They used sector analysis to pinpoint the weakness in coverage to the basal sectors, implying that seeds were being dragged away from the base as the applicator was withdrawn following the deposition of the most basal sources. This problem is user dependent and also can occur with preloaded needles.

According to the published reports, sector analysis has been used exclusively to study implant techniques. The practitioners have examined how the dose to different sectors compared over a series of implants, either to analyze their implant methods or to compare between two delivery systems. It is likely that sector analysis will become more important with regard to evaluating the dose distribution within individual implants. The introduction of saturation biopsies (typically using 30–80 cores; for example, Merrick *et al.* used a median of 50 cores and found transperineal template-guided saturation biopsy to be a useful diagnostic technique for patients with prior negative TRUS biopsies[36]) and metabolic imaging have given brachytherapists the ability to localize disease within the prostate gland, providing an impetus to concentrate the dose on specific regions and expect different dosimetric outcomes in these areas.

VI.B. Recommendations on sector analysis for prostate implants

In order to utilize fully the knowledge gained by recent pathology studies using biopsy data and advanced imaging techniques such as MR spectroscopy and single-photon-emission computed tomography,[37,38] it is important to start performing sector analysis of implant dose distributions in a research setting. It is recommended that treatment planning software vendors start providing the tools for such analysis. Further, the community should move from arbitrary (geometrically) defined sectors to "true" anatomical sectors. This could be performed via atlas matching of the contoured prostate volume.

VII. BIOPHYSICAL MODELS USED FOR PROSTATE IMPLANTS

While not in popular use and not available in commercially available treatment planning systems, it is of interest to the medical community to assess theoretical radiobiological effects for prostate implants. In permanent prostate brachytherapy, the tumor cells are subjected to continuous irradiation of low-energy photons with instantaneous dose rates varying in both space and time. The spatial variation in dose rate is caused by both the sharp dose falloff around the individual low-energy sources and the spatial relationship of the implanted sources. It is not uncommon to have dose rates differ by more than a factor of 2 within the prostate gland. The temporal variation in dose rate is caused primarily by the radioactive decay of the radionuclides and by the dynamic resolution of procedure-induced prostate edema. The prescribed initial dose rates vary from approximately 7 cGy/h for ^{125}I sources to more than 21 cGy/h for ^{103}Pd sources and more than 30 cGy/h for ^{131}Cs sources. The duration needed to deliver, for example, 80% of total dose varies from approximately 22 days for ^{131}Cs implants to 140 days for ^{125}I implants. With such diverse spatial and temporal variations, the dosimetric parameters such as D_{90}, V_{100}, V_{150}, and DVH discussed earlier in this report become insufficient to fully characterize the biological responses of different prostate implants because the cell repopulation and sublethal-damage repair can become significant during the course of dose delivery. There is a need to consider actively the interplay between the spatial-temporal patterns of dose delivery and the underlying cell kinetics in order to properly compare the permanent implants performed with different dose rates, spatial heterogeneities, and radionuclides, or to compare an implant to other treatment modalities such as HDR brachytherapy and EBRT for prostate cancer.

Various models have been used in research settings to characterize the interplay of spatial-temporal patterns of dose delivery with the underlying cell kinetics. For permanent implants, an analytic expression of BED [defined in the Appendix by Eq. (A1)] derived by Dale based on the linear-quadratic (LQ) cell-inactivation model has been used by many investigators in the examination of various issues related to prostate implant.[39–41] For example, Ling *et al.* and others used it to assess the effects of dose heterogeneity associated with prostate implants and the relative biological effectiveness of different radionuclides.[42–45,23,46] Other investigators used such a model to examine the relative effectiveness of low-dose-rate (LDR) and HDR irradiations, the radiobiological effects of mixing sources with different decay half-lives, the impact of tumor shrinkage during the implant, the effects of prostate edema, the probabilities of tumor control and long-term normal-tissue complication, the possibility of dose escalation, and the biological effect of combining prostate brachytherapy with external-beam radiotherapy.[47–62] Recently, Stock *et al.*[48] also performed a dose-response study for ^{125}I implants using BED as the implant quality index. Dale and Jones[40] presented an excellent review on the application of this BED model in brachytherapy. In addition, other models such as equivalent uniform dose (EUD) [defined in the Appendix by Eq. (A8)] and tumor-control probability (TCP) have also been used in permanent implant evaluations.[42,49–52] In most of these works, TCP was determined by the Poisson probability of inactivating all tumor cells, with the average surviving cells calculated according to Dale's BED. As shown in a study by Tucker *et al.*,[53] the Poisson model is known to underestimate the tumor cure rate when tumor-cell repopulation occurs during the treatment. Recently, Zaider and Minerbo[54] derived a more general TCP formalism capable of dealing with cell repopulation and applicable to different temporal patterns of dose delivery. A concern on the use of BED calculated at an "effective treatment time" in isoeffect comparison has also been raised recently in the literature.[55] Despite these new developments, the Dale formalism for BED is still used much more widely because of its mathematical tractability for inhomogeneous dose distributions. Nonetheless, medical physicists who are interested in or are engaged in using radiobiological indices should pay attention to these and future developments in radiobiological modeling.

To facilitate the proper use of radiobiological indices and to increase the comparability of indices reported by different institutions, the AAPM believes that it is important to establish a consensus model and its associated parameters for the purpose of reporting biophysical indices. After reviewing the currently available radiobiological models and the associated parameter values for prostate cancer, it is recommended that the Dale BED model and a set of self-consistent parameter values to be used as the interim biophysical models for permanent prostate brachytherapy. EUD can be used as a secondary index. Recognizing the evolving nature of radiobiological modeling, the use of other models, such as TCP or any new and improved models and/or parameters that become available in the future. When reporting these indices, it is recommended that adequate information about the model and the model parameters be included to facilitate easy relative comparison by others. It is well recognized that all models have limitations. Some models may be better than the others at describing or predicting a specific characteristic of the implant. *These recommendations do not imply that the selected models are superior to the others*. Also, the recommended parameter values should not be interpreted as the definitive radiobiological parameters for prostate cancer.

TABLE I. Examples of radiobiological indices for uniform dose distributions. (Calculated with $\alpha=0.15$ Gy^{-1}, $\beta=0.05$ Gy^{-2}, $\alpha/\beta=3.0$ Gy, $T_p=42$ days, repair half-life of 0.27 h, and $N_0=1\times10^6$.)

Indices	Radionuclide		
	^{125}I	^{103}Pd	^{131}Cs
Dose (Gy)	145.0	125.0	120.0
BED (Gy)	101.7	112.7	115.7
TCP (%)	79.0	95.5	97.1
T_{eff} (day)	236.2	94.1	61.0

These recommendations are intended primarily to help in establishing a level of consistency and comparability in the biophysical indices to be reported by different institutions for permanent prostate brachytherapy for relative comparisons.

Recommendations for reporting relative radiobiological response are as follows:

(1) When radiobiological indices are included in the reporting of permanent implant responses, adequate information on the radiobiological model and the model parameters should be included to facilitate easy comparison. Recognizing the evolving nature of radiobiological modeling, the BED [Eqs. (A5) and (A7) in Appendix] calculated with a set of nominal model parameters (see below) is recommended as an interim primary radiobiological index for permanent prostate brachytherapy. Other models such as EUD, TCP, or future new/improved models may also be used in accordance with the above reporting guidelines.

(2) For improved comparability, a set of model parameters with values representative of prostate cancer is recommended for the calculation of BED and EUD for permanent prostate implants. The recommended values are from the studies by Wang and co-workers:[56–58] $\alpha=0.15$ Gy^{-1}, $\beta=0.05$ Gy^{-2}, $\alpha/\beta=3.0$ Gy, $T_p=42$ days, and repair half-life of 0.27 h. It should be emphasized that these recommended values should not be interpreted as the radiobiological parameters of individual prostate cancer patients; also see the commentary by Fowler *et al.*[59] Typical values of BED, EUD, and TCP (Poisson model) using these parameters are shown in Table I, which can be used as a quality assurance check on algorithmic model implementation.

(3) Ideally, all dosimetric quantities needed for calculating the radiobiological indices should be reported so that these indices can be recalculated when new or improved models become available. However, it is not possible, at the present, to include these data (for example, differential dose-volume histograms of individual patients) in conventional publications. It would be ideal to have a centralized data center so that the data of individual patients can be electronically pooled together and analyzed systematically.

(4) The software vendors for brachytherapy are encouraged to incorporate calculations of radiobiological indices in their brachytherapy treatment planning system to facilitate reporting and relative comparison of radiobiological responses. The radiobiological parameters should be implemented as user-modifiable input fields so that the impact of different radiobiological characteristics on the calculated radiobiological indices can be easily examined. The currently accepted parameter set could be used as the default values.

VIII. DISCUSSION

In this report, we focus on LDR permanent interstitial brachytherapy for treatment of prostate cancer. In contrast to this modality are temporary implants using HDR brachytherapy techniques, in which hollow needles are placed into the prostate gland and a single high-activity radioactive source (nominally 10 Ci ^{192}Ir) dwells in selected locations in each needle for approximately 5–15 min to deliver the prescribed dose. This procedure is repeated two to three times over several days. After all treatment is completed, the needles are removed. Because of the major differences in LDR and HDR techniques, the dose-reporting requirements are fundamentally different. In this report, we address only the issues related to LDR permanent brachytherapy of the prostate because of its wide applicability and unique clinical issues.

The present recommendations do not include tissue-heterogeneity corrections and interseed-shielding effects primarily because the methods of their application have not been resolved at the present time. However, these issues need to be considered carefully once a practical model for their application is introduced. Dose calculations for transperineal implantation with ^{125}I or ^{103}Pd brachytherapy sources are typically performed assuming a point-source emitter in a homogeneous water phantom. The efficacy of this assumption has been investigated by several investigators using both experimental and Monte Carlo simulation techniques. For example, Chibani and colleagues have shown significant deviations for D_{90} due to calcifications.[60] Meigooni and Nath[61] found that the heterogeneity effect for different brachytherapy sources is a function of spatial location, tissue thickness, and photon energy. However, DeMarco *et al.*[62] observed that the effects of interseed attenuation in prostate implants with sources in the energy range of 20–36 keV are insignificant.

Presently, the dose at any point of a multiseed implant is calculated by adding the doses from each seed, assuming that the presence of the other seeds does not affect the radiation field. However, in a typical prostate implant there are 40–100 seeds in close proximity to each other that can cause seed-to-seed interference. Using a thermoluminescent dosimetry (TLD) technique, Meigooni *et al.*[63] showed a dose distortion of up to 10% in an assembly of 18 ^{125}I seeds. Furthermore, using the Monte Carlo simulation technique, Burns and Raeside[64] showed up to a 9.8% perturbation of the dose distribution around a single ^{125}I seed (models 6702 and 6711) by the presence of one or three nonradioactive neighboring seeds. Recently, DeMarco *et al.*[62] used the Monte Carlo

simulation method in a computed-tomography-based dosimetry calculation for ^{125}I prostate implants, which simulated clinical applications. Contrary to previous findings, they concluded that the interseed effects were negligible in their implant patterns. In an independent investigation, Carrier and co-workers[65,28] examined the effect of dose perturbation in a multiseed implant. They concluded based on an interseed attenuation study that computable dosimetric differences exist between plans with 0.38 and 0.76 U sources, two initial levels often used in clinical practice. Because more sources are necessary for a plan with 0.38 U, a 2% increase in the attenuation level was calculated for two different prostate sizes. The tissue-composition effect has the same impact for all prostate sizes and seed densities when the prostate is approximated to a homogeneous organ. However, they proposed that a more realistic study, taking into account local heterogeneities, would be necessary to establish the consequences of this effect. In addition, seed design was also shown to strongly influence interseed attenuation.[66] These discrepancies are not yet resolved, and there is still a need for further investigation into Monte Carlo simulations and TLD measurements for multiseed implants in heterogeneous media to clarify the role of interseed effects in patient dose delivery. Therefore, the recommendations in this report do not address the impact of heterogeneity on the final outcome, and these effects are excluded from the current recommendations.

ACKNOWLEDGMENTS

The authors wish to acknowledge the thoughtful criticisms and the generous assistance of our European colleagues, members of the BRAPHYQS and PROBATE working groups within GEC-ESTRO for reviewing this document. The authors have adopted many of the recommendations from their recent report. Some of this work (Z.C. and R.N.) was supported in part by a grant from the National Institutes of Health (Grant No. R01-CA134627).

APPENDIX: BED MODEL FOR PROSTATE IMPLANTS

The BED is defined to provide a direct measure of the amount of cell kill resulting from a given irradiation,[39]

$$\mathrm{BED} = \frac{1}{\alpha}\ln S \quad \text{or} \quad S = \exp[-\alpha \cdot \mathrm{BED}], \tag{A1}$$

where S and α denote the surviving fraction and the intrinsic radiosensitivity of the irradiated cells, respectively.

For acute irradiations, the LQ cell-inactivation model is often used to calculate the cell survival from a given irradiation. For acute single fraction irradiations, for which cell repopulation and sublethal-damage repair can be ignored during the irradiation, the LQ model gives the following well-known relationship between S and dose D,

$$S = \exp[-\alpha D - \beta D^2], \tag{A2}$$

where α and β are coefficients that characterize the average yield of cell kill resulting from the one- and two-track actions, respectively.[39] The BED for such an irradiation, according to Eq. (A1), is then given by

$$\mathrm{BED} = D[1 + D/(\alpha/\beta)]. \tag{A3}$$

I. BED for fractionated irradiations

For a course of radiotherapy given in N fractions with dose d per fraction, the LQ model predicts that

$$S = \exp\left[-\alpha N d - \beta N d^2 + \ln 2 \frac{(N-1)\gamma}{T_p}\right]. \tag{A4}$$

The last term in the exponent accounts for the cell repopulation during the course of the treatment, modeled by a potential doubling time T_p (in days) for tumor cells. It assumes that the repopulation is present at the start of the treatment and the treatment is given daily without interruption. The γ is the unit of the elapsed treatment time (in days) and equals 1 day. The intrafraction repair of sublethal damage was neglected in Eq. (A4), as the time needed to deliver a typical fraction (e.g., 2 Gy) is usually short, while the interfraction repair of sublethal damage was assumed complete within the 24 h break between fractions.[39]

II. BED for prostate implants assuming a uniform dose distribution

During the protracted dose delivery of permanent prostate brachytherapy, both cell repopulation and the repair of sublethal damage can become significant. Based on the LQ model, Dale[40,41] derived an analytical expression for the BED of permanent implants with a dose rate characterized by a single exponential decaying function. In his derivation, the cell repopulation was also modeled by a cell potential doubling time similar to that in Eq. (A4). A two-critical target model was used in modeling the repair of sublethal damage. In this model, a cell is considered to contain two critical targets susceptible to radiation damage. When only one of the critical targets is damaged by a radiation event, the damage is considered sublethal and is repairable. Cell inactivation occurs only when the damage to the other critical target occurs before the existing damage is fully repaired. It is assumed that the sublethal damage is repaired exponentially with time, i.e., if the sublethal damage was inflicted at time t_0, then the probability for it to persist to time t is given by $e^{-\mu(t-t_0)}$. The repair capability is modeled by the time constant μ. This model is fundamentally equivalent to the incomplete-repair model of Thames[67] for irradiations with constant dose rate. Dale obtained the following formula for the BED of permanent prostate implants:

$$\mathrm{BED} = D(T_{\mathrm{eff}})\mathrm{RE}(T_{\mathrm{eff}}) - \ln 2 \frac{T_{\mathrm{eff}}}{\alpha T_p}, \tag{A5a}$$

where

$$\mathrm{RE}(T_{\mathrm{eff}}) = 1 + \left(\frac{\beta}{\alpha}\right)\frac{\dot{D}_0}{(\mu-\lambda)} \times \frac{1}{1-e^{-\lambda T_{\mathrm{eff}}}} \times \left\{1 - e^{-2\lambda T_{\mathrm{eff}}} - \frac{2\lambda}{\mu+\lambda}(1-e^{-(\mu+\lambda)T_{\mathrm{eff}}})\right\}. \quad \text{(A5b)}$$

In Eq. (A5b), $\dot{D}_0$ is the initial dose rate, λ is the decay constant of the radionuclide, μ is the time constant for sublethal damage repair (inversely proportional to the repair half-time), T_{eff} is the effective treatment time for an implant, and $D(T_{\mathrm{eff}})$ is the total dose delivered by the implant within the time period of T_{eff}.

The existence of an effective treatment time arises from the two competing processes present in permanent implants, namely, the continuous cell repopulation and reduction in instantaneous dose rate. As the treatment time elapses, the rate of cell inactivation resulting from the instantaneous dose rate becomes exponentially smaller, while the rate of cell repopulation remains the same. The T_{eff} is defined as the time at which the rate of cell inactivation equals the rate of cell repopulation for any hypothetically remaining cell and is given by

$$T_{\mathrm{eff}} = T_{\mathrm{avg}} \ln\left[\alpha \cdot D \cdot \frac{T_p}{T_{1/2}}\right], \quad \text{(A6)}$$

where $T_{1/2}$ is the decay half-life of the radionuclide, $T_{\mathrm{avg}} = 1.44T_{1/2}$, and D is the total dose delivered during the full decay of the radionuclide. Beyond T_{eff}, a net cell kill is no longer attainable. While the definition of T_{eff} is physically intuitive, the need to use T_{eff} as the time point for BED calculation illustrates an inherent uncertainty in the application of this model to tumors that continuously repopulate during permanent implants. The BED value calculated at other time instances will be different from that calculated at T_{eff}. Even in relative comparisons of two implants, using BED calculated at T_{eff} versus using BED calculated at other time instances could lead to quantitatively different results. Recently, Zaider and Hanin[55] pointed out that the use of Eq. (A6) for proliferating tumors underestimates the isoeffective dose. For temporary implants with a source dwell time less than T_{eff}, the actual source dwell time should be used in Eq. (A5) for calculating the BED.

The BED derived by Dale is characterized by four parameters that take into account the effect of single-track lethality (α), intertrack quadratic interactions (β), as well as the first-order kinetics of sublethal damage repair (μ), and cell proliferation (T_p) in permanent prostate brachytherapy. It also takes into account the exponential decay of the instantaneous dose rates. The model shows that the effective cell kill depends not only on the delivered dose but also on the temporal patterns of the dose delivery in the presence of sublethal damage repair and cell repopulation. For implants with exponentially decaying radionuclides, the dose-delivery pattern is determined by the radioactive decay half-life, and the BED is a function of the radionuclides used. In general, the BED is greater if the total delivered dose is larger. For the same prescribed dose, the model indicates that the BED is always larger when the dose is delivered by radionuclides with shorter half-lives. The model has been used to compare different treatment techniques and other issues for which the absolute values of radiobiological parameters or model assumptions may not be critical. Note, however, that many radiobiological complexities are excluded by necessity, including nonexponential sublethal damage repair. In addition, as discussed earlier, concerns about the use of T_{eff} in BED calculations and its effect on isoeffect comparisons has been raised recently in literature.[55]

III. BED for inhomogeneous dose distributions in a prostate implant

The BED formulas discussed in Sec. VII have assumed that the dose-rate distribution is spatially uniform, which is not true in a real implant. The dose-rate distribution inside a prostate implant is highly nonuniform. The BED for such an implant can be calculated by partitioning the tumor volume into small subvolumes so that the dose-rate distribution in each subvolume can be considered uniform.[42,68] The BED_i for a subvolume i with initial dose rate of $\dot{D}_i(0)$ can then be calculated using the formulas discussed in Sec. VIII. Mathematically, the BED for a clinical prostate implant can be calculated as

$$\mathrm{BED} = -\frac{1}{\alpha}\ln\left(\sum_i \nu_i e^{-\alpha \cdot \mathrm{BED}_i}\right), \quad \text{(A7)}$$

where ν_i is the fractional volume receiving the dose rate $\dot{D}_i(0)$, with $\Sigma_i \nu_i = 1$. ν_i is directly related to the differential dose (or initial dose rate) histogram of a permanent implant. The BED calculated with Eq. (A7) takes into account not only the time-dependent dose-rate variation, cell repopulation, and sublethal damage repair during the dose delivery but also the spatial heterogeneity of the dose-rate distribution in permanent prostate brachytherapy. Ling *et al.*[42] used Eq. (A7) in studying the effects of dose heterogeneity in permanent interstitial implants.

The BED calculated according to Eq. (A7) is preferentially weighed by low-dose rates. To fully assess its significance, it may be beneficial to calculate the three-dimensional distribution of BED within a permanent prostate implant. The iso-BED distribution can be calculated by combining the BED formulas with the three-dimensional dose-rate distributions.[69,70] With the iso-BED distributions, one can evaluate the biological significance of "hot" or "cold" dose-rate regions based on underlying anatomy. Similar considerations have also been used to construct radiobiologically relevant dose-volume histograms in external-beam radiotherapy.[71–73] It should be pointed out that the calculation of iso-BED distribution with Eq. (A7) implicitly assumes that the tumor burden and their radiosensitivity is spatially uniform. Nonetheless, it would be straightforward to incorporate the spatial distribution of tumor burden and radiosensitivity into the calculation of BED or iso-BED distribution when such information is accurately known.

IV. EUD for inhomogeneous dose distributions in a prostate implant

Since the net cell survival produced by an implant of inhomogeneous dose distribution can be determined easily from Eqs. (A1) and (A7), one can also calculate an EUD, a concept introduced initially by Niemierko[49] for inhomogeneous distributions encountered in external-beam radiotherapy, for a prostate implant based on equal cell survival. The EUD for a permanent prostate implant can be obtained by equating the right-hand sides of Eq. (A5a) and Eq. (A7) and solving the resulting equation for EUD, i.e.,

$$\mathrm{EUD}\times \mathrm{RE}(\mathrm{EUD},T_{\mathrm{eff}})-\ln 2\frac{T_{\mathrm{eff}}}{\alpha T_p}=-\frac{1}{\alpha}\ln\left(\sum_i \nu_i e^{-\alpha\cdot \mathrm{BED}_i}\right). \tag{A8}$$

Note in Eq. (A8) that the $D(T_{\mathrm{eff}})$ in the right-hand side of Eq. (A5a) is now denoted as EUD. The equivalent uniform dose calculated in this fashion retains the temporal characteristics of dose delivery in permanent prostate brachytherapy.

Details of these calculations can be found in Sec. VIII.B.2 of the full TG-137 report available online.

[a]Electronic mail: ravinder.nath@yale.edu

[1]B. R. Thomadsen, K. Ayyanger, L. Anderson, G. Luxton, W. Hanson, and J. F. Wilson, in *Principles and Practice of Brachytherapy*, edited by S. Nag (Futura, Armonk, NY, 1997).
[2]W. L. Smith *et al.*, "Prostate volume contouring: A 3D analysis of segmentation using 3DTRUS, CT, and MR," Int. J. Radiat. Oncol., Biol., Phys. **67**, 1238–1247 (2007).
[3]C. Kirisits *et al.*, "Accuracy of volume and DVH parameters determined with different brachytherapy treatment planning systems," Radiother. Oncol. **84**, 290–297 (2007).
[4]F. A. Siebert *et al.*, "Phantom investigations on CT seed imaging for interstitial brachytherapy," Radiother. Oncol. **85**, 316–323 (2007).
[5]F. A. Siebert, P. Kohr, and G. Kovacs, "The design and testing of a solid phantom for the verification of a commercial 3D seed reconstruction algorithm," Radiother. Oncol. **74**, 169–175 (2005).
[6]K. R. Badiozamani *et al.*, "Anticipating prostatic volume changes due to prostate brachytherapy," Radiat. Oncol. Invest. **7**, 360–364 (1999).
[7]D. Taussky *et al.*, "Sequential evaluation of prostate edema after permanent seed prostate brachytherapy using CT-MRI fusion," Int. J. Radiat. Oncol., Biol., Phys. **62**, 974–980 (2005).
[8]F. M. Waterman *et al.*, "Edema associated with I-125 or Pd-103 prostate brachytherapy and its impact on post-implant dosimetry: An analysis based on serial CT acquisition," Int. J. Radiat. Oncol., Biol., Phys. **41**, 1069–1077 (1998).
[9]Y. Yamada *et al.*, "Impact of intraoperative edema during transperineal permanent prostate brachytherapy on computer-optimized and preimplant planning techniques," Am. J. Clin. Oncol. **26**, 130–135 (2003).
[10]F. M. Waterman and A. P. Dicker, "Impact of postimplant edema on V(100) and D(90) in prostate brachytherapy: Can implant quality be predicted on day 0?," Int. J. Radiat. Oncol., Biol., Phys. **53**, 610–621 (2002).
[11]L. Potters *et al.*, "A comprehensive and novel predictive modeling technique using detailed pathology factors in men with localized prostate carcinoma," Cancer **95**, 1451–1456 (2002).
[12]N. Yue *et al.*, "Optimum timing for image-based dose evaluation of 125I and 103PD prostate seed implants," Int. J. Radiat. Oncol., Biol., Phys. **45**, 1063–1072 (1999).
[13]Z. Chen *et al.*, "Dosimetric effects of edema in permanent prostate seed implants: A rigorous solution," Int. J. Radiat. Oncol., Biol., Phys. **47**, 1405–1419 (2000).
[14]N. N. Stone *et al.*, "Comparison of intraoperative dosimetric implant representation with postimplant dosimetry in patients receiving prostate brachytherapy," Brachytherapy **2**, 17–25 (2003).
[15]Z. Chen *et al.*, "Potential impact of prostate edema on the dosimetry of permanent seed implants using the new ^{131}Cs (model CS-1) seeds," Med. Phys. **33**, 968–975 (2006).
[16]R. G. Stock *et al.*, "A dose-response study for I-125 prostate implants," Int. J. Radiat. Oncol., Biol., Phys. **41**, 101–108 (1998).
[17]J. E. Sylvester, "The Seattle Prostate Institute approach to treatment planning for permanent implants," in *Basic and Advanced Techniques in Prostate Brachytherapy*, edited by A. P. Dicker, G. S. Merrick, F. M. Waterman, R. K. Valicenti, and L. G. Gomella (Taylor & Francis, London, 2005).
[18]K. Wallner, J. Roy, and L. Harrison, "Dosimetry guidelines to minimize urethral and rectal morbidity following transperineal I-125 prostate brachytherapy," Int. J. Radiat. Oncol., Biol., Phys. **32**, 465–471 (1995).
[19]C. Salembier *et al.*, "Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy," Radiother. Oncol. **83**, 3–10 (2007).
[20]J. F. Williamson *et al.*, "Guidance to users of Nycomed Amersham and North American Scientific, Inc., I-125 interstitial sources: Dosimetry and calibration changes: Recommendations of the American Association of Physicists in Medicine Radiation Therapy Committee Ad Hoc Subcommittee on low-energy seed dosimetry," Med. Phys. **26**, 570–573 (1999).
[21]J. F. Williamson *et al.*, "Recommendations of the American Association of Physicists in Medicine on ^{103}Pd interstitial source calibration and dosimetry: Implications for dose specification and prescription," Med. Phys. **27**, 634–642 (2000).
[22]B.R. Prestidge *et al.*, "Cesium-131 permanent prostate brachytherapy: An initial report," Int. J. Radiat. Oncol., Biol., Phys. **63**, S336–S337 (2005).
[23]N. Yue *et al.*, "Prescription dose in permanent (131)Cs seed prostate implants [Erratum appears in Med. Phys. **33**(7), 2655 (2006)]," Med. Phys. **32**, 2496–2502 (2005).
[24]J. Musmacher, R. Byrnes, K. Satchwill, and L. Rumpf, "Dosimetric computaion of cesium-131 and palladium-103 for permanent prostate brachytherapy," Med. Phys. **34**, 2440 (2007).
[25]W. S. Bice *et al.*, "Recommendations for permanent prostate brachytherapy with ^{131}Cs: a consensus report from the Cesium Advisory Group," Brachytherapy **7**, 290–296 (2008).
[26]R. A. Cormack *et al.*, "A clinical method for real-time dosimetric guidance of transperineal ^{125}I prostate implants using interventional magnetic resonance imaging," Int. J. Radiat. Oncol., Biol., Phys. **46**, 207–214 (2000).
[27]R. A. Cormack, C. M. Tempany, and A. V. D'Amico, "Optimizing target coverage by dosimetric feedback during prostate brachytherapy," Int. J. Radiat. Oncol., Biol., Phys. **48**, 1245–1249 (2000).
[28]J. F. Carrier *et al.*, "Postimplant dosimetry using a Monte Carlo dose calculation engine: A new clinical standard," Int. J. Radiat. Oncol., Biol., Phys. **68**, 1190–1198 (2007).
[29]G. K. Edmundson, D. Yan, and A. A. Martinez, "Intraoperative optimization of needle placement and dwell times for conformal prostate brachytherapy," Int. J. Radiat. Oncol., Biol., Phys. **33**, 1257–1263 (1995).
[30]J. Stromberg *et al.*, "Ultrasound-guided high dose rate conformal brachytherapy boost in prostate cancer: Treatment description and preliminary results of a phase I/II clinical trial," Int. J. Radiat. Oncol., Biol., Phys. **33**, 161–171 (1995).
[31]Y. Yu, T. Podder, Y. Zhang, W. S. Ng, V. Misic, J. Sherman, L. Fu, D. Fuller, E. Messing, D. Rubens, J. Strang, and R. Brasacchio, "Robot-assisted prostate brachytherapy," in *Medical Image Computing and Computer-Assisted Intervention—MICCAI 2006*, edited by R. Larsen, M. Nielsen, and J. Sporring (Springer, Heidelberg, 2006), Vol. 4190, pp. 41–49, Paper No. LNCS41900041.
[32]Z. Wei *et al.*, "Robot-assisted 3D-TRUS guided prostate brachytherapy: System integration and validation," Med. Phys. **31**, 539–548 (2004).
[33]G. Fichtinger *et al.*, "Robotically assisted prostate brachytherapy with transrectal ultrasound guidance—Phantom experiments," Brachytherapy **5**, 14–26 (2006).
[34]V. Misic, L. Fu, T. K. Podder, L. Liao, D. J. Rubens, R. Brasacchio, E. M. Messing, J. G. Strang, W. S. Ng, and Y. Yu, "Dynamic planning in single needle brachytherapy systems," Int. J. CARS **1**, 271–273 (2006).
[35]W. S. Bice, Jr., B. R. Prestidge, and M. F. Sarosdy, "Sector analysis of prostate implants," Med. Phys. **28**, 2561–2567 (2001).
[36]G. S. Merrick *et al.*, "Prostate cancer distribution in patients diagnosed by transperineal template-guided saturation biopsy," Eur. Urol. **52**, 715–723 (2007).
[37]A. S. Barnes *et al.*, "Magnetic resonance spectroscopy-guided transperineal prostate biopsy and brachytherapy for recurrent prostate cancer," Urology **66**, 1319 (2005).

[38]R. J. Ellis and D. A. Kaminsky, "Fused radioimmunoscintigraphy for treatment planning," Rev. Urol. **8**, S11–S19 (2006).
[39]J. F. Fowler, "The linear-quadratic formula and progress in fractionated radiotherapy," Br. J. Radiol. **62**, 679–694 (1989).
[40]R. G. Dale and B. Jones, "The clinical radiobiology of brachytherapy," Br. J. Radiol. **71**, 465–483 (1998).
[41]R. G. Dale, "The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy," Br. J. Radiol. **58**, 515–528 (1985).
[42]C. C. Ling *et al.*, "Quantifying the effect of dose inhomogeneity in brachytherapy: Application to permanent prostatic implant with ^{125}I seeds," Int. J. Radiat. Oncol., Biol., Phys. **28**, 971–978 (1994).
[43]C. C. Ling, "Permanent implants using Au-198, Pd-103 and I-125: Radiobiological considerations based on the linear quadratic model," Int. J. Radiat. Oncol., Biol., Phys. **23**, 81–87 (1992).
[44]G. R. Lazarescu and J. J. Battista, "Analysis of the radiobiology of ytterbium-169 and iodine-125 permanent brachytherapy implants," Phys. Med. Biol. **42**, 1727–1736 (1997).
[45]A. P. Dicker *et al.*, "Isotope selection for permanent prostate implants? An evaluation of ^{103}Pd versus ^{125}I based on radiobiological effectiveness and dosimetry," Semin Urol. Oncol. **18**, 152–159 (2000).
[46]C. I. Armpilia *et al.*, "The determination of radiobiologically optimized half-lives for radionuclides used in permanent brachytherapy implants," Int. J. Radiat. Oncol., Biol., Phys. **55**, 378–385 (2003).
[47]A. B. Jani *et al.*, "Biological effective dose for comparison and combination of external beam and low-dose rate interstitial brachytherapy prostate cancer treatment plans," Med. Dosim. **29**, 42–48 (2004).
[48]R. G. Stock *et al.*, "Biologically effective dose values for prostate brachytherapy: Effects on PSA failure and posttreatment biopsy results," Int. J. Radiat. Oncol., Biol., Phys. **64**, 527–533 (2006).
[49]A. Niemierko, "Reporting and analyzing dose distributions: A concept of equivalent uniform dose," Med. Phys. **24**, 103–110 (1997).
[50]X. A. Li *et al.*, "Dose escalation in permanent brachytherapy for prostate cancer: Dosimetric and biological considerations," Phys. Med. Biol. **48**, 2753–2765 (2003).
[51]A. Haworth *et al.*, "Assessment of I-125 prostate implants by tumor bioeffect," Int. J. Radiat. Oncol., Biol., Phys. **59**, 1405–1413 (2004).
[52]M. Zaider *et al.*, "Treatment planning for prostate implants using magnetic-resonance spectroscopy imaging," Int. J. Radiat. Oncol., Biol., Phys. **47**, 1085–1096 (2000).
[53]S. L. Tucker, H. D. Thames, and J. M. Taylor, "How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics? [see comment]," Radiat. Res. **124**, 273–282 (1990).
[54]M. Zaider and G. N. Minerbo, "Tumour control probability: A formulation applicable to any temporal protocol of dose delivery," Phys. Med. Biol. **45**, 279–293 (2000).
[55]M. Zaider and L. Hanin, "Biologically-equivalent dose and long-term survival time in radiation treatments," Phys. Med. Biol. **52**, 6355–6362 (2007).
[56]J. Z. Wang, M. Guerrero, and X. A. Li, "How low is the alpha/beta ratio for prostate cancer? [see comment]," Int. J. Radiat. Oncol., Biol., Phys. **55**, 194–203 (2003).
[57]J. Z. Wang *et al.*, "The low alpha/beta ratio for prostate cancer: What does the clinical outcome of HDR brachytherapy tell us?," Int. J. Radiat. Oncol., Biol., Phys. **57**, 1101–1108 (2003).
[58]J. Z. Wang *et al.*, "Effect of edema, relative biological effectiveness, and dose heterogeneity on prostate brachytherapy," Med. Phys. **33**, 1025–1032 (2006).
[59]J. F. Fowler *et al.*, "What hypofractionated protocols should be tested for prostate cancer?," Int. J. Radiat. Oncol., Biol., Phys. **56**, 1093–1104 (2003).
[60]O. Chibani and J. F. Williamson, "MCPI: A sub-minute Monte Carlo dose calculation engine for prostate implants," Med. Phys. **32**, 3688–3698 (2005).
[61]A. S. Meigooni and R. Nath, "Tissue inhomogeneity correction for brachytherapy sources in a heterogeneous phantom with cylindrical symmetry," Med. Phys. **19**, 401–407 (1992).
[62]J. J. DeMarco *et al.*, "CT-based dosimetry calculations for ^{125}I prostate implants," Int. J. Radiat. Oncol., Biol., Phys. **45**, 1347–1353 (1999).
[63]A. S. Meigooni, J. A. Meli, and R. Nath, "Interseed effects on dose for ^{125}I brachytherapy implants," Med. Phys. **19**, 385–390 (1992).
[64]G. S. Burns and D. E. Raeside, "The accuracy of single-seed dose superposition for I-125 implants," Med. Phys. **16**, 627–631 (1989).
[65]J. F. Carrier *et al.*, "Impact of interseed attenuation and tissue composition for permanent prostate implants," Med. Phys. **33**, 595–604 (2006).
[66]H. Afsharpour *et al.*, "A Monte Carlo study on the effect of seed design on the interseed attenuation in permanent prostate implants," Med. Phys. **35**, 3671–3681 (2008).
[67]H. D. Thames, "An 'incomplete-repair' model for survival after fractionated and continuous irradiations," Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med. **47**, 319–339 (1985).
[68]R. G. Dale *et al.*, "Calculation of integrated biological response in brachytherapy," Int. J. Radiat. Oncol., Biol., Phys. **38**, 633–642 (1997).
[69]S. P. Lee *et al.*, "Biologically effective dose distribution based on the linear quadratic model and its clinical relevance," Int. J. Radiat. Oncol., Biol., Phys. **33**, 375–389 (1995).
[70]Z. Chen and R. Nath, "Biologically effective dose (BED) for interstitial seed implants containing a mixture of radionuclides with different half-lives," Int. J. Radiat. Oncol., Biol., Phys. **55**, 825–834 (2003).
[71]T. E. Wheldon *et al.*, "The linear-quadratic transformation of dose-volume histograms in fractionated radiotherapy," Radiother. Oncol. **46**, 285–295 (1998).
[72]L. B. Marks *et al.*, "Incorporation of functional status into dose-volume analysis," Med. Phys. **26**, 196–199 (1999).
[73]Y. Lu, D. R. Spelbring, and G. T. Chen, "Functional dose-volume histograms for functionally heterogeneous normal organs," Phys. Med. Biol. **42**, 345–356 (1997).