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Special Article

Definition of medical event is to be based on the total source strength for evaluation of permanent prostate brachytherapy: A report from the American Society for Radiation Oncology

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Abstract

Purpose: The Nuclear Regulatory Commission deems it to be a medical event (ME) if the total dose delivered differs from the prescribed dose by 20% or more. A dose-based definition of ME is not appropriate for permanent prostate brachytherapy as it generates too many spurious MEs and thereby creates unnecessary apprehension in patients, and ties up regulatory bodies and the licensees in unnecessary and burdensome investigations. A more suitable definition of ME is required for permanent prostate brachytherapy.

Methods and Materials: The American Society for Radiation Oncology (ASTRO) formed a working group of experienced clinicians to review the literature, assess the validity of current regulations, and make specific recommendations about the definition of an ME in permanent prostate brachytherapy.

Results: The working group found that the current definition of ME in §35.3045 as "the total dose delivered differs from the prescribed dose by 20 percent or more" was not suitable for permanent

Conflicts of interest: Bruce R. Thomadsen, PhD, James S. Welsh, MD, Jeffrey F. Williamson, PhD, and Subir Nag, MD, have served on the Advisory Committee on the Medical use of Isotopes (ACMUI) of the Nuclear Regulatory Commission (NRC). Their opinions expressed here are in their private capacity as radiation oncologists and medical physicists and not as a representative of the NRC. While Mark J. Rivard, PhD, is a consultant to GE HealthCare, Inc., IsoRay Medical, Inc., Nucletron, B.V., Varian Medical Systems, Inc., and Xoft, Inc., he has not received any support directly related to this project. Jeffrey F. Williamson, PhD, is the principal investigator of a Varian and Philips research contract. Michael Hagan, MD has a research grant from Oncura Corp. James S. Welsh, MD, has received honorarium as a speaker from TomoTherapy, Inc. D. Jeffrey Demanes, MD, has not declared any conflict of interest.

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prostate brachytherapy since the prostate volume (and hence the resultant calculated prostate dose) is dependent on the timing of the imaging, the imaging modality used, the observer variability in prostate contouring, the planning margins used, inadequacies of brachytherapy treatment planning systems to calculate tissue doses, and seed migration within and outside the prostate. If a dose-based definition for permanent implants is applied strictly, many properly executed implants would be improperly classified as an ME leading to a detrimental effect on brachytherapy. The working group found that a source strength-based criterion, of >20% of source strength prescribed in the post-procedure written directive being implanted outside the planning target volume is more appropriate for defining ME in permanent prostate brachytherapy.

Conclusions: ASTRO recommends that the definition of ME for permanent prostate brachytherapy should not be dose based but should be based upon the source strength (air-kerma strength) administered.

Introduction

Brachytherapy in the United States is regulated by the Nuclear Regulatory Commission (NRC) under the Code of Federal Regulations (CFR) 10 Part 35. Under Part 35 section §35.3045 it is deemed to be a medical event (ME) (medical event was previously termed as "misadministration") if "the total dose delivered differs from the prescribed dose by 20 percent or more." Such a rule is not appropriate for permanent prostate brachytherapy since, during the several weeks time interval between the initial (preplan) volume study and the imaging performed for dosimetry, there are several changes that occur in the treatment volume (eg, the prostate gland) and the relative position of the radioactive sources within the treatment site which affect the final calculated dose. Further, the prostate volume and therefore the resultant calculated absorbed dose vary upon the imaging modality used, observer variability in prostate contouring, and variability in planning margins used among authorized users (AUs).

Due to the above factors, the final calculated dose may vary from the planned dose by >20% even if an implant is properly performed. If the NRC definition is rigidly applied, many properly executed implants will be deemed MEs, create unnecessary patient apprehension, and encumber regulatory bodies and the licensees with clinically irrelevant and costly investigations. Hence, a dose-based definition of ME is not suitable for permanent prostate brachytherapy. The American Society for Radiation Oncology (ASTRO) therefore formed a working group to offer recommendations regarding the appropriate definition of ME for permanent prostate brachytherapy.

Methods

ASTRO formed a working group of experts in brachytherapy to formulate recommendations about the appropriate definition of ME for permanent prostate brachytherapy. The working group members, listed in the acknowledgment section, are or have been leaders of professional radiation oncology and radiation physics organizations. They have collectively performed and evaluated tens of thousands of brachytherapy procedures and have published extensively on various aspects of brachytherapy. The working group reviewed the 2002 Code of Federal Regulations Part 35 sections on written directive (WD) in §35.40 and on ME in §35.3045 and identified sections of the rules that were not suitable for defining ME in permanent prostate implants. They formulated specific recommendations for defining ME for permanent prostate brachytherapy by a review of the pertinent literature and were guided by their clinical experience and consensus opinion. Selected members of the working group (the authors of this report) drafted the report. This document was then reviewed by the ASTRO prostate expert panel and posted on the ASTRO website to secure public comments. The document was then revised to reflect the consensus.

Results

The working group found that the current definition of ME in §35.3045 as the total dose delivered differs from the prescribed dose by 20% or more was not suitable for permanent prostate brachytherapy because the prostate volume (and hence the resultant calculated prostate absorbed dose) depends upon many factors including the following: (a) the timing of the imaging; (b) the imaging modality selected; (c) the observer variability in prostate contouring; and (d) the planning margins used. Additionally, the calculated dose could also vary due to seed migration within and outside the prostate. This variation in calculated dose exceeds 20% in prostate seed brachytherapy literature. Therefore, if the current dose-based ME definition was strictly applied, many properly executed implants would be improperly classified as an ME leading to a detrimental effect on brachytherapy. The working group recommends using a source strength-based rule. Source strength relates to the activity implanted. Activity, per se, poses a problem because, for the same activity within a source the attenuation of the source components produces different radiation fields for various source

models. ASTRO recommends a source strength-based criterion of >20% of source strength prescribed in the post-procedure written directive being implanted outside the planning target volume for defining ME in permanent prostate brachytherapy. The following sections detail the rationale for the working group's recommendation.

Prostate gland volume changes relative to time of implant

The shape and volume of the prostate gland can change secondary to the effects of androgen ablative therapy, postimplant edema, and variations in findings on different imaging modalities. The prostate volume determined on the initial volume study before the procedure and the prostate volume after the procedure used for dose calculation (also used to determine regulatory compliance) may be significantly different.[1,2] During the interval between planning volume study and the brachytherapy procedure, the prostate gland may shrink up to 33% when androgen ablative therapy is used.[3] During needle insertion, the prostate gland typically swells (ie, the prostate volume enlarges) from edema and hemorrhage due to needle and seed insertion, typically reaching a maximum volume within a few hours of procedure completion. The edema and hemorrhage gradually resolve over the next several weeks. The magnitude and time course of this volume change are highly variable from patient to patient and beyond the control of the AU. These changes can be as high as 50% in some cases.[1,2]

Institutions vary widely on timing of postimplant imaging. Some physicians obtain images for dosimetry on the day of the implant (while there is still significant edema) so they can evaluate the implant dosimetry promptly, while others wait about 4 weeks with iodine-125 (^{125}I) seed implants to allow resolution of the edema. Since the prostate volume may change markedly from the day of implant to day 30, the resultant calculated doses may vary in an individual patient by as much as 50% depending on when the imaging was performed.

The implications of these volume changes are twofold. First, to account for any volume changes occurring before and during the implant procedure ME must be based on the deviation from the WD completed after administration rather than the preimplant WD. Second, regulations for ME cannot be based upon comparisons of planned dose and calculated dose from postimplant images in permanent implants.

The prostate volume varies based upon the imaging modality used

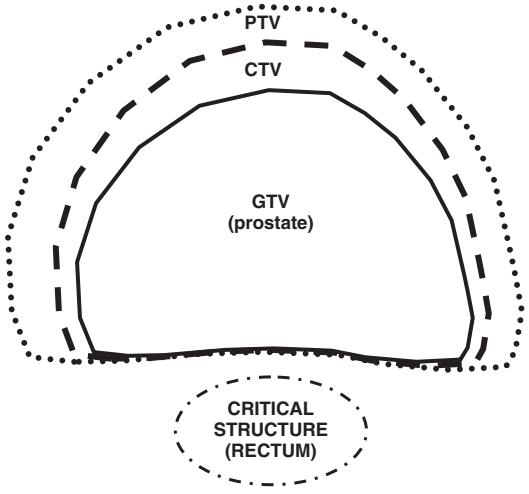
Different imaging modalities (eg, magnetic resonance imaging, computed tomography [CT], and ultrasound) estimate prostate volumes differently for the same patient.[4] For example, CT can overestimate the prostate volume by as much as 50% as compared with transrectal ultrasound.[5] If, as is usually the case, the preimplant volume study and the implant are performed using transrectal ultrasound images and the postimplant dosimetry is calculated using CT images, the volume differences will result in markedly different calculated doses. Such differences may be perfectly acceptable clinically but exceed the regulatory parameters if a dose-based criterion is used to define ME.

Observer variability in prostate contouring

In order to calculate dose, the prostate is outlined (contoured) on an image dataset. Different physicians contour the prostate differently due to imaging limitations and variability in image interpretation (acceptable variances in clinical judgment) that result from imaging artifacts from the seeds and indistinct prostate boundaries in postimplant CT images that are used for such dosimetry calculations. These factors can lead to large apparent differences in prostate volumes (interobserver variability) and thus the calculated doses in a given patient may vary considerably based upon interpretation alone and not actual dose differences.[6,7] In a study by Lee et al,[7] the mean prostate D_{90} (reported as percentage of the dose to 90% of the prostate) on the very same patients, varied from 75.1% to 102.6% ($P < .0001$) because 5 experienced reviewers interpreted the prostate volume differently during target contouring. Thus, if a dose-based criterion is used for a particular patient the implant could be classified as an ME by some observers and clinically suitable by others depending upon how the prostate was contoured, although the actual dose delivered to the prostate would be the same. There is even variability (albeit less) when the same individual physician contours a specific prostate image on different occasions (ie, intraobserver variability over time).

Variability in treatment planning margins used

An AU often treats a variable margin of normal tissues around the prostate gland to include possible microscopic spread. This volume is termed the clinical target volume (CTV). A margin is typically added around the prostate CTV to create a planning target volume within which the sources are distributed in order to ensure that the CTV is adequately treated (Figure 1). Physicians reasonably vary in how much margin they add around the prostate during the treatment planning process. Some physicians adjust the margin to account for possible edema and its resolution while others do not. This variation in the planning margins used can significantly affect the final calculated dose to the prostate and also explains why sources can justifiably be present outside the prostate gland.



GTV = gross tumor volume (usually the prostate).

CTV = clinical target volume which includes a variable margin of normal tissues. around the prostate gland to include possible microscopic spread.

PTV = planning target volume – includes a margin within which the sources are distributed in order to ensure that the CTV is adequately treated.

Figure 1 Expansion margins in prostate brachytherapy.

Seed migration within and outside the prostate

There are 2 types of seed migration in prostate brachytherapy procedures. (1) Some seeds could be deposited into the periprostatic blood vessels and then travel intravascularly to distant organs like the lung. This event is correctly recognized not to be ME by the NRC, which excludes sources that were implanted in the correct site but migrated outside the treatment site from ME definition. (2) There is a second method of seed migration which could trigger an ME if a rigid definition of ME is used. In this second method, some of the deposited seeds could migrate within and just outside the prostate during the radiation delivery. The effects of this second form of migration would lead to an alteration of the calculated prostate dose and thereby could trigger a spurious ME.[8]

Historical method of prescription for permanent brachytherapy

At its inception, the prescription of permanent prostate brachytherapy was defined in terms of apparent activity (in mCi) and has now been redefined in terms of source strength in air-kerma strength (U). For ^{125}I, the apparent activity (in mCi) to be implanted was initially given by the formula (5 × the average dimension of the tumor), which evolved into more complex nomograms with the activity based on the volume to be implanted for a desired peripheral dose. In the last 2 decades, due to the advent of CT scanning and 3-dimensional dosimetry, it has become possible to estimate the delivered dose. Several dosimetric parameters such as D_{100}, D_{90}, and D_{80} (ie, dose to 100%, 90%, and 80% of the prostate gland, respectively), and V_{100}, V_{150}, and V_{200} (ie, the percentage of prostate volume receiving 100%, 150%, and 200% of the prescribed dose, respectively) have been formulated to make clinical outcome comparisons.[1,9-11] These dosimetric parameters may be of prognostic significance but they were not designed for, nor are they suitable for, regulatory compliance.

Working group recommendation

Section 35.40 allows the WD to be prescribed in terms of the total dose or be prescribed in terms of the total source strength and exposure time. For permanent implants the "exposure time" is infinite, hence the WD would be the total source strength. As noted in sections 1 through 6 above, the total source strength implanted into the target volume is under control of the AU, but the subsequent prostate volume and the resultant dose to the prostate is not. The actual dose and the dosimetric parameters vary considerably depending upon when and how the images were obtained and how the prostate was contoured. Hence, a dose-based criterion for ME is not suitable for permanent prostate brachytherapy. On the other hand, a source strength-based criterion of >20% of source strength prescribed in the post-procedure written directive being implanted outside the planning target volume will correctly identify as ME cases in which a large number of sources have been improperly implanted outside the treatment site, but be less likely to generate spurious ME than a dose-based definition. Hence, ASTRO recommends using the implanted source strength-based metric to define ME in permanent prostate brachytherapy.

The working group recognized one scenario where an implanted source strength metric does not adequately identify an ME. It is when all or most of the sources are erroneously implanted within a small region of the target volume, leaving a substantial portion of the treatment site uncovered. Under this circumstance some of the target will be overdosed and other areas under dosed. This theoretical possibility is rarely observed in clinical practice. However, to address this scenario, ASTRO recommends that the AU be required to affirm in writing on the WD, after the implant is completed, that the distribution of the sources within the treatment site was as intended per the WD.

Illustrative case examples

The following diagrammatic representation (Figure 2) illustrates volumetric and dose changes that occur after prostate brachytherapy that may lead to an inappropriate classification as an ME. The preimplant WD for a patient was for 38 U (or 30 mCi apparent activity) in total, to achieve a goal of 144 Gy to a prostate volume of 32 cm^3.

Figure 2 Apparent under dose due to volume change which should not be categorized as a medical event.

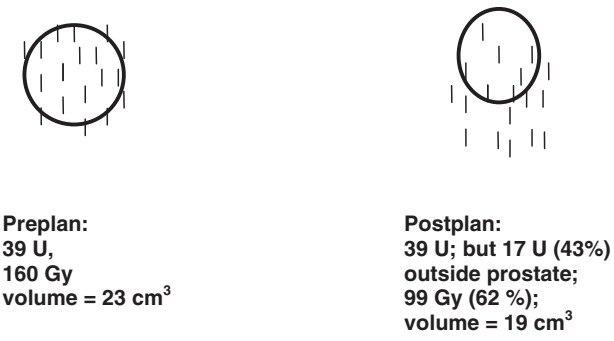


Figure 3 Under dose and medical event due to incorrect seed placement.

The seeds were implanted according to the treatment plan. The postimplant CT-based dosimetry, however, revealed D_{90} dose of 89 Gy (62 % of the original planned dose) because the prostate volume had swelled to 63 cm^3 at the time of the CT evaluation. The patient's disease was well controlled with no untoward effects. This implant would be deemed an ME if a dose-based rule is used, but it is correctly categorized not to be an ME if implanted source strength-based metric is used. Under the dose-based rule, the AU would have had to notify the patient that an ME had occurred, potentially causing unnecessary apprehension and distress to the patient who may have taken additional unnecessary treatments, which would have been poor clinical medical practice as well as poor regulatory policy. Note that if the CT scan had been taken at a different time interval when the edema had resolved and the prostate volume had shrunk close to its original volume, the resultant dose would have more closely approximated that in the WD. Using an implanted source strength-based metric to determine regulatory compliance would have noted that all of the sources were located within the treatment site regardless of the prostate volume change and therefore would not have classified it as an ME.

The above example contrasts with another case where the sources were improperly implanted with the seeds being displaced relative to the treatment site (Figure 3). The WD was for 39 U (or 31 mCi), 160 Gy for a prostate volume of 23 cm^3. The postimplant CT scan showed that the D_{90} was 99 Gy (62 %) for a prostate volume of 19 cm^3 but that 17 U (13 mCi) (43%) of implanted source strength was outside the treatment site. This error in the implant process resulted in a dose lower than the goal, which is correctly classified as an ME using the implanted source strength-based criteria.

Discussion

ASTRO is very much concerned that if the current dose-based definition for an ME is strictly applied for permanent seed brachytherapy, many properly executed medically acceptable implants will erroneously be labeled as MEs. It is difficult to accurately predict exactly how many implants in this country will be mislabeled as ME using the dose-based rules. However, if all the factors noted here are added it is estimated that at least 10%-25% of all permanent prostate seed implants done in the United States (ie, thousands of implants per year) could be considered as MEs, depending on how strictly the rules are applied and interpreted and how extensively a brachytherapy center is audited. Such a situation would be harmful to the public welfare as it will create undue apprehension in patients and the general public and likely occupy the NRC, state regulatory bodies, and the licensees in thousands of man-hours of unnecessary and clinically irrelevant costly investigations.

This outcome was unfortunately demonstrated in a recent Veterans Affairs Hospital (VAH) audit in which an unacceptable number of permanent prostate implant brachytherapy (97 out of 116 prostate cancer treatment procedures) were deemed as MEs using the existing dose-based ME criterion.[12] However, on reanalysis, 80 of these 97 were actually not considered MEs using an implanted source strength-based metric recommended by the "VAH blue ribbon panel" or the Advisory Committee for the Medical Use of Isotopes and the scientific organizations including ASTRO because many of these apparent MEs were due to prostate volume changes.[12] It should be noted that the implanted source strength-based ME criteria would still correctly identify the 17 medically unacceptable implants as MEs.

Another concern of ASTRO is that there is the very real risk that, as a result of these inappropriate rules, some practitioners will abandon permanent seed brachytherapy and thus access to this effective treatment modality could be impaired. We urge the NRC to heed the ASTRO recommendations to achieve an optimal balance between high sensitivity and high specificity in determining MEs for public safety while maintaining patient access and good clinical outcomes in permanent prostate brachytherapy.

Conclusions

ASTRO recommends that the definition of ME for permanent prostate brachytherapy should be based on the implanted source strength (>20% of source strength prescribed in the post-procedure written directive being implanted outside the planning target volume) and not be dose based. If a dose-based definition for permanent prostate implants is applied strictly many medically acceptable implants would be inappropriately classified as an ME, and rather than achieving the intended goal of patient safety there will be a detrimental effect on brachytherapy.

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