Advisory Committee on the Medical Uses of Isotopes (ACMUI)
Permanent Implant Brachytherapy Interim Report
October 20, 2010

Note: The ACMUI unanimously voted to approve this report at the October 20, 2010 meeting with the caveat that this is an interim report that may be revised in the future to consider additional input such as that received from stakeholders at public workshops.

Permanent Implant Brachytherapy Subcommittee Members

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Introduction

At the ACMUI meeting on October 27, 2008, the ACMUI and NRC staff discussed the proposed rule on medical use of byproduct material for permanent brachytherapy procedures ("permanent implants"). Several suggestions made at that meeting were incorporated into a formal Subcommittee report. On November 5, 2008 the formal report (*Advisory Committee on the Medical Uses of Isotopes (ACMUI) comments on the Proposed Rule for Medical Use of Byproduct Material—Amendments/Medical Event Definitions (RIN 3150-AI26, NRC-2008-0071)*) of the ACMUI Permanent Implant Brachytherapy Rulemaking Subcommittee was made available. (Report available on NRC's ACMUI web page at: http://www.nrc.gov/about-nrc/regulatory/advisory/acmui.html)

Since the time of the November 5, 2008 report, NRC has made extensive review of medical events involving permanent implant brachytherapy at the Department of Veterans Affairs (DVA) hospitals. As a result, NRC decided it was necessary to re-evaluate the proposed rules. This led NRC Staff to issue the following charge to the ACMUI permanent brachytherapy subcommittee:

Charge: The subcommittee should draft a report to provide recommendations on regulatory changes or improvements to the NRC's processes for permanent implant brachytherapy programs, as an outgrowth of the investigation of the Department of Veterans Affairs medical events.

In the interim, a re-proposed rule based partly on analysis of the medical events involving the VA was submitted for the Commission to consider. Thus, this Subcommittee Report addresses not only the above charge but also various aspects of the re-proposed rule.

Subcommittee Recommendations

The definition of a permanent implant brachytherapy medical event should be based on the following concepts:

I. A medical event ideally should be **of true medical significance** to a patient.

If this requirement is not fundamental, there is the risk of being overly sensitive and designating as "Medical Events" many cases that are of no potential harm to a patient and thereby inundating the regulatory and health care systems with many unnecessary investigations. The NRC definition of a "medical event" for permanent implant brachytherapy should be based on medical actions that could either cause harm to the patient, result in grossly inadequate treatment or identify patterns or trends that could lead to patient harm or inadequate treatment.

II. This concept should be balanced by the concept that: **The definition should be sensitive enough to detect any implant that is truly of potential harm to a patient.**

Furthermore, "harm" to a patient can be of two forms:

1.) Harm due to overdosing of sensitive normal structures and tissues
2.) Harm due to under-dosing the cancer and not curing the patient

III. Procedures with expected large changes in the source positions, such as permanent intra-operative lung implants, should be considered separately form more stable procedures, such as prostate implants. An appropriate Medical Event definition must balance the factors discussed above. This is a difficult task and could be even more difficult if an attempt is made at encompassing ALL forms of permanent implant brachytherapy under one set of Medical Event criteria. Therefore, the Subcommittee recommends that unless an activity-based (as opposed to dose-based) Medical Event set of criteria is adopted, consideration be given to separation of permanent brachytherapy procedures into various categories, e.g. permanent implant brachytherapy procedures which result in significant rearrangement of implant location during completion of the surgical implant procedure (such as operative lung implants) and those procedures that do not generally experience this phenomenon (such as prostate implants). The Subcommittee suggests that the former implant procedures be covered under separate categories within 10 CFR 35.400 or perhaps 10 CFR 35.1000 for the present.

IV. The Subcommittee strongly recommends that NRC seek specific help from stakeholders, particularly the medical community with expertise in permanent implant brachytherapy to discuss the definition of Medical Event for permanent implants, due to the complex nature of the issues.

V. The event metric should be source-strength based as opposed to dose based. The Subcommittee has focused on its primary charge above but is also aware of the recently re-proposed rule and has devoted considerable deliberation to this closely related subject. The Subcommittee is aware of certain circumstances in which the original

recommendations of ACMUI may be inadequate. Previously, the ACMUI was in favor of abandoning a dose-based metric in favor of an exclusively source-strength-based definition. The Subcommittee remains in favor of not using a dose-based metric for defining medical events. However, the Subcommittee is aware of certain clinical scenarios in which the ACMUI-proposed source-strength-based definition may fall short. For instance, the extremely unusual and unlikely situation in which all seeds are placed within the prostate but not distributed in the intended fashion. If they are all clumped into one location, this would not be a Medical Event under the source-strength-based proposed definitions. Consideration of this particular situation has caused the Subcommittee to reconsider its initial position on fully endorsing and advocating the previous activity-based definition.

V. If any dose-based criteria are to be applied, these criteria must be able to account for:

1.) True anatomic prostate volume or shape changes during and after the implant procedure,
2.) Differences in prostate volumes identified on CT vs. ultrasound (or any other modality),
3.) Inherent inter- and intra-observer differences in prostate contours (and thus volume estimates, which go into dose calculations), and
4.) Volume estimate uncertainties due to artifacts from the seeds and the indistinct prostate boundaries seen on post-implant CT images.

We recommend that if an apparent medical event were found to be due to anatomic prostate volume changes (item 1. above) after the administration, it would not be deemed a Medical Event, and that such cases be addressed in the fashion of other ***patient-related or patient-specific factors*** such as a patient removing a temporary implant, migration of properly implanted radioactive seeds, or incompletion of a Y-90 administration because of stasis.

Additionally, it should be kept in mind that brachytherapy is an art as well as a science and on occasion, skilled, experienced practitioners may intentionally "dose-intensify" certain regions within a target. Conversely, practitioners my elect to "dose de-escalate" in areas such as the urethra in a patient who has had a TURP (transurethral resection of the prostate) for example. Such aspects of the art and science of brachytherapy must be accommodated in any dose-based definitions of Medical Events and further strengthen the argument in favor of exclusively activity-based Medical Event definitions.

Discussion

In general, the Subcommittee finds that much of the intent of the Permanent Implant Brachytherapy Rulemaking Subcommittee Report of November 5, 2008 remains valid. The 97 medical events in 2008-09 within the Department of Veterans Affairs and the subsequent investigation of those medical events have not changed the

general recommendations of the ACMUI Permanent Implant Brachytherapy Rulemaking Subcommittee. Some relevant points include:

1.) Part § 35.3045(a)(3) reads, "A dose to the skin or an organ or tissue other than the treatment site that exceeds by 0.5 Sv (50 rem) to an organ or tissue and 50 percent or more of the dose expected from the administration defined in the written directive (excluding, for permanent implants, seeds that were implanted in the correct site but migrated outside the treatment site." In otherwise normal cases, this 0.5 Sv is a ***very*** small amount compared to therapeutic doses prescribed in most of these permanent brachytherapy cases (amounting typically to 0.35%). Also, a 50% overdose (as described in §35.3045(a)(3) could be medically inconsequential ***if the original expected dose to that normal tissue was very low*** (for example, the predicted skin dose in most permanent brachytherapy procedures or the penile bulb dose in prostate brachytherapy). With the very high gradients in the dose distributions and the inverse square law, very small shifts in a.) the source distribution b.) the target organ or c.) the normal tissues in question can cause much larger changes than 0.5 Sv or 50% of the expected dose with no consequences to the patient and constituting a perfectly normal and appropriate implant. A typical prostate implant may give 6 Gy to the skin 5 cm anterior to the prostate. If at the time of CT the prostate falls only 4 cm form the skin, not an uncommon occurrence, the dose to the skin would be twice that expected. Thus, if this criterion is applied strictly, some and perhaps many properly executed, medically acceptable implants could be inappropriately categorized as medical events. This underscores the concept that ideally Medical events should be of potential medical significance (or perhaps should identify trends that could lead to consequences of medical significance if not identified and acted upon). The 0.5 Sv threshold/20% definition of "Medical Event" is problematic when one considers the variability and inherent uncertainty in current medical practice, with dose uncertainties as high as 50% possible and medically acceptable. The inherently high level of uncertainty for many brachytherapy procedures *in absorbed dose estimation* is due to the variability of the tumor border, which is dependent on the imaging modality and imaging technique, normal movement of organs in the body, and significant volumetric changes associated with the surgical procedure itself resulting in inflammation and subsequent biological response.

Implanted amounts of radioactivity are not fully equivalent to absorbed dose and an appreciation that the spatial rearrangement of the same constant amount of activity can result in very different values of radiation dose. In current medical practice, the uncertainty in defining treatment volumes due to different imaging modalities and procedures and temporal variations due to the effects of the invasive procedures (e.g. edema) makes the 20% Medical Event criteria unrealistic.

The Subcommittee suggests defining specific volumes or areas of organs, tissues and skin if §35.3045(a)(3) is to remain. The Subcommittee suggests revision of §35.3045(a)(3) to adjust the nominal 0.5 Sv dose and the 50 percent figure to more appropriate figures and/or to specify an area of maximally irradiated skin and volume of maximally irradiated organ or tissues (e.g. 30 cm^2 of maximally irradiated skin or 5

cm^3 of maximally irradiated organs or tissues, based on Perera F, Chisela F, Stitt L, et al, TLD skin dose measurements and acute and late effects after lumpectomy and high-dose-rate brachytherapy only for early breast cancer. Int J Radiat Oncol Biol Phys. 62,1283-90; 2005 and S. L. Schoeppel, M. L. LaVigne, M. K. Martel *et al.*, "Three-dimensional treatment planning of intracavitary gynecologic implants: analysis of ten cases and implications for dose specification," Int J Radiat Oncol Biol Phys **28** (1), 277-83 (1994).).

The Subcommittee maintains that the units in the language above remain inconsistent and confusing in that absorbed dose (Gy or rads) and equivalent dose (Sv or rem) are used almost interchangeably. It is suggested that the final rule use appropriate units in a consistent manner.

2.) In the previous Subcommittee report, the ACMUI recommended that section § 35.3045(a)(2) (ii) be modified to "The total source strength implanted outside the treatment site (including the gross tumor, the clinical target volume plus a variable planning margin as defined by the AU) exceeding 20 percent of the total source strength documented in the written directive". This would take into account source migrations, seeds that become dislodged and seeds suctioned out of position but would still hold accountable cases in which the target organ was grossly misidentified and the wrong area was implanted.

The Subcommittee is aware of the preference for regulatory language that will broadly encompass all organs/situations rather than design regulations for each organ/situation. **However, it would be prudent to devise separate categories for: 1) permanent implant brachytherapy procedures that result in significant rearrangement of implant location during completion of the surgical implant procedure, e.g., mesh lung implants and 2) those procedures that do not generally experience this phenomenon, such as prostate or breast implants.** This would take into account the vast differences in sophistication and technology for pre-implantation treatment planning and post-implant dose distribution assessment between the two categories. Such separate classification could hopefully obviate the unnecessary assignment of the title of medical event to numerous medically acceptable non-prostate implants because of modifications to source geometries with the closing of surgery. The question of where to put such procedures in which implant relocation does occur was the subject of discussion within the Subcommittee with some favoring placement into 10CFR 35.1000 and others suggesting a revision within 10CFR 35.400.

3.) The Subcommittee felt that the old definition of "treatment site" (described in §35.2 as "the anatomical description of the tissue intended to receive a radiation dose, as described in a written directive") could lead to some uncertainty regarding the exact volume to which "treatment site" refers in §35.3045(a)(2)(ii). The Subcommittee recommends refinement of the previously ambiguous term "treatment site" to encompass the more rigorously defined concepts of gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) (*ICRU Report 62: Prescribing, Recording, and Reporting Photon Beam Therapy. Bethesda, MD:*

International Commission on Radiation Units and Measurements (ICRU), 1999). **The Subcommittee recommends that any revised rule and all subsequent matters dealing with this subject adopt the currently accepted nomenclature**. If a source-strength-based criterion is used, the basis for defining a medical event should be of the form of 20% of the source strength fall outside of the *planning target volume*, whereas a dose-based criterion should relate to the *clinical target volume*, both according to conventional clinical practice.

4.) The Subcommittee is in agreement that post-implant dosimetry is important and should be required. There was some discussion about the proposed requirement of licensees assessing the dose within 60 days from when the patient leaves the post-treatment recovery area. While imposing a timeline for such dosimetric evaluation may be challenging or difficult for some licensees, it is acknowledged that NRC desires some defined timeline for regulatory purposes. The 60-day timeline is acceptable as it is in alignment with recommendations of national organizations and guidelines. Situations in which a patient refuses or doesn't show up within the defined time-frame should be considered patient related factors and excluded from classification as Medical Events.

There was some discussion within the Subcommittee regarding the idea of using this post-implant dosimetry rule for regulatory purposes. Not all were in agreement that this requirement is appropriate for regulatory purposes (i.e. that if a licensee does not perform post-implant dosimetry within 60 days it would be a Medical Event). The decision of when to image and which modality to use for such imaging may be a medical decision. The main point is that after the treatment, there should be some imaging-based assessment with which dose can be re-estimated. Current practice varies enough that an NRC imposed regulatory requirement specifying the imaging modality could impede the development of good practice.

5.) ***Devising a truly acceptable, universally appropriate dose-based criterion for medical events remains challenging***. One challenge is the potential for difference in the prostate anatomy between the pre-procedure images and those performed afterwards that will affect the *calculated* total dose.

Prostate volume can be affected by:

1.) Anatomic changes such as edema or atrophy
2.) Contouring differences due to:
    a. different modalities (e.g CT vs ultrasound)
    b. inter- and intra-user contouring differences,
    c. artifacts introduced by the metallic seeds on CT, and
    d. Organ motion, which can be several centimeters, between the ultrasound and the CT.

Based on factor 1.) above, anatomic changes, depending on exactly when in the edema-resolution time course the post-implant dosimetric analysis is performed, the calculation of total dose can vary, although in general, the variations seem to fall in the range of less than 10% (AAPM recommendations on dose prescription and reporting methods for permanent interstitial brachytherapy for prostate cancer: report of Task

Group 137. Nath R, Bice WS, Butler WM, Chen Z, Meigooni AS, Narayana V, Rivard MJ, Yu Y; American Association of Physicists in Medicine. Med Phys. 2009 Nov;36(11):5310-22). Therefore, the Subcommittee continues to feel that dose-based assessments are not be ideal for regulatory purposes.

A dose-based definition must be capable of addressing all of the factors above that can affect prostate volume and calculated absorbed dose. To design a truly appropriate a dose-based criterion, it may be reasonable to introduce the concept of normalization to V_{init}, the initial pre-implant volume, so that any subsequent calculations of total dose afterwards are related back to this volume that the Authorized User based his/her initial dose prescription on. Thus, if in a prostate brachytherapy procedure, the prostate volume on which planned dose calculations are made is V_{init} but the post-implant dosimetry is done during the edematous period and the measured volume is 140% V_{init}, any deviations from the written directive prescribed dose due to this volume-related dose discrepancy should not be considered a Medical Event. The same concept would hold should the prostate shrink considerably following the implant due to the actions of hormonal therapy. In addition to addressing the concern about anatomic volume changes that affect dose calculations, the concept of normalizing back to V(init) also addresses the problems posed by the non-anatomic, contouring-related volume estimations. Any dose-based criteria for Medical Events must refer back to V_{init}, not the volume measured during the post-implant dosimetry procedure if there is a volume change. It is noted that normalization to V_{init} will eliminate categorization of many perfectly acceptable implants as Medical Events, but would not preclude identification of truly sub-standard implants irrespective of edema, atrophy or contouring discrepancies. In other words, a volume change should not be the basis for a Medical Event, but conversely just because a volume change occurred does not exclude the possibility of a Medical Event.

In general, alterations of a final brachytherapy dose due to "patient factors" such as a patient removing a temporary implant, migration of properly implanted radioactive seeds, or incompletion of a Y-90 administration because of stasis are not considered Medical Events. ***It is highly recommended that prostate volume changes due to edema, hematoma, hormone therapy-induced shrinkage, etc. also be considered "patient factors." Thus, item 1.) above, anatomic changes that cause alterations in volume that affect dose calculations should not be cause for the label of Medical Event***.

Additionally, brachytherapy dose is not homogenous. Authorized User brachytherapists often intentionally intensify dose (to perhaps 125-150% of the prescribed dose) to the high-risk areas of the prostate (e.g. the peripheral lobe where many tumors are located). In the opinion of many experts, the reason why brachytherapy is so effective is precisely because of this much higher dose to the tumor areas than stated in the prescription dose. This reality creates an intrinsic challenge to the use of dose-based criteria for regulatory purposes. The concept of intentional underdosing to certain areas within the clinical target volume (CTV) also poses a challenge to most dose-based criteria including those previously proposed by NRC.

The Subcommittee has decided to not put forth a proposition explicitly in writing at this time. But if requested the Subcommittee would be pleased to engage in further discussion with NRC staff on this complicated, important and sensitive matter in a highly efficient manner to help develop the regulatory wording.

Final Comments

Medical events are defined by the specific situations that constitute medical events. NRC's Policy Statement on Medical Uses (August 2000) states, "NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's directions." Therefore, it is important that the situations chosen to define a medical event for permanent implant brachytherapy be justified as having the potential of causing patient harm. In order to determine whether the use of the permanent implant is in accordance with the physician's directions, the requirements need to be understandable and unambiguously measurable for proper implementation and inspection and compatible with good medical practice.

Permanent implant brachytherapy is an effective, safe and convenient medical procedure that addresses a potentially lethal disease, cancer. Compared to other potentially cancer-curing treatment such as surgery and chemotherapy, permanent implant brachytherapy maintains a very safe overall clinical profile. Because of its safety, effectiveness and convenience, permanent implant brachytherapy is often the preferred first choice therapy. NRC should remain aware that compared to other modalities such as surgery and chemotherapy, permanent implant brachytherapy maintains its standing as a low-risk yet highly effective treatment. It would defeat our purpose if through overly restrictive regulations this treatment alternative were to fall out of fashion and become unavailable to those who could benefit. In the estimation of some, strict enforcement of the event rule could lead to many thousands of perfectly acceptable permanent brachytherapy cases (in prostate alone) being considered Medical Events. This would have obvious consequences on the practice and future availability of this proven effective medical option.

The Subcommittee recommends that the Subcommittee and all of ACMUI review any changes made to the rule before the Commission approves it for publication. It is also strongly recommended that NRC seek specific input from the medical community with expertise in permanent implant brachytherapy.

Finally, this Subcommittee has crafted what it believes is an important first step towards an understandable, unambiguously measurable and carefully considered solution for a dose-based criterion. The Subcommittee has decided to not put this proposition explicitly in proposed regulatory language within this report, but if requested, would be pleased to engage in further discussion on this complicated, important and sensitive matter in a highly efficient manner.

Addendum

This subject is presently hotly debated matter not just within the Subcommittee but in the radiation oncology community as a whole. Several points in the above report were not unanimously favored. Examples include:

The point about an exclusively activity-based metric rather than adding or switching to dose-based criteria was controversial. Three members were opposed to any dose-based criteria for the purposes of a medical event definition.

Two members felt strongly that this Subcommittee report should include a specific recommendation with regards to a dose-based metric. Three were opposed to dose-based criteria and did not wish to spell out any dose-based recommendations for fear that these would then be implemented when the preference was to steer clear of dose-based criteria altogether.

One member was opposed to the statement that brachytherapy is an "art" as well as science. Others were not opposed to such labeling. Three members felt that IF a dose-based definition were implemented, it would be more critical to emphasize this point about the art of medicine. Another member mentioned that this IS an art and therefore it will always be challenging for NRC to not encroach upon the practice of medicine in permanent implant brachytherapy. This difficulty in avoiding such encroachment will be compounded by attempts towards dose-based criteria.

One member was opposed to the concept of separating prostate brachytherapy (and other permanent brachytherapy procedures that do not typically experience significant rearrangement of seed location during completion of the procedure) from other permanent implant brachytherapy procedures that do result in significant rearrangement of implant location during completion of the surgical implant procedure, such as mesh lung implants.

One member was opposed to the requirement of post-implant dosimetry as a basis for medical events. Two others were not opposed to the requirement of post-implant dosimetry but were opposed to the idea of placing a 60-day limit for performing this.

Because three members were opposed to any dose-based criteria, (two adamant, the other not adamant), all matters related to dose-based criteria (such as including a specific recommendation) were controversial and one member suggested not including any discussion of the concept at all in this report.