Advisory Committee on the Medical Use of Isotopes (ACMUI)
Permanent Implant Brachytherapy Final Report
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Permanent Implant Brachytherapy Subcommittee Members

Susan Langhorst, Ph.D.
John Suh, M.D.
Bruce Thomadsen, Ph.D.
James Welsh, M.D., Chairman

Recommendations

A. Proposed Definition for Medical Event for Macroscopic Permanent Implants

1. For the target,

a. For the source locations (not resulting from patient-related causes such as edema or source migration after placement)

(i) 20% or more of the sources fall outside of the intended locations (planning target volume, PTV);

OR

(ii) Less than 5% of the sources occupy any octant of the PTV, ***except***

(a) by design for preservation of normal tissue; or

(b) intentional dose escalation to a particular region; or

(c) cases in which patient anatomy or technical limitations preclude physically reaching certain areas,

as specified in the Written Directive;

AND

b. Calculated dose to 90% of the clinical target volume (CTV) is less than 60% of the dose prescribed to the CTV (D_{90}<60%) within a timeframe to be determined by the Authorized User consistent with prevailing medical practice but not to exceed 60 days unless accompanied by written justification.

OR

2. For normal-tissue structures,

a. For neighboring structures (such as the bladder or rectum in prostate implants as an example), the dose to at least 5 cm^3 (contiguously) exceeds 150% of the dose prescribed to the CTV or PTV;

OR

b. For intra-target structures (such as the urethra in prostate implants as an example), the dose to at least 5 cm^3 (contiguously) exceeds 150% of *that*

structure's expected dose based on the approved pre-implant, dose distribution.

OR

3. A treatment is executed
- **a.** Using the wrong radionuclide;
- **b.** Using the wrong activity or source strength ($^{+}/_{-}$ 20%) as specified in the Written Directive
- **c.** Delivered to the wrong patient;
- **d.** Delivered directly to the wrong site or body part;
- **e.** Delivered using the wrong modality or
- **f.** Using leaking sources,

with the exceptions of seed migration, edema and other patient-related factors or source displacement following placement, as long as the criteria in 1a(i) is not violated.

B. Written Directive Completion

After implantation but before the patient is released from the Authorized User's control, the Authorized User shall complete the Written Directive to include the radionuclide, treatment site, number of sources, and the total source strength permanently implanted in accordance with 10 CFR 35.40(b)(6). Unusual aspects of the procedure, including patient-related limitations should be documented in this Written Directive completion. The permanent implant procedure shall be considered complete once the patient is released from the Authorized User's control.

Terminology

Gross Tumor Volume, GTV – The volume of the tumor proper as detected on imaging, visual observation or manual palpation on physical examination.

Clinical Target Volume, CTV – The volume containing the gross tumor and a margin that may contain malignant cells from the tumor. In the case of prostate implants, this usually is the whole prostate but can be more if there is "extra-capsular extension" of disease.

Planning Target Volume, PTV – The volume within which the sources are placed to deliver the prescribed dose to the CTV. This would include the CTV plus any additional margin used to assure adequate coverage.

D_{90} – The minimum dose to 90% of the CTV

Discussion

The ACMUI has previously issued two reports providing recommendations on the definition of Medical Event for permanent implant brachytherapy. In the 2008 report[1], ACMUI provided comments and recommendations on the proposed rule[2] to redefine Medical Event for permanent implants. The ACMUI issued an interim report[3] in 2010 at the NRC's charge to provide recommendations on regulatory changes or improvements to the NRC's processes for permanent implant brachytherapy programs. ACMUI's interim recommendations reiterated the principle that "a Medical Event should be potentially of true medical significance to a patient." In the time since the 2008 rulemaking[2], NRC and the medical community have discussed[4] possible Medical Event definitions that would identify those permanent implants (and ideally only those implants), that fall below clinically acceptable tolerances. This current ACMUI report proposes a definition that would capture appropriate Medical Events, utilizing metrics consistent with information currently required on the Written Directive and using standard medical guidelines for permanent implant brachytherapy. This proposed definition would identify cases where less-than-desirable dosimetry results from poor source distribution. Unlike previous definitions, dose changes due to edema or other patient-related factors would not trigger a Medical Event.

Because the vast majority of permanent implants are performed to treat prostate cancer, examples and guidance for these recommendations have drawn heavily on that procedure. However, the proposed definition (and everything else in this Subcommittee report) is intended to apply generally to all forms of permanent implants.

The Medical Event definition proposed in this report would catch an event where all the sources are bunched together. Using a template that limits source placement, the requirement of 5% of the sources occupy each octant (except by plan) is generally

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[1] Advisory Committee on the Medical Use of Isotopes (ACMUI) comments on the Proposed Rule for Medical Use of Byproduct Material – Amendment/Medical Event Definitions (RIN 3150-AI26, NRC-2008-0071-0058, November 5, 2008; http://pbadupws.nrc.gov/docs/ML0922/ML092220766.pdf).

[2] 73 FR 45635, Proposed Rule for Medical Use of Byproduct Material – Amendment/Medical Event Definitions (RIN 3150-AI26, NRC-2008-0071, August 6, 2008; http://edocket.access.gpo.gov/2008/pdf/E8-18014.pdf).

[3] Advisory Committee on the Medical Use of Isotopes (ACMUI) Permanent Implant Brachytherapy Interim Report (October 20, 2010; http://pbadupws.nrc.gov/docs/ML1035/ML103540385.pdf).

[4] Medical Rulemaking Workshops for Discussion of Topics Related to Medical Part 35 Regulations (New York, NY, June 20-21, 2011; Houston, TX, August 11-12, 2011; http://www.blsmeetings.net/NRCMedicalRulemakingWorkshop/presentations.cfm)

[5] Concept from "Sector analysis of prostate implants." William S. Bice, Jr., Bradley R. Prestidge, Michael F. Sarosdy. Medical Physics, Vol. 28, No. 12, December 2001.

[6] RTOG 0232: "A Phase III Study Comparing Combined External Beam Radiation And Transperineal Interstitial Permanent Brachytherapy With Brachytherapy Alone For Selected Patients With Intermediate Risk Prostatic Carcinoma," Radiation Therapy Oncology Group Protocol (9/6/2011 Version; http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0232).

practical. Octants simply define the prostate in half along each of the three axes and are unambiguous. The idea stems from a paper by Bice, Prestidge and Sarosdy.[5] Importantly, it would not identify as a Medical Event an implant with the sources missing an octant as long as the D_{90} is above 60%. The 60% criterion is recommended to prevent labeling as a Medical Event a less-than-ideal implant that is not medically significant to the treatment of that site.

This last criterion is based on the RTOG 0232,[6] a phase III trial comparing combined external beam radiation therapy and permanent implant with implant alone for selected patients with intermediate risk prostate cancer, where D_{90}<80% was considered an unacceptable deviation. Since a Medical Event should be more significant than a deviation in a clinical trial, a D_{90} threshold of 60% would be approximately 20% below the medically acceptable doses, which is consistent with other regulations. Additionally, for cases in which areas within the target are physically unreachable (because of patient anatomy or template and needle geometric limitations, such as the pubic arch limiting access to the anterior prostate) in which octants might therefore be underrepresented, the Written Directive (which should be completed after the implant but before the patient is released from control of the Authorized User) should reflect the clinical limitations encountered. Such cases should not be classified as Medical Events as long as the completed Written Directive documents why there might be octants with fewer sources than initially planned.

For the normal tissue, the D_{5cc} contiguous dose-volume specification avoids the high variation in dose sometimes seen in point doses and has literature to support it being a relevant quantity for toxicity. The rationale for the distinction between the bladder and rectum versus the urethra is that the latter falls within the target volume.

This final ACMUI report also provides recommendations of how the NRC should apply the current requirements for a permanent implant written directive. As stated in 10 CFR 35.40(b)(6), a written directive must contain for permanent implants:

> "(i) Before implantation: treatment site, the radionuclide, and dose; and
>
> (ii) After implantation but before completion of the procedure: the radionuclide, treatment site, number of sources, and total source strength and exposure time (or the total dose)."

Completion of the written directive after implantation reflects the need to document the implant based on the medical situation encountered during the procedure, for example adding sources where the source distribution appears to need additional coverage or noting that some sources could not be placed due to anatomical limitations. The completion of the procedure should be considered at the point when the patient is released from the Authorized User's control. This time frame is consistent with other types of surgical procedures allowing the physician to complete surgical documentation while the patient is in the surgical recovery area.

Adequate treatments require appropriate source-strength distributions that have been correlated over decades with successful clinical outcomes. As discussed in previous reports from this Subcommittee, post-implant evaluation forms an important part of Authorized User (and other members of the treatment team) self-assessment for correlating how actual source distributions compare with that on the pre-implant plan. It is acknowledged that dose distributions calculated on such post-implant dosimetry studies are fraught with problems, making calculated dose an unreliable metric for regulatory compliance purposes. Nonetheless, post-implant evaluation of this type provides some valuable medical feedback to the Authorized User. Post-implant evaluation provides the Authorized User and the regulating community with a more objective basis for inspecting implant compliance.

Basis for the Previous Subcommittee Recommendations

The Subcommittee has reaffirmed the principles that guided the definitions from the previous reports. The definition of a permanent implant brachytherapy Medical Event should be based on the following concepts:

A Medical Event ideally should be of true medical significance to a patient.

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.) Radiological and medical harm medically due to overdosing of sensitive normal structures and tissues
2.) Medical harm due to under-dosing the cancer and not curing the patient

An appropriate Medical Event definition must balance the above factors. This is a difficult task and is made even more difficult when attempting to encompass all forms of permanent implant brachytherapy under one set of Medical Event criteria. The Subcommittee was previously in favor of separating prostate from non-prostate permanent implants. With the presently proposed Medical Event definition, the Subcommittee no longer feels it is imperative to create such distinct categories.

The Subcommittee recognizes that a dose-based definition for the target, especially in prostate permanent implant brachytherapy, suffers from several limitations:

1.) True anatomic prostate volume or shape changes can occur during and after the implant procedure, particularly due to edema,

2.) Spurious differences in estimated prostate volumes can occur due to inherent limitations of identifying organ or target boundaries using CT and ultrasound (or any other modality),

3.) Volume estimate uncertainties due to artifacts caused by the seeds and the resultant indistinct prostate boundaries seen on post-implant CT images.

The Subcommittee also recommended in previous reports that if an apparent Medical Event were found to be due to true anatomic prostate volume changes (item 1. immediately above) after the administration, it should not be deemed a Medical Event. Such cases should be addressed in the fashion of other *patient-related or patient-specific factors* equivalent to a patient removing a temporary implant, migration of properly implanted radioactive seeds, or incompletion of a ^{90}Y microsphere administration because of stasis. An implant with potentially undertreated regions should not be considered a Medical Event if imaging identifies regions requiring additional radiation therapy.

The previous reports also reviewed aspects of the old definition that dealt with normal tissues. Consider the part of §35.3045 that 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." With the very high gradients in the dose distributions, very small and clinically insignificant 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. For example, a 1-cm shift in the position of the prostate due to gas in the bowel (a common amount of movement) can produce a 94% change in the calculated dose to the skin. It is worth noting that the difficulties in post-implant dose reconstruction for the prostate might also affect dose calculations for normal tissues – for instance, the above example of a 94% increase in the dose to the skin might not be seen if the same procedure were done the very next day if the bowel gas resolved. Such perfectly normal and clinically acceptable implants should not be categorized as Medical Events.

Thus, if this criterion were applied strictly, some (perhaps many) properly executed and medically acceptable implants might inappropriately be 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 proposed Medical Event definition herein adheres to these principles.