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Permanent brachytherapy subcommittee (PBSC) report

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Teleconference held 09/12/08, 1-3 pm EST

PERMANENT IMPLANT BRACHYTHERAPY NRC proposed rules

- § 35.40 (6) Written directive (WD) for permanent implant brachytherapy to be source strength-based rather than dose-based
- PBSC supports this proposed rule
- Comment: the word "activity" should be replaced by the correct term: "source strength" whenever it is applied to permanent brachytherapy in the document

PBSC concerns

- While these rules were developed with prostate brachytherapy in mind, they will nevertheless apply to all types of permanent brachytherapy in any organ of the body.
- Unintended consequences: The proposed language in some parts of §35.3045(a)(2) could result in inadvertently and inappropriately categorizing some properly executed, medically acceptable, implants as "medical events" (ME)

PBSC concerns

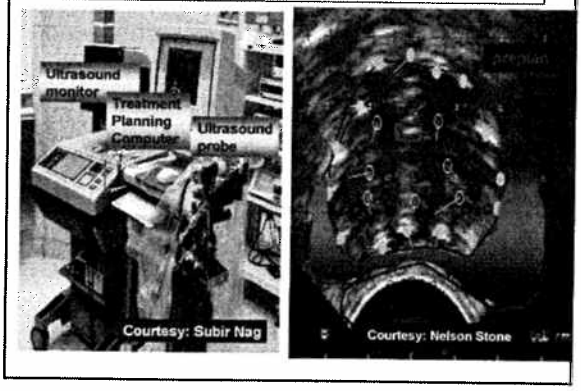
- § 35.3045(a)(2) (i) would deem it a medical event if the total source strength administered differed by 20 percent or more from the total source strength documented in the pre-implantation written directive.
- Further, NRC states pre-implantation WD cannot be changed since pre-implantation WD serves as basis for determining if an ME has occurred

PBSC clarifications

- Many Authorized Users (AU) perform real-time adaptive interactive planning
- WD and source strength implanted based on actual volume dynamically obtained during the procedure
- Not based on the pre-implant volume
- Real-time planning is more accurate
- Takes into account any alterations in the prostate volume and shape
- Plan constantly and dynamically updated as changes occurs during the procedure
- Even those performing preplanned techniques often modify their plan if intraoperative gland volume differs markedly from pre-implant volume

Ref: Nag S et al: ABS Report. IJROBP 2001;51:1422-30

Intraoperative planning/dosimetry – O.R. setup



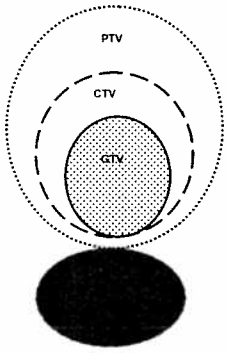
PBSC RECOMMENDATION

- In section § 35.3045 (a)(2)(i), basis for ME should be total source strength implanted after administration (but before patient leaves post-procedural recovery area)
  - Not be based on "pre-implantation" WD
  - Will allow intraoperative adaptation, if needed
  - Will apply both to preplanned technique and real time adaptive technique
- Similarly, the word "pre-implantation" be deleted from "pre-implantation written directive" in sections § 35.3045 (a)(2)(ii), (iii) and (iv) as well

PBSC concerns

- § 35.3045(a)(2) (ii) would deem it a ME if the total source strength implanted outside the treatment site and within 3 cm of the boundary of the treatment site exceeded 20 percent of the total source strength documented in the pre-implantation WD
- Definition of treatment site as "the anatomical description of the tissue intended to receive a radiation dose, as described in a written directive" leads to ambiguity regarding the exact volume referred to

Standard radiation oncology volumes defined (ICRU report #50)



- GTV = gross tumor volume - palpable or visible extent and location of tumor
- CTV = clinical target volume - margins added to the GTV to account for the subclinical microscopic spread of tumor
- PTV = planning target volume - additional margin to account for uncertainties in source positioning, tumor boundaries, isodose constrictions, etc.
- Expansion margins not constant nor uniform - vary for different clinical situations
- →Larger margin if high degree of uncertainty and/or if no adjacent critical structures
- →Margins smaller if boundary is distinct and/or if adjacent critical structures

PBSC concerns

- Determination of margins and source strength to be placed in the margin is a clinical decision
- NRC will be interfering with medical judgment if it dictates source strength AU can place in margin
- Unclear whether "treatment site" refers to
  - gross tumor volume or
  - includes margins as in clinical target volume or
  - includes margin as in planning target volume

PBSC RECOMMENDATION

- Clarify that to be considered a ME , 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) exceed 20 percent of the total source strength documented in the WD
- With this definition, NRC will not be interfering with clinical judgment but will be able to identify poor implants that need to be reported as MEs

PBSC concerns

- § 35.3045 (a)(2)(iii) would deem it a ME even if a single brachytherapy source were implanted beyond 3 cm from outside boundary of the treatment site....
- However, in normal course of brachytherapy properly executed implants, a few seeds end up beyond 3 cm from the outside boundary of the treatment site:

PBSC concerns

- Seeds can be deposited into periprostatic blood vessels and migrate to distant organs such as the lung (correctly recognized by the NRC not to be an ME)
- Deposited seeds could also travel to the adjacent pelvic area via the pelvic vessels and be more than 3 cm away from the prostate
- A few seeds can sometimes be implanted into the urethra or adjacent bladder - and normally are excreted in the urine
- Sometimes they move within the bladder or urethra and lodge more than 3 cm from the prostate
- In permanent implants of any organ, some seeds can be unknowingly sucked along the needle track while the needle is being retracted
- May end up more than 3 cm from the organ in the direction of the needle track (eg in prostate, >3 cm inferior to prostate)
- Patients inadvertently move during needle retraction - causing some seeds to be deposited more than 3 cm from treatment site

PBSC concerns

- While most permanent brachytherapy done in prostate, these rules will apply to other sites of permanent implant (eg. tumor beds after resection, deep seated liver tumors)
- At other sites, margins can be indistinct and have greater uncertainties
- After tumor resection no tissues to anchor the seeds – so seeds placed in gelfoam or vicryl mesh and attached to the tumor bed
- Some of these seeds can dislodge and travel in adjacent free cavity (e.g., abdominal, pelvic, or thoracic cavity)
- Finally deposited more than 3 cm away
- Virtually impossible to determine whether they were implanted there or were dislodged and migrated there
- Could be deemed to be an ME

PBSC RECOMMENDATION

- **§ 35.3045(a)(2) (ii) be modified to: ME if total source strength implanted outside the treatment site** (including the GTV, CTV, plus a variable planning margin as defined by the AU) **exceed 20 percent of the total source strength documented in the WD**
  - —would take into account source migrations, seeds being dislodged, etc, but would still hold accountable cases in which target organ grossly misidentified and wrong area implanted
- **§ 35.3045 (a)(2)(iii) will become superfluous and therefore should be eliminated**

PBSC concerns

- §35.3045(a): "A licensee shall report as a medical event any administration requiring a written directive if a written directive was not prepared ..."
- Not having a WD prior to administration of byproduct material is already a violation of NRC regulations
- Creating ME situations that are already regulatory violations serves only to add the number of reported MEs (i.e adding to the reporting burden without adding to safety)
- The proposed rule change will only add MEs that are rule violations but are not harmful to the patient
- Administrations done without required WD should be cited as regulation violation

Summary

- PBSC very much concerned that, with the proposed rules, above situations may be inappropriately deemed to be medical events when, in reality, they sometimes occur in the course of some normal, properly executed, brachytherapy implants and are beyond the control of the AU.
- PBSC is concerned that some practitioners will simply abandon permanent brachytherapy procedures rather than risk having medical events
- This will be detrimental to patient care

PBSC specific recommendations - summary

- In sections § 35.3045 (a)(2) (i), (ii), (iii) and (iv) "pre-implantation" should be deleted from "pre-implantation written directive"
- In § 35.3045(a)(2) (ii) clarify that "treatment site" includes the gross tumor, the clinical target volume, plus a variable planning margin as defined by AU.
- § 35.3045 (a)(2)(iii) will become superfluous and therefore should be eliminated
- "Activity" should be replaced by "source strength" whenever it is applied to permanent brachytherapy
- Administrations without WD should be cited as regulation violation and are not MEs *per se.*
- NRC should allow ACMUI to review and comment on any proposed rules BEFORE the proposed rules are published

Thanks to:

- **ASTRO**
- **ACRO**
- **ABS**

members for their input

ACMUI permanent brachytherapy subcommittee (PBSC) report of teleconference held 09/12/08, 1-3 pm EST

Members present:
Subir Nag (Chair)
Bruce Thomadson
James Welsh
Ralph Lieto

Background:

The PBSC reviewed the proposed rule on medical use of byproduct material for permanent implants published in the Federal Register Vol. 73. No. 152 issued on August 6, 2008. The PBSC concurs with many of the proposed rules drafted by the NRC for permanent brachytherapy, which are in accordance with the recommendations of the ACMUI. The PBSC notes that while these rules were developed with prostate brachytherapy in mind, they will nevertheless apply to all types of permanent brachytherapy in any organ of the body. In this regard, the PBSC wishes to reiterate to the NRC the following recommendations that the previous ACMUI Medical Event Subcommittee had made on 6/21/2003 under Section B 2) c) "The technology for image-guided seed positioning and verification is most developed and mature for prostate brachytherapy. However, even in this clinical setting, the precision with which the fraction of seeds implanted in the prostate can be determined from post-implant CT or intraoperative ultrasound imaging maybe limited, due either to image artifacts or operator variability in defining the treatment site. For some treatment sites, e.g., postoperative brachytherapy of a tumor bed, there is no well-encapsulated or radiographically visible target volume that can be used to precisely determine whether the implant is a treatment-site accuracy ME. In such cases, only grossly erroneous MEs can be determined with certainty. NRC enforcement policy must be based upon realistic expectations of the precision that can be achieved in ME determination in different clinical settings." The PBSC also notes that although the proposed rules were based on the recommendations of the ACMUI, the ACMUI was not offered an opportunity to review the proposed rules before the proposed rules were published in the Federal Register. The PBSC feels that some of the unintended consequences could have been avoided if the ACMUI had been able to review the proposed rules before publication.

Specific concerns:

The PBSC is concerned that the proposed language in some parts of §35.3045(a)(2) could result in inadvertently and inappropriately categorizing some properly executed, medically acceptable, implants as "medical events" as follows:

1. The proposed language for § 35.3045(a)(2) (i) on page 45643, column 3 would deem it a medical event if the total source strength administered differed by 20 percent or more from the total source strength documented in the

preimplantation written directive. Further in page 45637 column 3 it is noted *that* the preimplantation WD cannot be changed since the preimplantation WD serves as the basis for determining if an ME has occurred.

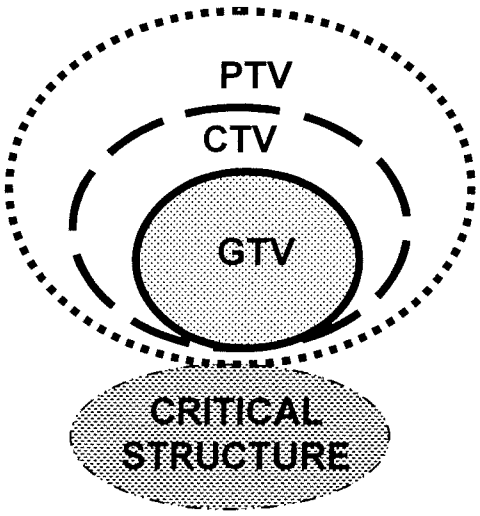
The PBSC wishes to clarify that many AU perform real-time adaptive interactive planning whereby the written directive and the source strength to be implanted are based on the actual volume dynamically obtained during the procedure rather than be based on the preimplant volume (Reference: Nag S, Ciezki JP, Cormack R, Doggett S, DeWyngaert K, Edmundson GK, Stock RG, Stone NN, Yu Y, Zelefsky M. Intraoperative Planning and Dosimetry for Permanent Prostate Brachytherapy: Report of The American Brachytherapy Society. Int J Radiat Oncol Biol Phys 2001;51:1422-30). Real-time planning is a more accurate method of implantation as it takes into account any alterations in the prostate volume and shape that occur between the time of the preplan and the implant procedure and therefore represents the actual prostate volume and implant situation. Hence for those performing real-time adaptive planning implantation, the total source strength to be implanted is determined intraoperatively during the implantation procedure and not preimplant. Further, even those performing permanent brachytherapy using preplanned techniques will often modify their plan if, intraoperatively, they find that the gland volume differs markedly from the volumes determined during the preplan. This is also reflected in the ACMUI directive (page 45636 column 3, sec.6) that "The AU is to complete any revisions to the WD for permanent implants to account for any medically necessary plan adaptations before the patient is released from licensee control after the implantation procedure and immediate post-operative period." Hence the basis for medical event should be the total source strength implanted after administration but before the patient leaves the post-treatment recovery area.

The PBSC recommends that: § 35.3045 (a)(2)(i) be modified to read "The administration of byproduct material or radiation from byproduct material for permanent implant brachytherapy (excluding sources that were implanted in the correct site but migrated outside the treatment site) results in the total source strength administered differing by 20 percent or more from the total source strength documented in the written directive." {ie delete "preimplantation"} It should be clarified that, in the written directive, the source strength implanted refers to the source strength implanted after administration but before the patient leaves the post-treatment recovery area. This wording would therefore apply both to those using the preplanned technique and those using real time adaptive technique. Similarly, the word "preimplantation" should be deleted from "preimplantation written directive" in sections § 35.3045 (a)(2)(ii), (iii) and (iv).

2. The proposed language for § 35.3045(a)(2) (ii)) on page 45643, column 3 would deem it a medical event if the total source strength implanted outside the treatment site and within 3 cm (1.2 in) of the boundary of the treatment site

exceeded 20 percent of the total source strength documented in the preimplantation written directive.

The PBSC wishes to point out that the definition of treatment site as described in § CFR35.2 as "the anatomical description of the tissue intended to receive a radiation dose, as described in a written directive" leads to some ambiguity regarding the exact volume of the treatment. ICRU report #50 has defined various standard volumes to be used in radiation oncology. These include the gross tumor volume (GTV), which is the gross palpable or visible extent and location of tumor. There are also two margins added to the GTV during the brachytherapy planning process. There is a margin added to account for the subclinical microscopic spread of tumor, which is termed the "clinical target volume" (CTV). There is an additional margin added to account for uncertainties in source positioning, tumor boundaries, isodose constrictions etc., which is termed the "planning target volume" (PTV). These expansion margins are neither constant nor uniform and vary for different clinical situations. Radiation oncologists use a larger margin if there is high degree of uncertainty and/or if there are no adjacent critical structures. Conversely, the margins are smaller if the boundary is distinct and/or if there are adjacent critical structures as illustrated in the following diagram.



Volume abbreviations:
GTV = gross tumor volume
CTV = clinical target volume
PTV = planning target

The determination of margins and the source strength to be placed in the margin is a clinical decision. The NRC will be interfering with medical judgment if it dictates the amount of source strength the authorized user can place in the margins. Using § 35.2 definition of treatment site as "the anatomical description of the tissue intended to receive a radiation dose, as described in a written directive" leads to ambiguity since it is unclear whether the "treatment site" refers to the gross tumor volume or includes the margins as in the clinical target volume or includes the margin as in the planning target volume.

For clarification, the PBSC recommends that to be considered a medical event, the sentence "The total source strength implanted outside the treatment site and within 3 cm (1.2 in) of the boundary of the treatment site exceeding 20

percent of the total source strength documented in the preimplantation written directive" be replaced by "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". With this clarification of the treatment site and deletion of "preimplantation", the NRC will not be interfering with clinical judgment but will still be able to identify poor implants that will need to be reported as medical events.

3. The proposed language for § 35.3045 (a)(2)(iii) on page 45643, column 3 would deem it a medical event if any brachytherapy source(s) were implanted beyond 3 cm (1.2 in) from the outside boundary of the treatment site, except for brachytherapy source(s) at other sites noted in the preimplantation written directive. Further in page 45638 column 2 it is noted that with the exception of sealed sources that migrate after implantation, even a single brachytherapy source implanted beyond 3 cm from the outside boundary of the treatment site would constitute an ME.

   The PBSC wishes to emphasize that in the normal course of some brachytherapy implants, a few seeds can end up beyond 3 cm (1.2 in) from the outside boundary of the treatment site due to a number of factors.
   a. In the prostate, seeds can be deposited into the periprostatic blood vessels and then travel to distant organs such as the lung. This is correctly recognized by the NRC, which excludes sources that were implanted in the correct site but have migrated outside the treatment site from medical event criteria. However, the deposited seeds could also travel to the adjacent pelvic area via the pelvic vessels and be more than 3 cm away from the prostate. This case could be determined to be a medical event as it would be impossible to distinguish whether it was wrongly deposited there or was correctly placed but migrated there.
   b. In prostate implants, a few seeds can sometimes be implanted into the urethra or adjacent bladder. Most of these seeds normally are excreted in the urine. However, sometimes they move within the bladder or urethra and lodge more than 3 cm from the prostate.
   c. In permanent implants of any organ, some seeds can be unknowingly sucked along the needle track while the needle is being retracted and may end up more than 3 cm from the organ in the direction of the needle track. In the prostate, they would end up inferior to the prostate.
   d. In permanent implants of any organ, patients could inadvertently cough or otherwise move during the needle retraction causing some seeds to be deposited more than 3 cm from the treatment site.
   e. While most permanent brachytherapy is done in the prostate, these rules will apply to other sites of permanent implant in addition to prostate. At other sites, for example the tumor beds after resection and deep seated liver tumors, the margins are indistinct and there are greater uncertainties. Therefore clinicians routinely implant beyond the tumor or tumor bed if

there are no critical structures in that area. Further, sometimes (especially after tumor resection) there may be no tissues to anchor the seeds to and so they are placed in gelfoam or vicryl mesh and attached to the tumor bed. Some of these seeds do dislodge and then can travel in an adjacent free cavity and be deposited more than 3 cm away (e.g., in the abdominal, pelvic, or thoracic cavity). It would be virtually impossible to determine whether they were implanted there or were dislodged and migrated there and therefore could be deemed to be a medical event.

The PBSC recommends 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 being dislodged, sucked out, etc, but would still hold accountable cases in which the target organ was grossly misidentified and the wrong area was implanted. Accordingly, § 35.3045 (a)(2)(iii) will become superfluous and therefore would be eliminated.

Other comments:

1. In addition to the above specific recommendations, the PBSC recommends that the word "activity" should be replaced by the term "source strength" whenever it is applied to permanent brachytherapy in the document.

2. Further, in the course of the review of these proposed rule changes, the PBSC wishes to comment on new wording that potentially affects any administration of byproduct material requiring a written directive (WD). The proposed language for §35.3045(a) on Federal Register, page 45643, column 2 currently reads, "A licensee shall report as a medical event any administration requiring a written directive if a written directive was not prepared or any event..."

The PBSC recommends that "...if a written directive was not prepared or..." be deleted from the proposed rules for the following reasons.
Not having a written directive prior to administration of byproduct material is already a violation of NRC regulations. 10 CFR §§35.40(a) and 35.41 require having a written directive prior to administration and the program and procedures to provide "high confidence" for verifying the written directive is done.
Creating medical events (ME) that are already regulatory violations serves only to add the number of reported deviations and establishes a undesirable precedent for making any medical regulation violation a ME. ME reporting is a national public notification within 24 hours that may initiate unneeded public embarrassment and scrutiny. Let us analyze the two scenarios where a non-emergent therapy administration requiring a WD was performed without a WD.
A. In the first scenario, the therapy is done following verbal orders/no WD but the patient receives the therapy administration as directed. While this is a clear

violation of regulations as described above, there is absolutely no resultant patient harm.
B. In the second scenario, the therapy is done following verbal orders/no WD but the patient receives more than ±20% of the intended therapy dose/dosage. Clearly, this not only violates regulations but also exceeds the medical event reporting criteria hence would be reported as a medical event anyway.

Therefore, the proposed rule change will only add events that are rule violations but are not harmful to the patient. Administration done without required WD should be handled as any citation of regulations by the regulatory enforcement agency (NRC or Agreement State). Licensees should be encouraged to self-identify such violations and implement documented remedial action with the clear understanding that the action would be reviewed during routine regulatory inspections. In addition, anything that would constitute an incomplete WD as required by the regulations (e.g., missing date or signature) would be considered an invalid directive and thus subject to the proposed ME reporting. This further establishes a precedent for any violation of regulations involving procedures requiring a written directive as being a ME.
The Discussion in the Federal Register (Item F, p. 45637) states that without a WD, "licensees do not have a basis for determining if a ME has occurred." This is not accurate. The NRC medical event database has a number of reported examples where *intended* diagnostic administrations of radioiodines, not requiring a WD, mistakenly received amounts in the therapeutic range. Licensees with quality written directive programs as required in §35.41 will have procedures that require a properly completed WD exists prior to administration, with the exception for already permitted emergent situations.

For almost two decades, overwhelming cause of medical events is human error. This new proposed change will provide only another process to add to MEs that are not harmful, without minimizing this cause. Contrary to the Discussion in the Federal Register, this new requirement will not add or improve to ensure the health and safety of patients is protected. The NRC has provided no justification that this rule violation merits being a reportable ME. This added requirement is not needed and will simply increase the number of reported medical events by creating only another process to add to the ME definition.

The PBSC recommends that the NRC staff issue a RIS emphasizing that administrations without the required WD are violations of regulations and procedures must exist to identify any deviations from this requirement. If violations should occur, the event must be documented with any appropriate remedial action. If the NRC feels this needs to be made more explicit in regulations, then the NRC should amend to §35.41 (a) (1) (Procedures for administrations requiring a written directive) to the effect "...to provide high confidence that: (1) The patient's or human research subject's identity is verified *and a properly written directive is done* before each administration;".

Summary:

The PBSC is very much concerned that, with the proposed rules, the above situations may be inappropriately deemed to be medical events when, in reality, they sometimes occur in the course of some normal, properly executed, brachytherapy implants and are beyond the control of the AU. Further, the PBSC is concerned that some practitioners will simply abandon permanent brachytherapy procedures rather than risk having medical events. This will be detrimental to patient care. Specifically, the PBSC recommends that:

- The word "preimplantation" should be deleted from "preimplantation written directive" in sections § 35.3045 (a)(2) (i), (ii), (iii) and (iv).
- § 35.3045(a)(2) (ii)) be clarified to read "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".
- § 35.3045 (a)(2)(iii) will become superfluous and therefore should be eliminated.
- The word "activity" should be replaced by the term "source strength" whenever it is applied to permanent brachytherapy in the document.
- A RIS be issued emphasizing that administrations without the required WD are violations of regulations and are not ME *per se*. Procedures must exist to identify any deviations from this requirement.
- The NRC should allow the ACMUI an opportunity to review and comment on any proposed rules BEFORE the proposed rules are published in the Federal Register. This will avoid unintended consequences.

Thank you for affording us this opportunity to provide comments on the NRC's preliminary draft rule changes to 10 CFR 35.40 and 35.3045 related to medical events in brachytherapy.