Statement of
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Thank you for the opportunity to make this statement on behalf of the American Society for Radiation Oncology. I am Dr. Danny Song, an Associate Professor and Clinical Director for the Department of Radiation Oncology and Molecular Radiation Sciences at Johns Hopkins University School of Medicine. I am also director of brachytherapy services at Johns Hopkins and have over 7 years' experience in performing prostate as well as endobronchial brachytherapy, and maintain an active brachytherapy service as well as a federally funded research program in prostate brachytherapy.

ASTRO is the largest radiation oncology society in the world, with more than 10,000 members who specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, biology and physics, the Society is dedicated to improving patient care through education, clinical practice, advancement of science and advocacy. ASTRO's highest priority has always been ensuring patients receive the safest, most effective treatments.

ASTRO believes that the current definition of medical event for permanent implant brachytherapy – one that relies on absorbed dose – is peculiarly problematic and requires practitioners to report events that may very well fall within the range of what is considered to be medically acceptable.

As you know, radiation therapy is the use of various forms of ionizing and in some cases, non-ionizing radiation to safely and effectively treat cancer and other diseases. Radiation Oncologists use radiation therapy to eradicate cancer, to control the growth of the cancer or to relieve symptoms, such as pain. Patients receive radiation therapy in one of two ways: externally or internally. During external beam radiation, a beam of radiation is directed to the tumor and immediate surrounding area in order to destroy the tumor and any nearby cancer cells. Internal radiation or brachytherapy is the placement of radioactive sources in or next to a tumor.

Permanent Implant Brachytherapy and Prostate Cancer

Brachytherapy is a highly effective way of delivering radiation tailored to the shape of the tumor while sparing surrounding normal tissues. Over the last 15 years, sophisticated computerized treatment planning and advances in medical imaging have helped to achieve increased accuracy and superior, optimized dose distribution for cancer patients.

The benefits of brachytherapy vary depending on the patient, their age and diagnosis, stage and preferences. Permanent implant brachytherapy is a cost-effective, minimally invasive outpatient procedure that avoids hospitalization and allows the patient a rapid recovery and rapid return to normal activity. It produces excellent 10-year outcomes with relatively low morbidity. The benefits of using this form of brachytherapy in the treatment of early stage prostate cancer are quite pronounced and include a lower incidence of impotence and incontinence than is commonly

reported with a radical prostatectomy. The high degree of accuracy achievable in prostate implants is partly due to technological improvements, but quality implants still require skill, adequate training, and attention to detail.

Brachytherapy Clinical Practice Guidelines

Permanent prostate brachytherapy, is given by inserting small seeds of radioactive iodine, cesium or palladium directly into the prostate gland. These radioactive sources have relatively low energy levels and half lives of between 10 and 60 days. Patients are under spinal or general anesthesia during this outpatient surgical procedure. The seeds are temporarily radioactive and deliver the radiation to the prostate over several weeks to months. After losing their radioactivity, the seeds remain in the prostate. The seeds are then harmless and should not bother the patient.

It is essential that post-implant dosimetry be performed on all patients undergoing permanent prostate brachytherapy as a quality assessment measure. It is recognized that the dose distributions following implantation are never exactly the same for each patient as those planned prior to the implant because the prostate gland swells and or changes shape during and after the procedure. Because the dose distributions may differ, it is important to document the actual dose that the prostate and normal adjacent tissues will receive over the life of the implant. This can only be determined if a post-implant dosimetric assessment is performed.

The information obtained from post-implant dosimetry is essential for optimal patient care. Significant over-dosing of the prostate may increase the risk of side-effects. Significant under-dosing of the prostate can lead to treatment failure. The latter can potentially be rectified using supplemental external beam radiation therapy or additional seed implants. While the timing may vary in part due to the half-life of the particular isotope involved, post-implant dosimetry scans are generally obtained at intervals varying from one day to one month post-implant.

At the conclusion of the course of treatment, a written summary of the treatment delivery parameters is generated, including the total prescribed dose of brachytherapy and the total dose of external beam therapy if given, treatment technique, treatment volume, acute side effects, clinical course, and patient disposition. Patients treated with brachytherapy should be evaluated after treatment at regular intervals by the radiation oncologist for response and, early and late effects on normal tissues.

Definition of Medical Event

Under Part 35 section 35.3045 it is deemed to be a medical event if “the total dose delivered differs from the prescribed dose by 20 percent or more.” However, ASTRO believes that such a rule is not appropriate for permanent implant brachytherapy. If the NRC definition is rigidly applied, many medically acceptable and appropriate implants will be deemed to be medical events, creating unnecessary patient apprehension. Further, we are concerned the dose-based measure is medically inappropriate and encumbers regulatory bodies (such as the NRC) and the licensees with clinically irrelevant and costly investigations. Hence, a dose-based definition of medical event is not suitable for permanent implant brachytherapy.

One key reason for this is that during the time interval between the initial or preplan volume study and the end of the implant, there are several changes that occur in the treatment volume (e.g., 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 varies upon the post-implant imaging modality used (CT or MRI), observer variability in prostate contouring. An ASTRO working group found that the current definition of medical events was not suitable for permanent implant brachytherapy because the prostate volume (and hence the resultant calculated prostate absorbed dose) depends upon many factors including a) the timing of the imaging; b) the imaging modality

selected; c) the observer variability in prostate contouring (both inter-observer and intra-observer); and d) the planning margins used. If the current dose-based medical event definition remains in force, many properly executed implants would be improperly classified as a medical event leading to a detrimental effect on brachytherapy.

Instead of a rule based on absorbed dose, ASTRO strongly recommends using an activity (i.e., source strength) based rule (>20 percent of source strength implanted outside the treatment site) to define medical events for regulatory purposes. This is because the total source strength implanted within and around the prostate is under control of the authorized user, but the subsequent prostate volume and the resultant dose to the prostate is not. The actual dose and the dosimetric parameters will vary considerably depending upon when and how the images were obtained, how the prostate was contoured, and the amount of swelling or edema. A source strength based criterion, (>20 percent of source strength implanted outside the planning target volume) will correctly identify as medical events cases in which a large number of sources have been improperly implanted outside the treatment site but be less likely to generate spurious medical events than a dose based definition. ASTRO recommends using the source strength-based rule for regulatory purposes.

ASTRO acknowledges one scenario where a source strength-based criterion would not adequately identify a medical event. This would be 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 over-dosed and other areas under-dosed. To address this rare event, ASTRO recommends that the authorized user be required to affirm in writing on the written directive, after the implant is completed, that the distribution of the sources within the treatment site was as intended per the pre-implant written directive.

The investigation of the permanent implant brachytherapy procedures at the Philadelphia Veterans Administration has brought attention to this issue, and a Blue Ribbon Panel was assembled to review the cases to determine if the implants were medically inappropriate. This panel found that many of those implants, previously considered to be medical events under the current definition, were, in fact, medically acceptable and proper. Thus, ASTRO is very concerned that if the current dose-based definition for permanent implant brachytherapy medical events remains, many properly executed and medically acceptable implants will erroneously be labeled as medical events.

In the absence of reforming the definition of medical event that relies on dose-based rules, it is difficult to accurately predict exactly how many medically acceptable implants in this country will be mislabeled as medical events. Such a situation would be harmful to the public welfare as it will create undue apprehension in patients and the general public about this safe and effective medical procedure, and it would likely continue to occupy the NRC, state regulatory bodies and the licensees with thousands of man-hours of unnecessary and clinically irrelevant costly investigations. Enforcement of this rule would also lead to decreased patient access to what is well-accepted as a successful and cost-effective treatment which will not be in our patients' best interest.

Written Directive

Another factor compounding the definition of medical event is the revision of medical directives. It is very important that the definition of medical event and the rules surrounding written directives take into account clinical practice realities so that certain medically acceptable implants are not labeled as medical events. Current regulations require that revisions to the written directive be made before implantation begins. The reason the pre-implantation written directive cannot be changed is that the pre-implantation written directive serves as the basis for determining if a medical event has occurred. ASTRO would like to emphasize that many authorized users perform real-time, adaptive, interactive planning, whereby the written directive and the source strength to be implanted are based on the actual volume dynamically determined during the procedure rather than based on the pre-implant volume. ASTRO believes

that real-time planning is a more accurate method of implantation because it takes into account any alterations in the prostate volume and shape. While real-time planning is most developed and most commonly used in the prostate, it can also be used in other brachytherapy procedures as long as the organ is easily imaged in real time.

For those performing real-time adaptive planning implantation, the total source strength to be implanted is determined intraoperatively during the implantation procedure and not pre-implant. Further, even those performing permanent brachytherapy using preplanned techniques will often modify their plan if intraoperatively they find major discrepancies in the gland or organ volume from the volumes determined during the pre-plan. Allowing flexibility to deal with real life clinical situations that become apparent during the operation improves clinical outcomes.

Accordingly, ASTRO recommends that the written directive refer to the total source strength implanted after administration, but before the patient leaves the post-treatment recovery area rather than an arbitrary pre-implantation written directive.

Conclusion

We appreciate both the ACMUI and NRC's deliberations on this issue and look forward to working with the NRC to revise this definition so that patients have access to safe, medically appropriate procedures.