Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Use of Isotopes (ACMUI)

Subcommittee on
Radioactive Seed Localization for Non-Palpable Breast Lesions
Revision 1
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Introduction

Radioactive seed localization (RSL) is a relatively new medical procedure, the first such procedures being performed in early 2000s. The first Guidance regarding RSL was issued by the NRC in 2006. This Subcommittee was formed in response to a request for modifications to the regulatory Guidance for RSL. The subcommittee also felt enough time had elapsed since the initial issuance of the Guidance to warrant a review of the Guidance.

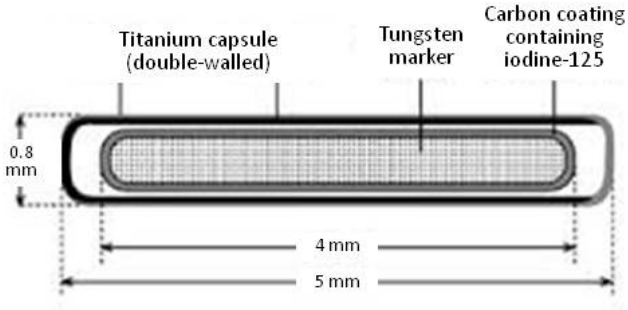
Background

The main current use of RSL is in localization of non-palpable breast lesions prior to surgical excision, although other indications are emerging. In the breast, RSL is an alternative to the traditional localization procedure to guide breast surgery, wherein a non-radioactive radio-opaque percutaneous wire is implanted into the lesion and excised with the suspicious tissue. The RSL technique offers the following main advantages over the wire-implantation technique: scheduling is more flexible, as RSL can be performed up to a week (or longer) before surgery; wires protruding from the skin, which some patients find disconcerting, are avoided; and cosmesis is potentially improved, as the surgeon can place the incision at the optimal location and is not restricted to the sites of the localization needles.

RSL uses the same radioactive seeds as those used for brachytherapy. Iodine-125 or palladium-103 seeds (typically only one but as many as four) containing 200-300 μCi each are implanted percutaneously by a radiologist under image (mammography or ultrasound) Guidance into the breast lesion using a needle; iodine-125 seeds are used far more commonly than palladium-103 seeds. The surgical procedure and removal of the seeds are typically performed 2 to 7 days post-implantation, although seed implantation is sometimes performed on the same day as the surgical procedure. The radioactive seed(s) and thus the lesions can be localized with an intraoperative gamma probe identical to that use for sentinel node biopsy and surgically removed. The seed(s) may be removed from the tissue specimen in surgery or, more commonly, the tissue specimen containing the seed(s) are sent to Pathology for removal of the seed and analysis. The seed or seeds are then disposed of in accordance with 10 CFR 35.92 or the equivalent Agreement-State regulations.

Physical and dosimetric properties of iodine-125 seeds

Iodine-125 seeds used for localization of non-palpable breast masses as well as for permanent-implant brachytherapy are comparable in size and shape to a grain of rice and are comprised of a double-walled titanium capsule containing an iodine-125-containing carbon-based material coating a radiographically imageable tungsten marker (See the figure below).

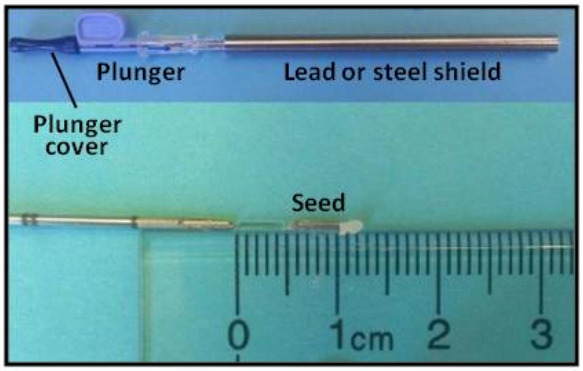


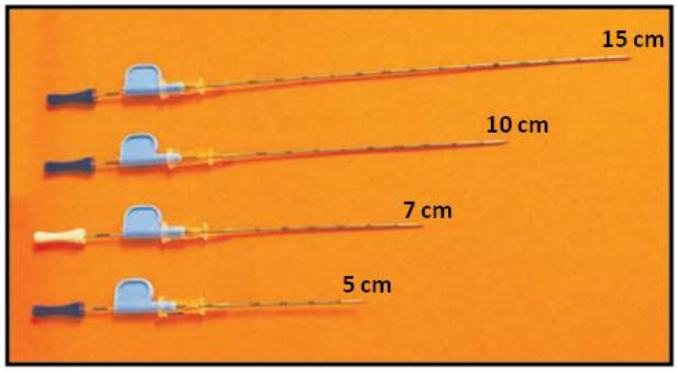
Iodine-125, with a physical half-life of 60.1 days, decays by electron capture accompanied by the emission of low-energy gamma rays and a cascade of characteristic x-rays ranging in energy from ~4 to ~45 keV; its most abundant photon emissions (3 x-rays with a collective abundance of 128%) are in the energy range 27-31 keV. Its overall half-value layer is only 0.02 mm in lead and 1.7 cm in water or soft tissue. Its gamma constant is 0.27 mR/h/mCi at 1 m, yielding an exposure rate from a 300-μCi (0.3-mCi) iodine-125 seed of ~0.081 mR/h at 1 m. Therefore, the absorbed dose at 1 m from such an iodine-125 seed would be only 58 mrad if an implanted seed were not removed (i.e., for complete decay) and only 7 mrad if the seed were removed 7 days post-implantation, assuming the seed was implanted at a depth of 1.7 cm (or 1 half-value layer) in the breast; the actual doses to individuals at 1 m from the patient would be 15 and 1.8 mrad, respectively, assuming the standard occupancy factor value of 0.25 for such individuals. The corresponding absorbed doses at 0.3 m (approximating the position of a child being held by the patient, for example) would be 640 and 78 mrad, respectively; the actual doses to a held child at 0.3 m would be 130 and 16 mrad, respectively, assuming an occupancy factor of 0.2 for such a child. Realistically, therefore, the absorbed doses from a patient implanted with an iodine-125 seed for localization of a breast lesion are extremely low, of the order of those received by passengers over the course of a trans-continental airline flight or less. Accordingly, there is no need for the patient or her family members to follow any radiation safety precautions in the time interval between seed implantation and explantation.

The radiation doses to a patient implanted with a 300-μCi iodine-125 seed may be estimated using the OLINDA/EXM computer code. If an implanted seed were not removed (i.e., for complete decay), the mean absorbed dose to the breasts would be 120 rad and the effective dose 6.1 rem; the absorbed doses to tissues other than the breasts would of the order of 1 rad or less. However, the doses to the tissue immediately adjacent to the seed(s) would be substantially higher than this. If these tissues are not subsequently excised at surgery along with the seed(s), long term consequences such as fibrosis are possible. More realistically, if the seed were removed 7 days post-implantation, the mean absorbed dose to the breasts would be 5 rad and the effective dose 0.23 rem; the absorbed doses to tissues other than the breasts would less than 0.1 rad. Importantly, the foregoing first-order dose estimates are conservative in that they assume a maximal seed activity of 300-μCi (0.3-mCi) and maximal time interval of 7 days from implantation to explantation. The actual doses would be proportionately lower for lower activities and/or shorter time intervals. (The dose estimates based on

the assumption that the implanted seed was not removed and underwent complete decay in situ represent the doses for a rare, worst-case scenario.) In addition, it should be noted that OLINDA/EXM slightly overestimates the dose.

Iodine-125 seeds for localization of non-palpable breast masses are packaged in a sterile pre-loaded needle assembly (See the figure below) and are thus ready-to-use. The available needle lengths are 5, 7, 10, and 15 cm and the seeds themselves are shielded by a lead or steel sleeve. Once the shield





is removed and the tip of the needle percutaneously positioned in the lesion, as guided by mammographic or ultrasound imaging, the plunger cover is removed and the plunger pushed to implant the seed within the lesion. As marketed, the seed and needle assembly have a shelf life of 90 days; this is dictated not by the physical decay of the iodine-125 but rather by the sterility of the assembly. The supplier of the iodine-125 seeds can, and should, provide the Sealed Source and Device Registry (SSDR) certificate.

Changes to Guidance Considered by the Subcommittee and its Recommendations

Title of Guidance

The subcommittee recommends that the title of the Guidance be changed by removing references to specific isotopes. The guidance is generic to any isotope used. Although I-125 is the most commonly used isotope to date, others could be used as well; so, there is no reason to specifically single out one or two isotopes. Although the sources are not being used for therapy, they are commonly called "brachytherapy sources." Therefore, the use of that term in the title is only meant for clarity and not to imply this is a brachytherapy procedure. Thus, the Guidance should be entitled "Low Dose Rate Brachytherapy Seeds Used for Localization of Non-palpable Lesions."

Similarly, references to I-125 and Pd-103 should be struck from the section headings "Safety Precautions and Instructions for Iodine-125 and Palladium-103 Seed Localization for Non-Palpable Lesions" and "Suggested Revisions to Existing Iodine-125 and Palladium-103 Seed Localization Programs to Conform to this Licensing Guidance" which should be changed to "Safety Precautions and Instructions for Brachytherapy Seed Localization for Non-Palpable Lesions" and "Suggested Revisions to Existing Brachytherapy Seed Localization Programs to Conform to this Licensing Guidance", respectively.

Purpose
The subcommittee recommends that the wording in the beginning of this section should be modified to address the current use of RSL which includes possible non-breast (e.g. axilla) applications, as follows: "The purpose of radioactive seed localization (RSL) of non-palpable lesions is to localize suspicious tissues for excision with the use of radioactive seeds. Most commonly this is being used in the breast where RSL differs from current localization procedures…"

Footnote #1 should be deleted.

Waste Disposal
The Guidance currently states: "The seed or seeds are then disposed of in accordance with 10 CFR 35.92 or the equivalent Agreement State regulations."

The Sub-committee feels that seeds can also be returned to the supplier following proper procedures and do not have to be retained at the facility that used them. Therefore, this sentence should be modified as follows: "The seed or seeds can be returned to the supplier following proper procedures or disposed of in accordance with 10 CFR 35.92 or the equivalent Agreement State regulations."

General
Radionuclides, Form, Possession Limits

Since RSL is not a treatment, the subcommittee recommends that the following text in the Guidance be changed: from "Authorization 8: 1.5 millicuries maximum per treatment and 15 millicuries total," to, "Authorization 8: 1.5 millicuries maximum per procedure and 15 millicuries total,"

Authorized User
Some radiologists who routinely place needles into breast or other tissue for the purposes of biopsies or placement of guidewires do not have the adequate training to be authorized users (AU) according to the current Guidance. The subcommittee acknowledges the difficulty in such a radiologist acquiring the needed training to be an AU once he/she has completed radiology training while also acknowledging the important knowledge and judgment acquired in such training to assure the safe use of radioactive materials in this setting.

Regarding training, the subcommittee recommends that an AU under 10 CFR 35.290 be allowed to be supervised by a 10 CFR 35.290 AU who has been previously trained in RSL in addition to the option of supervision under a 10 CFR 35.490 AU. Thus, the AU section of the Guidance should state:
The authorized user should be considered qualified for implementation, localization and removal of the seeds if the individual is listed on a license (NRC or Agreement State) and meets the criteria in:

> 10 CFR 35.490 or the equivalent Agreement State regulations; or
> 10 CFR 35.290, including supervised work experience under the supervision of a 10 CFR 35.490 authorized user and preceptor or under the supervision of a 10 CFR 35.290 AU and preceptor who has previously been approved for RSL on an NRC or Agreement State license. Training and supervised work experience should include the following:…"

For clarity, in the AU section of the Guidance that begins, "Pathology personnel…", the following statement should be added "This training should be provided by the AU described above or the Radiation Safety Officer, as applicable." This would provide consistency between pathology and surgical personnel with respect to the requisite radiation safety training.

The subcommittee feels that the work experience required for the AU should not include "removing RSL sources safely," since this is performed by the breast surgeon. The subcommittee also feels that radiation safety training for surgeons working under the supervision of the AU should not include preparing and implanting brachytherapy sources, since these procedures are not performed by the surgeon.

Written Directive

Pursuant to §35.40, a WD is required when a therapeutic dose of byproduct material is being delivered. Although the goal of the procedure is guidance of surgery rather than therapy, from the perspective of patient safety these sources may deliver doses considered to be in the therapeutic dose range close to the source or when left in for long periods of time. Therefore, the subcommittee feels the WD is an integral component of the proper regulatory requirements to assure safe RSL.

Regarding the specific elements of a WD, The subcommittee feels that dose should be eliminated as one of the required elements of the pre-procedure WD. In addition, the language of the requirement regarding the location into which the seed will be implanted should be modified from "treatment site" to "implant site," consistent with the non-therapeutic intent of RSL. Thus, prior to the procedure, the WD must specify the implant site (i.e., location within patient's body), the radionuclide to be used and the activity of the source. The post-procedure part of the WD must specify the implant site, radionuclide, number of sources implanted, total activity implanted and total time planned until surgery. If a violation of the WD occurs, a report must be completed as required in §35.3045.

The subcommittee, therefore, recommends the following language in the revised Guidance:
"A written directive must be dated and signed by an authorized user before the administration of brachytherapy seeds for seed localization. The written directive must contain the patient or human research subject's name and the following information –
(i) Before implantation: implantation site, the radionuclide, and activity per source; and
(ii) After implantation, but before completion of the procedure: the radionuclide, implantation site, number of sources, and total activity implanted and time planned before surgery."

The subcommittee also recommends the following language in the revised Guidance:
Medical Event Reporting -
(a) A licensee shall report any event, except for an event that results from patient intervention, in which the administration of byproduct material or radiation from byproduct material results in-
(i) An administration of radioactive byproduct material to the wrong individual or human research subject;
(ii) An administration of the wrong radioactive byproduct material;
(ii) An administration of the radioactive byproduct material to the wrong site (part of body)
(iii) Administration of radioactive byproduct material for more than 20% longer than planned. It should be noted, that if this is the result of the patient not showing up for the planned surgery, this

shall be considered "patient intervention" and not reportable as a Medical Event in accordance with 10 CFR 353045.
(iv) An administration of the radioactive byproduct material activity of more than 20% of the intended activity
(v) A leaking sealed source.
(b) A licensee shall report any event resulting from intervention of a patient or human research subject in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician.

Safety Precautions

The precautions regarding source rupture or cutting are warranted, as such incidents have been reported. In addition, to written emergency procedures for such an occurrence, the subcommittee recommends written emergency procedures be required for other abnormal situations including: loss of a seed, implant of a seed in the wrong location or wrong patient, inability to locate an implanted seed during surgery or pathological processing, and if a patient implanted with a radioactive seed does not present for scheduled surgery. Finally, we recommend patients be advised not to breast feed from a breast into which a seed(s) has(ve) been implanted and not yet removed. Breast feeding is, of course, permissible once the seed(s) has(ve) been removed. In the event of seed rupture within the breast, the subcommittee recommends the patient be advised not to breast feed from that breast for 10 half-lives.

Verification of Source Activity

Verification of source activity by the recipient is a crucial element of quality control and should remain in place. The subcommittee recommends, however, the following revision of the pertinent language in the revised Guidance: "The activity of sealed sources will be determined prior to each patient implant, either through direct measurement or based on manufacturer's indicated activity after correcting for decay". The foregoing language not only maintains consistency with the allowance to use the source manufacturer's measurements for brachytherapy source activity in 10CFR35.432(3)(b) but also recognizes that the manufacturer-provided calibration of dose calibrators is not applicable to the physical configuration of prepackaged sterile seeds in needles.

Training

The subcommittee feels that training on topics described in §35.410 should not be required. These apply to brachytherapy procedure after which the patient cannot be released from the medical facility; this does not apply to RSL.

Survey Instrumentation and Radiation Survey Requirements

Seed removal is required to be verified on the basis of a radiation survey. The subcommittee, however, recommends the removal of mention of any specific devices but rather recommends the Guidance state "licensee should possess and use a portable, properly calibrated radiation survey instrument capable of detecting low dose rate brachytherapy seeds. Calibration of the device shall be performed as required for the proper use of the particular device. " While imaging, such as a specimen radiograph or ultrasound, can visualize a seed as well, confusion could arise if the patient has also had the placement of items such as surgical clips prior to this procedure (e.g., at the time of biopsy).

Performance of a radiation survey avoids any such potential confusion and should continue to be required.

Change in Physical Conditions of Use
This section should be modified as follows, given that the radioactive seeds are currently approved by FDA for localization procedures:
If the physical conditions of use exceed those reported in the Sealed Source and Device (SS&D) certificate, the limited specific medical use licensee should request an amendment for the new conditions, and a broad scope licensee should perform its own engineering and radiation safety evaluation addressing those differences.

Procedures
The subcommittee feels that the procedures described in §35.410 are not necessary, since patients are always released from the medical facility following RSL. These procedures should be removed from the Guidance.

The subcommittee also feels that §35.41 should be changed to §35.41 (a), (b) (1), (2), (c), excluding §35.41 (b) (3) and (b) (4), which require dose calculations.

Respectfully submitted, August 11, 2015,
***Subcommittee on* Radioactive Seed Localization for Non-Palpable Breast Lesions,**
Advisory Committee on the Medical Use of Isotopes (ACMUI),
Nuclear Regulatory Commission (NRC)