

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

Sub-Committee on
Radioactive Seed Localization for Non-Palpable Breast Lesions

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Introduction

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

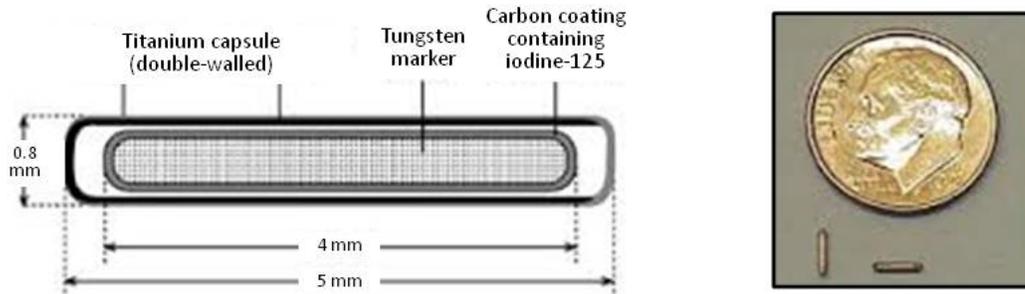
Background

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(s) 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).

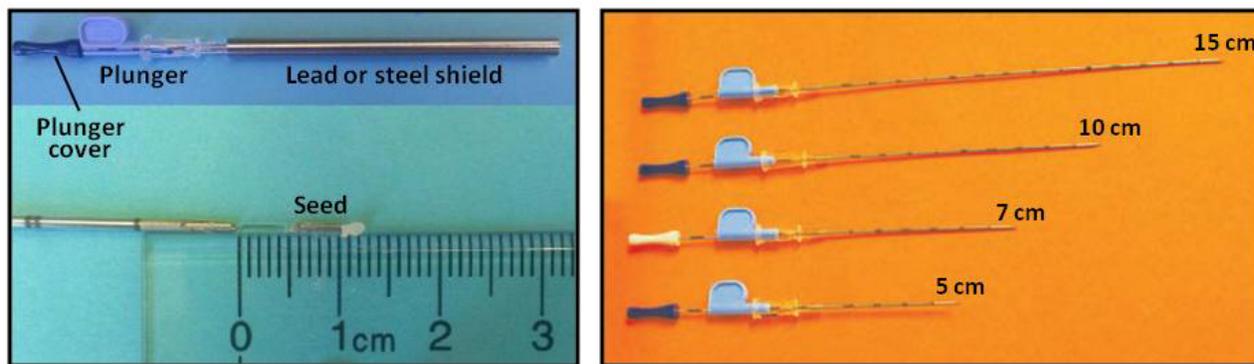


Iodine-125, with a physical half-life of 60.1 days, decays by electron capture accompanied by the emission of low-energy gamma rays and a cascade of characteristic x-rays ranging in energy from ~4 to ~45 keV; its most abundant photon emissions (3 x-rays with a collective abundance of 128%) are in the 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- μ Ci (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- μ Ci 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 be 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 be less than 0.1 rad. Importantly, the foregoing first-order dose estimates are conservative in that they assume a maximal seed activity of 300- μ Ci (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.)

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 Sub-committee and its Recommendations

Title of Guidance

No change in the title of the Guidance is recommended. 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. In addition, although Pd-103 has not been used to date for this procedure, the Sub-committee sees no reason to exclude this isotope and therefore recommends retaining the reference to it in the title.

Purpose

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 also 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 agrees that seeds can 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 to state the following:

“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 following text in the Guidance should be changed:

“Authorization 8: 1.5 millicuries maximum per procedure and 15 millicuries total,”

Authorized User

Seed placement must be performed by the Authorized User (AU) as defined in the existing Guidance. The Sub-committee considered changes to this requirement, but feels that the proper handling of the radioactive source used in this procedure require this level of expertise in radiation protection.

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 Sub-committee agrees that the work experience required for the AU should not include “removing RSL sources safely,” since this is performed by the breast surgeon. The Sub-committee also agrees 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

The Sub-committee also considered a request to remove the requirement for a Written Directive (WD) for RSL. 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 Sub-committee feels the WD is an integral component of the proper regulatory requirements to assure safe RSL. The Sub-committee does agree, however, with the suggestion to modify the specific elements of the WD and to eliminate dose 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 Sub-committee, 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 I-125 or Pd-103 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 exposure time/time planned before surgery.

Medical Event Reporting

The Sub-committee 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;
 - (iii) An administration of the radioactive byproduct material to the wrong site (part of body)
 - (iv) Administration of radioactive byproduct material for more than 20% longer than planned
 - (v) An administration of the radioactive byproduct material activity of more than 20% of the intended activity
 - (vi) 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 Sub-committee feels 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 Sub-Committee 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, the Sub-committee recommends 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.

Verification of Source Activity

Independent verification (i.e., assay) of source activity by the recipient is a crucial element of quality control and should remain in place.

Training

The Sub-committee agrees that training on topics described in §35.410 should not be required. These apply to brachytherapy procedures 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 using a sodium iodide (NaI) or Geiger-Muller (GM) meter. 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 using a NaI or GM meter avoids any such potential confusion and should continue to be required. The Sub-committee does recommend, however, that the preference for NaI meter over a GM meter be removed from the Guidance, since both are effective for this task given that the I-125 activities used for RSL are easily detected by both types of meters. The Sub-Committee also agrees that annual calibration of the survey meter is not required for the purpose of verifying seed removal, since the meter is used in this context simply for source detection and not, for example, for an exposure-rate measurement.

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 Sub-committee agrees 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 Sub-committee 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.

In addition, §35.432 should be changed to include only 35.432 (a) and (c) because (b) allows the licensee to rely on source strength measurements provided by the manufacturer. The Sub-committee believes, as stated elsewhere in the guidance, that the licensee must make their own measurement to verify source strength.

Therefore, the language in the guidance should be modified to state the following:

Because the iodine and palladium seeds are temporarily implanted, the applicant may simplify its submission by confirming that it will:

Meet the requirements for temporary implants and develop, implement, and maintain the appropriate procedures in the following regulations: 10 CFR 35.40(a), (c), (d), and as modified above in the Written Directions Section, 35.41(a), (b)(1), (b)(2) and (c), 35.67, 35.75, 35.310, 35.404, 35.406, 35.432(a) and (c), or the equivalent Agreement State regulations.

**Respectfully submitted, May 29, 2015,
Sub-Committee on Radioactive Seed Localization for Non-Palpable Breast Lesions,
Advisory Committee on the Medical Use of Isotopes (ACMUI),
Nuclear Regulatory Commission (NRC)**

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