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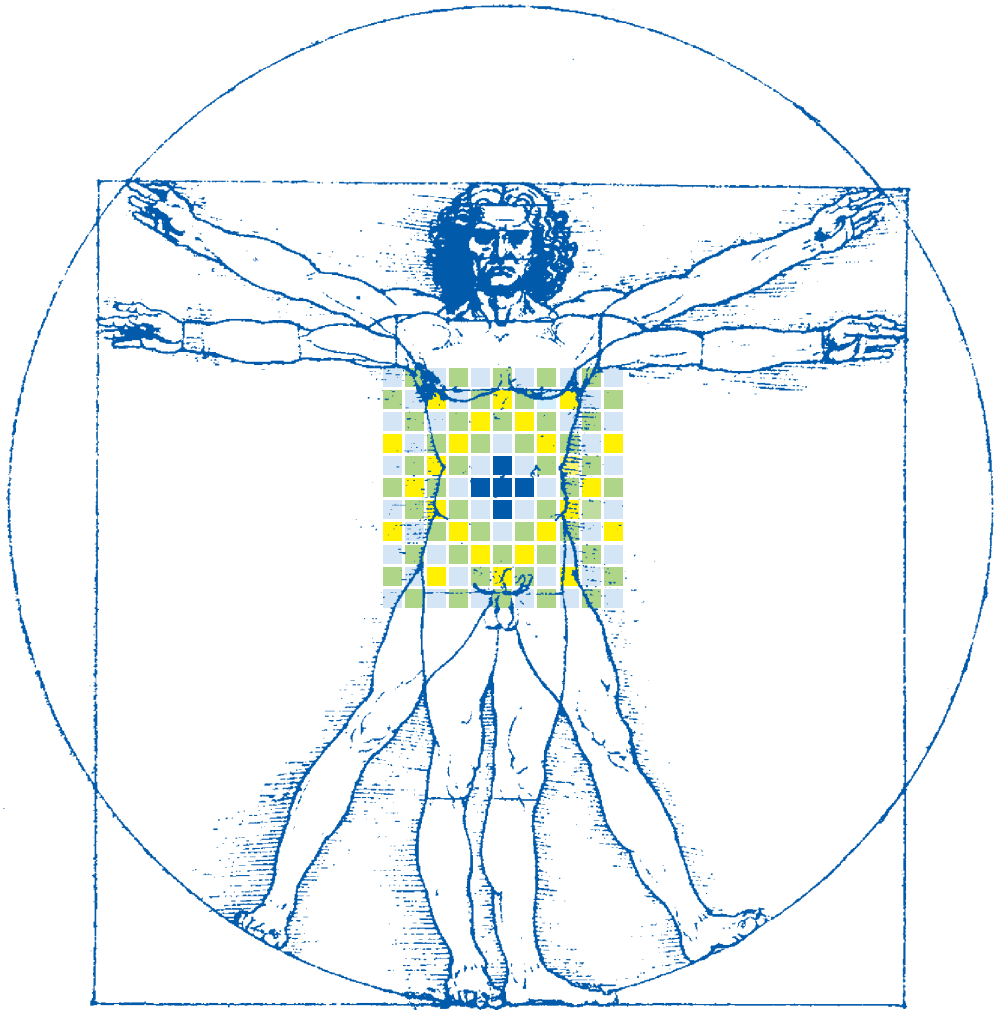

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REVIEW

IMAGE GUIDED SURGERY: FROM CLASSICAL TECHNIQUES TO NOVEL ASPECTS AND APPROACHES

Therapeutic applications of radioactive sources: from image-guided brachytherapy to radio-guided surgical resection

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ABSTRACT

It is well known nowadays that radioactivity can destroy the living cells it interacts with. It is therefore unsurprising that radioactive sources, such as iodine-125, were historically developed for treatment purposes within radiation oncology with the goal of damaging malignant cells. However, since then, new techniques have been invented that make creative use of the same radioactivity properties of these sources for medical applications. Here, we review two distinct kinds of therapeutic uses of radioactive sources with applications to prostate, cervical, and breast cancer: brachytherapy and radioactive seed localization. In brachytherapy (BT), the radioactive sources are used for internal radiation treatment. Current approaches make use of real-time image guidance, for instance by means of magnetic resonance imaging, ultrasound, computed tomography, and sometimes positron emission tomography, depending on clinical availability and cancer type. Such image-guided BT for prostate and cervical cancer presents a promising alternative and/or addition to external beam radiation treatments or surgical resections. Radioactive sources can also be used for radio-guided tumor localization during surgery, for which the example of iodine-125 seed use in breast cancer is given. Radioactive seed localization (RSL) is increasingly popular as an alternative tumor localization technique during breast cancer surgery. Advantages of applying RSL include added flexibility in the clinical scheduling logistics, an increase in tumor localization accuracy, and higher patient satisfaction; safety measures do however have to be employed. We exemply the implementation of RSL in a clinic through our experiences at the Netherlands Cancer Institute.

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After Wilhelm Röntgen's discovery of X-rays, Henri Becquerel's detection of emitted uranium radiation, and Pierre and Marie Curie's experiments with radium, which happened in the early 19th to 20th century, it was soon discovered that the rays of these radioactive materials could be used for therapeutic goals.[1] Since the interaction of ionizing radiation with cancerous cells was quickly found to lead to the potential destruction of the latter, the treatment of cancer with radiation has grown to be an undeniable part of modern medicine. In the field of radiation oncology, radioactive sources are now used for treatment of cancer. Radioactive materials (drugs and sources) are however also utilized for diagnostic and treatment planning purposes. Medical imaging presents an excellent template for demarcation of the tumor before intervention to present a basis for the choice of treatment, including

chemotherapy, surgery, and different types of radiation treatment. However, in order to increase accuracy and efficiency – and thereby the recovery rates of patients – also more and more real-time guidance is used during these kinds of treatments.

Such guidance is traditionally provided by imaging, of which the most used modalities include magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US), and positron emission tomography (PET).[2] These techniques are most known for their communality in that waves or rays are directed towards the patient and reflected, after which changes are caught by appropriate detectors. Some of these modalities have been elevated by introducing substances or tracers into the patient, *e.g.*, contrast agents in MRI or radioactive tracers in PET.[3] The previously mentioned radioactive sources, historically only used for the treatment of tumors, together with this idea of image guidance has led to ground-breaking newly developed techniques, during which the sources are alternatively used to effectively guide surgical procedures from within the patient.

In this article, we review two different kinds of therapeutic applications of radioactive sources. First, a classical example of the sources used for treatment purposes is exemplified by image-guided brachytherapy (BT), during which the radioactivity is meant to destroy malignant cells while imaging is used for guidance. Second, these radioactive sources, together with a gamma ray detector, can be used for radio-guided tumor localization during therapeutic surgery to accurately resect the tumor.

We focused on three main indications where radioactive sources are used either as a therapeutic or guidance tool during intervention or treatment, namely cervical and prostate cancer for image-guided BT, and breast cancer for radio-guided tumor localization during surgery.

Image-guided brachytherapy

Overview

BT is a form of radiation treatment which has been used since the early 20th century and involves placing sealed radioactive sources near or inside the targeted tumor. The emitted radiation destroys cells by damaging the deoxyribonucleic acid (DNA) chain and thereby poses a threat to surrounding organs at risk (OARs), as well as fulfils its purpose in destroying malignant cells. The sources are placed using catheters and/or applicators, in each of which they can reside at defined so-called dwell positions, for different times, called dwell times. An afterloader is used to propagate the sources from the shielded safe through guide tubes to their respective dwell positions.

BT procedures can be divided into distinct techniques consisting of low-dose-rate (LDR), high-dose-rate (HDR), and pulsed-dose-rate (PDR). During LDR, the radioactive sources (also referred to as seeds) are implanted for at least several days or often even permanently, the radiation is thus continuous and defined by a dose of 0.4 to 2 Gy/h.[4] PDR is characterized by low-intensity pulses which are repeated every hour to every few days. Finally, HDR is nowadays the most used technique and, depending on the type of cancer, consists either of a single-dose treatment or is divided into a few fractions of doses above 12 Gy/h each.[4]

Different radionuclides are used as radioactive sources for each of these techniques. Some of them are iodine-125 (^{125}I), palladium-103 (^{103}Pd), and cobalt-60 (^{60}Co), whereas the most common one is iridium-192.[5] They have half-lives of 59.41 d, 16.99 d, 5.2714 y, and 73.83 d,[6] respectively, and are chosen because of these longer half-lives, combined with their emitted energy range and ease of production. The ones with shorter half-lives and lower photon energy are generally used in LDR BT, whereas the other ones are rather used in HDR procedures to generate higher doses in shorter times.

BT procedures can furthermore be of intracavitary and/or interstitial nature. The former makes use of applicators and involves the placement of radioactive sources inside a natural body cavity, whereas the latter includes the implantation of sources using catheters (needles) in order to place them inside the tumor or organ. One type of cancer to which both techniques can be applied is breast cancer, for which BT in general has proven to be as effective as external beam radiation treatment (EBRT) while considerably shortening the overall treatment time.[7] There are different ways to perform BT for breast cancer, all of which are considered part of accelerated partial breast irradiation, a kind of radiation treatment which exclusively treats the adjacent breast tissue around the surgical cavity.[8] The more traditional form of BT is multi-catheter interstitial BT,[9] which is comparable to how prostate cancer is treated and which is described below. Alternatively, intracavitary BT for breast cancer includes a MammoSite lumen balloon that is inserted either during a lumpectomy surgery or as a separate procedure.[10] Note that intraoperative BT, where the treatment takes less than an hour straight after the lumpectomy, is also a possibility.[11] A more specific example for which

only the interstitial technique is used is prostate cancer. Cervical cancer treatments are always of intracavitary nature, but they are often combined with an interstitial implantation of additional catheters. Cervical and prostate cancer are two of the main types of cancer tackled using BT, which is why they are further discussed in the following sections.

Cervical and prostate cancer

Cervical cancer is the second most common cause of cancer death in females.[12] The most common treatment for locally advanced cervical cancer consists of EBRT with concomitant cisplatin-based chemotherapy, which is then followed by BT.[5] The latter can rarely also be used alone as treatment for early-stage cervical tumors, but is mostly used as a boost, either as a postoperative treatment or after EBRT in inoperable patients. The 5-year disease-free survival rate of a treatment including chemoradiation and BT was found to increase from 69.3% to 76.7% as compared to chemotherapy and surgery.[5] In all cases, this type of intracavitary BT predominantly uses HDR and remote afterloaders, since LDR (and PDR) entails an increased risk of manual error (*e.g.*, during selection and implantation of the sources) as well as higher radiation doses to physicians and assistants.[13] While dose fractionation and survival and complication rates in LDR are historically more established and have been confirmed by data and experts, HDR is much more promising in relation to adaptive image-guided BT, allowing the technique to grow with modern imaging modalities. There are no proven benefits of HDR as compared to LDR in terms of local control and target coverage – only late complications and toxicity are found to be slightly reduced in HDR.[14]

BT is also one of the most used treatments for prostate cancer, the second most common type of cancer in men worldwide, since it is minimally invasive, and has been shown to lead to fewer side effects (such as potency or urination disorders) with similar 10-year survival rates as radical prostatectomy.[15] It can both be used as a sole therapy in patients with expected survival of at least 10 years, or as a boost after EBRT for patients who are symptomatic or have an unfavorable intermediate risk factor.[5] HDR BT has been on the rise over the past 20 years, but LDR permanent ^{125}I (or sometimes ^{103}Pd or cesium-131 (^{131}Cs)) seed implantation is still widely used, especially in tumors that have not spread beyond the prostate gland.[15] This can be due to the interstitial nature of the procedure, which is by definition more invasive than intracavitary BT. If one adds to this that multiple implantations are necessary for HDR, and that the number of catheters used is higher for prostate cancer than *e.g.*, for cervical cancer, choosing LDR over HDR limits the invasiveness of the procedure. However, HDR is generally believed to give rise to a higher rate of erectile preservation than LDR,[16] though not all studies agree.[17] Furthermore, HDR is often associated with a higher radiobiological advantage.[18] The final choice between HDR, LDR, and PDR is therefore highly dependent on the patient, physician, patient geometry, and tumor properties.[19]

Workflow

In order to unfold the role of modern medical imaging in relation to BT, it is essential to be guided by the workflow of a standard image-guided BT treatment. Examples of used imaging modalities differ per cancer type and include MRI, CT, US, or even PET – specific choices for each of the steps for cervical and prostate cancer are laid out in the following section. The mentioned workflow is visualized in Figure 1, which is kept as general as possible with the intention of being broadly applicable across BT procedures for breast, prostate, and cervical cancer. Medical imaging precedes the start of the actual BT procedure and

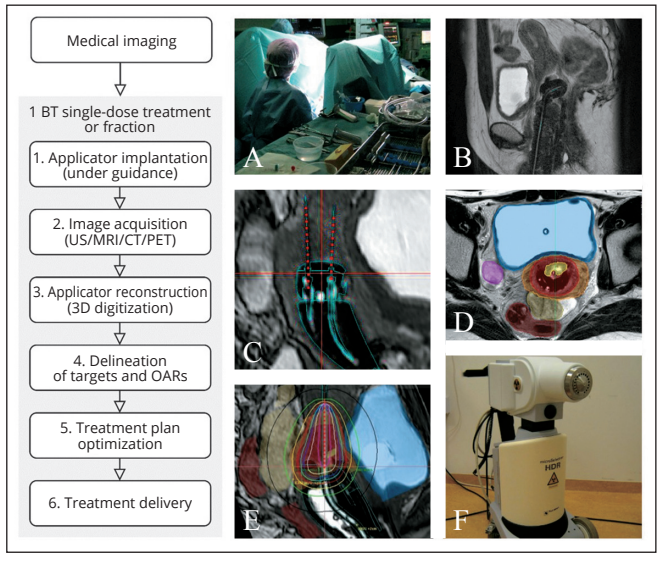

Figure 1.—Succession of steps before and during one single-dose treatment or fraction of a standard BT treatment. The cervical cancer case is used as an example for the illustrations: A) surgical implantation of the applicator and potentially catheter(s); B) image acquisition with applicator/catheter(s) in place; C) applicator/catheter reconstruction (turquoise in the online version), the dots (red in the online version) denote active dwell positions; D) organ and target delineation; E) treatment plan optimization, the dose distribution is visible through isodose lines; and F) an afterloader used for propagation of the radioactive source in order to deliver treatment.

includes imaging used for diagnosis and preplanning. The BT workflow of one single-dose treatment or fraction can be subdivided into six different steps as follows.

First, after the kind of applicator and/or number of catheter(s) to use have been chosen based on patient and tumor geometry, they are implanted in the patient. This is considered a surgical procedure during which the patient is under general or spinal anesthesia, and for which real-time image guidance is often used. Then, with the applicator/catheter(s) in place, a more precise image of the implanted instruments and their exact location is obtained using one of different imaging modalities. Next, the applicator/catheter(s) are reconstructed, which means being digitized into a 3D reconstruction using available software. Subsequently, based on the imaging and other clinical findings, the OARs and targets are delineated. At some institutes this is first done by a radiation treatment technologist, but always with a check (and adjustment if necessary) by a radiation oncologist. Thereafter, during treatment plan optimization, a treatment plan, consisting of a set of dwell times for each of the dwell positions, is optimized with respect to aspiration values regarding the minimum (target volume) and maximum (OARs) amounts of dose for the given patient. Finally, the radioactive sources are introduced into the catheters using an afterloader, and according to the optimized treatment plan the therapeutic doses are delivered.

It is worth noting that for LDR BT, the treatment ends after step 6 (as shown in Figure 1), followed by a seed extraction procedure if the seeds are meant to be non-permanent. For HDR cervical cancer BT, steps 1-6 correspond to one fraction and are thus repeated 2-4 times with intervals of days to weeks, depending on the local clinical practice. During PDR, the applicator/catheter(s) are usually not removed between fractions, which are then called pulses.

Imaging techniques

The portrayed workflow reveals that medical imaging is utilized at three distinct times in relation to a BT procedure. Firstly, imaging done before the treatment itself serves for preplanning purposes in terms of applicator/catheter choice. Secondly, it provides guidance during the applicator/catheter implantation phase. Thirdly, images obtained after applicator/catheter insertion are the basis for 3D applicator/catheter reconstruction and OARs and target delineation. The following sections provide an overview of different imaging modalities used for cervical and prostate cancer.

Cervical cancer

Before a cervical cancer patient is treated with BT for the first time, imaging for diagnostic purposes is done, at the tumor detection stage and potentially after tumor regression following EBRT treatment. An EBRT treatment is planned based on a planning CT, as well as a diagnostic T2 weighted MRI. EBRT involves several daily treatments (fractions). Cone-beam CT is used for daily pretreatment patient setup verification. Therefore, when EBRT preceded the BT treatment, the cone-beam CT scans are utilized for BT preplanning, while otherwise, MRI scans are used. It is worth noting that these are the most general choices, but standard clinical practice at specific local clinics can of course diverge.

With regard to applicator and potentially catheter implantation guidance for HDR cervical cancer BT, US is the current golden standard, since it offers real-time images, while being cheap, easy to use, and widely available.[20] As to post-implantation image acquisition to serve as the basis for OARs and target delineation, MRI is highly recommended, its main benefit being the easy discrimination between the cervix soft tissue and the tumor. It also displays unique properties of functional imaging that allow for dose painting, *i.e.*, targeting areas with increased radioresistance.[2] However, the applicator, catheters, and OARs are often at least as easily recognizable in CT images.[21] An advantage of the latter is that uterine perforation, which is one of the most well-known complications, is easily detectable.[22] Some studies claim that PET is another accurate method for cervical cancer treatment planning,[23] but clinical studies are limited. All in all, MRI is the preferred modality, but CT is widely accepted in smaller-scale hospitals with reduced MRI availability.

Prostate cancer

US is sufficient for preplanning in prostate cancer cases and then provides the basis for the choice of catheter number and source/seed positions, but MRI is becoming increasingly popular.[24] Then, regarding image-guidance, comparably to cervical cancer, transrectal US is conventionally most widely used for guidance during catheter implantation since it gives an outstanding view of the prostate gland and is easily applicable.[25] There are nonetheless observable errors that arise during US-based catheter reconstruction due to bright echoes and shadow artefacts.[2] Hence, as a basis for postimplant dosimetry, most frequently CT imaging is used, which provides an easy identification of the implanted seeds and catheters for LDR and HDR treat-

ments, respectively. Since, however, the delineation of the prostate itself (and of the OARs) can be difficult because of the ineffectiveness of CT scans in distinguishing soft tissues such as the prostate base or apex, MRI has been used more and more since 1997 - whenever available.[26] PET imaging has merely shown limited sensitivity for the detection of prostate cancer, and no clinical studies addressing the use of PET within BT have been conducted.[27]

Dosimetric optimization

For BT treatment planning, doses given by the set of dwell positions and dwell times are calculated before treatment delivery, as depicted in Figure 1. For breast, prostate, and cervical cancer, affected tissues are of limited density; therefore, the patient is approximated as containing purely water. The detailed dose calculations, followed by the clinical objectives in order to optimize the resulting calculated dose distribution, are presented below.

AAPM TG-43 formalism

The international standard for dose calculations in BT is since 2012 the AAPM TG-43 formalism.[28-32] It includes a description of the accepted available sources, corresponding datasets, and source production and handling. The recommended dose calculation formalism is divided into a one-dimensional (1D) and a two-dimensional (2D) dose-rate equation. These are defined for a point of interest P(r, θ), in which r denotes the distance from the center of the source to the point, and θ denotes the polar angle between this point relative to the source longitudinal axis. For the reference point $P(r_0, \theta_0)$, r_0 denotes the reference distance of 1 cm from the source, and the reference angle, θ_0, defines the source transverse plane, and equals 90°.[30] The 2D dose-rate is then defined by:

$$\dot{D}(r,\theta) = S_k \cdot \Lambda \cdot \frac{G_L(r,\theta)}{G_L(r_0,\theta_0)} \cdot g_L(r) \cdot F(r,\theta)$$

where S_K symbolizes the air kerma strength and Λ the dose rate constant, $G_L(r,\theta)$ represents the geometry factor for a line-source (L) approximation, $g_L(r)$ is the radial dose function, and $F(r,\theta)$ corresponds to the 2D anisotropy function.

Clinical objectives

The TG-43 formalism allows for the calculation of the dose rate for different dose calculation (DC) points in the MRI/CT images, but the specific clinical goals must still be defined. To this end, radiation oncologists first define a planning-aim dose, equivalent to the dose deemed sufficient for tumor treatment. They then also make use of parameters called dose-volume indices, which designate maximum and minimum doses that cover a given volume of an organ, and maximum and minimum volumes of an organ that are covered by a specific amount of dose. In this way, clinical goals are clearly defined and can thus provide a basis for the optimization of the doses in the treatment plan, based in turn on dose rate calculations of the DC points within the delineated target(s) and OARs. Different doses are naturally defined by a different combination of dwell times for each of the dwell positions. It is also worth noting that for some types of cancer such as that of the cervix, the clinical protocol includes dose-point indices, representing maximum doses given to specific locations with respect to the applicator or organs.

Because of the necessity to include multiple different dose-volume indices for all organs and regions of interest, the optimization is of an inherently multi-objective (MO) nature. This is caused by conflicting objectives: target volumes should be covered as much as possible with the planning-aim dose, whereas OARs should receive as little dose as possible. The problem at hand therefore has multiple optimal solutions with different trade-offs between the objectives. Apart from manual optimization, different algorithms are used for treatment planning optimization: deterministic methods such as the Nelder–Mead simplex (NMS) and stochastic ones like simulated annealing (SA).[33] While these types of algorithms generate one single treatment plan, MO optimization methods approximating a Pareto front of multiple plans, of which the radiation oncologist can then pick one, have recently been developed for prostate HDR BT.[34, 35] Studies show that physicians prefer plans automatically optimized in this way over the manually optimized clinical plan,[36] as is also the case for other optimization approaches for prostate[37] and cervix HDR BT.[38]

Outlook

The future of image-guided BT is mostly comprised of automating processes that are currently done by hand. An example would be organ delineation that is carried out by radiation treatment technologists or radiation oncologists, which can be error prone and most of all time consuming. Therefore, numerous studies focus on developing machine learning algorithms in order to automatically detect targets and organs based on many previously delineated images.[39, 40]

The automation of the applicator/catheter reconstruction

step can be accomplished through electromagnetic tracking.[41, 42] For this approach, induction coils are inserted into the applicator or into the catheters such that when they are placed in an area under a field generator, their precise position and orientation can be determined. Currently, only preclinical studies for interstitial BT have been conducted: as part of the afterloader as a position assessment method between implantation and treatment,[43] and as an integration into US-guided HDR prostate BT.[44] Furthermore, as for delineation, deep learning is another method for automatic catheter detection and reconstruction.[45]

Another promising method of BT treatment consists in online imaging, which strongly differs from the workflow presented in this article in that all imaging and dose delivery is carried out in the same room.[46] Advantages include increased patient comfort, efficient use of resources, and higher imaging precision due to decreased patient and therefore organ movement. On-site use of US is already part of the clinical practice for prostate treatments at some institutes[24] and has laid out the groundwork needed for MRI integration,[47] which recently has been successfully applied at some treatment centers.[48]

There is naturally also other research which could lead to better future treatment quality in BT. First, examples of biologically based optimization include taking into account individual patients' tumor and normal tissue biological characteristics, as well as the use of radiosensitive nanoparticles in order to enhance radiation doses given to the tumor. Then, biomarkers can be used for diagnostic, prognostic, and predictive reasons, and facilitate studying precise biological molecules and pathways related to the procedure. Finally, self-shielded applicators, of which the most advanced ones are applicable to intracavitary types of BT, allow for intensity and direction modulation.[49]

Radioactive iodine seed use in breast cancer treatment

Overview

Radioactive ^{125}I seeds consist of a welded titanium capsule containing ^{125}I adsorbed onto a nickel/copper coated, gold-cord aluminum wire. ^{125}I has a half-life of 59.41 days and decays by electron capture with the emission of characteristic photons and Auger electrons. The seeds were developed for BT which is described in the previous section. In 2001 radioactive seed localization (RSL) was introduced as an alternative tumor localization technique[50] in breast cancer surgery. With RSL, a radioactive ^{125}I-labelled seed is preoperatively implanted in the center of the tumor area using ultrasonic or stereotactic guidance. The surgeon uses a gamma detector probe during surgery to localize the ^{125}I seed and thus the tumor center (Figure 2).

Table I summarizes the current clinical applications of radioactive ^{125}I seeds when treating patients with breast cancer.

The seeds of the different brands[51-58] vary little with respect to design, dose-rate constant, anisotropy function, radial dose function, and anisotropy factor. Additionally, all types are approximately of the same size (±4 mm long axis, 0.8 mm short axis), a typical example is presented in Figure 3.

Different institutes used a variety of activities, ranging from 3 to 13 MBq. In the more recent studies, a trend is evolving towards the use of seeds with lower activities (even below 3 MBq). This might be the result of a changing paradigm, from the early days when hot ^{125}I BT seeds were used, to a more standardized procedure in which low-activity ^{125}I seeds dedicated for RSL are used.

Breast cancer

Breast cancer is the most common type of cancer in women worldwide.[59] Breast cancer treatment consist of a multidisciplinary approach combining surgery, radiation treatment, and systemic treatment. The last few decades this multidisciplinary treatment was focused on patient and tumor tailored treatment resulting in de-escalation of treatment whenever possible. A large shift in surgery de-escalation started when large prospective randomized trials showed that survival rates between patients that underwent breast conserving treatment, consisting of breast conserving surgery (BCS) followed by radiation treatment

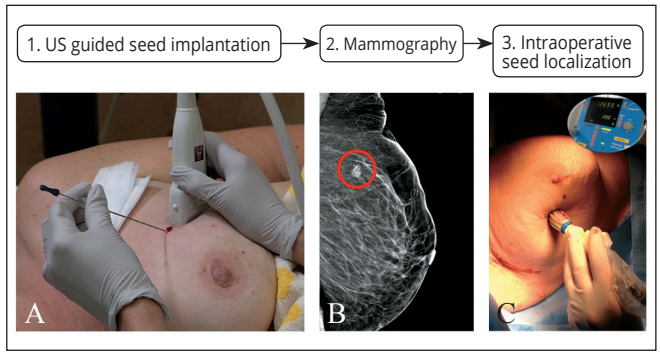

Figure 2.—Succession of steps during RSL: A) implantation of an ^{125}I seed by US guidance; B) post-implantation mammography to validate the implantation location; and C) intraoperative ^{125}I seed localization while using a gamma probe.

TABLE I.—*Current clinical applications of radioactive seed localization for breast cancer treatment.*

	Localization in the breast	Localization in the axillary nodes
Diagnostics	Diagnostic excision of breast lesion	Diagnostic excision of lymph node
Primary breast conserving surgery	In non-palpable breast cancer In non-palpable multicentric breast cancer In non-palpable DCIS In eDCIS (multiple seeds)	
Breast conserving surgery after NST	In T1-2-3 breast cancer treated with NST	
Axillary staging after NST		In cNplus breast cancer patients treated with NST MARI procedure TAD procedure RISAS procedure

DCIS: ductal carcinoma *in situ*; eDCIS: extensive DCIS; cNplus: clinical node positive; MARI: Marking of Axillary lymph node by Radioactive Iodine seed; NST: neoadjuvant systemic therapy; RISAS: Radioactive Iodine Seed localisation in the Axilla in axillary node positive breast cancer combined with a Sentinel node procedure; TAD: targeted axillary dissection; T1-2-3: T categories for breast cancer (T1: tumor size is 2 cm or less across; T2: tumor size is more than 2 cm but no more than 5 cm across; T3: tumor size is more than 5 cm across).

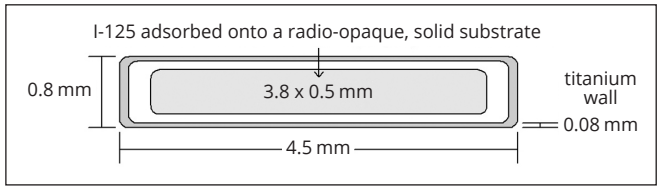

Figure 3.—Schematic and measurements of a radioactive ^{125}I seed.

(RT), and mastectomy were similar.[59-61] Therefore, today more than 60% of breast cancer patients are being treated with BCS.

Following the introduction and improvement of different breast screening programs, more early-stage and non-palpable tumors, including both invasive cancer and ductal carcinoma in situ (DCIS), are being detected.[51] In addition, the use of neoadjuvant systemic therapy (NST) is increasing. These NST regimen have been increasingly tailored to specific patient and tumor characteristics, resulting in effective downsizing of the tumor before surgery to lesions that are suitable for BCS instead of mastectomy.[62, 63] NST based on tailored therapy regimens even leads to many pathologic near-complete or complete responses, resulting in many more non-palpable lesions.

The main goal of BCS is removal of the whole tumor, surrounded by a margin of healthy breast tissue. Simultaneously, the surgeon aims to spare as much healthy breast tissue as possible to ensure good cosmetic outcome. Especially in non-palpable lesions, BCS is challenging. To improve the surgical outcome of BCS for non-palpable lesions, several tumor localization methods have been developed. Currently there are three important techniques for tumor localization prior to surgery: wire-guided, ultrasound guided, and radio-guided localization. For more than 20 years, the standard method has been wire-guided localization (WGL). This involves a wire being inserted into the center of the tumor under ultrasound or stereotactic guidance shortly before surgery. During surgery, the wire is used as a guide to estimate the center and borders of the tumor. Several studies have shown that WGL is associated with high rates of positive resection margins, varying between 13 and 58%.[55-65] Other major disadvantages of WGL are possible dislocation of the wire, patient discomfort, and poor cosmetic outcome.[66-68]

Intraoperative US is another technique that provides perioperative visualization of the tumor and has been shown to lead to fewer positive resection margins than WGL.[69, 70] With US guided localization the tumor borders are visualized during the surgical procedure. However, since not all tumors are visible on US, for example DCIS or tumors with a complete clinical response after NST, the use of US is still limited in clinical practice.

With radio-guided localization techniques, the surgeon is guided by a radionuclide. One method is the Radioactive Occult Lesion Localization (ROLL) in which a small amount of radioactive liquid technetium is injected into the tumor, shortly before surgery. The location with the highest radioactive signal is subsequently localized during surgery with a portable gamma probe. However, the diffuse uptake of technetium in the breast hampers precise tumor localization. In order to overcome this issue, RSL has been developed in which a radioactive ^{125}I seed is preoperatively implanted.[50, 71-75] For localization of unifocal spherical tumors the ^{125}I seed is preferably implanted in the center of the tumor, using US or stereotactic X-ray guidance. Similar to ROLL, a gamma probe provides intraoperative guidance to the radioactive ^{125}I seed and thus the tumor location. With RSL the surgeon is guided by point-source localization of the ^{125}I seed, instead of the dif-

fuse radioactive signal throughout the breast with ROLL. Transcutaneous measurements with the gamma probe determine the location of the maximum ^{125}I-gamma counts, which is marked on the skin, and subsequently the incision is made at this site. The gamma probe is further used to guide the excision of the ^{125}I-seed and lesion. Correct ^{125}I-seed removal is confirmed by a measurement of no ^{125}I-signal in the wound and an ^{125}I-signal measurement in the excised specimen (Figure 2).

Several randomized clinical trials and cohort studies have shown that, firstly, the use of ROLL or RSL results in lower rates of incomplete tumor removal and re-excisions when compared to WGL. Secondly, cosmetic outcome improved.[76, 77]

RSL has several advantages over ROLL. The point-source activity of the seed used in RSL allows more precise tumor localization in comparison with the diffuse activity of the liquid ^{99m}Tc-labelled tracer. Furthermore, multiple seeds could be used to bracket the edges of extensive DCIS or multifocal invasive tumors; this has been demonstrated previously using multiple wires in, for example, large clusters of calcifications.[78-80] Another advantage of ^{125}I-labelled seeds is the long half-life of 59.41 days, allowing seed implantation up to 12 months before surgery, which is useful in patients treated with NST.[53, 75-81] Even after completion of several courses of NST, which can be several months after seed implantation, the radioactive signal of the ^{125}I seed can still be localized at the time of surgery, guiding the surgeon towards the original tumor location.

Finally, seed implantation is also possible in metastatic axillary lymph nodes before the start of NST in order to tailor axillary treatment after NST. Tumor-positive axillary lymph nodes can be marked with a seed before NST and selectively removed after NST to analyze axillary response, a procedure known as MARI (Marking of Axillary lymph node by Radioactive Iodine seed).[82, 83] For this purpose, an ^{125}I seed (STM1251, Bard Brachytherapy Inc., Carol Stream, IL, USA) with an apparent activity varying from 0.2 to 1.0 MBq at time of implementation was placed under ultrasound guidance in the largest pathology proven tumor-positive axillary lymph node (*i.e.*, MARI-node) prior to the start of the first NST cycle. The activity of ^{125}I seeds used for MARI-node localization is lower than for breast tumor localization (apparent activity 1.0–7.6 MBq) to minimize irradiation of the node. The MARI procedure was introduced in 2008 at the Netherlands Cancer Institute. We first showed that the MARI-procedure has a false negative rate of 7% for predicting pathologic complete response (pCR) in the additional axillary nodes. Marking the positive axillary nodes with a conventional marker (*e.g.*, a hydrogel-based biopsy marker) before NST followed by placement of an ^{125}I seed after NST, just before surgery, has also been described. When combining this with a sentinel lymph node biopsy (also known as targeted axillary dissection), a false negative rate of 4% can be reached[84] as was also shown in the Dutch RISAS trial.[85] It is therefore possible to stage the axilla adequately after NST, with a false negative rate below 10%.

Hereafter, an axillary treatment protocol was developed (*i.e.*, MARI-protocol) which combined the outcome of the MARI-procedure (ypMARI-neg or ypMARI-pos) with a pre-NST acquired fluorodeoxyglucose (FDG)-PET/CT scan to determine the presence of less or more than four tumor-positive axillary lymph nodes (ALNs) (cN(<4) or cN(4+)) prior to NST. Patients staged cN(<4), ypMARI-neg received no further axillary treatment, patients staged cN(<4), ypMARI-pos and cN(4+), ypMARI-neg received axillary radiation treatment (ART), and patients staged cN(4+), ypMARI-pos received axillary lymph node dissection (ALND) plus ART (Figure 4).[86, 87]

We have recently demonstrated that MARI-protocol is an effective axillary staging and treatment protocol which resulted in omission of ALND in 80% of cNplus patients undergoing NST while maintaining excellent three-year axillary- and regional recurrence free survival rates of 98% and 96%.[88]

Implementation of RSL in the clinic; an example

As mentioned in Table I and explored above, there are several useful applications for the introduction of ^{125}I seed localization in the clinical workflow for breast cancer treatment.

Although ^{125}I seeds are increasingly being used for tumor localization due to improved surgical planning and diminished patient discomfort, extensive regulations often apply for handling and disposal of the seeds requiring extensive protocols and administrative work[89] which may keep people from starting this type of localization technique.

For instance, despite the dose of the seeds used in RSL for the breast being low, in the Netherlands, RSL in the breast requires authorization by the government and some safety issues need to be addressed.[52] More specifically, personnel handling the ^{125}I seed are required to receive training in radiation safety. In addition, the seed should be traceable during all phases of care with an electric accompaniment form containing the dose at time of implantation. Next, to confirm correct placement of the seed, patients

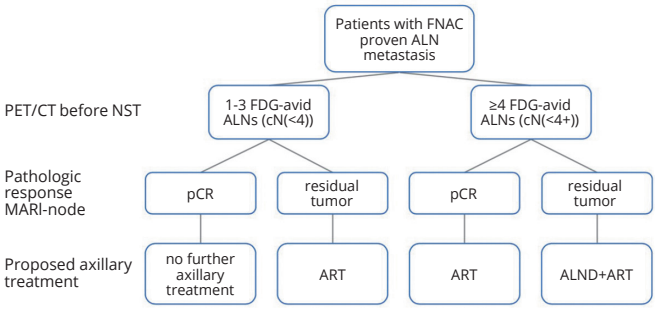

Figure 4.—Axillary treatment protocol at the Netherlands Cancer Institute for patients presenting with axillary disease before NST.
FNAC: fine-needle aspiration cytology; ALN: axillary lymph node; PET/CT: positron emission tomography combined with computed tomography; MARI: marking axillary lymph nodes with radioactive ^{125}I seeds; pCR: pathologic complete response; ALND: axillary lymph node dissection; ART: axillary radiation treatment.

receive mammograms directly after RSL; whenever the seed is not visible, other imaging is applied to visualize the location of the seed. Further, after placement of the resection specimen in the cup used for transportation to the pathology department, the resection specimen needs to be scanned with a gamma detector probe to confirm the presence of the ^{125}I-labelled seed. The excision cavity in the breast must be scanned with a gamma detector probe to ensure removal of the seed from the patient.[90] Special care needs only to be taken in case of contact with small infants. All in all, it is worth noting that national regulations on radioactive seed handling can differ, and it is therefore essential to get acquainted with and follow them when clinically introducing RSL.

However, the effort of implementing RSL is worthwhile and is only a hazzle in the beginning. An example of implementation which could encourage others is given by our institute: at the Netherlands Cancer Institute we treat around 500 to 600 newly diagnosed breast cancer patients per year. RSL was implemented in 2008. In Figure 5A we show the total amount of ^{125}I seeds being used over the years. It is visible that the implementation of RSL took about 5 years, and that, since then, RSL is routinely being used in our daily clinical practice. In Figure 5B we show the use in one year (2020) in both the breast and axillary nodes.

Summary

RSL is an increasingly popular technique to localize breast lesions and/or axillary nodes as part of breast cancer treatment. It provides many clear advantages over other localization procedures used. RSL adds flexibility to the clinical schedules as well as the planning of the localization approach and surgical incision site. RSL allows more accurate lesion localization and improves patient satisfaction in comparison with *e.g.*, wire localization. Safety measures must be employed when radioactive seeds are used, including guidelines and precautions for the safe and secure handling of the radioactive seeds to prevent any mishaps.

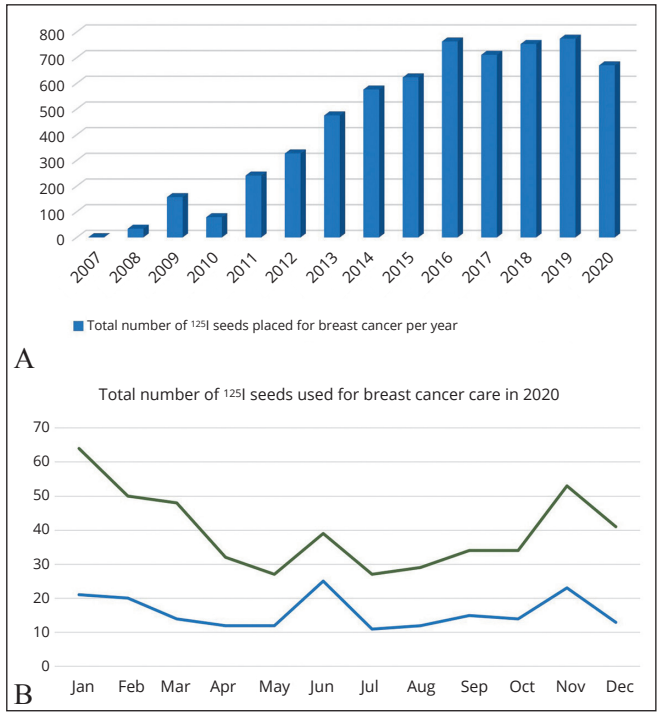

Figure 5.—A) The total number of used ^{125}I seeds used for breast cancer care at the Netherlands Cancer Institute over the last 10 years. B) The total number of ^{125}I seeds used for breast cancer care at the Netherlands Cancer Institute in 2020. The dark line (green in the online version) represents the number of seeds placed in the breast, the light line (blue in the online version) the number of seeds placed in an axillary node for the MARI procedure.

Conclusions

Today, radioactive sources have a variety of therapeutic applications. Key examples of this are image-guided brachytherapy for prostate and cervical cancer in which the sources are directly used for treatment purposes, while radioactive seed localization for breast conserving surgery demonstrates that they can also be used for real-time guidance during surgery. Once incorporated in the clinical workflow, both procedures present advantages in setup, efficiency, and/or outcomes when compared to respective alternative methods.

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