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Radioactive seed immobilization techniques for interstitial brachytherapy

K. Yan
Thomas Jefferson University

T. Podder
Thomas Jefferson University

I. Buzurovic
Thomas Jefferson University

Y. Hu
Thomas Jefferson University

E. Messing
University of Rochester

See next page for additional authors

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Authors

K. Yan, T. Podder, I. Buzurovic, Y. Hu, E. Messing, D. Rubens, A. Dicker, R. Valicenti, N. Sarkar, W. Ng, and Y. Yu

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K. Yan[1], T. Podder[1], I. Buzurovic[1], Y.Hu[1], E. Messing[1], D. Rubens[1], A. Dicker[1], R. Valicenti[1], N. Sarkar[1], W. Ng[2] and Y. Yu[1]

[1]*Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA*

[2]*School of Mechanical & Aerospace Engineering, Nangyang Tech. University, Singapore*

Phone: 01-215-955-6043

Email: Kaiguo.Yan@jeffersonhospital.org

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ABSTRACT

Purpose: In prostate brachytherapy, seeds can detach from their deposited sites and move locally in the pelvis or migrate to distant sites including the pulmonary and cardiac regions. Undesirable consequences of seed migration include inadequate dose coverage of the prostate and tissue irradiation effects at the site of migration. Thus, it is clinically important to develop seed immobilization techniques.

Methods: We first analyze the possible causes for seed movement, and propose three potential techniques for seed immobilization: (1) surgical glue, (2) laser coagulation and (3) diathermy coagulation. The feasibility of each method is explored. Experiments were carried out using fresh bovine livers to investigate the efficacy of seed immobilization using surgical glue.

Results: Results have shown that the surgical glue can effectively immobilize the seeds. Evaluation of the radiation dose distribution revealed that the non-immobilized seed movement would change the planned isodose distribution considerably; while by using surgical glue method to immobilize the seeds, the changes were negligible.

Conclusions: Prostate brachytherapy seed immobilization is necessary and three alternative mechanisms are promising for addressing this issue. Experiments for exploring the efficacy of the other two proposed methods are ongoing. Devices compatible with the brachytherapy procedure will be designed in future.

Keywords: Seed movement, Seed immobilization techniques, Interstitial Brachytherapy

1 Introduction

Prostate cancer is one of the leading causes of cancer death in American men. In 2007, the National Cancer Institute (NCI) estimated new prostate cancer cases in the United States are 218,890, and around 27,050 persons will die from prostate cancer [1]. With the advent of prostate-specific antigen (PSA) screening, most prostate cancer diagnosed is made in the early stages. An increasingly used option in the management of early-stage prostate cancer is transperineal interstitial permanent prostate brachytherapy (TIPPB), which is an outpatient procedure to carefully place the radioactive “seeds” inside of the cancerous tissue in a manner that will deliver a tumorocidal dose most efficiently [2]. Except for prostate cancer, other diseases now treated with brachytherapy include cervical cancer, endometrial cancer, and coronary artery disease. Brachytherapy has been proven to be very effective and safe, providing a good alternative to surgical removal of the prostate, breast, and cervix, while reducing the risk of certain long-term side effects.

In brachytherapy, depending on different variables, normally around 50 - 100 radioactive seeds are implanted into the prostate using long, slender needles (200mm long, 1.3-1.5mm diameter). The types of seed also vary and may include Iodine-125, Palladium-103, and echnogenic Iodine-125 seeds. A typical seed is a titanium capsule (0.8mm in diameter and 4.5 mm in length), which contains a radioactive isotope and a marker made of radio-opaque material for identification in computed tomography (CT) and X-ray images. The seeds provide significant radiation dose to a relatively small volume, which requires accurate seed placement to ensure complete treatment. Sensitivity of the urethra and rectal mucosa to radiation are other factors that heighten the need for careful seed placement.

In TIPPB, it is a known phenomenon that seeds can detach from their insertion sites and move locally as well as migrate to distant places like the pulmonary region and cardiac region. By way of the same pathway, seeds may enter the systemic circulation through right-to-left cardiac shunts [3]. In 1988, Hempel *et al.* reported seed movement on a patient who underwent interstitial therapy for carcinoma of the anus and was later found to have metallic seeds on a chest X-ray [4]. Subsequently, the increased use of TIPPB has led to multiple reports of radioactive seed migration to the chest [5]-[14]. Several clinicians have reported seed migration for about 30-40% of the patients that they have treated and the number of migrated seeds ranging from 1 to 10 per patient [16, 17]. The occurrence and number of seed migration vary with the patient and treatment variables. Two possible consequences of seed migration are inadequate dose coverage of the prostate [15] and potential effects of tissue irradiation at the site of migration. Although stranded seeds embedded in vicrylsutures migrate less (about 1%) than loose seeds (about 10%) [17]-[19], to accurately deliver the linked seeds is quite challenging. Therefore, the actual delivered dose may significantly deviate from the planned dose.

Murali *et al.* [23] shows that there is no consistent relationship between the movement and the type of seeds used. Up to date, the exact mechanism for seed movement is still unknown. In this paper, we first analyze the possible causes for seed movement, and then propose three potential techniques for seed immobilization: (1) surgical glue, (2) laser coagulation and (3) diathermy coagulation. A rocking platform has been designed and fabricated for seed movement and local migration experiments. Experiments have been carried out to first prove that the seeds implanted into the animal tissue phantom will move when rocking in current platform. After that, seed immobilization experiment is performed with the surgical glue. Details are presented in the following sections. Discussion and future work are given at the end.

2 Investigation of Causes of Seed Movement

It is important to understand the possible causes of seed movement and migration for developing feasible seed immobilization techniques. In this section, we investigate several possible causes of seed movement, as discussed below.

Vacuum created during needle withdrawal: During needle penetration, the pressure in the needle channel is similar to that of the atmosphere, since small gaps between the cannula and stylet allow air to flow freely. Upon withdrawal of the stylet and cannula, a small amount of air may be trapped within the prostate, which can form a vacuum. This small pressure difference can create a suction force on the seed and thus pull the seed along as the needle is withdrawn. Some researchers and physicians have reported such phenomena [24, 25].

Collision of needle and deposited seeds: Due to needle bending, tissue deformation and lack of efficient imaging guidance during needle insertion, some needles may collide with seeds deposited earlier. Such collision can also shift the deposited seeds positions.

Prostate edema: Due to the blockage of blood vessels by the intruding needles and tissue injury, prostate edema occurs during brachytherapy, which can increase the size of the prostate by around 20-130% [25, 30], and thus result in the seed displacement in later imaging.

Presence of cysts in prostate: The prostate may contain tiny water sacs or cysts. At the prostatic urethra region, bodily fluid could be released from the surrounding walls due to traumatism, which can move the free seeds. In some extreme cases, seeds may be placed accidentally into water sacs or cysts, thus causing seed movement.

Seed migration through blood vessel: The prostatic capsule has a rich venous plexus with vessels large enough to accommodate the small seeds. Seeds placed extraprostatically have access to this plexus and often migrate away from their intended position via access to the venous circulation. Through the venous pathway, seeds may be gradually carried by the blood flow and migrate through the inferior vena cava, right chambers of the heart and into the pulmonary circulation [3]. This process probably takes about one day. Thus, the seeds are normally not seen on chest radiographs obtained on the day of brachytherapy, but appear on subsequent radiographs as shown by Nag *et al.* [26].

Forces from prostate contractions, relaxations and from neighboring organs and muscle: If the prostatic tissue is loose due to aging or cancer etc., stretching and distortion of the prostatic tissue can contribute to the seed movement. In addition, as the prostate functions as a gland to create the seminal fluid required to nourish the sperm, the muscle fibers will contract and relax during sexual behavior, which can result in seed displacement. Even throughout the patients daily activities, the surrounding tissues and organs such as bladder, pubic bone, seminal vesicle, urethra and rectum may “bombard” the prostate constantly, thus causing seed movement.

3. Potential Seed Immobilization Techniques

Of the above mentioned causes, single or multiple causes may be enough to move some seeds away from the deposited place. Therefore, in this study, we mainly emphasize on seed immobilization techniques. Three of such techniques have been described below.

1) *Surgical glue:*

The sealing capability of various surgical glues has been studied and used by many researchers and clinicians [20]-[22]. The threat of getting infection from agents of the fibrin adhesive limits the widespread usage of the surgical glue in surgery, especially in the United States. Thus, the production of fibrin adhesive has been limited to quantities obtained from the patients own blood to reduce the risk, which makes it costly and time consuming. In this research, we propose to use a FDA approved surgical glue called BioGlue® Surgical Adhesive (Cryolife Inc., GA, USA) for seed immobilization. BioGlue is a two-component adhesive composed of purified bovine serum albumin (BSA), a cow protein, and a chemical called glutaraldehyde. The glutaraldehyde molecules covalently bond (cross-link) the BSA molecules to each other and, upon application to the tissue proteins at the repair site, create a flexible mechanical seal independently of the body's clotting mechanism. Premixing of glutaraldehyde with BSA eliminates the potential hazards associated with clinical applications. The whole glue seal will be absorbed by tissue in a few months. The advantages of using such fibrin glue are biocompatibility, biodegradability, decreased operative time, effective control of localized bleeding, and reduced postoperative blood loss. How effective the surgical glue in sealing the seeds is currently under investigation.

2) Laser coagulation:

Interstitial laser coagulation technique has been used to treat various neoplasms and benign prostatic hyperplasia (BPH) in recent years [27]-[29]. The laser energy can activate tissue bonds between the surgical surfaces, thus fusing them together. Irreversible tissue damage does not occur below 45°C. As the temperature rises to 45°C-50°C, there is damage to enzymes and cell membranes, which is described by the term hyperthermia. Denaturation of proteins occurs when tissue is heated to 60°C, giving rise to coagulation of tissue and necrosis of cells, which is visibly manifested by a whitish discoloration. Direct heating of the tissues may lead to considerable thermal damage of the tissue, hindering tissue regeneration. Thus, low strength anastomoses and thermal damage of tissue are of major concern. In this research, we will perform experiments to investigate the best tissue sealing sites for effective seed immobilization, and the optimal laser configuration (e.g. optimal power, exposure time and beam size, etc.) for minimum tissue overheating and seed damage. Based on this study, a special laser applicator will be designed to apply heat to the desired sites for seed immobilization.

3) Diathermy coagulation:

Diathermy is a method of using high frequency electric current to heat tissue for therapeutic purposes in medicine (e.g. cutting, destroying or coagulating tissue). Coagulating tissues with diathermy is possible because the tissue itself acts as the pathway through which electrical current travels. Coagulation requires a high enough voltage to produce sparks, but a low current. This can be achieved by intermittent short bursts of high voltages. The temperature of the cell increases when it is hit by sparks and returns during the prolonged period without any electron bombardment, which will result in coagulation. Diathermy has proven to be a major advance in surgery by minimizing blood loss, reducing operative time and providing a dry surgical field without the need to tie all blood vessels [25]. In this research, we will design and develop a device/system for monopolar diathermy, so that the required current can be precisely delivered to the desired location through brachytherapy needle cannula without shocking the patient and overcooking of the surrounding tissue.

4. Preliminary experiment for seed immobilization using surgical glue

Material and method

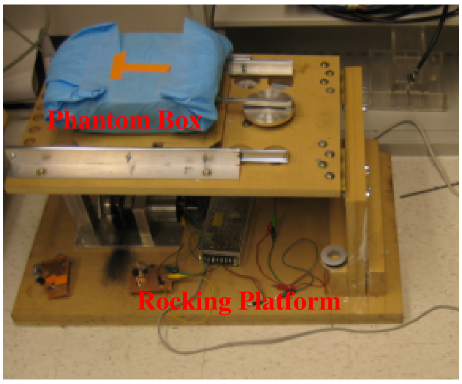
This paper presents the preliminary work for seed immobilization using surgical glue. A controlled delivery system, which consists of a reusable delivery device, applicator tips, and applicator tip extenders, is currently used to dispense the solution during the experiment as shown in Fig. 1 a. A motorized 2 degree-of-freedom rocking platform (Fig. 1 b) has been designed and fabricated, which can move both horizontally and vertically with adjustable speeds. At current stage, fresh animal organ (bovine liver) was used. Two long needles were inserted into the liver as references. The objectives of current experiments are

1) to prove that the seeds will move using current setting;

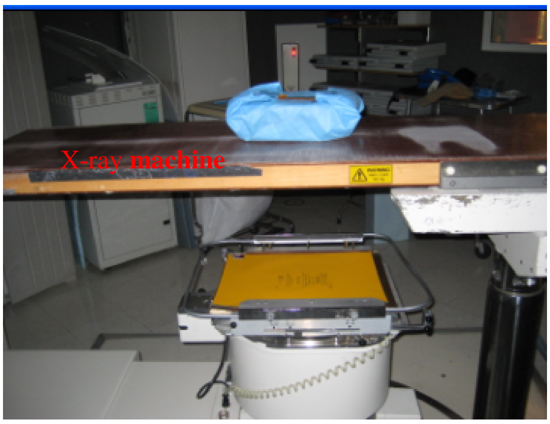
2) to test the effectiveness of seed immobilization using surgical glue.

After the seeds were implanted into the phantom, an initial X-ray scan was taken to record the reference positions of these seeds using an X-ray machine (Fig. 1 c), before putting the phantom onto the rocking platform to simulate accelerated testing scenario. Two subsequent scans were taken at around 10-h intervals to observe the seed movement.

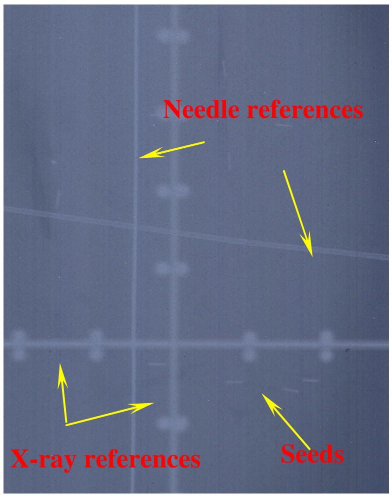
(a)



(b)



(c)



(d)

Figure 1: (a) delivery system for dispense glue (b) experimental setup (c) x-ray scanning of the phantom (d) X-ray scan of seed distribution and needle references

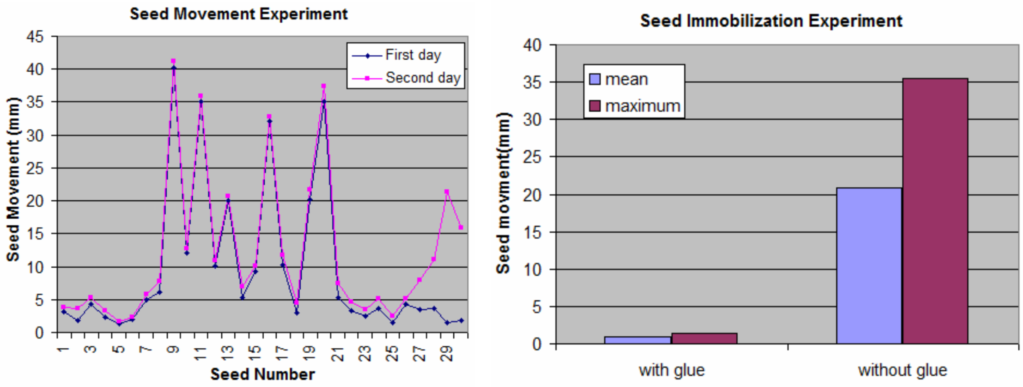
The current experiment setup has some limitations. The livers used in the experiment did not have the functions that a live organ would have, such as blood flow, which is an important cause for seed movement. The first trial with the setup shows that the seeds tend to be held in the sticky dead liver and can only move around 1-3mm even rocking by the platform. To overcome the limitation of the current experiment platform, water was put into the phantom box and dripped into the cut during seed movement and immobilization experiment to create some “blood flow” in the dead liver. It has showed (as presented below in Results and discussion) that this method can effectively move some of the free seeds not well-lodged inside the tissue during platform rocking. Since we use the same method in both types of experiments without and with surgical glue, the results are comparable.

Results and discussion

Three sets of seed movement experiments were carried out first, with ten seeds in each set. As observed from the X-ray scans, the seeds can move both parallelly and axially (even rotating) compared with their original reference orientations. The parallel movement was mainly caused by tissue deformation, which has been measured ranging from 1 to 2mm in current experiment. The axial movement that would carry the seeds away from the intended tissue position, was caused by tissue movement, blood flow, and so on, and currently is our main interest. The seed immobilization techniques that we are investigating focus on reducing the axial seed movement. The axial displacements of the 30 seeds in the seed movement experiment are shown in Fig. 2 a. As clearly shown in the figure, the seeds significantly moved in current setup. The maximum and mean movements are 41.1 and 12.2mm respectively, which provides a significant baseline and comparison for the following seed immobilization experiment.

BioGlue was used in the seed immobilization experiment. In each set, ten seeds were implanted into the phantom, of which five seeds were deposited with BioGlue, and the other five seeds were without BioGlue. BioGlue began to polymerize within 20 - 30 seconds and reached its bonding strength within 2min. The maximum and mean movements of the seeds without BioGlue are 35.5mm and 20.9mm respectively; while the ones with BioGlue are 1.1mm and 0.9mm (see Fig. 2 b), respectively. Currently, we only considered the seed movements in one x-ray scanning plane due to some imaging problem caused by the X-ray machine. The out-of-plane movement was neglected. In future, we will try to scan in another direction to accurately measure the seed movements.

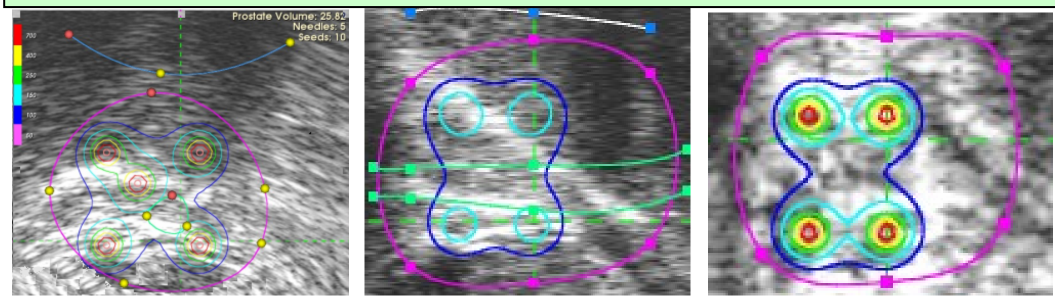
We evaluate the changes in radiation dose distribution using two sets of data, one from the seed movement experiment and the other from the seed immobilization experiment. A dosimetric plan was generated using a FDA-approved PIPER™ (Prostate Implantation Planning Engine for Radiotherapy) planning engine to determine the optimal distribution of seeds given a prostate size, patient histology and anatomy. Inverse planning method was chosen with prescribed dose 145Gy. Ten seeds (type I-125 Amersham 6711) were used in the plan and Air Kerma Strength per seed was 0.695U. The results are presented in Fig. 3. The original isodose distribution and distributions after applying the seed movements detected in seed movement experiment and seed immobilization experiment are shown in Fig. 3 a, b and c, respectively. As can be observed from the figure, the seed movement without applying BioGlue significantly affects the isodose distribution; while after using the BioGlue, the effects are neglectable (see sagittal and coronal views).



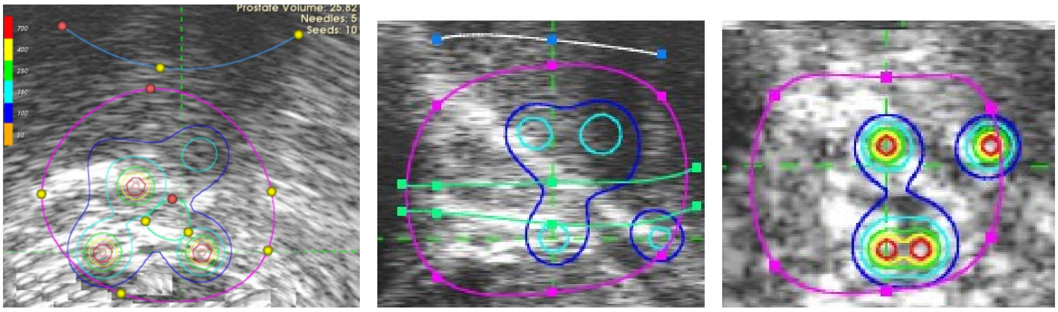
(a) (b)

Figure 2: Seed movement in two days (a) seed movement without glue (b) seed movement with & without glue

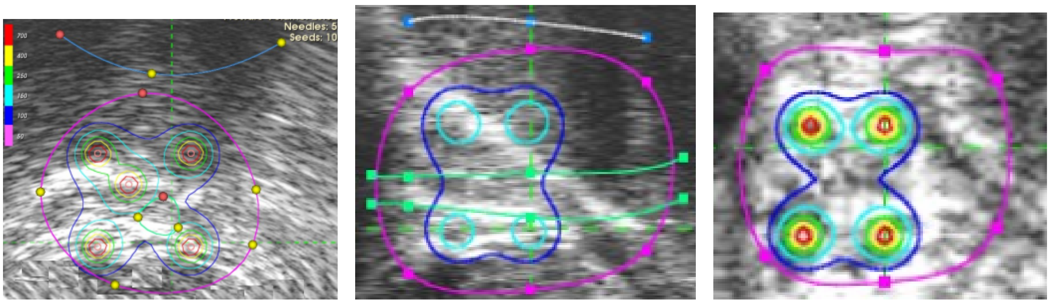
Transversal View	Sagittal View	Coronal View



(a)



(b)



(c)

Figure 3: Transversal (left), sagittal (middle) and coronal (right) views of isodose distribution. (a) original isodose distribution; (b) isodose distributions after rocking the tissue phantom with seeds without applying BioGlue; (c) isodose distribution after rocking and with application of BioGlue to immobilize seeds.

5. Future work

Experimental results have revealed that the surgical glue can effectively reduce the seed movements, thus can potentially deliver more accurate radiation dose as per the dosimetric plan. More experiments are ongoing for further investigation of this method. In the near future, we will also carry out experiments to investigate the efficacy of using laser and diathermy coagulation for seed immobilization. The optimal configuration of these two methods in achieving minimum seed movement, as well as least overheating of surrounding tissue will also be investigated. Devices compatible with the brachytherapy procedure will be designed to dispense the surgical glue, or deliver corresponding laser or diathermy coagulation.

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