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**Teresa Gawlik-Jakubczak, Marcin Matuszewski**

Klinika Urologii, Gdański Uniwersytet Medyczny

# Fiducial markers in the treatment of prostate cancer: technique and short term observation

**Address for correspondence:**

Dr n. med. Teresa Gawlik-Jakubczak

Klinika Urologii

Gdański Uniwersytet Medyczny

e-mail: teresaj@gumed.edu.pl

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## ABSTRACT

**Introduction:** Prostate cancer (PC) is one of the most common cancers in the elderly population. The incidence is constantly growing. Radiotherapy for PC is rapidly evolving, which contributes to better cancer control. The escalation of RT dose requires better target localisation in order to avoid RT complications. Fiducial markers are improvements widely used for better accuracy of radiation.

**Material and method:** We implanted gold markers to 56 patients with confirmed PC between January and August 2014. After the procedure we controlled complication rate and proper localisation of the markers.

**Results:** No serious complication occurred. We observed a few cases of epididymitis, dysuria, and blood trace in urine. Four patients lost one seed.

**Conclusions:** Implantation of fiducial markers is simple and save ambulatory procedure and improves the results of radical radiotherapy in PC due to exact positioning.

**Key words**: prostate cancer, radiotherapy, markers

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## Introduction

In Europe and United States prostate cancer is one of the most common male cancers [1]. The incidence in Poland in 2000 year was 8%. It was the third most common cancer in males after lung cancer (27%) and colon cancer (10%) [2]. Radical treatment options for local disease are radical prostatectomy or radiotherapy (brachytherapy or teletherapy). Current radiotherapy techniques compared to conventional 2DXRT are evolving towards dose escalation and more precise planning. However, we know that incidence of complication after radiotherapy depends on dose and amount of irradiated volume beyond the prostate margins. In order to improve the results of treatment new technologies, such as three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), were put to use worldwide in the last few years [3–5]. The procedures of treatment include applying many fractions, so it is crucial to repeatedly deliver radiation to target. Image-guided radiation therapy (IGRT) uses real-time imaging to mould radiation beams to the tumour. The linear accelerator delivers precise radiation dose different for the prostate, lymph nodes, seminal vesicles, and margins. Usually time of single irradiation in IMRT technique lasts 15–20 minutes. Using further refinement, such as RapidArc, improves dose conformity with significant shortening of treatment time to 5–7 minutes, so more patients can be irradiated during the day. RapidArc allows for changing simultaneously three parameters during treatment — rotation speed of gantry, shape of the treatment aperture using the movement of multi-leaf collimator leaves and delivery dose rate. Other way to further improve the radiotherapy results may be possible by better following inter-fractional movements of the treated organ.

Prostate is not prone to large movements but it may shift slightly depending on respiration and rectum or bladder filling [6, 7]. Motions are predominantly in

the posteroanterior and cephalocaudal directions. However, as both organs — bladder and rectum — are located very close to prostate, they may easily get into the irradiation zone with danger of serious complications, even with the very small movements. Bladder and, especially, rectum wall are very vulnerable organs. External beam therapy produces rectal and genitourinary toxicities that can be early, which occur during or immediately after treatment, and late appearing after 6 months. The incidence differs much between the authors, but about 30% of patients present symptoms of acute proctitis or cystitis during therapy of prostate cancer. Other, usually late gastrointestinal symptoms are pain, bleeding, mucosal loss, higher stool frequency, ulceration, stricture, lymphedema and worse sphincter control [6]. Symptoms from genitourinary system are dysuria, frequency, haematuria, severe nocturia, decreased stream and incontinence of urine. We observe that despite the treatment 5% to 10% of patients have permanent post-radiotherapy symptoms like irritable bowel, cystitis, intermittent rectal or bladder bleeding.

Controlling the exact location of the prostate during subsequent sessions of image-guided external beam radiotherapy (IGRT) is an obvious method to improve precision and reproducibility of delivered doses [9, 10]. In order to achieve it, the utilization of fiducial markers has been proposed. The first use of gold markers for prostate localization was described by Crook and Raymond in 1995 in 56 patients treated with conventional teletherapy 2DXRT [11]. These markers are also currently used with IMRT techniques. Use of 3 gold fiducials allows for reducing clinical target volume and planning target volume margins. The fiducials markers are effective method of localizing prostate displacement. The gold seed markers are radio-opaque and easily identified in x-ray, CT and MRI. They are also small and chemically inert in man. The implantation of fiducial markers is a simple procedure and is well tolerated by patients [12–14]. What is important, is that the markers must be positioned so they are forming 3D triangle. Implantation can be performed by transperineal or transrectal way with ultrasound guide [15]. Usually, 3 seeds are implanted although in same centres 4 seeds were used. There are few types of seeds. They are pure gold cylinders specially knurled to avoid migration; they differ in size and type of incisions. Seeds for soft tissue usually are 3 mm or 5mm long and 0.8; 0,9; 1,0; 1,2; 1,6 mm in diameter. Needle is 20 or 30 cm long and 18, 17 or 14 Ga of thickness. They are available in sterilized preloaded needles or alone [8].

Majority of articles describing the use of fiducial seeds are written by oncologist. In this article we would like to present urological aspect. Implantation is the simple and short procedure. In this study we present our experience in insertion of fiducial markers before radiotherapy of the prostate cancer

## Material and method

Between January 2014 and August 2014 we performed 56 implantations by transrectal mode. All patients had confirmed prostate cancer on biopsy and were qualified for radical IMRT treatment. Diagnostic biopsies were performed in several local urological centres. Patients were qualified to set markers by a team of radiation oncologists. All 56 patients had cancer limited to the prostate. Mean age of the patients was 69.5 years. Gleason grade ranged from 5 (in one case) to 10, mean 7. Gleason score 5 was recognized in 2003, but patient was submitted to the radiation only in 2014. PSA level ranged from 1.99 ng/ml to 287 ng/ml. Seven patients had PSA between 46 and 287 ng/ml at the time of biopsy (287, 110, 91, 78, 66, 49, 46). These patients received neoadjuvant hormonotherapy after biopsy. Then they underwent CT of the abdomen and pelvis and a bone scan which excluded the spread of cancer. The patient with PSA 287 ng/ml in whom the diagnosis had been established in 2012, after 2 years of hormonotherapy was categorised to the radiotherapy at the PSA level 9.36 ng/ml. In CT and scintigraphy a guild of dissemination wasn't found. All 55 patients had acinar carcinoma, but one patient had ductal carcinoma with PSA level 1.99 ng/ml. Mean PSA was 25.3 ng/ml.

## Technique

The used needle was 18 Ga, 20 cm long with cylindrical marker 1 mm × 3 mm (Riverpoint Medical Portland, Pre-Waxed Brachytherapy Needle). We inserted 1 seed in right lobe near apex, 1 in left lobe laterally in the middle of gland and 1 more in right lobe near bladder neck and urethra trying to create the tringle. Such a location was suggested by oncologists.

Procedures were performed by 3 urologists. Before implantation patients received 2 doses of ciprofloxacin — 500 mg orally. We didn't use bowel preparation. During the procedure the patients were positioned on left lateral position. Only local anaesthesia with lignocaine gel was applied to the rectum few minutes before the procedure. The insertion was performed under TRUS control on simultaneous two cross-section picture. The needle was slowly inserted in the direction marked by the ultrasound tag and when the planned location has been reached the fiducial was released from the needle guide. Position correction was possible until the seed ejects from the needle. After implantation every patient underwent plain X-ray as a control of location of seeds

and usually 2–3 weeks later CT and MRI scan for planning EBRT. Patients have had radiotherapy conducted IMRT or RapidArc method.

## Results

All 56 patients well tolerated the insertion. No complication occurred during procedure. No significant complications in the post-implantation period were seen. No urosepsis, gross haematuria, serious rectal bleeding or urinary retention were reported. No patient required hospitalization.

However small complications were observed. Two patients developed epididymitis which was treated with the antibiotic. The patients received ciprofloxacin for 10 days with a good clinical outcome. One patient had small rectal bleeding lasting 3 days. One patient complained of dysuria due to insertion of 1 seed into the wall of intraprostatic urethra. Complains passed after about 3 weeks. In CT scans 1 seed wasn't found. The marker was probably expelled with urine, so after all the patient didn't require additional treatment procedures. Some patients reported slight increase in urinary frequency, dysuria, and trace of blood in urine. These symptoms disappeared spontaneously within a few days and did not require special treatment. A total of four patients have lost one seed. Probably 3 markers were excreted with stool and 1 with urine. The absence of seed was detected in control CT. The plausible explanation of this lost is that marker was implanted to the rectum wall. The patients who lost 1 seed were irradiated according to the earlier established schedule. We didn't implant the fiducial seed in to replace the lost one, and no different technique of irradiation was used. No other complication during procedure occurred.

## Discussion

Implantation of radio-opaque markers to the prostate gland helps in locating the gland during radiotherapy course [9–11]. Modern technology IGRT enables very precise planning of the dose. IMRT and VMAT allow dose escalation, but what is crucial for patient safety is a strict control of target position. The problem not completely solved even by the new modalities is how to secure the surrounding organs. The dose must be delivered to the same site during all subsequent fractions. Therefore the key issues are exact positioning and adjusting the irradiation field to any movement of the treated organ. Movement of prostate is related to respiratory movement and to rectal and bladder filling. The movements are small (2–4 mm) and occur mainly in the anterior-posterior axis and superior-inferior axis, but because the organs are within very close proximity to the prostate, it creates the risk of side effects. Movement in lateral axis may be up to 1–2 mm [14, 16]. The benefit of higher doses is better cancer control, but disadvantage of this is higher toxicity to adjacent organs. All side effects of radiation significantly reduce the quality of life of patients even long time after completion of radiotherapy. Treatment of side effects is difficult. Only grade 2 toxicities which respond to simple management are reported between 26–35% [8]. Symptomatic treatment is long and very often ineffective. Symptoms tend to recur for many years. Serious complications from urinary and gastrointestinal system, such as faecal incontinence, rectal stricture or fistula, sometimes require urinary diversion and faecal stoma. The incidence of severe complications is decreasing despite of dose escalation due to the use of three-dimensional imaging systems. Fiducial markers are simple method to accomplish precise maintenance of the treated field. The procedure is easy, similar to the transrectal biopsy [12, 15]. The idea of positioning the seeds is to create spatial block from 3 or 4 seeds inserted inside prostate gland. Prostate motion known as inter-fractional motion occur between daily treatments and the other type intra-fractional motion occur during RT fraction. Radio-opaque marker and the use of electronic portal imaging give a direct evaluation of prostatic motion during radiation treatment. The CT scanner is part of the linear accelerator and determines the current location of the tumour and the prostate gland with submillimetre accuracy [9, 10, 14, 16, 17]. Every day before treatment, location of gold seeds has been verified and compared with CT and MRI reference images. There is no need to implant seeds far from each other, because in such case some seeds are usually located in the rectal or urethra wall and are lost. The minimal space between markers should be 1 cm for better position verification. Other technical point is that the seed moves forward from applying needle and so the needle must be applied properly.. But the most important is the feed-back information from the radiotherapy team informing urologists how they can improve positioning.

## Conclusion

Implantation of fiducial markers to prostate is save and rather easy for urologists. In our group, we have seen that it helps in reducing the risk of irradiation of bladder and rectum and in this way prevents complications. The location of the prostate during radiotherapy is very accurate and precise. It is another example of the fact that close multidisciplinary cooperation brings a lot of merits to our patients.

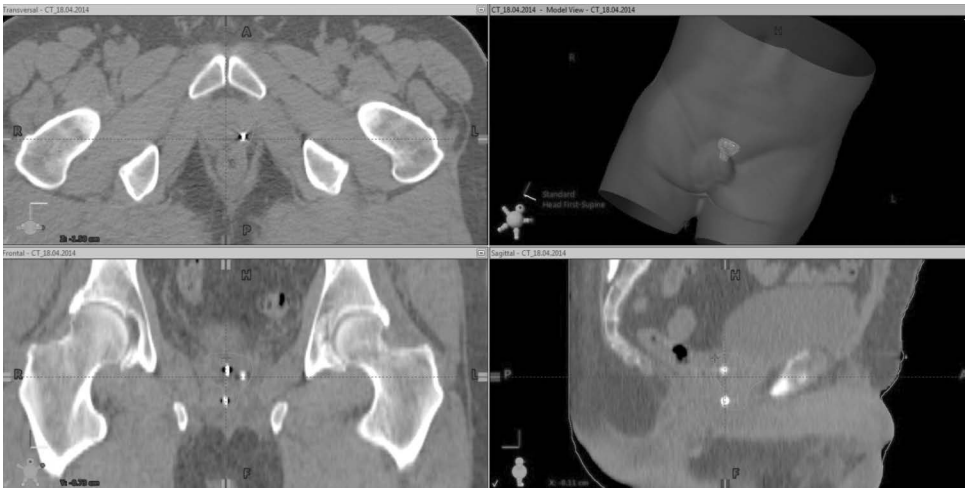

**Figure 1.** Patient no 1. CT of pelvis in 3 dimensions and a 3-D reconstruction of the body with marked position of prostate. Fiducial seed in rectum wall — small arrow

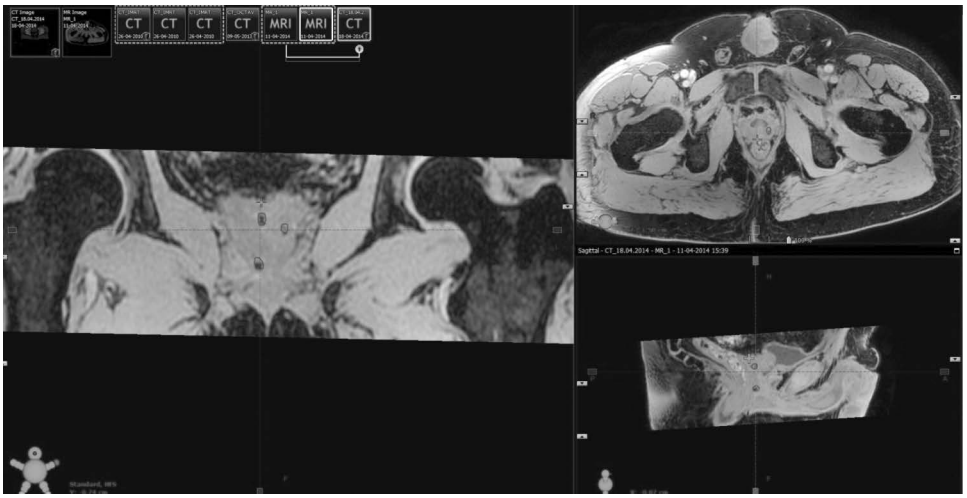


**Figure 2.** Patient no 1 and his MRI of pelvis in 3 dimensions, three fiducial seeds appear as dark spots

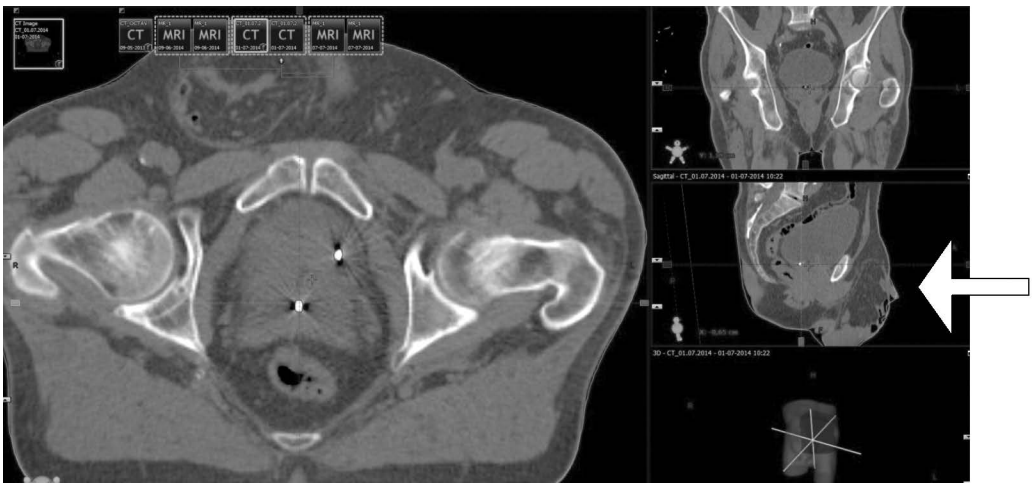


**Figure 3.** CT of pelvis, two markers visible as bright spots. Big scrotal hernia marked by arrow

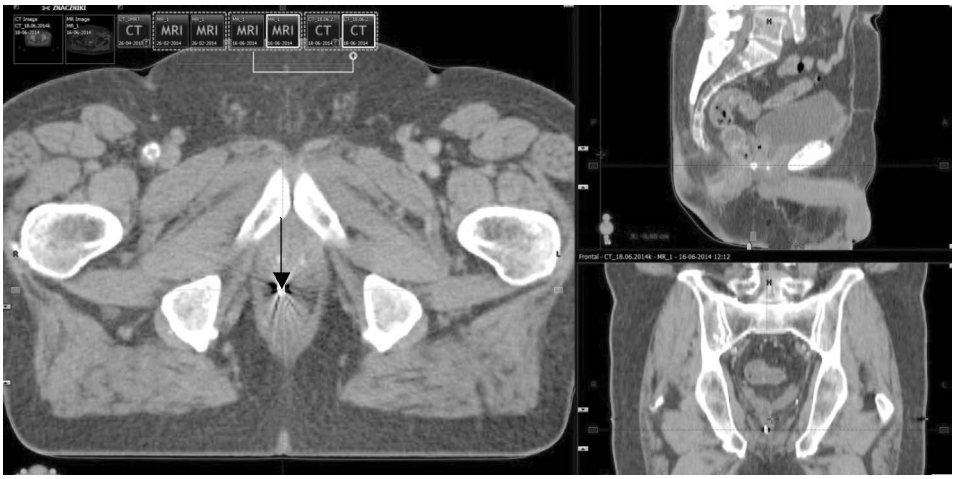

**Figure 4.** CT scans, image for radiotherapy planning with markers. Calcification in prostate marked by arrow

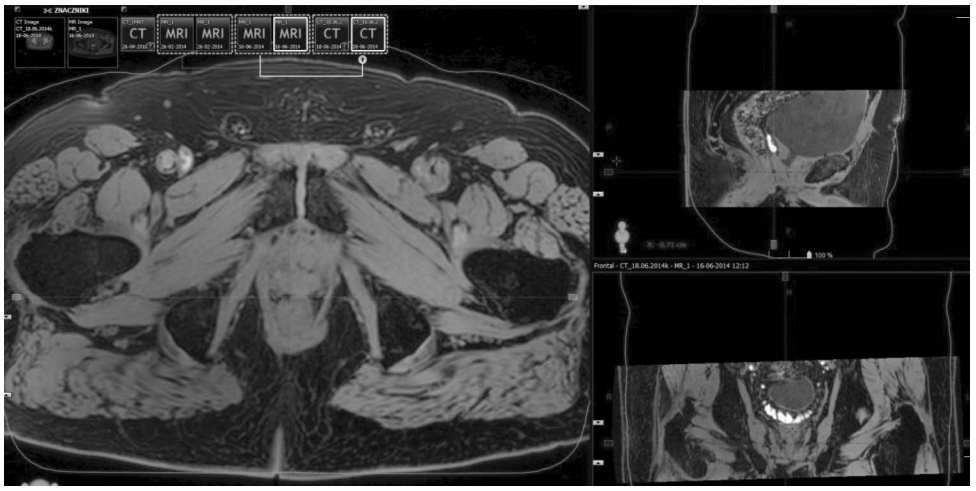

**Figure 5.** MRI of pelvis before radiotherapy with markers

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