White paper

Rectal cancer

BioXmark®

The liquid fiducial marker

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1. Introduction

This white paper covers the clinical use of BioXmark® in patients with rectal cancer. We present background knowledge on rectal cancer and the use of fiducial markers to improve radiotherapy. Furthermore, we introduce BioXmark® - the liquid fiducial marker, and the clinical evidence supporting that BioXmark® can be implanted safely in rectal cancer patients to guide high precision radiotherapy.

2. Rectal cancer background

In North America and Europe, rectal cancer ranks 7th based on incidence with approximately 236,000 new cases and 8th based on mortality with approximately 100,000 deaths in 2020 [1].
Rectal cancer is often grouped with colon cancer (i.e. colorectal cancer) epidemiologically, in which case it ranks as the 4th most common cancer and ranks 2nd based on mortality (in North America and Europe). The majority of rectal cancers are adenocarcinomas[2].

3. Radiation therapy background

Radiation therapy in cancer can have different aims. It may be given with curative intent in cases with localized disease. It can be given as neoadjuvant therapy for tumor shrinkage before surgery or may be used as part of adjuvant therapy, to prevent tumor recurrence after surgical resection of the primary malignant tumor. Radiation therapy is synergistic with chemotherapy. It may also be used as palliative treatment, where cure is not possible[3,4].

The total dose of radiation used in radiation therapy varies depending on the cancer type and is fractionated into smaller doses for several reasons. Fractionation allows healthy cells time to recover, while tumor cells are generally less efficient in repair between fractions. Fractionation also allows tumor cells that were in a relatively radio-resistant phase of the cell cycle during one treatment to cycle into a sensitive phase of the cycle before the next fraction is given. A type of fractionation schedule that is increasingly being used and continues to be studied is hypofractionation. This is a radiation treatment in which the total dose of radiation is divided into fewer and larger doses. This type of radiation therapy necessitates a high degree of accuracy since just a single fraction missing the target will mean a huge decrease in total amount of radiation delivered to the tumor and an equally high dose wrongly delivered to healthy tissue[3,4].

3.1 Radiotherapy for rectal cancer

The primary treatment for rectal cancer patients is surgical resection of the primary tumor[2]. Radiotherapy also plays an important role in the treatment of rectal cancer, since approximately

60% percent of rectal cancer patients have an evidence-based indication for receiving radiotherapy[5].

For rectal cancer stage I patients, where the tumor only extends into the submucosa (T1) or into the bowel muscular layer (T2), surgery with or without chemoradiation therapy is the standard treatment option [2].

For rectal cancer stages II and III patients (T3-T4 or node-positive disease stages), preoperative chemoradiation therapy has become the standard of care. Furthermore, clinical evidence suggest that for patients with a complete clinical response to the chemoradiation it is reasonable to consider this treatment curative and follow these patients by active surveillance (watch and wait approach) [2]. Radiotherapy also plays a role together with surgery in the treatment of stage IV patients and may be used in palliative treatment[2].

Radiation dose escalation is expected to result in an increased clinical complete response rate in rectal cancer patients. Dose escalation may enable more patients to qualify for an organ sparing approach by omission of surgery[6].

4. Fiducial markers background

A fiducial marker is an object placed in the field of view of an imaging system that appears in the image produced, for use as a point of reference. Methods to secure a target reference point in radiation therapy have a long history and were initially seen in the form of a cross penciled or tattooed mark on the skin of the patient to guide the entry point of the radiation beam. Later, when Image Guided Radiation Therapy (IGRT) was introduced, bony structures in close relation to the tumor were used as landmarks on images for patient set-up at the point of treatment and as a guide for better target precision. Most of the imaging modalities available at the point of treatment are however not able to differentiate sufficiently between different soft tissues, including the tumor and the surrounding non-cancerous tissue. Furthermore, inter fractional and intra-fractional movement of the tumor target complicates the precise delivery of the radiation dose to the tumor[4,7,8].

For a fiducial marker to be a relevant tool through all phases of radiation therapy the following features are needed:

- Feasible to implant with low risk of procedure related complications
- Visible on relevant imaging modalities
- Positional stable throughout the entire treatment course and through follow-up

Advantages of using fiducial markers:

- Accurate identification of tumor target location for better treatment planning, treatment, and follow-up
- Maximization of radiation to the tumor target and minimization of radiation to healthy surrounding tissue
- Makes it possible to locate the tumor target despite day-to-day variation on the treatment unit and help overcome the challenge of inter-fractional target movement
- Makes it possible to live monitor tumor motion during a fraction of radiation treatment and help overcome the challenge of intra-fractional target movement
- Allowing accurate re-identification of the tumor target in the time of follow-up

4.1 Fiducial markers for rectal cancer

The acute side effects of radiotherapy for rectal cancer are primarily related to gastrointestinal toxicity, are normally self-limiting, and usually resolve within 4-6 weeks of completing treatment [2]. Long term side effects include damage to the small bowel, which is the dose limiting organ at risk. The associated risks include fibrosis, structuring and obstruction. The risk of small bowel toxicity is related to the dose delivered to the small bowel and with careful planning the risk of significant small bowel toxicity can be reduced to around 5%. Other long-term toxicities include impotence in male patients, loss of fertility and insufficiency fractures [4].

To facilitate precision radiotherapy with minimized radiation to organs at risk in patients with rectal cancer, use of fiducial markers has been evaluated. However, the number of published studies on this use is limited[9–14].

Vorwerk *et al.* demonstrated the use of gold fiducial markers in a study with 9 patients. Each patient had 2-3 markers (Additec, Germany) implanted in the mesorectal tissue of the tumor region, mainly at the lower border of the tumor. All markers, but one, were visible at planning CT. All markers were stable during radiotherapy, but 85% of the markers got lost prior to histopathologic examination. The study concludes that: *"The proposed method improved target volume delineation, thus enhancing the accuracy of radiotherapy and especially protection of anal structures"*[11].

Moningi *et al.* have described the visibility and stability of two types of fiducial markers placed under EUS guidance for use in high-dose rate endorectal brachytherapy[12]. The fiducial markers used were traditional fiducials (Best Medical International Inc, USA) (5 mm in length, 0.80 mm in diameter) and X-mark fiducials (ONC Solutions Inc, USA) (1, 2, or 3 cm in length, 0.85 mm in diameter). The study included 11 patient in total. 3 patients received traditional fiducial markers and 8 received X-mark fiducials. It is concluded that both types of fiducial markers had good visibility. Furthermore, it is concluded that the markers may be used to target rectal tumors for additional treatments that require millimeter accuracy such as stereotactic radiotherapy.

Dhadham *et al.* [9] have reported on the use of fiducial markers in large cohort of patients with gastrointestinal malignancies who underwent EUS guided fiducial marker placement for IGRT without fluoroscopy. In the study, 54 patients with rectal cancer had 103 fiducials placed (Visicoil, RadioMed, USA). The technical success is described to be 100% and no migration is reported. For 70.3% fiducial marker placement was possible in both proximal and distal aspects of rectal tumors. Among the conclusions of the study, it is stated (not specifically for rectal cancers) that EUS-guided fiducial marker placement without fluoroscopy is technically feasible and safe.

Rigter *et al.* [10] evaluated the technical success rate and safety of two endoscopic ultrasound (EUS)-guided placement strategies and four fiducial types for rectal cancer patients. The study included 20 patients. A total of 64 fiducials were placed. The two placement strategies were (1): for 10 patients the fiducial markers were placed into the tumor (one proximal, one central and one distal) and (2): for 10 patients the goal was to place at least two fiducial markers in the mesorectal fat (one proximal and one distal from the tumor) and one in the center of the tumor. The 4 fiducial markers used were Visicoil 0.75 mm × 5 mm and Visicoil 0.50 mm × 5 mm (IBA Dosimetry GmbH, Germany), Cook 0.64 mm × 3.4 mm (Cook Medical, Limerick, Ireland) and Gold Anchor 0.28 mm × 20 mm (unfolded length, Naslund Medical AB, Sweden).
The results showed that 55% of intratumoral fiducials were present on CBCT after a median follow-up of 17 days, in comparison with 90% of fiducials placed in the mesorectal fat. The study concludes that "*EUS-guided placement of fiducials for rectal cancer is feasible and safe, but adequate position remains a challenge. Placement of fiducials in the mesorectal fat leads to a higher rate of retention of fiducials, however, these results could be influenced by other factors (e.g. fiducial type) and should be confirmed in a larger study*".

Van den Ende *et al.* have analyzed the MRI visibility of the four fiducial markers based on the same study. They conclude that the Visicoil 0.75 and Gold Anchor fiducials were the most visible fiducials on MRI [13].

In another publication based on the same data, Van den Ende *et al.* have evaluated the feasibility of fiducial markers as a surrogate for gross tumor volume (GTV) position in image-guided radiation therapy for rectal cancer. For this analysis, 19 of the 20 patients were included. 35 of the 64 injected markers were available for analysis on CBCT. 22 were identified on the first MRI and 17 on the second MRI. Of those 14 were injected in the tumor and 3 in the mesorectum. The study concludes that "*despite the observed fiducial displacement relative to the GTV, the use of fiducials as a surrogate for GTV position reduces required margins the AP and CC directions for a GTV boost using image guided radiation therapy of rectal cancer. The reduction of required margins may be higher in patients with a proximal compared with a distal tumor. However, this needs to be confirmed in a larger study*" [14].

5. BioXmark® - the liquid fiducial marker

BioXmark® is a unique carbohydrate/iodine-based liquid low density fiducial marker. The liquid nature of BioXmark® enables implantation of multiple size-adaptable markers in the same uninterrupted procedure. BioXmark® can be implanted with thin needles and flexible scopes guided visually, by fluoroscopy and/or ultrasound. Upon injection of the BioXmark® liquid into soft tissue, efflux of ethanol leads to the *in-vivo* formation of a radiopaque and gel-like fiducial marker.

5.1 BioXmark® - Indications for use

5.1.1 Europe

BioXmark® is indicated for use to radiographically mark soft tissue.
BioXmark® is intended to mark tissue for at least 2 months after implantation.

5.1.2 United States

BioXmark® has De Novo clearance from the US FDA with an indication for use to radiographically mark lung, bladder, and lymph nodes in adult patients for whom it has been determined that radiographical marking of tissue for radiation treatment is indicated for their cancer treatment.

BioXmark® is implanted via image-guided injection into tissue relevant for radiotherapy planning at a healthcare facility. BioXmark® can be implanted in the tumor, lymph nodes or tissue adjacent to the tumor subject to irradiation or in healthy tissue which should not be irradiated.

BioXmark® is intended to mark tissue for at least 3 months after implantation.

5.2 Positional stability and long-term visibility

BioXmark® is positional stable and visible on CT and MRI during treatment planning, treatment, and follow-up. Long-term visibility on CT has been demonstrated up to 6 years[a].

5.3 Low level of artifact and MR safe

Streaking and shadowing artifacts are commonly encountered in CT with currently used metal-based markers. These artifacts are problematic since they induce a loss of clarity and increase inaccuracy in dose calculation during tumor target delineation in treatment planning and in the patient positioning during treatment[16].

[a] Additional follow up on patients from clinical investigation by de Blanck *et al*. [15]

Fiducial markers creating a lower level of artifacts allows for better dose calculation accuracy due to better image quality, including the area around the marker, than for markers with higher level of artifacts.

Due to its non-metallic composition BioXmark® has been found to generate a low level of artifacts in CT. This has been demonstrated in a study by Scherman *et al.* using a water phantom in a clinical diagnostic CT-scanner using various tube voltages from 80kV to 140kV in 20kV steps (Figure 1)[17] and has been confirmed by clinical investigations in bladder and lung[18,19]

The non-metallic composition is also an advantage in MR since there are no displacements of BioXmark®. The product is labelled MR safe according to ASTM F2503.

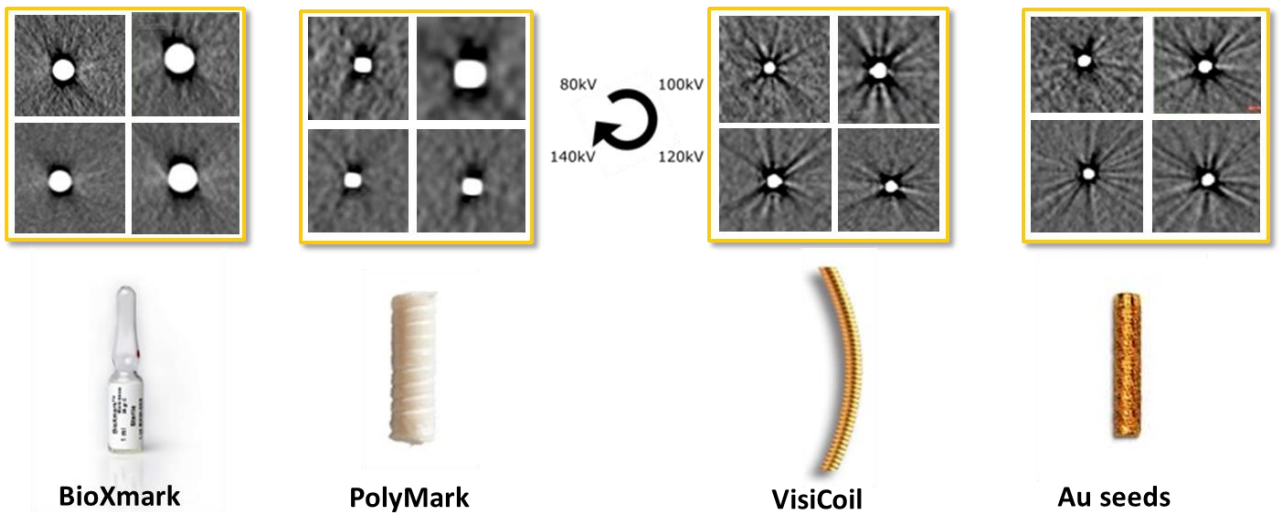

Figure 1. Artifacts of different markers on CT images at different tube voltages.

5.4 Low dose perturbation

For the use of a fiducial marker to be beneficial, an improved positioning accuracy must not be offset by marker-induced dose distortion. This constitutes a negligible challenge in photon therapy, but is a significant consideration in proton therapy, where fiducials can cause severe perturbations of the proton dose and lead to cold-spots downstream the marker, where the tissue will not receive the intended radiation dose. This interaction is described as the Relative Stopping Power (RSP), which is high in metals.

The ideal fiducial marker for proton therapy combines a low RSP value with good visibility on 2D X-ray and CBCT with a low level of artifacts.

BioXmark®'s non-metallic composition gives a low RSP, compared to metal, which ensures low dose perturbation in proton radiation therapy combined with the low levels of artifacts described above.

The RSP of BioXmark® has been calculated to be 1.174 and measured to be 1.164 by Troost et al. in a phantom model[20]. Furthermore, the BioXmark® markers were evaluated after being exposed to normofractionated and extremely hypofractionated proton therapy and no chemical degradation was observed[20].

Rydhög and colleagues has, in collaboration with Professor Lomax from the Paul Scherrer Institute, performed a gelatin phantom study where BioXmark® markers of 0.01-0.1 ml were investigated for dose perturbation in proton therapy. The largest of the BioXmark marker (0.1 ml) perturbed the proton beam in a spread-out Bragg Peak with a maximum of 4.8% as measured in the film placed the furthest from the phantom meant to capture downstream shadowing effects. The dose perturbation shall be taken into account when planning treatment doses in proton therapy in accordance with local procedures and national guidelines[21].

5.5 Injectable with thin needles

Injection of BioXmark® is possible with percutaneous and endoscopic needles. The liquid formulation can be injected using thin needles up to 25G. The use of thin needles gives lower risk of procedure related complications such as bleedings and pneumothorax.

5.6 Endoscopic implantation

BioXmark® can be implanted using flexibles scopes, making it possible to access tumors located at anatomical locations not accessible with rigid scopes or percutaneously.

The possibility of implanting BioXmark® endoscopically has been evaluated in several different types of endoscopes, e.g., flexcystoscopy[18], endoscopic ultrasound, endobronchial ultrasound and video bronchoscope[15].

5.7 Implantation of multiple size-adaptable markers in the same procedure

BioXmark® enables the implantation of multiple markers in the same uninterrupted endoscopic or percutaneous procedure, with no need for retraction of endoscope and/or needle for reloading. This has been demonstrated by de Blanck S. *et al.* concluding: *"The liquid formulation also allows for the placement of several markers in one session without needing to reload the endoscopy needle between each implantation […]"*[15]. Fewer injections are associated with less risk of procedure related complications.

The optimal injection volume depends on the intended target site, planned treatment, and the applied image modality as well as desired visibility and artifact level. In general, both visibility and artifacts increase with larger injection volumes[16]. The volume of each BioXmark® marker can be determined prior to, or adapted during, the implantation procedure.

5.8 Implantation guided by ultrasound and fluoroscopy

During the marker implantation procedure, the location of the needle and BioXmark® marker can be visualized and guided by fluoroscopy and/or ultrasound, ensuring precision and safety during marker placement and verification of marker location. The feasibility of guiding BioXmark® implantation by fluoroscopy and/or ultrasound has been demonstrated, incl. clinical investigation in lung and bladder cancer[15,18].

5.9 Biocompatible

BioXmark has been biologically evaluated and tested in compliance with ISO standards and FDA guidance related to the biocompatibility of medical devices. It was found to be safe and biocompatible within the intended use.

6. Clinical use of BioXmark® in rectal cancer

The clinical use of BioXmark® as fiducial marker for radiotherapy of rectal adenocarcinoma has been tested in a prospective, non-randomized, single-arm feasibility trial performed at MAASTRO Clinic Maastricht[22]. In this study, BioXmark® markers were injected into the rectal wall preparation using a sigmoidoscopy via thin needles (<25 Gauge) by two experienced gastroenterologists. A two-step marking method was used to minimize the risk of extra-luminal injection of the marker. First, a saline solution was injected into the submucosal space to create a bleb of 0.5 ml, where after the marker was injected into the bleb. A total of four marker spots with a volume of 80 µL were injected into the rectal wall approximately one-centimeter lateral from the tumor, two in caudal and two in cranial direction with a one-centimeter margin to the tumor. The total procedure time was around 15 minutes.

The markers' performance was analyzed regarding positional stability, visibility, safety, and possible influence on pathology review. A total of 20 patients had 4 markers implanted.

6.1 Positional stability

Eight out of 80 injected markers (10 %) were not available for analysis: two were lost, four markers could not be followed during the entire radiation course due to missing imaging data, and two

markers were too close to an adjacent marker and were evaluated as a single marker. This resulted in a total of 106 marker pair distances being available for analysis. Total migration per marker pair distance showed an average total migration of 0.5 cm (SD: 0.1 cm). One marker was found to migrate significantly through the mesorectal fat based on a large variation in day-to-day location. In total, three out of eighty markers (3.8 %) were scored as unstable; two were lost and one migrated. The authors evaluate that the liquid fiducial marker demonstrated good positional stability.

6.2 Visibility

BioXmark® demonstrated good visibility with all markers still in situ were clearly visible on the planning CT-scan and 98.5 % of the markers were clearly visible on daily CBCTs. Minor beam hardening artifacts were present on CBCT without significantly impacting image interpretation. BioXmark® in rectal cancer can be seen in figure 2 and 3.

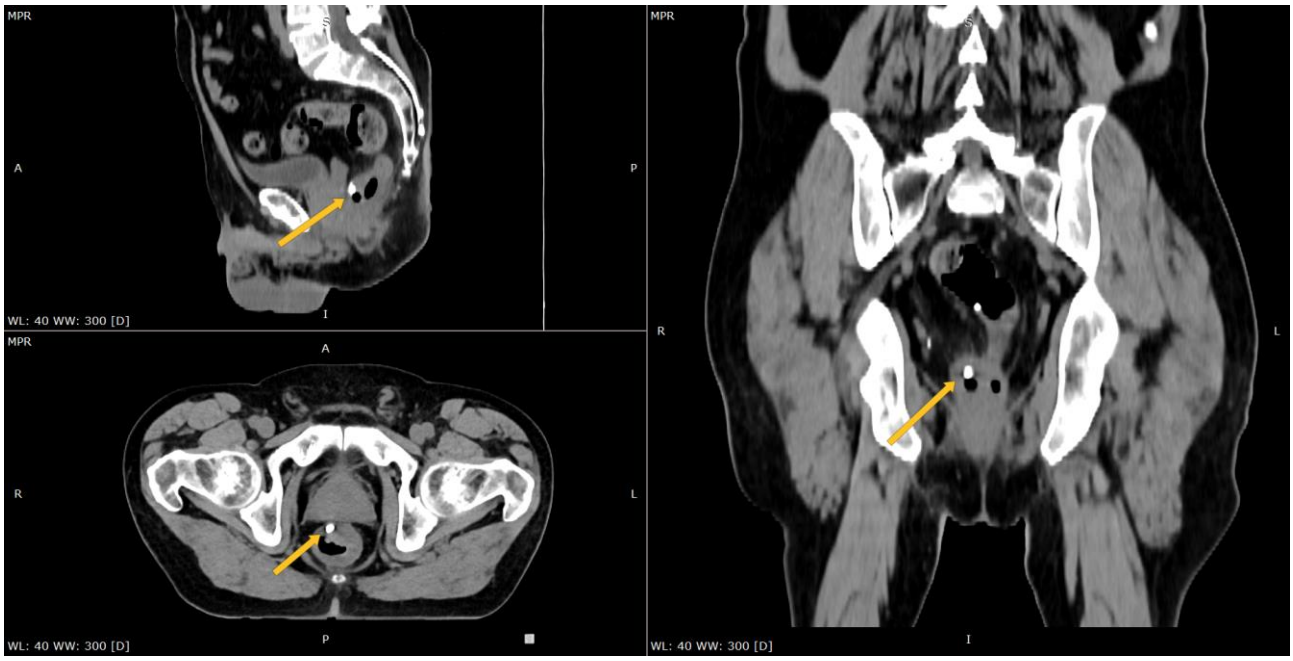

Figure 2: Planning CT showing BioXmark® in the rectal wall of patient with rectal adenocarcinoma.

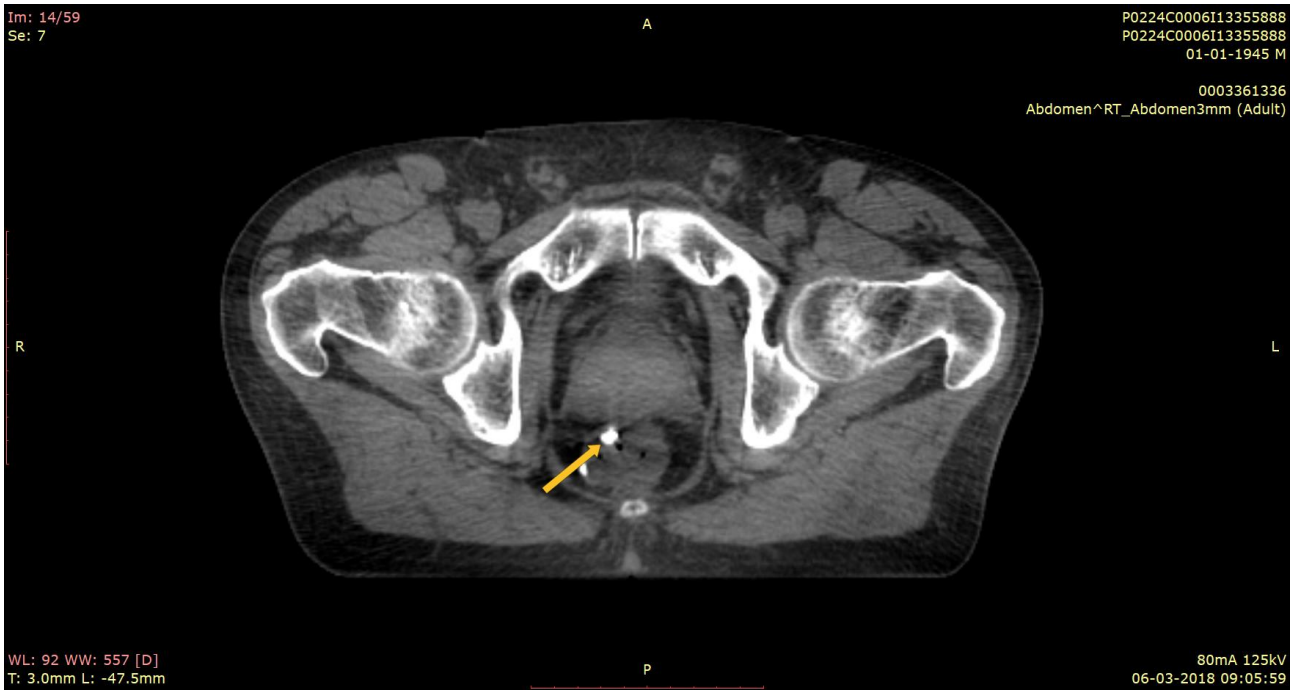

Figure 3: CBCT showing BioXmark® in the rectal wall of patient with rectal adenocarcinoma.

6.3 Safety and pathology

One patient experienced a vagal reaction during marker injection with spontaneous recovery and no late side effects. In three patients, technical difficulties with marker injection were experienced with possible leakage of the fiducial into the lumen of the rectum. No adverse events were reported shortly after injection or during radiotherapy in any of the patients. At two months follow-up, the only treatment-related acute toxicities were Grade 1 proctitis in 7/20 patients (35 %) and Grade 2 proctitis in 1/20 patients (5%). No injection or marker related acute or late toxicity was encountered during follow-up. Moreover, pathology did not report any substantial local tissue inflammation.

6.4 PTV margin analysis for tumor boosting

In another study on the same cohort from the MAASTRO (NL), Willems et al. aimed to determine the required PTV margins for external beam radiotherapy (EBRT) boosting in rectal cancer patients when using BioXmark® fiducials[6]. 19 of the 20 patients were included in the analysis. Alignment before each fraction was based on both bone and anatomical CBCT matching. An additional CBCT was performed after every fraction. For GTV boost, one centre of mass of all eligible fiducial markers during treatment was calculated for every fraction. The results showed that for GTV boost, PTV margins to ensure a minimum dose to the CTV of 95% for 90% of patients were 0.3 cm, 0.8 cm, and 0.3 cm for the lateral, craniocaudal, and anteroposterior directions, respectively. The PTV margin to cover 90% of all fractions was 1.2 cm for the elective target volume (CTVelec).

The study concludes that: "The calculated PTV margins are less than the margins that are generally used in CBCT based EBRT boost treatments for rectal cancer patients. Therefore, implantation of BioXmark® fiducials and CBCT marker matching using these fiducials may allow for significantly increased dose escalation to target volumes and reduced dose to normal tissue compared to CBCT based boosting without fiducial implantation and could be an alternative to MRI-linac based boosting"[6].

7. Conclusion

The use of BioXmark® for rectal cancer has been clinically tested and demonstrated technical feasibility and safety.

Placement of BioXmark® in the rectum wall can be done endoscopically.

BioXmark® has shown high positional stability and clear visibility on planning CT scan and day-to-day cone beam CT.

Use of BioXmark® may allow for significantly increased dose escalation to target volumes and reduced dose to normal tissue in connection with radiotherapy treatment of rectal cancer.

Use of BioXmark® enables precision radiotherapy for rectal cancer.

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