Whitepaper
Rectal cancer

The liquid fiducial marker

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Table of contents

Rectal cancer ................................................................................................................................................ 2
1. Background ............................................................................................................................................... 2
2. Radiation therapy ..................................................................................................................................... 2
   2.1 Radiotherapy for rectal cancer ............................................................................................................. 2
3. Fiducial markers background .................................................................................................................. 3
   3.1 Fiducial markers for rectal cancer ........................................................................................................ 4
4. Clinical use of BioXmark® ...................................................................................................................... 6
5. Conclusion .................................................................................................................................................. 7
6. List of references ...................................................................................................................................... 7
Rectal cancer

This whitepaper covers the clinical use of Nanovi’s BioXmark in patients with rectal cancer. We present the clinical evidence demonstrating that BioXmark® can support high precision radiotherapy in rectal cancer.

1. 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].

2. Radiation therapy

Radiation therapy 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 being treated 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. One 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 to the tumor and an equally high dose wrongly delivered to healthy tissue [3,4].

2.1 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 radiotherapy treatment [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].

3. 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
- Visibility on relevant imaging modalities
- Positional stable throughout the entire treatment course and through follow-up

Advantages of using fiducial markers
- Identification of tumor target location with greater accuracy for better treatment planning, treatment and follow-up
• Maximization of radiation to the tumor target and minimization of radiation to healthy surrounding tissue
• Fiducial markers make 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
• Fiducial markers make it possible to live monitor tumor motion during a fraction of radiation treatment and help overcome the challenge of intra-fractional target movement
• Fiducial markers allow the precise re-identification of the tumor target in the time of follow-up

3.1 Fiducial markers for rectal cancer

The acute side effects of radiotherapy for rectal cancer are mainly 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].

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

Vorwerk et al. [11] 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”.

Moningi et al. [12] have described the visibility and stability of two types of fiducial markers placed under EUS guidance for use in high-dose rate endorectal brachytherapy. 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 patients, and 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. [13] 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.

In another publication based on the same data, Van den Ende et al. [14] 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”.

4. Clinical use of BioXmark®

The clinical use of BioXmark® as fiducial marker for radiotherapy of rectal cancer has been tested in a prospective, non-randomized, single-arm feasibility trial performed at MAASTRO Clinic Maastricht [15]. In this study, BioXmark® markers were injected into the rectal wall after proper enema preparation using a sigmoidoscopy via thin needles (<25 Gauge) by two experienced gastroenterologists. A two-step marker 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, where after the marker was injected into the bleb. A total of four marker spots with a volume of 80uL were injected into the rectal wall an approximately one-centimeter lateral from the tumor, two in caudal and two in cranial direction. One-centimeter margins were chosen in agreement with the gastroenterologist. The markers were injected with an angle of approximately 45 degrees to limit perforation risk.

The preliminary conclusions of the study have been presented in a master thesis with a publication to follow [15]. The results showed that BioXmark® did not migrate in 95.8% out of 72 analysed markers and was clearly visible on planning CT scan and day-to-day cone beam CT. The thesis concludes that “BioXmark® showed to be feasible to act as a tumor location surrogate on daily cone beam CT for image guided radiotherapy. BioXmark® may provide us a tool to follow day-to-day tumor location and may thereby enable dose escalation in rectal cancer patients”.

In another publication from the same institution, 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”.

5. 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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6. List of references


