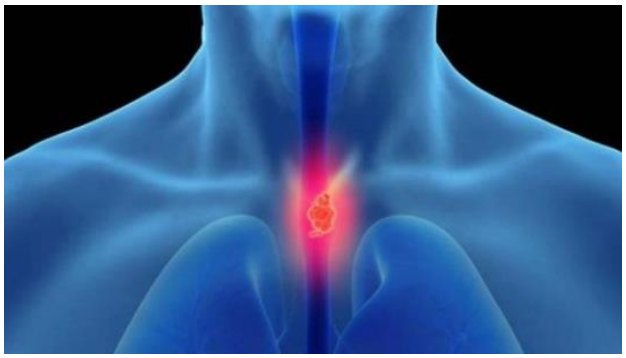
White paper

Esophageal and stomach cancer



BioXmark®

The liquid fiducial marker

Table of Contents

1. Introduction 2
2. Esophageal and stomach cancer background 2
2.1 Esophageal cancer 2
2.2 Stomach cancer 2
3. Radiation therapy background 3
3.1 Radiotherapy for esophageal and stomach cancer 3
4. Fiducial markers background 4
4.1 Fiducial markers for esophageal and stomach cancer 4
4.1.1 Esophageal cancer 5
4.1.2 Stomach cancer 5
5. BioXmark® - the liquid fiducial marker 5
5.1 BioXmark® - Indications for use 6
5.1.1 Europe 6
5.1.2 United States 6
5.2 Positional stability and long-term visibility 6
5.3 Low level of artifact and MR safe 6
5.4 Low dose perturbation 7
5.5 Injectable with thin needles 8
5.6 Endoscopic implantation 8
5.7 Implantation of multiple size-adaptable markers in the same procedure 8
5.8 Implantation guided by ultrasound and fluoroscopy 9
5.9 Biocompatible 9
6. Clinical use of BioXmark® in esophageal and stomach cancer 9
6.1 Esophageal cancer 9
6.2 Stomach cancer 11
7. Conclusion 11
8. References 12

NANOVI
Diplomvej 378
DK-2800 Lyngby
+45 31 42 11 86
www.nanovi.com

1. Introduction

This white paper covers the clinical use of BioXmark® in patients with esophageal and stomach cancer. We present background knowledge on esophageal and stomach 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 esophageal and stomach cancer patients to guide high precision radiotherapy.

2. Esophageal and stomach cancer background

2.1 Esophageal cancer

In North America and Europe, esophageal cancer ranks 20th based on incidence with approximately 74,000 new cases and 14th based on mortality with approximately 64,000 deaths in 2020 [1]. Esophageal cancer has a relatively poor prognosis with a 5-year survival of ~ 20% and it is a highly lethal disease as evidenced by the case fatality rate of 90% [2]. In terms of cancer-related deaths worldwide, esophageal cancer ranks 6th, accounting for 5.5% of cancer-related deaths worldwide [1].

There are two main histological types of esophageal cancer: Squamous cell carcinoma, which develops throughout esophagus and adenocarcinoma, which primarily develops in the distal esophagus [3].

2.2 Stomach cancer

Stomach cancer is more common than esophageal cancer and ranks 13th based on incidence with approx. 166,000 new cases and 7th based on mortality with approximately 110,000 deaths in 2020 (North America and Europe) [1]. The 5-year survival rate is ~ 32% [4]. Adenocarcinoma of the stomach was the leading cause of cancer-related death worldwide through most of the 20th century [2]. In the West, the incidence has decreased. It now ranks 4th in terms of cancer-related number of deaths, accounting for 7.8% of cancer-related deaths worldwide [1].

90-95% of gastric malignancies are adenocarcinomas. The two major types of gastric adenocarcinomas are intestinal (well differentiated, arranged in tubular or glandular structures) and diffuse (poorly differentiated, lack of gland formation) [5]. Some adenocarcinomas are located in the gastroesophageal junction (GEJ). According to the generally accepted Siewerts classification system, Siewerts type I lesions are considered cancers of the distal esophagus, and type II and III lesions are considered gastric cancers (cardia and subcardia) [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[2,6].

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[2,6].

3.1 Radiotherapy for esophageal and stomach cancer

For patients with minimally invasive resectable esophageal cancer and gastric cancer confined to the mucosa, surgical resection alone holds potential for cure. At more advanced stages of cancer surgery alone is insufficient to prevent local or metastatic relapse and therefore multimodal therapy is standard of care. In this multimodal approach radiotherapy plays an important role for both esophageal and stomach cancers [5].

Therapeutic management of patients with locally advanced esophageal cancer has evolved significantly over the last few decades [3]. The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) has demonstrated a survival benefit for preoperative chemoradiation compared with surgery alone in locally advanced esophageal cancer [7]. For locally advanced disease, neoadjuvant chemoradiation followed by surgery is currently the standard of care [8].

For resectable stomach cancers perioperative chemotherapy and postoperative chemoradiotherapy are the two standards of care of adjuvant therapy in addition to surgery [5,9]. For both treatment options, trials have shown superior outcome compared to surgery alone (the MAGIC and the INT0116 trials) [10,11]. However, a trial with a direct comparison of the two methods (the CRITICS trial) did not show a benefit for postoperative chemoradiotherapy compared with postoperative chemotherapy alone [12]. Research is ongoing to clarify if preoperative radiotherapy can lead to a

better outcome and become standard of care, as have been seen for other gastrointestinal tumor types including esophageal cancer [13].

Radiotherapy additionally has a role in palliation in both esophageal and stomach cancers of advanced stages where surgery is not an option.

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[6,14,15].

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 esophageal and stomach cancer

Delivering precision radiotherapy maximizing radiation to the tumor target and minimizing radiation to healthy surrounding tissue is challenging for esophageal and stomach cancer, due to similar

contrast values in normal and malignant tissue in the mediastinum and upper abdomen, poor visibility of mucosal tumor tissue and due to mobility of the organs depending on gastric filling, cardiac and respiratory motion [16].

4.1.1 Esophageal cancer

The feasibility and safety of using fiducial markers in esophageal cancer has been demonstrated in several studies [17–19]. It has also been shown that fiducial markers can make delineation more accurate.

In a retrospective study with 60 patients, *Fernandez et al.* reported on the stability and utilization of EUS-guided placement of fiducial markers for esophageal cancer. The study concludes that fiducial marker placement for esophageal cancer aids in target delineation for radiation planning and daily IGRT and mentions that use of fiducial markers for radiotherapy treatment of esophageal cancer patients is routine practice at their institution [17].

In another study, Machiels *et al.* demonstrated how using fiducial markers led to a more precise delineation. The study investigated inter- and intra-observer variation in esophageal gross tumor volume (GTV) delineation and the impact of endoscopically implanted fiducial markers on the variations. Marker implantation at the craniocaudal tumor borders led to significantly reduced inter- and intra-observer variation. The results of the study endorse the use of markers in esophageal GTV delineation to reduce the geometric uncertainty and provide a higher treatment accuracy [20].

4.1.2 Stomach cancer

The feasibility and safety of using fiducial markers in stomach cancer has also been demonstrated in studies, but the use of fiducial markers in stomach cancers is less common than in esophageal cancer. Chandran *et al.* demonstrated the safety and feasibility of gold fiducials in gastric cancers in a study with 8 patients [21]. In a later study concerning both esophageal and gastric cancers (26 patients, incl. 5 gastric and 4 junctional Siewert 3), Chandran *et al.* demonstrated that placement of a novel endoscopic marker (mixture of lipiodol and n-butyl-2-cyanoacrylate) was successful in the majority of cases and that marker placement resulted in improved radiological localization in the majority of the cohort and allowed for IGRT [22].

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[24].

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.

[a] Additional follow up on patients from clinical investigation by de Blanck *et al*. [23]

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)[25] and has been confirmed by clinical investigations in bladder and lung[26,27]

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.

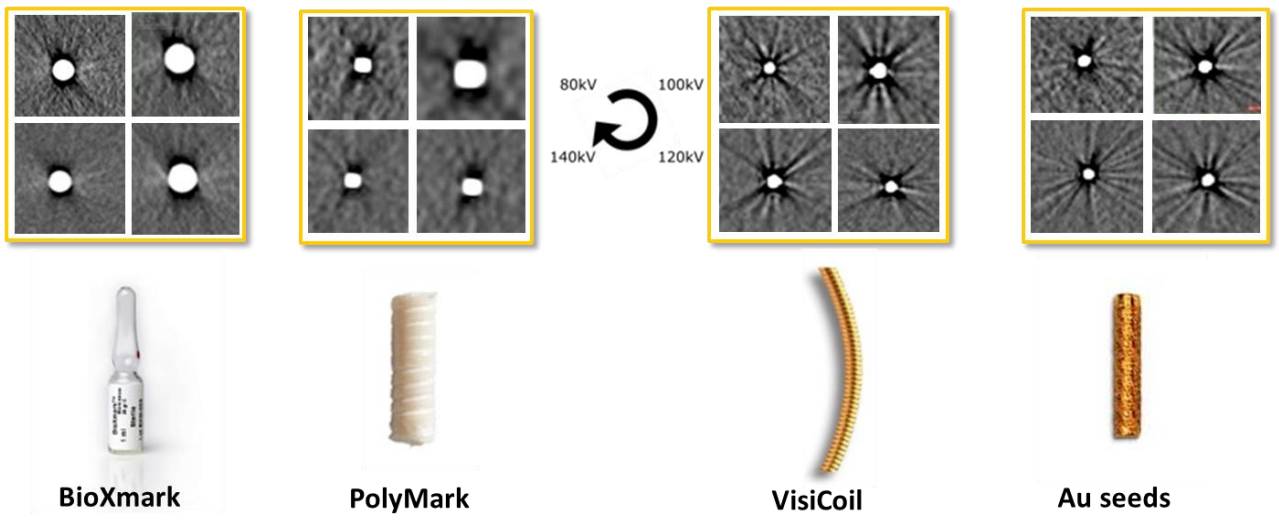


Figure 1. Artifacts of different markers on CT images at different tube voltages.

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[28]. Furthermore, the BioXmark® markers were evaluated after being exposed to

normofractionated and extremely hypofractionated proton therapy and no chemical degradation was observed[28].

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[29].

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[26], endoscopic ultrasound, endobronchial ultrasound and video bronchoscope[23].

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 […]"*[23]. 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[24]. 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[23,26].

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 esophageal and stomach cancer

6.1 Esophageal cancer

Riisgaard de Blanck *et al.* [16] and Machiels *et al.* [30] have shown that the placement in the esophagus of BioXmark® is safe and technically feasible.

Riisgaard de Blanck *et al.* demonstrated excellent continuous radiopacity of BioXmark® in CT and CBCT images during the treatment course and throughout the follow-up period up to 12 months (the follow-up period varied, being 3 months for one patient, 6 months for 2 patients and 12 months for one patient). 12 out of 16 implanted markers were available at planning-CT and there was no marker loss during the treatment period, with all 12 markers present at the last treatment CBCT and the last follow up CT. This can be compared to a study that reported marker availability for three types of endoscopic/EUS-guided placed fiducial markers, including a solid gold marker, a flexible coilshaped gold marker and a polyethylene glycol-based hydrogel marker, which showed a marker loss from planning-CT to last CBCT for all three marker types [31]. See table **Error! Reference source not found.** below for a comparison of the results from that study with the results for BioXmark® from Riisgaard de Blanck *et al.* and Machiels *et al.* [30] (described below).

Marker type [study reference]	Im-planted	Available at planning-CT	Available at first CBCT	Available at last CBCT
BioXmark® [16]	16	12	12/12 (100%)	12/12 (100%)
BioXmark® [30]	24*	19	19/19 (100%)	18/19 (94.7%)
Solid gold marker [31]	32	28	21/28 (75%)	20/28 (71%)
Coilshaped gold marker [31]	51	50	42/50 (84%)	41/50 (82%)
Hydrogel marker [31]	18	16	4/16 (25%)	2/16 (13%)

Table XXXX: Comparison of BioXmark® with different fiducial markers. *The table shows results from 3 different studies. As such any direct comparison is subject to potential differences in design, available technical equipment, experience of implanting surgeon etc.*

*Solid gold marker = a smooth-surface, solid, rigid, gold marker measuring 5 mm in length by 0.43 to 0.64 mm in diameter (Cook Medical, Limerick, Ireland or in-house manufactured); Coilshaped gold marker = a flexible, coilshaped, gold Visicoil marker (Visicoil; Core Oncology, Santa Barbara, Calif) with a diameter of 0.35 mm and handcut length of 2 to 3, 5, 8, or 10 mm; Hydrogel marker = an injectable radiopaque polyethylene glycol-based hydrogel marker (TraceIT Tissue Marker; Augmenix Inc, Waltham, Mass). *28 markers were implanted, however the first four markers (2 patients) were left out of the clinical performance analysis and labeled as learning cases.*

Machiels *et al*. [30] showed that out of 19 successfully implanted markers visible on planning-CT, 18 (94.7%) remained visible on CBCT images during the treatment course. On MRI, 3 out of 4 markers had a distinct hypointense signal on T2-weighted images with a moderate visibility score.

The positional stability was analyzed by identifying the pairwise distances. The results suggest that the pairwise distance variation observed most likely is explained by tissue deformation and not marker migration.

No procedure-related adverse events were encountered.

The study states that the easier and faster endoscopic injection procedure, especially when multiple markers are needed, is a large advantage over the gold fiducial markers.

The study concludes that BioXmark® has an appropriate visibility on CT, CBCT and MRI with excellent positional stability. Figure 2 and 3 shows BioXmark® in a patient with esophageal cancer on pre-treatment planning CT and follow-up CT, respectively.

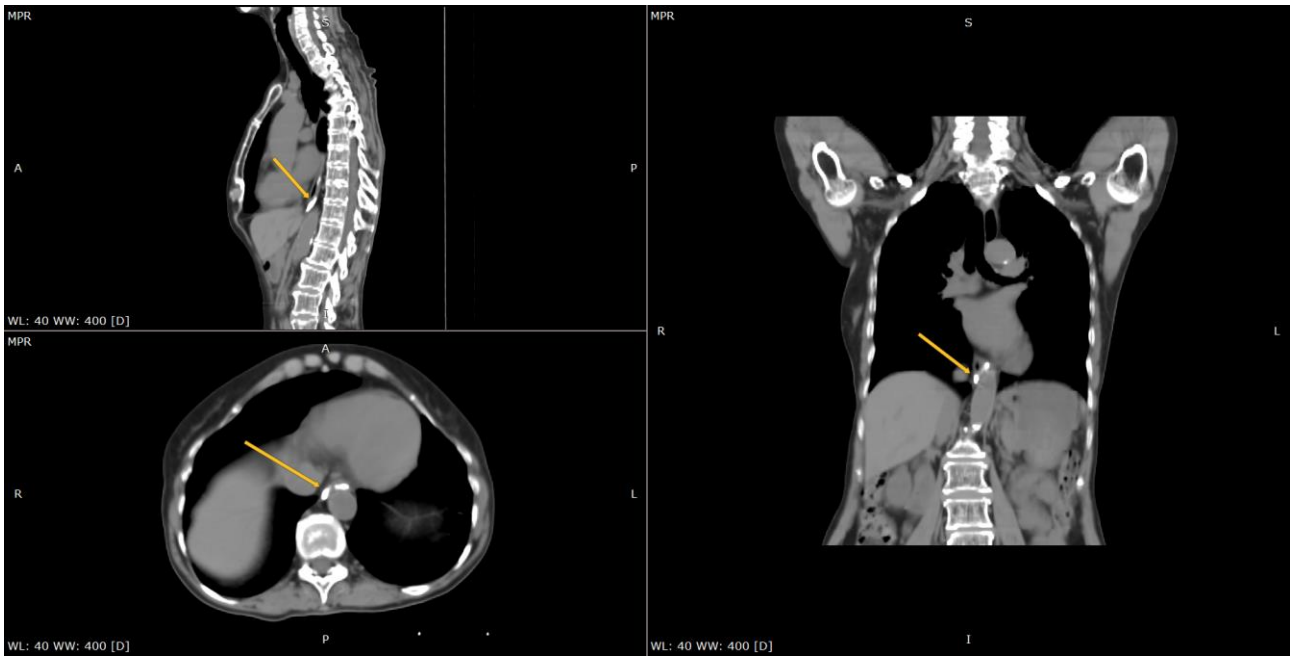


Figure 2: BioXmark® (yellow arrow) in the esophagus on planning CT.

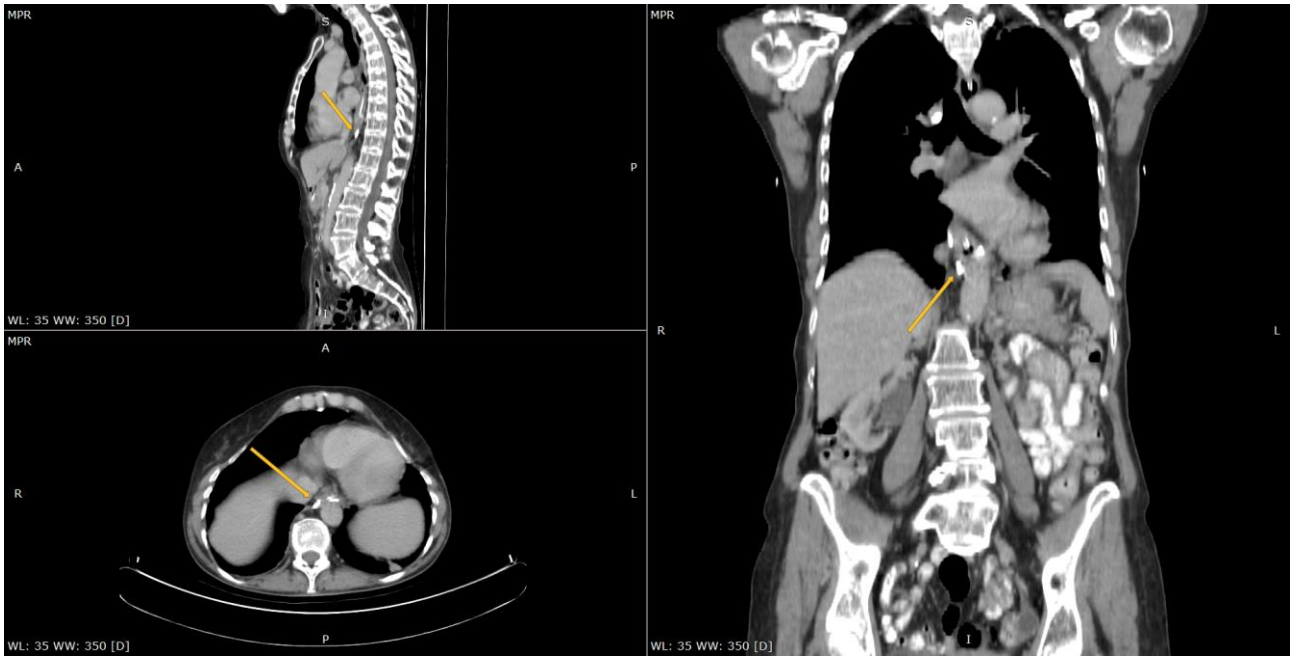


Figure 3: BioXmark® (yellow arrow) in the esophagus on 62 days follow-up CT.

6.2 Stomach cancer

Bleeker *et al.* have shown that implantation of BioXmark® in the stomach is technically feasible [32]. In the study with 12 patients, all patients received gold markers (Visicoil, Core Oncology, CA, USA; Ø 3.5mm x 10mm length) and 5 of the patients also received BioXmark®.

The study showed that placement in the stomach was technically feasible and successful, for the gold marker in 62% of the attempts and for BioXmark® in 94% of the attempts. At the last CT scan, 42 out of 61 gold markers and 17 out of 18 BioXmark® markers were present, demonstrating the strong positional stability of BioXmark®.

7. Conclusion

The use of BioXmark® in the esophagus and stomach is safe and technically feasible.

Using BioXmark® involves an easy and fast endoscopic implantation procedure.

BioXmark® has shown excellent positional stability and continuous radiopacity in CT and CBCT images.

BioXmark® enables precision radiation therapy in esophageal and stomach cancer.

8. References

1. GLOBOCAN 2020. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. [Internet]. [cited 2022 Mar 10]. Available from: http://gco.iarc.fr/today/home

2. DeVita VT, Lawrence TS, Rosenberg SA, editors. DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology. 11th edition. Philadelphia: Wolters Kluwer; 2019. 2390 p.

3. PDQ® Adult Treatment Editorial Board. PDQ Esophageal Cancer Treatment (Adult). Bethesda, MD: National Cancer Institute. Updated 07/15/2021. [Internet]. 2022 [cited 2022 Mar 11]. Available from: https://www.cancer.gov/types/esophageal/hp/esophageal-treatment-pdq

4. Stomach Cancer — Cancer Stat Facts [Internet]. [cited 2022 Mar 11]. Available from: https://seer.cancer.gov/statfacts/html/stomach.html

5. PDQ® Adult Treatment Editorial Board. PDQ Gastric Cancer Treatment. Bethesda, MD: National Cancer Institute. Updated 01/27/2022 [Internet]. 2022 [cited 2022 Mar 11]. Available from: https://www.cancer.gov/types/stomach/hp/stomach-treatment-pdq

6. Symonds P, Mills JA, Duxbury A, Walter J, Miller H, editors. Walter and Miller's textbook of radiotherapy: radiation physics, therapy and oncology. Eighth edition. Amsterdam: Elsevier; 2019. 615 p.

7. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, Henegouwen MI van B, Wijnhoven BPL, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. N Engl J Med. 2012 May 31;366(22):2074–84.

8. Thomas M, De Roover R, van der Merwe S, Lambrecht M, Defraene G, Haustermans K. The use of tumour markers in oesophageal cancer to quantify setup errors and baseline shifts during treatment. Clinical and Translational Radiation Oncology. 2021 Jan;26:8–14.

9. Leong T. A CRITICal period for chemoradiotherapy in gastric cancer. The Lancet Oncology. 2018 May;19(5):581–3.

10. Cunningham D. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. n engl j med. 2006;10.

11. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, et al. Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection. JCO. 2012 Jul 1;30(19):2327–33.

12. Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. The Lancet Oncology. 2018 May;19(5):616–28.

13. Leong T, Smithers BM, Michael M, Gebski V, Boussioutas A, Miller D, et al. TOPGEAR: a randomised phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG). BMC Cancer. 2015 Dec;15(1):532.

14. O'Neill AGM, Jain S, Hounsell AR, O'Sullivan JM. Fiducial marker guided prostate radiotherapy: a review. BJR. 2016 Dec;89(1068):20160296.

15. Choi JH, Seo DW, Park DH, Lee SK, Kim MH. Fiducial Placement for Stereotactic Body Radiation Therapy under Only Endoscopic Ultrasonography Guidance in Pancreatic and Hepatic Malignancy: Practical Feasibility and Safety. Gut Liver. 2014 Jan 15;8(1):88–93.

16. de Blanck SR, Scherman-Rydhög J, Siemsen M, Christensen M, Baeksgaard L, Irming Jølck R, et al. Feasibility of a novel liquid fiducial marker for use in image guided radiotherapy of oesophageal cancer. Br J Radiol. 2018 Dec;91(1092):20180236.

17. Fernandez DC, Hoffe SE, Barthel JS, Vignesh S, Klapman JB, Harris C, et al. Stability of endoscopic ultrasound-guided fiducial marker placement for esophageal cancer target delineation and image-guided radiation therapy. Practical Radiation Oncology. 2013 Jan;3(1):32–9.

18. DiMaio CJ, Nagula S, Goodman KA, Ho AY, Markowitz AJ, Schattner MA, et al. EUS-guided fiducial placement for image-guided radiation therapy in GI malignancies by using a 22-gauge needle (with videos). Gastrointestinal Endoscopy. 2010 Jun;71(7):1204–10.

19. Coronel E, Cazacu IM, Sakuraba A, Luzuriaga Chavez AA, Uberoi A, Geng Y, et al. EUS-guided fiducial placement for GI malignancies: a systematic review and meta-analysis. Gastrointestinal Endoscopy. 2019 Apr;89(4):659-670.e18.

20. Machiels M, Jin P, van Hooft JE, Gurney-Champion OJ, Jelvehgaran P, Geijsen ED, et al. Reduced inter-observer and intra-observer delineation variation in esophageal cancer radiotherapy by use of fiducial markers. Acta Oncologica. 2019 Jun 3;58(6):943–50.

21. Chandran S, Vaughan R, Efthymiou M, Sia J, Hamilton C. A pilot study of EUS-guided fiducial insertion for the multidisciplinary management of gastric cancer. Endosc Int Open. 2014 Sep;2(3):E153-159.

22. Chandran S, Vaughan R, Jacob A, Hamilton C, Joon DL, Lim K, et al. A novel endoscopic marker for radiological localization and image-guided radiotherapy in esophageal and gastric cancers (with video). Gastrointestinal Endoscopy. 2016 Feb;83(2):309–17.

23. de Blanck SR, Rydhög JS, Larsen KR, Clementsen PF, Josipovic M, Aznar MC, et al. Long term safety and visibility of a novel liquid fiducial marker for use in image guided radiotherapy of non-small cell lung cancer. Clinical and Translational Radiation Oncology. 2018 Nov;13:24–8.

24. De Roover R, Crijns W, Poels K, Peeters R, Draulans C, Haustermans K, et al. Characterization of a novel liquid fiducial marker for multimodal image guidance in stereotactic body radiotherapy of prostate cancer. Med Phys. 2018 May;45(5):2205–17.

25. Rydhog Scherman J, Irming Jølck R, Andresen TL, Munck af Rosenschöld P. Quantification and comparison of visibility and image artifacts of a new liquid fiducial marker in a lung phantom for image-guided radiation therapy: A new liquid fiducial marker for IGRT. Med Phys. 2015 May 15;42(6Part1):2818–26.

26. de Ridder M, Gerbrandy LC, de Reijke TM, Hinnen KA, Hulshof MCCM. BioXmark® liquid fiducial markers for image-guided radiotherapy in muscle invasive bladder cancer: a safety and performance trial. BJR. 2020 Jun 1;20200241.

27. Rydhög JS, Mortensen SR, Larsen KR, Clementsen P, Jølck RI, Josipovic M, et al. Liquid fiducial marker performance during radiotherapy of locally advanced non small cell lung cancer. Radiotherapy and Oncology. 2016 Oct;121(1):64–9.

28. Troost E, Menkel S, Enghardt W, Hytry J, Kunath D, Makocki S, et al. EP-1710: Chemical stability of BioXmark® following normofractionated and single-fraction proton beam therapy. Radiotherapy and Oncology. 2017 May 1;123:S937–8.

29. Rydhög Scherman J, Perrin R, Jølck RI, Gagnon-Moisan F, Larsen KR, Clementsen P, et al. Liquid fiducial marker applicability in proton therapy of locally advanced lung cancer. Radiotherapy and Oncology. 2017 Mar;122(3):393–9.

30. Machiels M, Voncken FEM, Jin P, Dieren JM van, Bartels-Rutten A, Alderliesten T, et al. A Novel Liquid Fiducial Marker in Esophageal Cancer Image Guided Radiation Therapy: Technical Feasibility and Visibility on Imaging. Practical Radiation Oncology. 2019 Nov 1;9(6):e506–15.

31. Machiels M, van Hooft J, Jin P, van Berge Henegouwen MI, van Laarhoven HM, Alderliesten T, et al. Endoscopy/EUS-guided fiducial marker placement in patients with esophageal cancer: a comparative analysis of 3 types of markers. Gastrointestinal Endoscopy. 2015 Oct;82(4):641–9.

32. Bleeker, Pouw, Bel, Sonke, Hulshof, van der Horst. Feasibility of endoscopic fiducial marker implantation in the stomach for use in image-guided RT. Poster presentation, ESTRO 2022;

NANOVI
Diplomvej 378
DK-2800 Lyngby
+45 31 42 11 86
www.nanovi.com