White paper

Head and neck cancer

BioXmark®

The liquid fiducial marker

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1. Introduction

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

2. Head and neck cancer background

The term "Head and neck cancer" is used to describe several different cancers of the head and neck region and generally includes cancers of larynx, pharynx (naso-, oro- and hypopharynx), lip and oral cavity, salivary glands, paranasal sinuses and nasal cavity [1].

In North America and Europe, head and neck cancer ranks 7th based on incidence with approximately 234,000 new cases and 8th based on mortality with approximately 89,000 deaths in 2020 [2]. Cancer of the oral cavity and lips, larynx and pharynx constitute the majority of head and neck cancers, while cancers of the salivary glands and paranasal sinuses and nasal cavity are less common [3].

90% of head and neck cancers are squamous cell carcinomas, which is a lethal disease with a mortality rate of ~50% for patients with advanced disease [1].

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[1,4].

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[1,4].

3.1 Radiotherapy for head and neck cancer

The use of radiotherapy for head and neck cancers depends on the type and stage of the cancer. In general, radiotherapy plays an important role in the treatment of head and neck cancer and can, potentially, be curative. For many primary head and neck cancers, radiotherapy yields better functional outcomes than surgery and is often preferred for localized disease. For locoregionally advanced head and neck cancers, radiotherapy is often used in combination with chemotherapy as a definitive organ function-preserving approach, or after surgery as adjuvant postoperative radiotherapy [5].

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[4,6,7].

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 head and neck cancer

Delivering precision radiotherapy maximizing radiation to the tumor target and minimizing radiation to healthy surrounding tissue is challenging for head and neck cancer. Radiotherapy administered to the head and neck region is burdened by a high rate of acute and late side effects. The side effects (apart from fatigue) relate to the structures in the radiation field and acute side effects include mucositis, dysphagia, loss of taste, loss of appetite, thickened secretions (together often leading to weight loss) and skin reactions while late side effects include skin pigmentation, alopecia, xerostomia, breakdown of the bone and myelitis [4].

The feasibility and safety of using gold fiducial markers in head and neck cancer has been demonstrated [8,9].

In a study with 27 patients Hamming-Vrieze *et al*. showed that gold marker (Visicoil™, RadioMed Corporation, Tyngsboro, MA, US) implantation was feasible without complications. The study aimed to quantify tumor shape variability in head and neck cancer patients during radiation therapy using implanted markers. The study concluded that large differences in fiducial marker patterns were observed and that the cranial and caudal borders in the posterior pharyngeal wall are at highest risk to be covered insufficiently during radiation therapy. Furthermore, the study concluded that "*implanted markers could help identify patients with an actual shrinkage of GTV who might benefit from mid-radiation therapy re-delineation to reduce toxicity*" [9].

The feasibility and safety of using surgical clips in head and neck cancer has also been demonstrated. Bitterman *et al.* [10], performed a clinical investigation with the purpose of analyzing the use of surgical clips placed in the tumor resection margins for use as radiographic markers to facilitate focused adjuvant radiation therapy. This prospective single arm study was conducted on 16 patients and in total 282 clips were evaluated. The study concluded that "*placement of surgical clips in the cavity walls after complete tumor resection provides an easy and inexpensive approach for defining resection margins and allows for increased accuracy of adjuvant treatment*".

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[12].

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*. [11]

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)[13] and has been confirmed by clinical investigations in bladder and lung[14,15]

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.

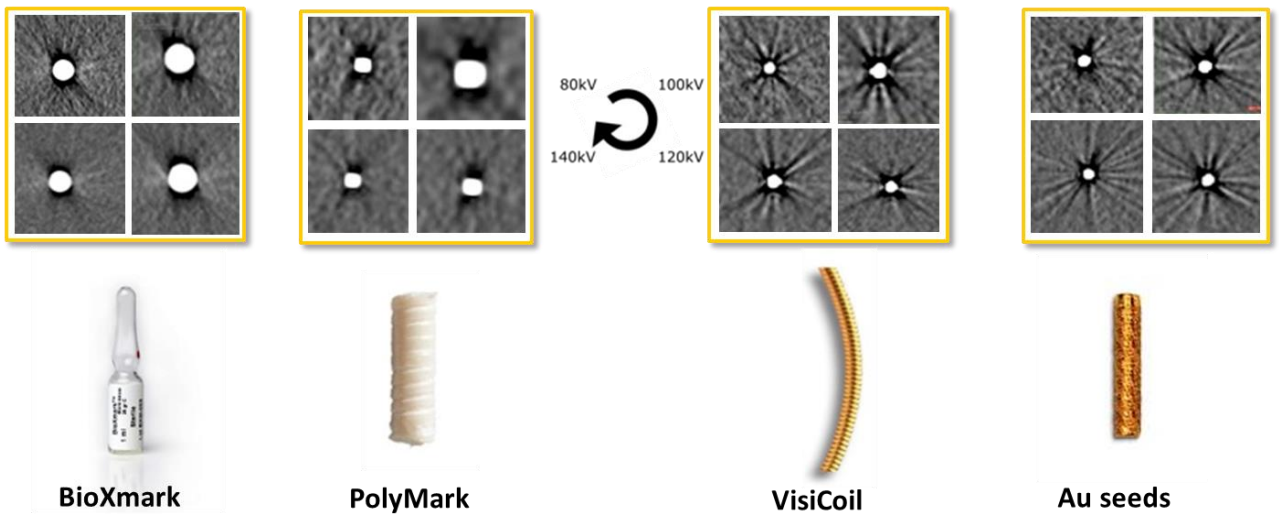

Figure 1. Artifacts of different markers on CT images at different tube voltages.

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

normofractionated and extremely hypofractionated proton therapy and no chemical degradation was observed[16].

Rydhög and colleagues have, 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 markers (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[17].

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[14], endoscopic ultrasound, endobronchial ultrasound and video bronchoscope[11].

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 […]"*[11]. 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[12]. 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[11,14].

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 head and neck cancer

In a clinical investigation with two patients, Steybe *et al*. demonstrated that a high number of markers with very low dose injections of BioXmark® (10-30 µl) is a feasible approach to mark oral soft tissue resection surfaces. The study adds information on the applicability of low dose injections to facilitate identification of the tumor bed in postoperative CT and on performance of the marker at different kV settings used in clinical routine [18]. This approach made it feasible to create a 3D grid structure for visualization of the tumor bed cavity in head and neck cancer.

In the clinical study one patient had 66 BioXmark® markers (64 × 10 µl; 2 × 30 µl) injected at the soft tissue tumor resection surface after undergoing surgical resection of a squamous cell carcinoma, located at the base and lateral margin of the tongue, while the other patient had 52 markers (48 × 10 µl; 4 × 30 µl) injected after resection of a tumor of the parotid gland and undergoing defect reconstruction with a scapula and latissimus dorsi flap. The injections were performed at the soft tissue resection surface once the results of frozen section analysis were available and surgical removal of the tumor was considered to be adequate [18]. The results showed that in single energy CT imaging, 57 of the 66 markers were easily identifiable as hyperdense structures in postoperative CT imaging. 10 µl injections showed relatively homogenous, circular markers, while 30 µl injections resulted in a larger and more heterogenous, non-circular shape, distinguishable from 10 µl injections. In dual-energy CT imaging, 43 of the 52 markers resulted in hyperdense structures well identifiable and providing basis for three-dimensional reconstruction of the tumor resection surface (flap volume). Fig. 4 below (image and text copied directly from figure 4 of the publication [18]) shows BioXmark® in a postoperative CT.

The study concludes that amounts as low as 10 µl of BioXmark® were clearly visible in head and neck CT imaging at kV settings applied in clinical routine and that intraoperative injection of low doses of

BioXmark® "*can be considered a promising option to facilitate identification of the tumor resection surface in postoperative CT imaging for RT planning and follow-up imaging*".

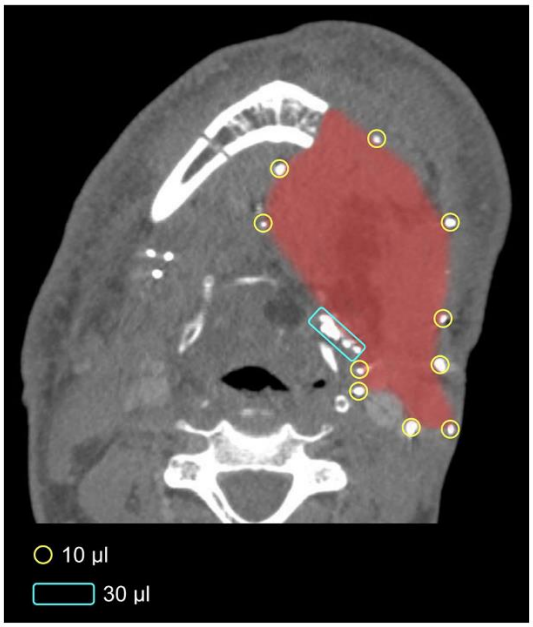

Fig. 4 Markers created by injection of 10 µl of SAIB/x-SAIB guide delineation of the tumor resection surface in postoperative CT imaging. Moreover, markers created by the injection of 30 µl of SAIB/x-SAIB can be visually differentiated from the 10 µl markers and thus be applied to mark regions which require special attention in the postoperative setting

7. Conclusion

The use of BioXmark® in connection with radiotherapy of head and neck cancer has been demonstrated.

BioXmark® in amounts as low as 10 µl is visible in the head and neck region on CT imaging at kV settings applied in clinical routine and 30 µl injections were distinguishable from 10 µl injections.

Intraoperative injection of multiple low doses of BioXmark® can be considered a promising option to facilitate identification of the tumor resection surface in postoperative CT imaging for radiotherapy planning and follow-up imaging.

8. References

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