White paper

Lung cancer

BioXmark®

The liquid fiducial marker

Table of Contents

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1. Introduction

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

2. Lung cancer background

In North America and Europe, lung cancer ranks 2nd based on incidence with approximately 730,000 new cases (~11% of new cancer cases) and it is the leading cause of cancer-related mortality with approximately 544,000 deaths (~ 21% of cancer related mortality) in 2020[1]. The 5-year relative survival rate is around 22% (2011-2017, in the US) and varies significantly for patients diagnosed with local (60%), regional (33%) or metastatic disease (6%)[2,3].

Lung cancers are divided into non-small-cell lung cancer (NSCLC) (80-85%) and small-cell lung cancer (SCLC) (15% to 20%) based on histologic, clinical, and neuroendocrine characteristics. NSCLC is any type of epithelial lung cancer other than SCLC and is further subdivided based on histology, with the three main subtypes of NSCLC being squamous cell carcinoma (~25% of lung cancers), adenocarcinoma (~40% of lung cancers) and large cell carcinoma (~10% of lung cancers)[2,4].

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 [4,5].

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[4,5].

3.1 Radiotherapy for lung cancer

Treatment of lung cancer is complex. Radiotherapy plays an important role in the treatment. 77% percent of all lung cancer patients have an evidence-based indication for radiotherapy, however it is often utilized less[6,7]. The use of radiotherapy for lung cancer depends on the subtype and stage.

SCLC is highly radiosensitive and thoracic radiation therapy has been shown to improve survival of SCLC patients[8]. Chemotherapy combined with radiation therapy is considered the standard of care for this group of patients[6]. However, complete recovery is difficult to achieve because SCLC has a greater tendency to be widely disseminated by the time of diagnosis, and the prognosis for SCLC is generally poor with an overall 5 year survival rate around 5-10%[8].

For NSCLC surgical resection is the treatment option with the highest potential to achieve full recovery[2]. Radiotherapy is used to cure patients where surgery is contraindicated because of local spread and/or the patient is not fit for surgery because of comorbidity[5].

For patients medically unfit for surgery or refusing surgery and having peripherally located stage I-IIA NSCLC, Stereotactic Body Radiation Therapy (SBRT) or Stereotactic Ablative Body Radiotherapy (SABR) has become the standard of care. For inoperable stage I-II patients where SBRT/SABR is not feasible (due to tumor location or node positive disease), conventionally fractioned or hypofractionated radiotherapy remains the standard of care[6]. There is an ongoing debate about the role of SABR in patients who are fit to undergo surgery, with the ongoing VALOR trial (NCT02984761) aiming to evaluate the two treatments in a randomized trial[9].

For most patients with stage III NSCLC, radiotherapy with concomitant chemotherapy is the standard of care. The addition of surgery has not been shown to be of benefit to overall survival, compared to definitive chemoradiotherapy[9].

For patients with stage IV NSCLC radiotherapy is primarily used with a palliative aim, where it has a well-established role. Moreover, there may be a group of patients with oligometastatic disease where ablative treatment may result in long-term survival[6].

The U.S. Preventive Services Task Force has recommended annual screening for lung cancer with low-dose CT in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years[10]. In many European countries national authorities are assessing implantation of similar risk based lung cancer screening[11]. There has been an increase in the detection of peripheral pulmonary nodules in recent years and the implementation of low dose CT screening programs is expected to increase this trend, underpinning the need for less invasive strategies for diagnostic and therapeutic management of such nodules, which for the majority of cases are benign[12,13].

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[5,14,15].

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 lung cancer

Delivering precision radiotherapy, i.e. maximizing radiation to the tumor target and minimizing radiation to healthy surrounding tissue is challenging in lung cancer patients as the tumor, due to respiratory and cardiac induced movements, is a moving target and is situated within an area surrounded by critical and radiosensitive healthy tissues (such as lung parenchyma, the esophagus, heart and spinal cord)[9,16].

For stereotactic body radiation therapy (SBRT) fiducial markers are commonly used to act as internal radiographic markers. This technique is especially useful for certain radiation delivery techniques

which use kV imaging such as CyberKnife® (Accuray, Sunnyvale, CA, USA)[16]. With the advance of SBRT in the treatment of lung cancers, it is likely that the number of patients requiring fiducial markers will increase. The most commonly used fiducial markers are gold seeds, while titanium clips and coils have also been used[17].

Several studies have demonstrated the value of fiducial markers in lung cancer[17–39]. Different implantation methods have been used, including percutaneous (transthoracic) insertion, endovascular placement and implantation using bronchoscopy, endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB). Different challenges and benefits are associated with the different techniques and marker types.

The percutaneous insertion of gold fiducial markers is widely available but involves penetrating the pleura and is associated with a high rate of pneumothorax in the order of 30-67%[13,38]. Various migration rates have been reported in the order of 9-19%[27].

The endobronchial method respects the natural airway pathway to reach pulmonary lesions. It has been reported to have a lower rate of pneumothorax (0-6%). Among the early studies using the bronchoscopic approach a higher migration was reported, with the fiducial marker dropping into the airway in 22% of the cases[27]. This migration has been associated with linear fiducial markers and to minimize fiducial marker migration coil-tailed and coil-shaped fiducial markers have been designed. In a study with 30 patients, Lachkar *et al.* reported on the use of coil-tailed fiducial markers (SuperLock™ Nitinol Coil fiducial markers) placed using EBUS and reported of a very low rate of secondary migration after long term follow-up[27]. In a retrospective study with 52 patients and 207 fiducial markers, Casutt *et al.* investigated the use of endobronchial inserted coil-shaped fiducial markers (Tornado®, Cook Medical)[38]. Tracking was found to be successful for 93% of the peripheral pulmonary lesions and migration of the fiducial marker occurred for 8% of the markers. The study concludes that the use of bronchoscopic coil-shaped fiducial markers is "*associated with a low migration rate and allows precise SBRT delivery*".

Insertion of coils-shaped fiducial markers by way of electromagnetic navigation bronchoscopy (ENB) have been demonstrated feasible and accurate, but procedures require a complex infrastructure limiting its large-scale use [13].

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 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[41].

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

[a] Additional follow up on patients from clinical investigation by de Blanck *et al*. [40]

diagnostic CT-scanner using various tube voltages from 80kV to 140kV in 20kV steps (Figure 1)[42] and has been confirmed by clinical investigations in bladder and lung[43,44]

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 F2503-13.

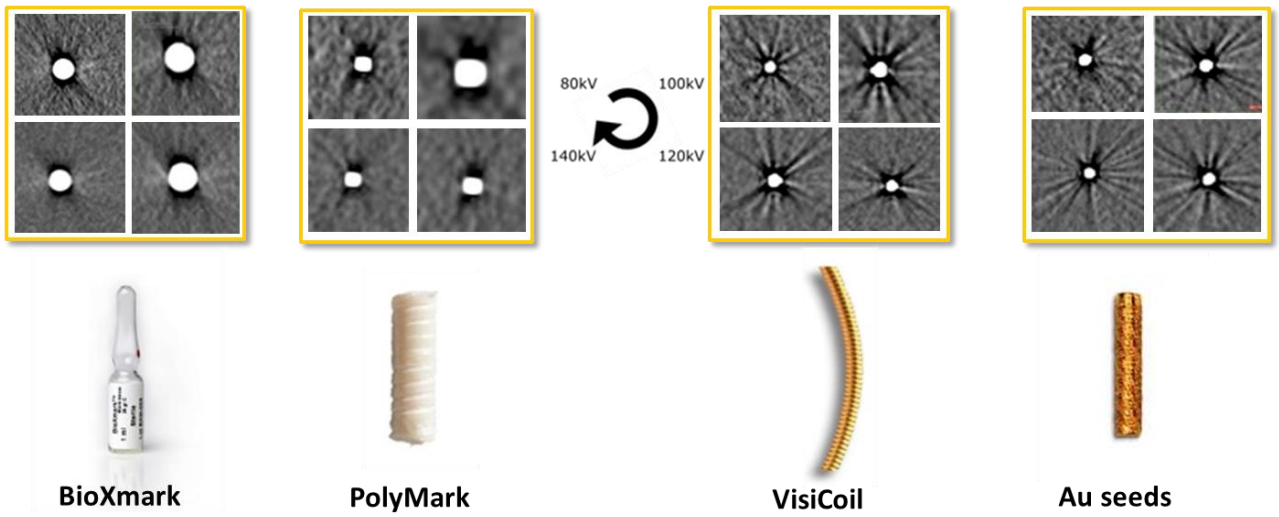


Figure 1. Artifacts of different markers on CT images at different tube voltages.

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[45]. Furthermore, the BioXmark® markers were evaluated after being exposed to normofractionated and extremely hypofractionated proton therapy and no chemical degradation was observed[45].

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[46].

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[[43], endoscopic ultrasound, endobronchial ultrasound and video bronchoscope[40].

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 […]"*[40]. 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[41]. 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[40,43].

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 lung cancer

The performance of BioXmark® as fiducial marker for radiotherapy of lung cancer[44] and its long term safety and visibility has been thoroughly evaluated[40].

In a study by Rydhög *et al.* 15 patients had in total 35 BioXmark® fiducial markers implanted, 1-4 markers in each patient[44]. The patients were referred for concomitant chemoradiotherapy (66 Gy in 33 fractions, 5 weekly fractions). Markers were placed into the tumor or in the healthy tissue near the primary tumor and into the mediastinal lymph nodes. The markers were implanted using a 22G needle using either a conventional video-bronchoscope or an endobronchial ultrasound bronchoscope (EBUS) or an esophageal endoscopic ultrasound (EUS) device and furthermore fluoroscopy was used for all patients except 1. Doppler ultrasound was used to minimize the risk of endovascular injection. 2 patients did not proceed to radiotherapy leaving 32 markers injected in 13 patients receiving radiotherapy. 29 of the 32 markers (91%) were suitable as fiducial markers on the planning CT and these markers remained fully visible on the CBCT-images throughout the treatment course[44].

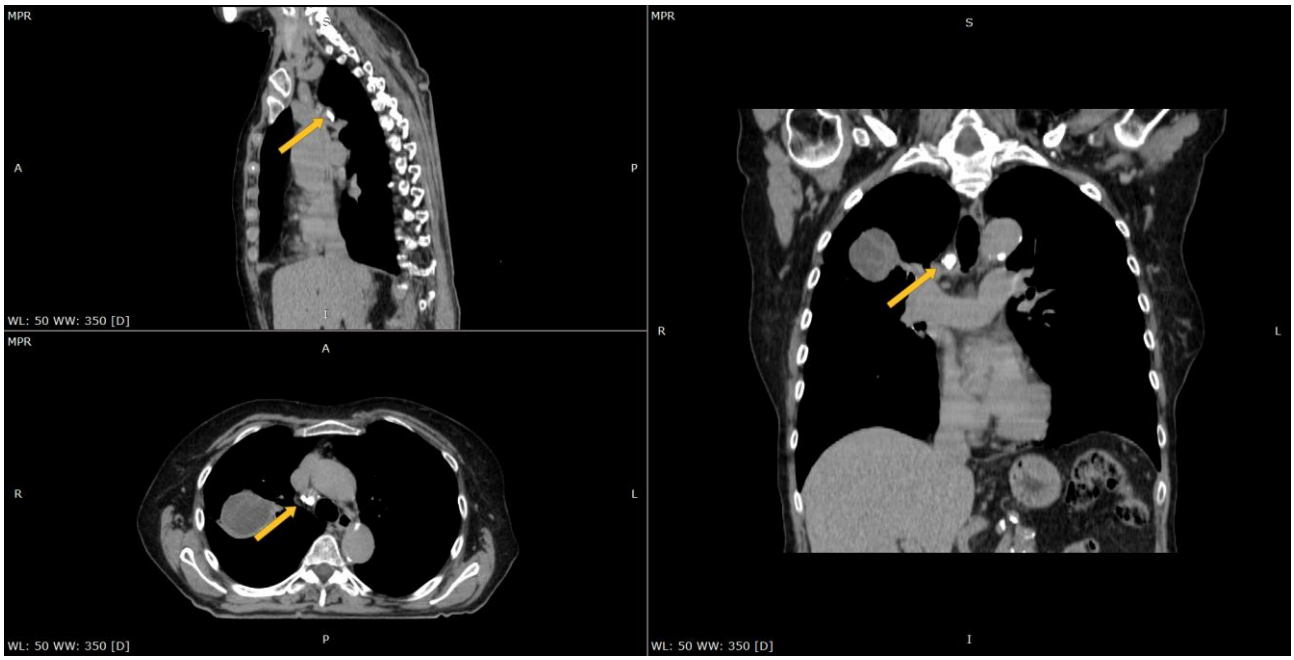
2 of the markers not visible were the ones injected by conventional video-bronchoscope. Markers appeared more condensed when injected in the lymph nodes than in the tumors. No marker migration relative to the injection site was found in CT images up to 36 months after end of treatment. No pneumothorax was observed in any of the 15 patients included in the study.
An analysis of degradation showed that the markers underwent some degradation until approximately 9 months, after which a steady state with no further degradation was seen[40].

Rydhög *et al*. conclude on the performance: "*We found that the injected liquid fiducial markers were suitable for IGRT for locally advanced lung cancer patients. Three liquid fiducial markers were lost*

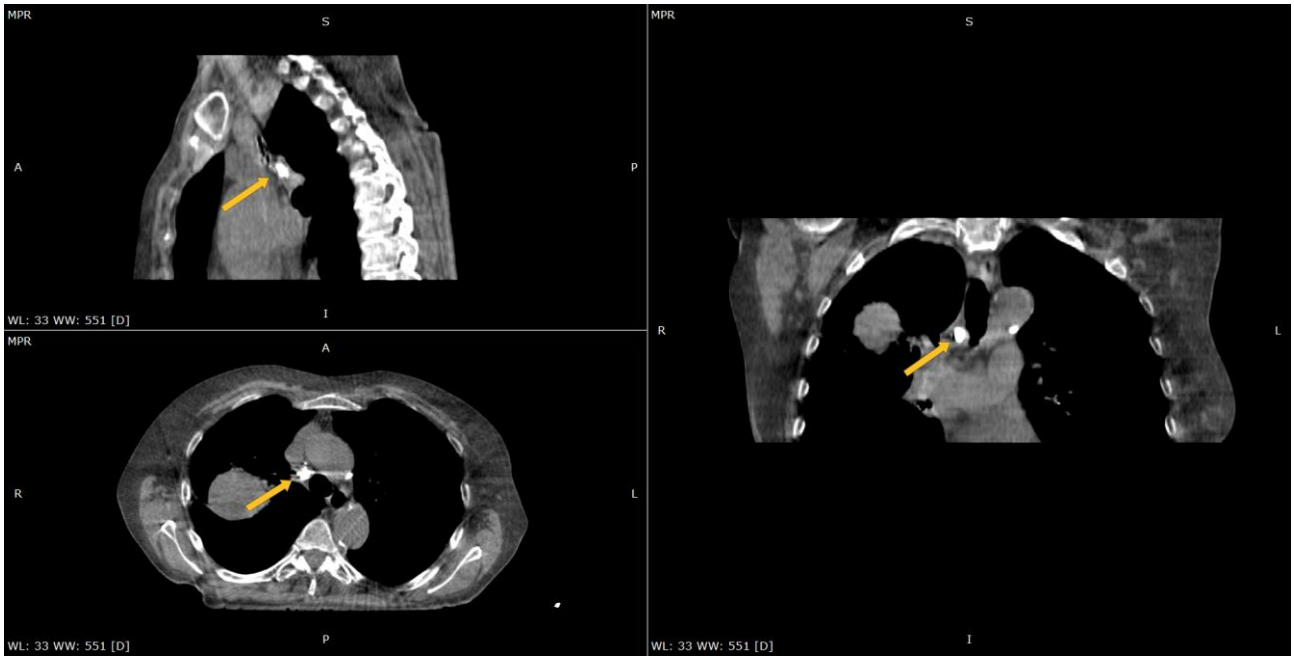
between injection and treatment planning CT-scan. No liquid fiducial markers implanted into either the tumor mass or into lymph nodes were lost during the treatment period, and importantly, the marker volumes and density were stable. The injected markers stayed within the tumor and/or node position during the course of radiotherapy and were most stable for lymph node injection. We observed positional shifts for patients with large anatomical changes. The liquid fiducial marker is an adequate surrogate for IGRT of the mediastinal targets"[44].

Riisgaard de Blanck *et al*. conclude on the long-term safety and visibility that BioXmark® "*was safe to endoscopically inject into primary tumors and lymph nodes in patients with locally advanced NSCLC and provided adequate visibility and stability when acting as fiducial markers for image guided radiotherapy. The marker was partially degraded during a three year follow up. No post-RT marker migration or complication were found*" [40].

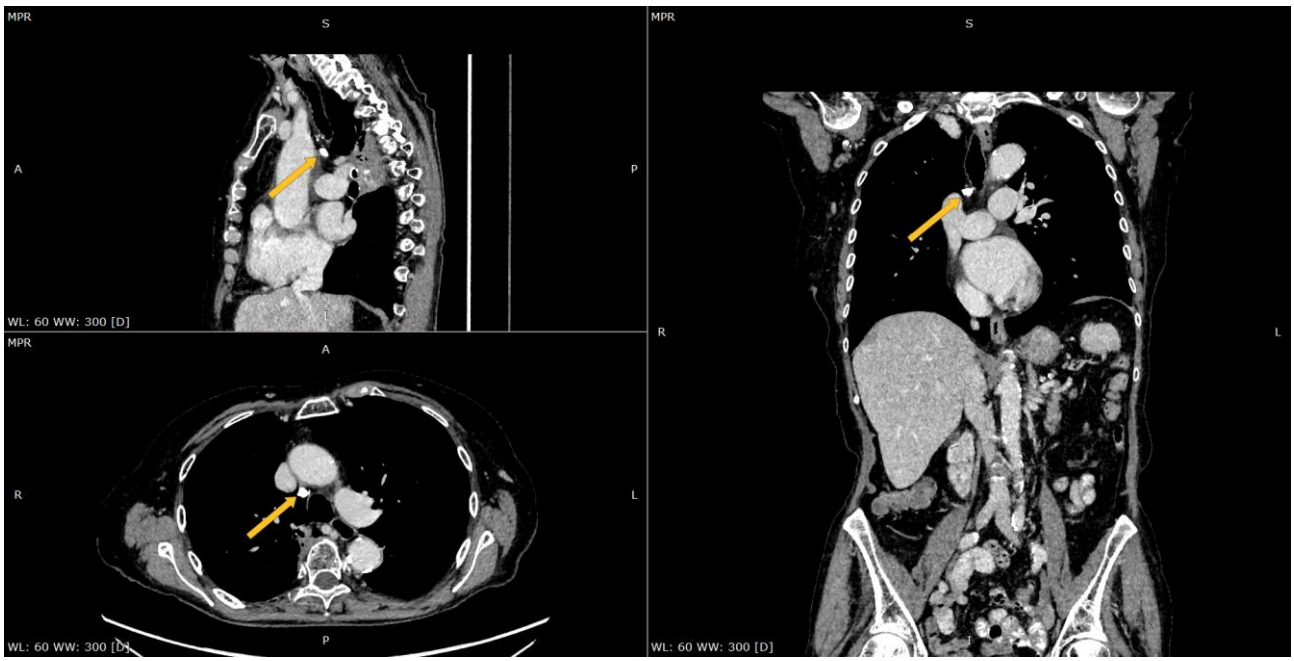
Below clinical images show BioXmark® in lung cancer patients. Two different patients with BioXmark® placed in a central mediastinal lymph node and a peripheral lung tumor, respectively, are shown during planning, treatment and long-term follow-up:



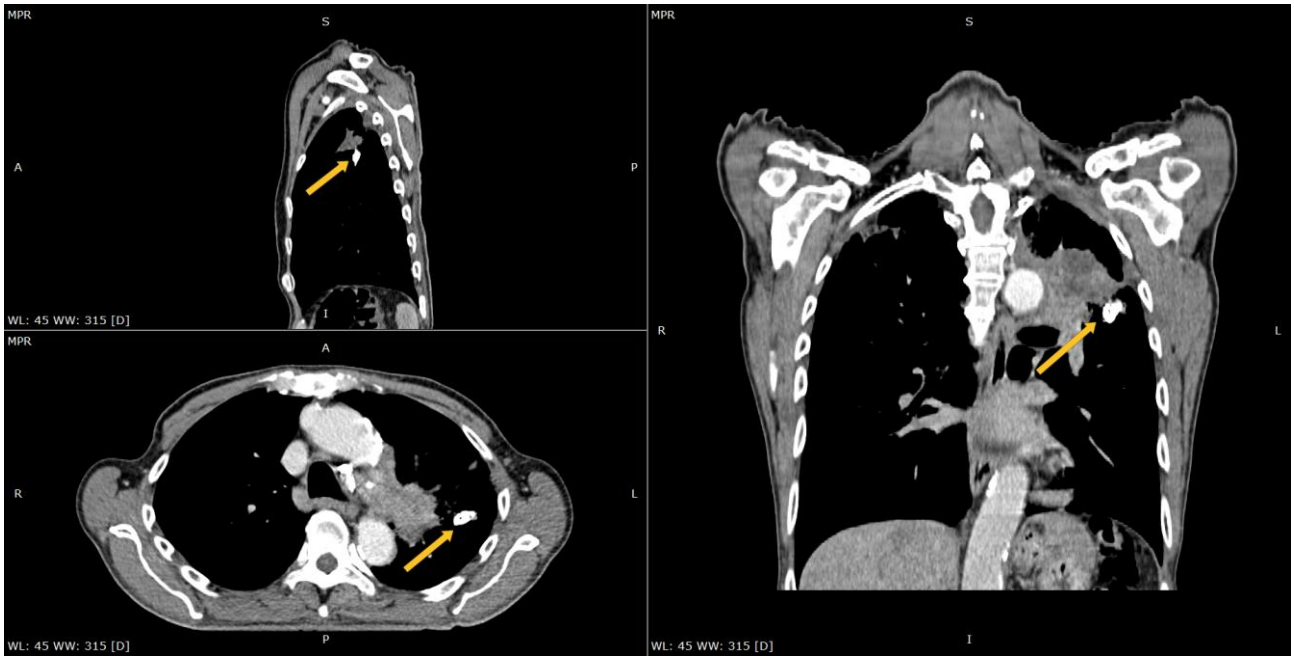
BioXmark® in a central lymph node on a planning CT scan.



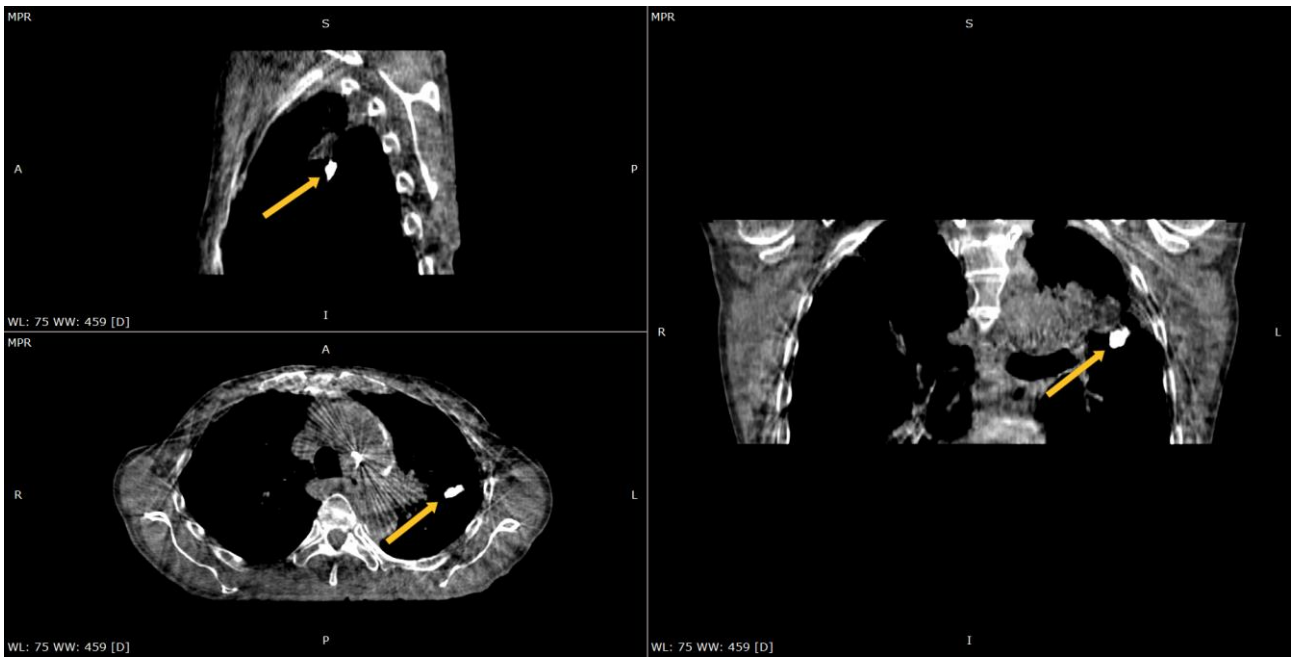
BioXmark® in a central lymph node on CBCT.



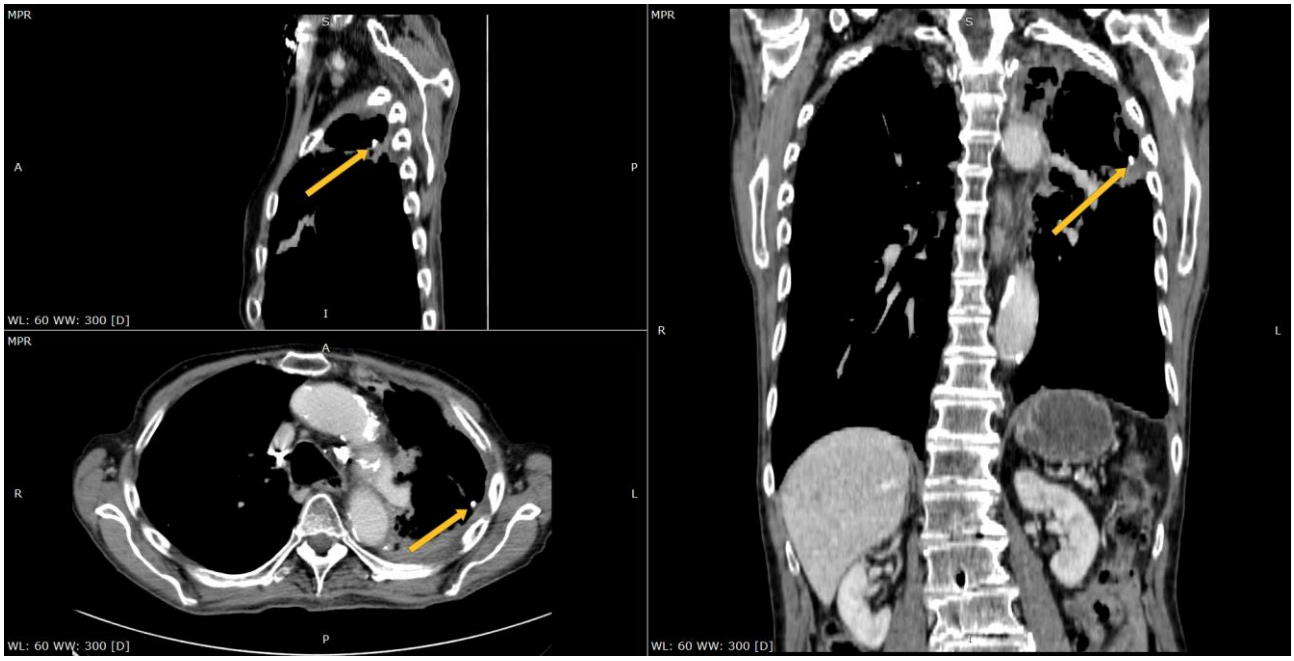
BioXmark® in a central lymph node on a follow-up CT scan (73 months).



BioXmark® in a lung tumor on a planning CT SCAN.



BioXmark® in a lung tumor on a CBCT scan.



BioXmark® in a lung tumor on a follow-up CT scan (33 months).

7. Conclusion

It is demonstrated that BioXmark® enables precision radiation therapy in patients with lung cancer.

The use of BioXmark® in patients with lung cancer demonstrated to is safe and technically feasible and BioXmark® has sustained visibility and positional stability during the entire treatment course and throughout the follow-up period.

Implantation of BioXmark® in lung cancer can be done with thin needles percutaneously or by video bronchoscope or endobronchial ultrasound. BioXmark® can be implanted in the tumor tissue, in adjacent healthy lung parenchyma or in any lymph nodes.

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