Whitepaper
Head and neck cancer

BioXmark®

The liquid fiducial marker

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Head and neck cancer

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

1. 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].

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 [1,4].

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 [1,4].

2.1 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].

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 [4,6,7].

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
- 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 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*".

4. Clinical use of BioXmark®

In a recent 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 [11]. 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 [11].

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 [11]) shows BioXmark® in a postoperative CT.

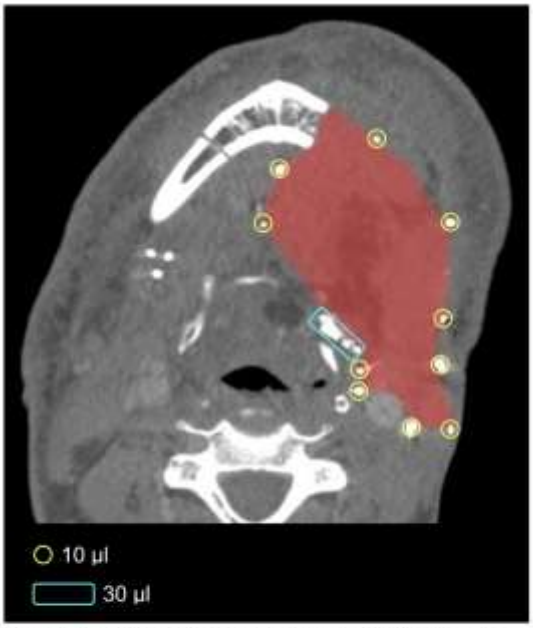

Fig. 4 Markers created by injection of 10 µl of SAIB/x-SAIB guide delineation of the tumor resection surface in postoperative CT imaging. Moreover, markers created by the injection of 30 µl of SAIB/x SAIB can be visually differentiated from the 10 µl markers and thus be applied to mark regions which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

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*".

5. 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.

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