Received:
06 March 2018

Revised:
25 June 2018

Accepted:
27 June 2018

<https://doi.org/10.1259/bjr.20180236>

Cite this article as:

de Blanck SR, Scherman-Rydhög J, Siemsen M, Christensen M, Bæksgaard L, Irming Jøelck R, et al. Feasibility of a novel liquid fiducial marker for use in image guided radiotherapy of oesophageal cancer. *Br J Radiol* 2018; **91**: 20180236.

SHORT COMMUNICATION

Feasibility of a novel liquid fiducial marker for use in image guided radiotherapy of oesophageal cancer

¹STEEN RIISGAARD DE BLANCK, MD, ^{2,3}JONAS SCHERMAN-RYDHÖG, M.Sc. PhD, ⁴METTE SIEMSEN, MD, PhD, ⁴MERETE CHRISTENSEN, MD, ¹LENE BÆKSGAARD, MD, PhD, ^{5,6}RASMUS IRMING JØLCK, M.Sc., PhD, ¹LENA SPECHT, MD, DMSc, ⁵THOMAS LARS ANDRESEN, M.Sc., PhD and ¹GITTE FREDBERG PERSSON, MD, PhD

¹Department of Oncology, Section of Radiotherapy, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

²Department of Physics, Niels Bohr Institute, University of Copenhagen, Copenhagen, Denmark

³Department of Radiation Physics, Skane University Hospital, Lund, Sweden

⁴Department of Thoracic Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

⁵DTU Nanotech, Department of Micro-and Nanotechnology, Center for Nanomedicine and Theranostics, Technical University of Denmark, Kongens Lyngby, Denmark

⁶Nanovi A/S, DTU Scion, Kongens Lyngby, Denmark

Address correspondence to: Steen Riisgaard de Blanck

E-mail: steen.riisgaard.de.blanck@regionh.dk

Objective: To evaluate the feasibility of a new liquid fiducial marker for use in image-guided radiotherapy for oesophageal cancer.

Methods: Liquid fiducial markers were implanted in patients with metastatic or inoperable locally advanced oesophageal or gastro-oesophageal junction cancer receiving radiotherapy. Markers were implanted using a conventional gastroscope equipped with a 22 G Wang needle. Marker visibility was evaluated on fluoroscopy, CT, MRI and cone beam CT scans.

Results: Liquid markers ($n = 16$) were injected in four patients. No Grade 2 or worse adverse events were observed in relation to the implantation procedure, during treatment or in the follow-up period. 12/16 (75%)

markers were available at the planning CT-scan and throughout the treatment- and follow-up period. The implanted markers were adequately visible in CT and cone beam CT but were difficult to distinguish in fluoroscopy and MRI without information from the corresponding CT image.

Conclusion: Liquid fiducial marker placement in the oesophagus proved safe and clinically feasible.

Advances in knowledge: This paper presents the first clinical use of a new liquid fiducial marker in patients with oesophageal cancer and demonstrates that marker implantation using standard gastroscopic equipment and subsequent use in three-dimensional image-guided radiation therapy is safe and clinically feasible.

INTRODUCTION

Radiotherapy (RT) plays a significant role in the treatment of tumours in the oesophagus and gastro-oesophageal junction (GEJ) area.¹ Accurate target volume delineation is challenging as the true tumour extent is difficult to visualize in planning computed tomography (CT) images, due to similar contrast values in normal- and malignant tissue in the mediastinum and upper abdomen, in combination with poor visibility of mucosal tumour tissue.^{2,3} The similar contrast values also impact the accuracy of image-guided RT and the possibility to correct for physiological and anatomical changes occurring during the treatment course. These uncertainties in RT planning and delivery, necessitate large treatment margins, leading to increased risks of normal tissue toxicity.^{4,5}

Endoscopy is the commonly used standard for determination of the mucosal tumour extent. Implantation

of radiopaque fiducial markers at the cranial and caudal borders of the tumour as surrogates for tumour extension may aid in target delineation and increase RT treatment precision resulting in reduced normal tissue toxicity.⁶

Several studies have investigated the use of solid metal fiducial markers including clips, linear gold seeds and coils in RT of oesophageal cancer. These markers provide good X-ray visibility and are safe to use. However, loss of markers between placement and RT planning has been reported.^{7–11}

BioXmark® is a novel liquid fiducial marker developed for use in RT. The marker consists of sucrose acetate isobutyrate and organoiodinated sucrose acetate isobutyrate mixed with ethanol. After injection into soft tissue, ethanol diffuses out of the marker, causing a rapid increase in marker viscosity resulting in a sticky highly viscous gel-like

marker. The initial low viscosity allows for minimal invasive implantation using up to 25 G needles and standard endoscopic equipment.¹²

In this study, we evaluated the safety of the implantation procedure, as well as the visibility and visually verified positional stability of the liquid fiducial marker during and after RT in four patients with inoperable/metastatic oesophageal cancer.

METHODS AND MATERIALS

Patients with biopsy proven metastatic or inoperable locally advanced oesophageal or GEJ cancer referred for palliative RT with 30 Gy in 10 fractions, were eligible for inclusion during a fixed inclusion period (March–December 2015). Exclusion criteria were tumours located <25 cm from the oral orifice, allergy to iodine, allergy to iodinated contrast or contraindications to MRI. The study adheres to the standard of ethics in the Helsinki declaration, and was approved by the regional ethics committee (H-4-2014-092) and by the Danish Health and Medicines Authority (Application# 2014071880). All patients provided written consent to participate in the study.

All patients underwent endoscopy-guided liquid fiducial marker placement as an outpatient procedure by two experienced surgeons using a conventional gastroscope equipped with a 22 G Wang needle. The procedure was performed under general anaesthesia according to standard of care for endoscopic biopsy procedures.

The dead volume of the Wang needle was replaced with the liquid marker (approximately 1.5 ml) immediately before the injection procedure. Two submucosal injections (0.1–0.25 ml per injection) were performed at both the cranial and caudal border of the visible tumour extensions resulting in four markers per patient. After the implantation procedure, patients were monitored at least 3 h before discharge.

RT planning CT-scans were acquired within 4 days of the injection procedure. A free-breathing (FB) CT, three consecutive deep inspiration breath-hold (DIBH) CTs and a respiratory correlated four-dimensional CT was acquired using a Siemens Somatom Definition AS Open CT-scanner. FBCT images were used for treatment planning. MRI was performed on a 1.5 T MR-scanner. Two T_1 weighted sequences (FLASH tra 4 mm and 5 mm) acquired during multiple DIBHs and four T_2 weighted (HASTE cor/sag/tra 6 mm in DIBH and one BLADE tra 3 mm, diaphragm triggered) sequences were acquired. CT and MRI images were co-registered (bone match).

Patients were treated using volumetric arc technique in FB using a Varian TrueBeam STx linear accelerator. Daily FB cone beam CT (CBCT) images were acquired prior to treatment for patient positioning and orthogonal fluoroscopy images were acquired at fraction two and nine for 2D X-ray visibility evaluation. Continuous marker visibility and positional stability during the treatment period were assessed based on the acquired CBCT scans. Safety visits with registration of toxicity were performed prior to start of treatment, and after the last fraction. Toxicity was

graded according to CTCAE v. 4.0. After end of RT, patients were followed with regular visits, including CT scans, at 3 month intervals until death.

RESULTS

Four patients (age 68–78) were included. Reason for referral were dysphagia and haemorrhage.

Patient, tumour and marker characteristics are listed in [Table 1](#). Follow-up time was 5–12 months.

In total, 16 markers were injected. Endoscopic implantation of the markers was technically feasible, and the liquid marker composition enabled multiple markers implantations to be conducted during the same endoscopic procedure.

One CTCAE (Common Terminology Criteria for Adverse Events) Grade 1 complication was observed during the injection procedure: a case of minor bleeding from the implantation site immediately after the injection. The patient had no clinical symptoms from the bleeding, but visual guidance during the following implantations was limited. No complications requiring intervention were noted in relation to the injection procedure and no post-implantation haemorrhage or other complications were encountered.

Three markers (19%) were lost between implantation and planning CT-scan acquisition (1–4 days). The proximal markers in Patient 1 had conjoined and was analysed as one marker. All remaining 12 markers were retained during the treatment and follow-up period.

The implanted markers showed excellent continuous radiopacity in CT and CBCT images both during the treatment course and throughout the follow-up period up to 12 months ([Figures 1a,b, 2](#)) and all markers remained positionally stable with no registered migration relative to implantation site during the follow up period. In both T_1/T_2 weighted MRI, the markers appeared hypo intense (signal void) ([Figure 1c](#)). Identification of individual marker deposits on MRI was challenging without information from the corresponding CT-images and thus marker-based co-registration of CT/MRI was not feasible. 3 of the 12 retained markers were visible in fluoroscopy images during the treatment course ([Figure 1d](#)).

DISCUSSION

Within the limitations of this study, implantation of the novel liquid fiducial marker using standard gastroscopic equipment in patients with tumours in mid- and distal oesophagus/GEJ area proved safe and clinically feasible.

Other studies have reported the technical feasibility and safety of endoscopy-guide marker placement of both solid and liquid markers in oesophageal cancer.^{13–15} In a study by Machiels *et al*¹³ three types of markers including gold seeds, flexible coils and a liquid polymer based fiducial marker were investigated. Marker retention rate varied to a large extend between the three marker types. Markers available at planning-CT, first CBCT and last

Table 1. Patient and marker placement data *Proximal markers conjugated, analysed as one marker

Patient	Age/ gender (M/F)	Stage (TNM)	ECOG status (0-4)	Primary oesophageal tumour location	Reason for referral	Volume, proximal/ distal markers (ml)	Time from marker implantation to RT (days)	Markers visible on planning CT/last treatment CBCT	Markers within treatment volume (PTV)	Visible markers on last follow up CT (markers/months)
1	75/M	T3N2M1	1	Distal/GEJ	Dysphagia	0.1 + 0.1/0.1+0.1	2	3*/3*	2	3*/12
2	78/M	T3N1M1	2	GEJ	Haemorrhage	0.1 + 0.1/0.1+0.1	2	3/3	1	3/6
3	68/F	T3N0M0	2	Middle	Dysphagia	0.1 + 0.2/ 0.1 + 0.2	4	4/4	4	4/6
4	74/M	T3N0M0	2	Distal/GEJ	Dysphagia	0.25 + 0.2/ 0.2 + 0.2	3	2/2	2	2/3

ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; TNM, TNM Classification of Malignant Tumours.

CBCT recorded during treatment were reported as; gold seeds: 88, 66 and 63%; gold coils: 98, 82 and 80% and liquid polymer based fiducial marker: 89, 22 and 11%.

In our study, 75% of the implanted markers were available at planning-CT, first CBCT and last CBCT images recorded during treatment. In addition, the liquid markers implanted in this study were also continuously visible and positionally stable in CT images throughout the follow-up period up to 12 months (Figure 2). The number of markers available at the planning-CT scan in our study was comparable to the performance of other solid fiducial markers used in oesophageal cancer and more importantly, no markers were lost during treatment.

Precision of marker placement is important for delineation purposes, whereas volumetric and positional stability during RT is important for treatment precision. In the present study, visual guidance was used during marker implantation to enable visualisation of mucosal target lesions in CT images. Another option is using endoscopic ultrasound guidance to improve precision of placement and include submucosal tumour extension, as the tested liquid marker is sonographically visible. A further advantage of using ultrasound guidance during marker injections is better verification of correct marker placement depth in the submucosal tissue, reducing the risk of marker detachment immediately or shortly after implantation. It is suspected that the three markers lost after implantation were subsequently swallowed. In one patient, a small radiopaque element, most likely representing a lost marker, was noticed in the ventricle on the planning CT images. The involved patients were not affected by the detachment of the markers. We have previously evaluated the liquid fiducial marker in a population of non-small cell lung cancer (NSCLC) patients, where endobronchial ultrasound guided injections were successfully used during implantation in lung- and mediastinal lymph node lesions. All markers injected under guidance of endoscopic ultrasound in the NSCLC study (29 markers in total) were available for analysis in planning CT and treatment CBCT images.¹²

This study was planned in patients receiving short course palliative RT. The design of the study did not allow for inclusion of patients receiving long term definitive RT as the time frame for marker injection between referral to and beginning of RT in this group of patients was too short. In the NSCLC study, the liquid fiducial marker was evaluated in a RT course of 33 fractions, showing good positional stability and visibility in tumours and lymph nodes throughout the treatment course.¹²

The visibility of the liquid marker in 2D kV images was limited in this study with only 25% (3/12) of the implanted markers being visible during treatment. This is most likely due to high density tissue and bony structures in the mediastinum/GEJ area blocking the liquid marker, or marker adaptation in the mucosal tissue limiting the marker size/radiopacity in the imaging plane.

Figure 1. Treatment CBCT (a), planning CT (b), T_1 W MRI (c) and fluoroscopy image (d) of marker in patient four.

In a recent study, the visibility of the liquid fiducial marker in T_1/T_2 weighted MRI in a pancreatic phantom was investigated. The marker showed good visibility in MRI and the authors concluded that volumes $> 25 \mu\text{l}$ should be used for creating a sufficient signal void.¹⁶ In this clinical study, the marker visibility in T_1/T_2 weighted MRI was limited. In good accordance with previous findings, the markers appeared hypointense (signal void) in both T_1/T_2 weighted MRI.

It is important to note that the primary objective of this study was to evaluate the safety and feasibility of injecting the novel liquid fiducial marker as well as the performance during

the RT course. No changes in the delineation procedure, comparison with similar cases without implanted markers or changes in margin sizes were made. No conclusions on clinical outcome or possible margin reductions can be made from this study. Results from studies including larger patient groups are warranted.

CONCLUSION

Endoscopy assisted liquid fiducial marker placement is safe and technically feasible in patients with tumours in the oesophagus and gastro-oesophageal junction area. Endoscopic ultrasound guidance is recommended if available.

Figure 2. Marker in Patient 1 on RT planning CT (a), treatment CBCT after nine fractions (b) and 1 year follow-up CT (c).

ACKNOWLEDGEMENTS

This work was funded by the Danish Council for Strategic Research (Nanoguide, sagsnr. 0603-00442B), the Novo Foundation, Hellerup, Denmark and The Niels Bohr Institute, Copenhagen, Denmark.

CONFLICTS OF INTEREST

RIJ was previously employed by Nanovi A/S. TLA is a board member of Nanovi A/S. JSR has received travel expenses from Nanovi A/S for another project.

REFERENCES

1. Stahl M, Mariette C, Haustermans K, Cervantes A, Arnold D, Group GW. clinical practice guidelines Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis treatment and follow-up clinical practice guidelines, vol. 24, August 2003. 2013.
2. Sillah K, Williams LR, Laasch HU, Saleem A, Watkins G, Pritchard SA, et al. Computed tomography overestimation of esophageal tumor length: Implications for radiotherapy planning. *World J Gastrointest Oncol* 2010; 2:197–204. doi: <https://doi.org/10.4251/wjgo.v2.i4.197>
3. Konski A, Doss M, Milestone B, Haluszka O, Hanlon A, Freedman G, et al. The integration of 18-fluoro-deoxy-glucose positron emission tomography and endoscopic ultrasound in the treatment-planning process for esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2005; 61:1123–8. doi: <https://doi.org/10.1016/j.ijrobp.2004.07.717>
4. Kong FM, Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys* 2011; 81: 1442–57. doi: <https://doi.org/10.1016/j.ijrobp.2010.07.1977>
5. Cohen RJ, Paskalev K, Litwin S, Feigenberg, and a Konski, “Esophageal motion during radiotherapy: Quantification and margin implications”. *Dis Esophagus* 2010; 23: 473–9.
6. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. *J Clin Oncol* 2007; 25: 938–46. doi: <https://doi.org/10.1200/JCO.2006.09.9515>
7. Jin P, van der Horst A, de Jong R, van Hooft JE, Kamphuis M, van Wieringen N, et al. Marker-based quantification of interfractional tumor position variation and the use of markers for setup verification in radiation therapy for esophageal cancer. *Radiother Oncol* 2015; 117: 412–8. doi: <https://doi.org/10.1016/j.radonc.2015.10.005>
8. Fukada J, Hanada T, Kawaguchi O, Ohashi T, Takeuchi H, Kitagawa Y, et al. Detection of esophageal fiducial marker displacement during radiation therapy with a 2-dimensional on-board imager: analysis of internal margin for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2013; 85: 991–8. doi: <https://doi.org/10.1016/j.ijrobp.2012.07.2358>
9. 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). *Gastrointest Endosc* 2010; 71: 1204–10. doi: <https://doi.org/10.1016/j.gie.2010.01.003>
10. Shin EJ, Ko CW, Magno P, Giday SA, Clarke JO, Buscaglia JM, et al. Comparative study of endoscopic clips: duration of attachment at the site of clip application. *Gastrointest Endosc* 2007; 66: 757–61. doi: <https://doi.org/10.1016/j.gie.2007.03.1049>
11. 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. *Pract Radiat Oncol* 2013; 3: 32–9. doi: <https://doi.org/10.1016/j.prro.2012.02.006>
12. Rydhög JS, Mortensen SR, Larsen KR, Clementsen P, Jølc RI, Josipovic M, et al. Liquid fiducial marker performance during radiotherapy of locally advanced non small cell lung cancer. *Radiother Oncol* 2016; 121: 64–9. doi: <https://doi.org/10.1016/j.radonc.2016.06.012>
13. 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. *Gastrointest Endosc* 2015; 82: 641–9. doi: <https://doi.org/10.1016/j.gie.2015.03.1972>
14. 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). *Gastrointest Endosc* 2016; 83: 309–17. doi: <https://doi.org/10.1016/j.gie.2015.06.042>
15. de Souza Lawrence L, Ford E, Gilbert C, Yarmus L, Meneshian A, Feller-Kopman D, et al. Novel applications of an injectable radiopaque hydrogel tissue marker for management of thoracic malignancies. *Chest* 2013; 143: 1635–41. doi: <https://doi.org/10.1378/chest.12-1691>
16. Schneider S, Jølc RI, Troost EGC, Hoffmann AL. Quantification of MRI visibility and artifacts at 3T of liquid fiducial marker in a pancreas tissue-mimicking phantom. *Med Phys* 2018; 45: 37–47. doi: <https://doi.org/10.1002/mp.12670>