OPEN ACCESS

GAVIN PUBLISHERS

Journal of Oncology Research and Therapy

Malik A. J Oncol Res Ther: JONT-148.

DOI: 10.29011/2574-710X. 000048

Research Article

Feasibility and Safety of Ultrasound Guided Fiducial Placement Before Robotic Stereotactic Radiotherapy in Primary Hepatic Malignancies: A Tertiary Care Experience

Abhidha Malik*

Department of Radiotherapy, CMC Hospital, Ludhiana, India

***Corresponding author:** Abhidha Malik, Department of Radiotherapy, CMC Hospital, Ludhiana, India. Email: dr.abhidha@gmail.com

Citation: Malik A (2018) Feasibility and Safety of Ultrasound Guided Fiducial Placement Before Robotic Stereotactic Radiotherapy in Primary Hepatic Malignancies: A Tertiary Care Experience. J Oncol Res Ther: JONT-148. DOI: 10.29011/2574-710X. 000048

Received Date: 19 February, 2018; **Accepted Date:** 27 March, 2018; **Published Date:** 03 April, 2018

Abstract

Introduction: Advances in radiation medicine have enabled the use of several special types of external beam radiation therapies for the precise localization and delivery of intra tumoral high fractional radiation doses.

Aims: This study is aimed to determine the safety and technical feasibility of ultrasound (USG) guided fiducial placement.

Material and Methods: Retrospective analysis of 30 patients was done. All patients underwent USG guided percutaneous placement of at-least three to six gold fiducials under all aseptic precautions by an in-house intervention radiologist with extensive experience. When performing the fiducial implantation, it was advised to keep a minimum of two cm spacing, and a minimum 15° angle between the fiducials. After fiducial implantation oblique, orthogonal X-ray imaging was done and fiducial placement with respect to their usability to guide Stereotactic Body Radiotherapy (SBRT) treatment was verified by the radiation oncologist. Any peri-procedural complication (minor or major) was assessed to determine the feasibility and safety of the above-mentioned procedure.

Results: No major complication like bleeding or marker migration occurred (zero percent). The minor complication rate was ten percent. One patient developed fever which was managed conservatively with i.v. antibiotics and i.v. antipyretics. The other two patients developed thrombocytopenia & hepatic encephalopathy which could be either procedure related or disease related. Both the patients settled with conservative management.

Conclusions: USG guided percutaneous placement of gold fiducials is a safe procedure and is associated with a high technical success rate. However, it carries a variety of small risks of which intervention radiologist, radiation oncologists and patients should be aware off.

Keywords: Cyberknife; Fiducial; Hepatocellular Carcinoma

Introduction

Hepatocellular Carcinoma (HCC) is the most common primary malignancy of the liver. It is the second leading cause of cancer related mortality in the world [1,2]. Although Liver Transplant (LT) represents the most efficient treatment in patients with small HCC, <30% of patients are eligible for LT [3]. In the past, radiation therapy has not often been used to treat HCC due to the relatively low tolerance of the whole liver to Radiotherapy (RT). However, higher tolerances of partial liver volumes to radiation and recent technological developments have made it possible to spare the volume of uninvolved liver from RT [4]. With the Robotic Cyber Knife (CK) system, SBRT is delivered in the setting of near real-time tracking of implanted fiducial markers combined with respiratory motion modelling to achieve sub-millimetre accuracy by continuously detecting and correcting for tumour motion throughout treatment. Fiducial markers serve as surrogates of tumour position therefore are used as reference points on Computed Tomography (CT) planning and also allow for simultaneous correction of target motion [5]. We evaluated percutaneous placement of fiducial marker under USG guidance

with respect to safety and technical success rate in the preparation for CK based radiation therapy.

Material and Methods

Patients: All patients with histopathological diagnosis of hepatocellular carcinoma with or without portal vein tumour thrombosis scheduled to receive cyber knife based SBRT comprised the study cohort. Patients with coagulopathy (international standardized ratio >1.5, platelets <50,000) were transfused with appropriate blood products for correction of coagulopathy. Ascitis, if any at presentation was drained before fiducial placement. Any allergy to gold was considered as a contraindication for fiducial placement and CK based SBRT. All procedures were performed under ultrasonography guidance by in house intervention radiologists with extensive experience. Informed written consent was obtained before each procedure [6].

Preparation: Peri-procedural intravenous antibiotics and analgesics injection Magnex two grams IV BD and injection Tramadol IV stat respectively were administered prophylactically in all patients for day one. Anticoagulant and anti-platelet medications were discontinued at-least 72-96 hours before the procedure.

Instruments: Needle: 18 gauge coaxial; Fiducial marker: Gold fiducial marker (Figure 1) 17gm x 20 cm GF 1003 size 1.2mm x3mm (IZI Meditronix Medical product); System for SBRT-: Cyber Knife VSI® Radiosurgery System (Accuray Inc., Sunnyvale, CA, USA)

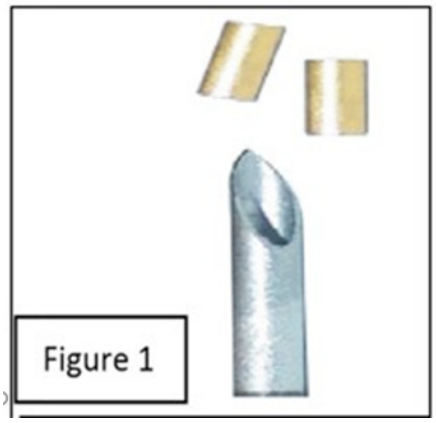

Figure 1: Gold fiducial marker GF 1003 (IZI Meditronix Medical product).

Technique: Ultrasonography along with USG Doppler was performed with a convex probe (2-5 MHz). A gold flexible linear marker (3 mm in diameter and 1.2 mm in length, Figure 1) contained in an 18-gauge coaxial needle was used. Local anaesthesia was achieved via the subcutaneous administration of 2% lignocaine. After confirming that the needle tip had reached the target lesion, the fiducial marker was deployed, and then the needle was removed (Figure 2). When performing the fiducial implantation, it was advised to keep a minimum of two cm spacing, and a minimum 15° angle between the fiducials. Moreover, the fiducials should not be more than five to six cm away from the target lesion. A minimum of three and on an average four to five fiducials were deployed taking into account possibility of fiducial migration.

Figure 2: USG guided deployment of Gold fiducial around the target lesion.

Outcome: Technical success was defined as the ability to implant at least three fiducials in the appropriate location for SBRT. After fiducial implantation obliques, orthogonal X-ray imaging was done in Cyber knife suite, and fiducial placement with respect to their usability to guide SBRT treatment was verified by a radiation oncologist (Figure 3). Fiducial migration was defined as seed dislodgement outside the volume of the original injection site [7].

Figure 3: Oblique orthogonal X-ray imaging done in Cyber knife suite.

Treatment Planning and Delivery: The SBRT technique followed at our institute is described as follows. First patients were immobilized in supine position hands over head in a vacuum mattress. CT simulations were performed 1-3 days after fiducial marker placement. RT planning CT scans were taken after giving intravenous contrast 2ml/kg of body weight. Four hours fasting was needed prior to the scan as per contrast protocol. The planning scans were acquired without contrast in normal end inspiration and end expiration along with triple phase scan with contrast (arterial, portal and delayed phase) in normal end expiration (figure four). Planning images were taken from thoracic inlet till pelvic brim

with 1mm slice thickness in Siemens Biograph™ PET CT scanner (Siemens healthcare, Erlangen, Germany). The planning images were transferred to Multiplan® (Accuray) treatment planning software and Synchrony® (Accuray) respiratory tracking system. The Gross Tumor Volume (GTV) was contoured as the contrast enhancing disease visible on the normal end expiration CT scan. Planning Target Volume (PTV) was defined as the Clinical Target Volume (CTV) with 5mm radial and 7mm cranio-caudal margin to GTV. A total dose ranging between 36-60 Gy in 3-5 fractions was prescribed to 80% isodose line with 95% PTV coverage. Treatment was delivered to PTV in three to ten days. The dose was adjusted to remain within the dose constraints of normal tissues and surrounding organs at risks Figure 4.

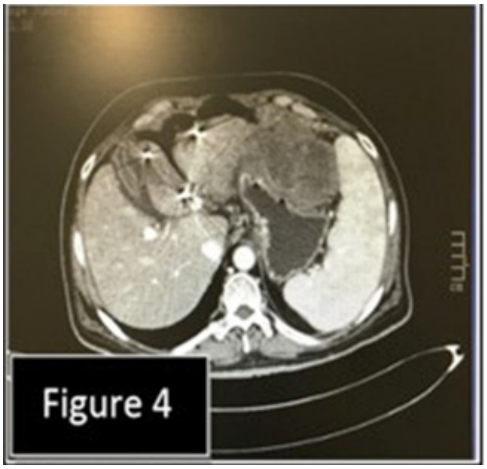

Figure 4: Triple Phase normal end expiratory planning CT scan.

Results

The fiducial marker placement was successful in all cases thus, the technical success rate was 100%. The median hospitalization period was two days (Range 1-3 days). Cyber knife based SBRT was successfully performed in all 30 cases. The median period between marker implantation and RT planning CT scan was three days (Range 1-15 days). (Table 1).

Patients (n= 30)	N (%)
Male/Female	27 (90) /3(10)
Mean age ± SD	52.67 ± 13.06
HBV/HCV/Both/None	13(43.3) /5(16.7) /1(3.3) /2(6.6)
HCC alone /HCC+PVTT	2(6.7) /28(93.3)
Location (Right/left/both)	5 (16.7) /17 (56.7) /8(26.7)
Child Pugh score A/B	20(66.7)/10(33.3)
Portal HTN (Present/Absent)	12(40) / 18(60)
Previous treatment details	
RFA/TACE/TARE/Systemic therapy	4(13.3) /9(30) /9(30) /6(20)
Patients given anticoagulants	4(13.3)
No of fiducials	3.27 ± 0.49
Complications Major/Minor	0(0)/ 3(10)

Table 1: Summary of patient demographics and tumor characteristics.

No major complication like bleeding or marker migration occurred (0%; 0/30). The minor complication rate was (10%; 3/30). One patient developed fever which was managed conservatively with IV. antibiotics and IV. antipyretics. The other two patients developed thrombocytopenia & hepatic encephalopathy which could be either procedure related, or disease related. Both the patients got settled in few days with conservative management. In all three patients SBRT was performed as planned.

Discussion

SBRT in primary hepatocellular carcinoma has evolved tremendously in last two decades. Implantation of USG guided fiducial markers are increasingly being used by radiation oncologists for treatment localization and delivery in liver stereotactic radiation therapy. There is scarcity of literature on risk associated with marker implantation. Till date the complications associated with fiducial marker placement in liver have either been reported as case reports or as component of large retrospective series of percutaneous intervention procedures in gastrointestinal malignancies (Table 2). In our study, we examine the feasibility and safety of US guided fiducial placement before Cyber knife based stereotactic body radiotherapy in primary hepatic malignancy.

S No	Ref	Published Year	Type of study	No of cases	Needle used, gauge	Type of fiducials diameter x length (mm)	Success rate No (%)	Adverse events (No of cases)
1.	6	2003	R	21	NIA	2 mm spherical Ag	95.24	1/21 (4.7%)Migration
2.	7	2006	P	13	19	0.8 x 3mm(Ag)	85	1/13 (7.6%)Cholangitis
3.	8	2009	R	34	19	0.8 x 5 (Ag)	100	1/34 (2.9%) Minor
4.	9	2010	R	9	19	0.8 x 5 (Ag)	100	None
5.	10	2010	P	57	19	0.8 x2.5(V)	98	1/57 (1.7%)Minor bleeding
6.	11	2010	R	30	22	0.35 x 10 (V)	97	1/30 (3.3%)Fever
7.	12	2010	P	51	19	0.8 x 5 (Ag)	90	1/ 51 (1.9%)Mild pancreatitis
8.	13	2010	R	13	22	08 x 5 (Ag)	100	None
9	14	2012	R	29	19 22	0.8 x 5(Ag) 0.35 x 10 (V)	100	None
10.	15	2012	R	24	18	0.9 x 3 (Ag)	96.8	1/24 (4.1%) Biloma + pleural effusion + pain
11.	16	2013	R	12	19	0.75 x 5 (V)	100	None
12.	17	2013	R	60	19 22	0.75 x 10 (V) 0.35/0.5 x 10 (V)	100	None
13.	18	2014	R	32	19	0.8x3 (Ag)	100	1/32 (3.1%) Mild pancreatitis
14.	19	2014	R	69	19	0.8 x 3 (Ag)	99.3	2/69 (2.8%) pneumothorax
15.	20	2014	R	39	18	NIA	100	2/39 (5%) Pain
16.	21	2014	P	8	19	0.35 x 10 (V)	88	None
17.	22	2015	R	11	19	0.8 X 5(Ag)	100	None
18.	23	2015	P	30	22	0.35 X10 (V)	100	1/30 (3.3%)Pneumothorax 2/30 (6.6%) Mediastinitis
19.	24	2016	R	514	19	0.35 x 10 (V) 0.75 x 10 (V)	99.8	9/514 (1.7%) minor bleeding
20.	25	2015	P	38	18	3mm	100	2/38 (5.2%) Pneumothorax
21.	26	2016	P	18	18	0.75 x 5 (V)	100	1/18 (5.5%) Pneumothorax

22	27	2016	R	30	19	0.8x5mm (Ag)	100	1/30 (3.3%) Perihepatic hematoma
23	Current study	2017	R	30	18	1.2 x 3mm (Ag)	100	3/30 (10%) fever, TCP,

Table 2: Summary of published studies on EUS guided fiducial placement in Liver. Abbreviations: R: Retrospective, P- Prospective, Ag- Gold, V-Visicoil, TCP- Thrombocytopenia.

Fiducial placement is a source of several inconveniences. It leads to delay in treatment. The procedure is associated with additional cost [8]. The fiducials can create significant imaging artefacts on CT, in addition percutaneous procedures have a variety of risks. Minor complications are noted in 17.3% and major complications in 3% cases [9-14]. Risk factors associated with percutaneous procedure are pain, pneumothorax, and hemothorax, perforation of non-targets (most commonly gall bladder), bile peritonitis, infection, hemobilia, neuralgia and possibility of tumour seedlings. Three to six markers are recommended to be implanted in or around a tumour for image-guided radiotherapy, such as Cyber Knife therapy [15]. Another study suggested that, at least three markers that do not appear superimposed on orthogonal views are required to give positional information about the tumour [8]. In our study average of 3.27 ± 0.49 markers were placed per patient. The value is in accordance with recommended range [16].

Fiducials are typically made of a biologically inert metal with a high atomic number. Several issues are to be considered while choosing a marker. These include price, convenience, availability as well as the specific imaging system used for radiotherapy guidance. Modern radiotherapy equipment will most often be purchased with an integrated kilovoltage imaging source dedicated to image guidance. These systems should be able to easily resolve small gold markers with a diameter of 0.5mm (or less) but will be influenced by body habitus and overlying structures. To be visible with a megavoltage radiotherapy beam, the markers will need to be thicker or longer [17]. In our study, Cyber Knife (Accuray, Inc.) system uses roof mounted orthogonal X-rays (kilo voltage imaging) to visualize radiopaque fiducials therefore cylindrical gold marker of 1.2x3 mm were easily picked up by the real-time imaging done during radiation delivery.

CT is the preferred modality for guided trans-abdominal fiducial marker placement as it gives better contrast and three-dimensional spatial accuracy, which are critical in confirming the position of implanted fiducial markers [8]. Ultrasound provides real-time monitoring of the whole procedure and a more comfortable handling during an intra-abdominal procedure. Therefore, we thought ultrasound guided implantation could raise the success rate over currently used methods. Ultrasound can also reduce radiation hazard compared to a CT guided procedure. In our study, all marker placements were USG guided and we had 100% technical success rate. Our results were in accordance to Kulkarni N et al [18]. According to their study complication rates and technical efficacy are similar when fiducial placement is performed without the need for CT fluoroscopy [16-21], thereby avoiding additional radiation burden to both the operator and patient [21-23].

Ohta K et al. reported that the trans-arterial placement of a fiducial markers resulted in low complications rate (two percent) [24,25] and a high technical success rate (100%) [26,27]. Brook OR et al, concluded that percutaneous fiducial marker placement exhibits a higher complication rate than trans-arterial placement in the abdomen or pelvis [28]. However, outcomes of such procedures were considered to depend on the tumour site and the anatomy of the hepatic artery. Celiac artery stenosis makes it difficult to identify the hepatic artery [29]. CT and angiography is required to confirm tumour site and the anatomy of the hepatic artery. Del CA et al, reported complication of femoral pseudo aneurysms after angiographic fiducial marker placement [30]. This study did not aim to compare the efficacy of trans-arterial and percutaneous procedures. A joint decision by oncologists and interventional radiologists was reached to follow percutaneous approach as marker placement is easy and less time consuming if done percutaneously. There exists a clear need for additional research to address the issue of gold standard technique for fiducial marker placement [31].

Conclusion

Cyber knife based SBRT treatment adds to the armamentarium of local treatment modalities as complementary or salvage therapy in primary liver tumours. The fiducial markers placed percutaneously facilitate accurate targeting of tumour during SBRT. Our study concludes that ultrasound guided percutaneous placement of gold fiducials is a safe procedure and is associated with high technical success rate. However, it carries a variety of small risks of which intervention radiologist, radiation oncologists and patients should be aware off.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet TJ, et al. (2015) Global cancer statistics,2012 CA Cancer J Clin 65: 87-108.
2. World Health Organization (2008) Mortality Database. WHO Statistical Information System 36-47 .
3. Belghiti J, Kianmanesh R (2005) Surgical treatment of hepatocellular carcinoma HPB (Oxford) 7: 42-49.
4. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, et al. (1995) Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 30: 1237-1248.

5. Goyal K, Einstein D, Yao M, Kunos C, Barton F, et al. (2010) Cyber knife stereotactic body radiation therapy for nonresectable tumors of the liver: Preliminary results. HPB Surg 2010.

6. Shirato H, Harada T, Harabayashi T, Hida K, Endo H, et al. (2003) Feasibility of insertion/implantation of 2.0-mm-diameter gold internal fiducial markers for precise setup and real-time tumor tracking in radiotherapy. Int J Radiat Oncol Biol Phys 56: 240-247.

7. Pishvaian AC, Collins B, Gagnon G, Ahlawat S, Haddad NG (2006) EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. Gastrointest Endosc 64: 412-417.

8. Kothary N, Heit JJ, Louie JD, Kuo WT, Loo BW Jr, et al. (2009) Safety and efficacy of percutaneous fiducial marker implantation for image-guided radiation therapy. J Vasc Interv Radiol 20: 235-239.

9. Varadarajulu S, Trevino JM, Shen S, Jacob R (2010) The use of endoscopic ultrasound-guided gold markers in image-guided radiation therapy of pancreatic cancers: a case series. Endoscopy 42: 423-425.

10. Park WG, Yan BM, Schellenberg D, Kim J, Chang DT, et al. (2010) EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. GastrointestEndosc 71: 513-518.

11. DiMaio CJ, Nagula S, Goodman KA, Ho AY, Markowitz AJ, et al. (2010) EUS-guided fiducial placement for image-guided radiation therapy in GI malignancies by using a 22-gauge needle. Gastrointest Endosc 71: 1204-1210.

12. Sanders MK, Moser AJ, Khalid A, Fasanella KE, Zeh HJ, et al. (2010) EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. Gastrointest Endosc 71: 1178-1184.

13. Ammar T, Coté GA, Creach KM, Kohlmeier C, Parikh PJ, et al. (2010) Fiducial placement for stereotactic radiation by using EUS: feasibility when using a marker compatible with a standard 22-gauge needle. GastrointestEndosc 71: 630-633.

14. Khashab MA, Kim KJ, Tryggestad EJ, Wild AT, Roland T, et al. (2012) Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. Gastrointest Endosc 76: 962-971.

15. Kim JH, Hong SS, Kim JH, Park HJ, Chang YW, et al. (2012) Safety and efficacy of ultrasound-guided fiducial marker implantation for Cyberknife radiation therapy. Korean J Radiol 3: 307-313.

16. Patel A, Khalsa B, Lord B, Sandrasegaran K, Lall C (2013) Planting the seeds of success: CT-guided gold seed fiducial marker placement to guide robotic radiosurgery. J Med Imaging Radiat Oncol 57: 207-211.

17. Roberge D, Cabrera T (2011) Percutaneous Liver Fiducial Implants: Techniques, Materials and Complications. In: Mizuguchi Y, editor. Liver Biopsy in Modern Medicine, In: 1st ed. Croatia: In Tech: 107-116.

18. Kulkarni N, HonG TS, kambadakoneA, Arellano RS (2015) CT-Guided Implantation of Intrahepatic Fiducial Markers for Proton Beam Therapy of Liver Lesions: Assessment of Success Rate and Complications. AJR Am J Roentgenol 204: 207-213.

19. Choi J-H, Seo D-W, Park DH, Lee SK, Kim M-H (2014) Fiducial Placement for Stereotactic Body Radiation Therapy under Only Endoscopic Ultrasonography Guidance in Pancreatic and Hepatic Malignancy: Practical Feasibility and Safety. Gut and Liver 8: 88-93.

20. Valentine K, Cabrera T, Roberge D (2014) Implanting metal fiducials to guide stereotactic liver radiation: McGill experience and review of current devices, techniques and complications. Technol Cancer Res Treat 3: 253-258.

21. Chandran S, Vaughan R, Efthymiou M, Sia J, Hamilton C (2014) A pilot study of EUS-guided fiducial insertion for the multidisciplinary management of gastric cancer. Endoscopy International Open 2: E153-E159.

22. Moningi S, Walker AJ, Malayeri AA, Rosati LM, Gearhart SL, et al. (2015) Analysis of fiducials implanted during EUS for patients with localized rectal cancer receiving high-dose rate endorectal brachytherapy. Gastrointestinal endoscopy 81: 765-769.

23. Machiels M, Hooft JV, Jin P, van Berge Henegouwen MI, van Laarhoven HM, et al. (2015) Endoscopy/EUS-guided fiducial marker placement in patients with esophageal cancer: a comparative analysis of 3 types of markers. Gastrointest Endosc 82: 641-649.

24. Dhadham GC, Hoffe S, Harris CL, Klapman JB (2016) Endoscopic ultrasound-guided fiducial marker placement for image-guided radiation therapy without fluoroscopy: safety and technical feasibility. Endoscopy International Open 4: E378-E382.

25. Oldrini G, George HT, Oldrini SR, Baumann AS, Marchesi V, et al. (2015) Implantation of fiducial markers in the liver for stereotactic body radiation therapy: Feasibility and results. Diagn Interv Imaging 96: 589-592.

26. Ohta K, Shimohira M, Murai T, Nishimura J, Iwata H, et al. (2016) Percutaneous fiducial marker placement prior to stereotactic body radiotherapy for malignant liver tumors: an initial experience. J Radiat Res 57: 174-177.

27. Liu CH, Yu CY, Lin TP, Chao HL, Chen HC, et al. (2015) Sonographic-guided percutaneous fiducial marker implantation of hepatic malignancies for Cyberknife radiation therapy: Evaluation of safety and technical efficacy. J Med Sci 35: 92-96.

28. Brook OR, Gourtsoyianni S, Mendiratta-Lala M, Mahadevan A, Siewert B, et al. (2012) Safety profile and technical success of imaging-guided percutaneous fiducial seed placement with and without core biopsy in the abdomen and pelvis. AJR Am J Roentgenol 198: 466-470.

29. Bargellini I, Turini F, Bozzi E, Lauretti D, Cicorelli A, et al. (2013) Image fusion of preprocedural CTA with real-time fluoroscopy to guide proper hepatic artery catheterization during transarterial chemoembolization of hepatocellular carcinoma: a feasibility study. Cardiovasc Intervent Radiol 36: 526-530.

30. Del Corso A, Vergaro G (2013) Percutaneous treatment of iatrogenic pseudoaneurysms by cyano acrylate-based wall-gluing. Cardiovasc Intervent Radiol 36: 669-675.

31. Fernandez DC, Hoffe SE, Barthel JS, Vignesh S, Klapman JB, et al. (2013) Stability of endoscopic ultrasound-guided fiducial marker placement for esophageal cancer target delineation and image-guided radiation therapy. Pract Radiat Oncol 3: 32-39.