Multimodality Guidance for Accurate Bronchoscopic Insertion of Fiducial Markers

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Introduction: Fiducial markers act as visible surrogates of tumor position during image-guided radiotherapy. Marker placement has been attempted percutaneously but is associated with high rates of pneumothorax and chest drain placement.

Methods: Patients undergoing radical radiation treatment for non–small-cell lung cancer underwent bronchoscopic implantation of gold fiducials using radial probe endobronchial ultrasound (EBUS) with virtual bronchoscopy and fluoroscopic guidance to achieve tumor localization and placement within/adjacent to peripheral lung tumors. For tumors not localized using radial EBUS, fiducial placement was achieved by electromagnetic navigation to the vicinity of the tumor.

Results: Eighteen fiducials were placed to mark 16 lesions in 15 patients. In nine patients (60%), fiducials were implanted at the time of diagnostic bronchoscopy. No procedural complications occurred. EBUS localization allowed marker implantation within the target lesion in 12 cases. In four lesions, electromagnetic navigation bronchoscopy-guided implantation achieved a median fiducial–lesion distance of 6 mm (mean 12 mm). No marker migration occurred after the implantation of two-band markers; however, early migration was observed in two of eight (25%) of the smaller linear fiducials. No migration during the course of radiation therapy was observed.

Conclusion: Fiducial marker placement is easily and safely performed bronchoscopically, including at the time of diagnostic bronchoscopy. Marker geometry appears important in stability of bronchoscopically inserted fiducials. Future studies are required to confirm the optimal marker size, geometry, and spatial relationship with the target lesion.

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DOI: 10.1097/JTO.0000000000000389

ISSN: 1556-0864/15/1002-0324

Key Words: Stereotactic radiotherapy, Lung cancer, Endobronchial ultrasound.

(*J Thorac Oncol.* 2015;10: 324–330)

Fiducial markers are frequently used in management of pulmonary lesions to either aid localization of pulmonary lesions during minimally invasive surgery,[1,2] or precisely identify the location of pulmonary lesions being targeted with external beam radiotherapy.[3] Failure to locate small nodules at thoracoscopic surgery may result in incomplete resection or conversion to open thoracotomy. Peripheral lung tumors may demonstrate significant respiratory-induced motion, with large variations in magnitude and direction from patient to patient, fraction to fraction, and importantly, cycle to cycle.[4] The ensuing suboptimal targeting of radiation can result in excess toxicity and geographic tumor miss. There has particularly been an increasing interest in fiducial markers for image guidance for stereotactic ablative body radiotherapy.[5,6] Markers allowing reliable and accurate determination of lung lesion position have the potential to significantly improve treatment safety and outcomes.

Marker insertion through a percutaneous route has been associated with a high rate of complications.[7–9] Bronchoscopic placement is feasible but requires guidance tools to achieve accurate localization as lesions are not visible at bronchoscopy. Previous reports suggest that electromagnetic navigation guidance may allow marker placement in the vicinity of parenchymal lesions[10,11] though accuracy of placement remains poorly described. Only one previous study has utilized endobronchial ultrasound (EBUS), with electromagnetic navigation bronchoscopy (ENB) in selected cases, to guide marker placement. The authors reported a high degree of accuracy using the combination of guidance tools, though the exact contribution of each modality to accuracy is unclear.[12] The optimal methods to aid bronchoscopic marker implantation therefore remain uncertain, and no examination of marker features (size, shape, geometry) have been published.

Our institution utilizes numerous techniques to aid bronchoscopic localization of peripheral pulmonary lesions, including radial EBUS, virtual bronchoscopy (VB), and ENB. We have used fiducial markers to localize small pulmonary nodules, with a sequential approach to use of bronchoscopic techniques. In this report, we describe our preliminary

experience in implantation of two different types of lung fiducial markers and present our experience regarding the components of bronchoscopic fiducial marker placement and describe our preliminary experience in implantation of two different types of lung fiducial markers.

PATIENTS AND METHODS

Institutional review board approval was granted for performance of this prospective observational study. All patients provided written informed consent.

Consecutive patients referred for bronchoscopic fiducial marker placement were selected on the basis of the following:

1. Confirmed early stage peripheral lung malignancy in patients deemed medically inoperable, where fiducial marker placement was performed to aid external beam tumor irradiation, and
2. Presumed/confirmed pulmonary metastases, where marker placement was performed to aid stereotactic ablative body radiotherapy or to aid thoracoscopic resection of pulmonary metastases.

Bronchoscopic Localization of Target Lesion

Bronchoscopy was performed with a standard videobronchoscope (BF-MP160F or BF-P180; Olympus, Tokyo, Japan) under conscious sedation as previously described.[13] Guidance tools to ensure accurate marker placement were utilized in as "sequential" fashion, with VB planning and radial EBUS (described below) used to locate the target lesion in all patients. In patients where lesion position could not be confirmed by EBUS, within the same procedure ENB was used to identify the position within the bronchial tree closest to the target lesion.

Randomized trials have indicated VB significantly improves localization of small peripheral lesions.[14] We therefore completed VB preprocedure planning using multiplanar formatting of Digital Imaging and Communications in Medicine (DICOM) data from computed tomography (CT) chest (slice thickness 1.0 mm with 0.8 mm overlap). Three-dimensional reconstruction of the bronchial tree from DICOM images was performed using iLogic software (SuperDimension Inc., Plymouth, MN). A bronchoscopic pathway was determined using the iLogic software and localization of lesions was first attempted using radial EBUS as previously described,[13] based on the "virtual bronchoscopy" pathway.

If EBUS findings indicated successful localization of the lesion, the radial EBUS probe was removed, with the guide sheath remaining in situ. For lesions where preprocedure tissue diagnosis was known, we proceeded to placement of the fiducial marker. In patients where tissue diagnosis was unconfirmed, bronchial brushings from the lesion were performed and subject to rapid on-site cytologic evaluation.[15] Only when brushings confirmed the presence of diagnostic malignant material was placement of fiducial marker performed.

In patients where radial EBUS was unable to confirm the location of the target lesion, we proceeded to ENB (inReach system, SuperDimension Ltd, Minneapolis, MN). Performance of this technique has been described in detail previously.[16] Briefly, bronchoscopic direction was controlled using a steerable locator guide emits low frequency electromagnetic waves. Electromagnetic signal is detected by an electromagnetic location board which lies underneath the patient. The position of the probe within the bronchial tree is localized within a virtual bronchoscopic tree which is constructed by the iLogic software from the DICOM images, as described above. Navigation to the lesion location is undertaken and the minimum average fiducial target registration error (AFTRE) was recorded. The locator guide was withdrawn from an extended working channel (EWC) and repeat EBUS examination was performed. Subsequently, sampling (brushings, TBLB, washings) was performed under fluoroscopic vision.

Marker Placement

Markers used were determined by marker availability. Markers were either a linear fiducial 10 × 0.75 mm linear marker (Visicoil; Robertson Medical, Coffs Harbour, Australia), or a two-band 13 × 0.9 mm marker (superLock; SuperDimension Ltd, Minneapolis, MN) (Fig. 1).

Before the removal of the radial EBUS probe, or steerable locator guide, fluoroscopic imaging was used to determine the location of the lesion within the lung fields. Markers were then inserted into the guide sheath (EBUS-located lesions) or EWC (ENB procedures) and advanced to the tip of the sheath using sampling instruments. Insertion was performed under fluoroscopic vision to ensure that the location was the same as where the lesion had been located.

Postprocedure Imaging

Patients underwent chest x-ray (CXR) within 2 hours of their procedure to confirm marker position and retention. More detailed imaging was performed with 4D planning CT 7 to 12 days postprocedure. This study confirmed the positioning of the marker relative to the target lesion (marker accuracy). Confirmation of retention of the marker (marker stability) was also noted at this study. Subsequent imaging was performed according to clinical need.

The positioning of the marker relative to the target lesion (marker accuracy) was established was bas based on imaging obtained at the 4D planning CT.

RESULTS

From September 26, 2012 to February 19, 2014, 18 fiducials were placed bronchoscopically to mark 16 lesions

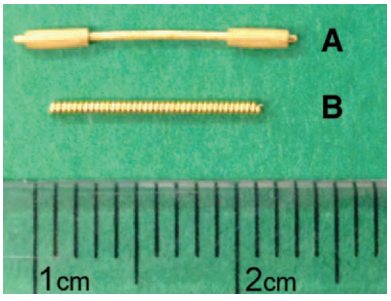

FIGURE 1. Fiducial markers used. *A,* 10 × 0.75 mm linear marker and (*B*) two-band 13 × 0.9 mm marker.

in 15 patients. One lesion was marked by two fiducials, and one lesion was subjected to a second marker placement procedure as, after the initial ENB-directed placement, lesion–marker distance was thought to be too great to adequately aid external beam irradiation (see Supplementary Video file 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A730). No procedural complications occurred. Clinical scenario and procedural outcomes are recorded in Table 1.

The indications for placement of fiducial markers were for guidance of external beam irradiation in 14 patients (15 lesions), and to aid surgical resection of a presumed pulmonary metastasis in one patient. Only three patients had a confirmed tissue diagnosis before marker placement. A further four lesions were presumed metastatic on the basis of prior history of carcinoma and observed growth of pulmonary nodules. The remaining nine lesions underwent placement at the time of diagnostic bronchoscopy, with on-site cytology examination of bronchial brushings indicating malignancy, and final pathology examination confirming non–small-cell lung cancer in all 10 lesions.

Marker Accuracy

EBUS successfully located 12 of the target lesions, allowing marker placement within the target lesion (Fig. 2). In the remaining four lesions, ENB was used to guide placement with a median and mean intraprocedure AFTRE of 8 mm. Postprocedure planning CT indicated a median marker–lesion distance of 6 mm (mean 12 mm), but with one lesion showing significant marker–lesion discrepancy of 35 mm despite an intraprocedural AFTRE of 9 mm. This patient underwent repeat EMN-guided marker placement through a different lobar subsegment and achieved a marker–lesion distance of 4 mm.

Marker Stability

No marker migration was observed after the insertion of the two-band markers. Early marker migration was observed in two of eight patients (25%) in whom Visicoil markers were placed. One marker was presumed expectorated as it was not seen on imaging at day 10 postimplantation despite being observed in situ on CXR performed day 2 postimplantation. The marker was placed within a cavitating lesion 65 mm from a lobar bronchus. The other marker was noted to have migrated down toward the lung base after the placement within the lesion only 14 mm from the lobar bronchus. It was subsequently visualized at the diaphragmatic pleura (Fig. 3) on imaging performed day 1 postprocedure.

DISCUSSION

Our experience confirms that bronchoscopic insertion of fiducial markers for localization of peripheral lung lesions is accurate and safe and demonstrates that EBUS is able to target marker placement with excellent marker accuracy. Advantages of bronchoscopic insertion are the ability to perform diagnostic biopsy and marker placement in the one procedure, the excellent safety profile of bronchoscopy, procedural cost minimization, and the ability of radial EBUS to confirm localization of the tumor and enable highly accurate placement of markers *within* lesions of interest. Our rate of intratumor localization (75%), achieved using EBUS, is superior to the rate previously reported for percutaneous fiducial lung implantation.[19]

Fiducial markers are used to facilitate image guidance for radiotherapy in lung tumors or to aid in intraoperative nodule localization during minimally invasive surgery.[1,2,20] Percutaneous marker insertion into lung lesions was first reported in 2001,[21] but this approach has been associated with a very high rate of complications, with reports suggesting pneumothorax rates from 13%[22] to over 60%.[7–9] Intercostal tube insertion to manage pneumothorax is required in 3% to 44%.[7,9,22,23] Complication rates after marker insertion seem consistent with reported pneumothorax/intercostal drainage rates after percutaneous lung biopsy.[13,24] Significantly, a markedly higher rate of pneumothorax in patients undergoing concurrent biopsy at the time of marker placement has been reported.[7]

Bronchoscopy offers an appealing alternative to percutaneous fiducial marker insertion given its superior safety profile. As peripheral lung lesions, by definition, are beyond bronchoscopic vision, guidance systems must be utilized to ensure that accurate placement of markers is achieved. Bronchoscopic fiducial marker insertion was first reported in 2002 using fluoroscopic guidance to achieve placement near to peripheral lung tumors[3]; however, no subsequent studies have describe this technique. This almost certainly is due to the limitations of fluoroscopic guidance, which are illustrated by the modest diagnostic yields associated with bronchoscopic investigation of peripheral pulmonary lesions.[25,26] Up to 65% of peripheral lung cancers may be radiographically invisible,[27] and prospective studies have demonstrated that lung malignancies are not visible on CXR/fluoroscopy until an average size of 2.4 cm is reached.

Development of more advanced bronchoscopic guidance tools such as EBUS,[28,29] VB,[30] and electromagnetic navigation[31] has significantly improved the diagnostic accuracy of bronchoscopy in the assessment of peripheral pulmonary lesions. EBUS is an excellent tool to guide fiducial marker placement due to the ability to precisely locate the position of a tumor within the lung; up to 85% of malignant lesions may be located using EBUS,[32,33] with the success rate of localization exceeding 90% for lesions within 50 mm of the pulmonary hilum, and exceeding 80% for lesion greater than 10 mm diameter.[33]

Reports of VB-guided[34] and ENB-directed[5,10,11] marker placement have been published. Only one prior study has described the use of EBUS to guide marker placement.[12] As we did, these authors used ENB to support bronchoscopic placement in cases where EBUS was unable to locate the lesion. Their rate of EBUS-localization (72%) was slightly inferior to ours (81%), which may reflect the added value of VB in successful lesion localization.[14] In addition, no reports to date have examined the geometric relationship between inserted markers and target lesions. Our study is therefore the first to our knowledge to utilize VB in association with EBUS to aid fiducial marker placement, and the first to describe the geometric proximity between inserted markers and target tumors.

Our findings suggest that EBUS is the ideal modality to guide marker placement as it is able to achieve *and confirm* an

TABLE 1. Clinical Scenario and Procedural Outcomes for Lesions Marked by Bronchoscopic Fiducial Marker Placement

Lesion	Relevant Past History	Preprocedural Diagnosis (*Method*)	Size (mm)	Lobar Location	Distance from Lobar Bronchus (mm)	Lesion Located by EBUS	Diagnosis Established by ROSE[c]	EMN used/*AFTRE* (mm)	Procedure Time (min)	Marker Used	Marker–Lesion[h] Distance (mm)	Marker Migration
1	Previous RULobectomy for NSCLC. FEV_1 0.9 L	SCC (*CT-guided biopsy*)	17	LLL	105	N	–	Y (3)	21	superLock	6	No
2	Severe COPD, previous LVRS	None	17	RLL	24	Y	NSCLC-NOS	N	46	superLock	0	No
3	FEV_1 0.8 L	None	13	RUL	66	Y	Lung adenoca.	N	22	Visicoil	0	No
4	Severe COPD	None	34	RUL	38	Y	Adenoca.	N	17	Visicoil	0	No
5	Enlarging nodule. Prior history CRC metastases	CRC metastasis (*CT-guided biopsy*)	28	LUL	36	Y	–	N	9	superLock	0	No
6	FEV_1 1.0 L	None	33	RUL	34	Y	SCC	N	32	Visicoil	0	No
7	FER 36%	None	18	RUL	52	Y	Adenoca.	N	–	Visicoil	0	No
8	Enlarging nodule. Prior history CRC metastases	Presumed new CRC metastasis	9	RUL	79	N	–	Y (11)	34	superLock	5	No
9	T4 tumor	None	27	LUL	65	Y	Adenoca.	N	38	Visicoil	0	Yes[g]
10	T1 N0 M1 tumor—high-dose palliative XRT	None	19	RUL	39	Y	Adenoca.	N	36	Visicoil	0	No
11	Previous resection of pulmonary PEComa metastases. New nodule	Presumed new PEComa metastasis	5	LUL	59	N	–[d]	Y (9)	34	superLock	12	No
12i[i,a]	Enlarging nodule. Prior history CRC metastases	None	15	LLL	68	N	–[e]	Y (9)[f]	48	superLock	35	No
12ii[i,a]	Enlarging nodule. Prior history CRC metastases	None	15	LLL	68	N	–[e]	Y (7)[f]	31	superLock	4	No
13	Limited performance status. Patient declined risks of surgical treatment	None	33	LUL	31	Y	SCC	N	24	superLock	0	No
14	Previous pneumonectomy for NSCLC. New lung mass	None	48	RLL	34	Y	SCC	N	17	Visicoil	0	No
15	T4 tumor	SCC (*bronchoscopy*)	59	RLL	14	Y	–	N	18	Visicoil	0	Yes[b]
16[a]	Enlarging nodule. Prior history CRC metastases	Presumed new CRC metastasis	16	RUL	67	Y	–[e]	N	38	superLock	0	No

[a]Same patient.
[b]Marker observed to migrate toward lung base (see Fig. 3).
[c]Sole diagnostic specimen was obtained during the same procedure as fiducial placement.
[d]Resection successfully performed through VATS, confirming metastatic perivascular epithelioid cell tumor (PEComa).
[e]Fiducial-guided stereotactic ablative radiotherapy delivered despite confirmed tissue diagnosis as both patients had previously had pathologically confirmed CRC pulmonary metastases, and current lesion had been observed to grow over serial imaging.
[f]First marker position was felt to be too far from lesion to aid SABR, so a second marker was placed in an adjacent airway (see Fig. 4, Supplementary Video file 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A730).
[g]Marker presumed expectorated.
[h]Measured by the shortest distance visualized on any CT slice (axial, coronal, or sagittal).
[i]Same lesion, with repeat procedure undertaken given large fiducial–tumor distance see with first marker placement.

COPD, chronic obstructive pulmonary disease; LVRS, lung volume reduction surgery; NSCLC, non–small cell lung cancer; NSCLC-NOS, non–small cell carcinoma not otherwise specified; SCC, squamous cell carcinoma; CRC, colorectal carcinoma; FEV_1, forced expiratory volume in 1 second; FER, forced expiratory ratio; EBUS, endobronchial ultrasound; EMN, electromagnetic navigation; AFTRE, average fiducial-target registration error; CT, computed tomography. ; ROSE, rapid on-site examination; LLL, left lower lobe; RLL, right lower lobe; RUL, right upper lobe; LUL, left upper lobe; VATS, video-assisted thoracoscopic surgery; SABR, stereotactic ablative body radiotherapy.

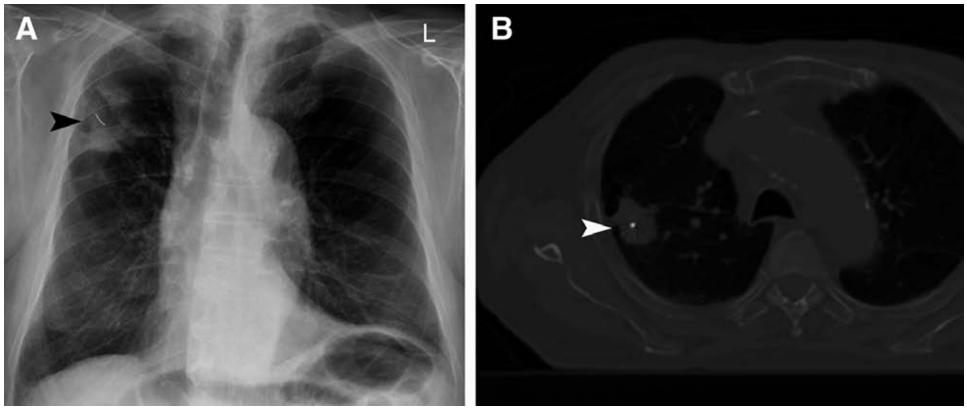

FIGURE 2. Postprocedure (*A*) CXR and (*B*) planning CT, demonstrating successful implantation of fiducial marker within target lesion after EBUS localization of peripheral lung tumor. CT, computed tomography; CXR, chest x-ray; EBUS, endobronchial ultrasound.

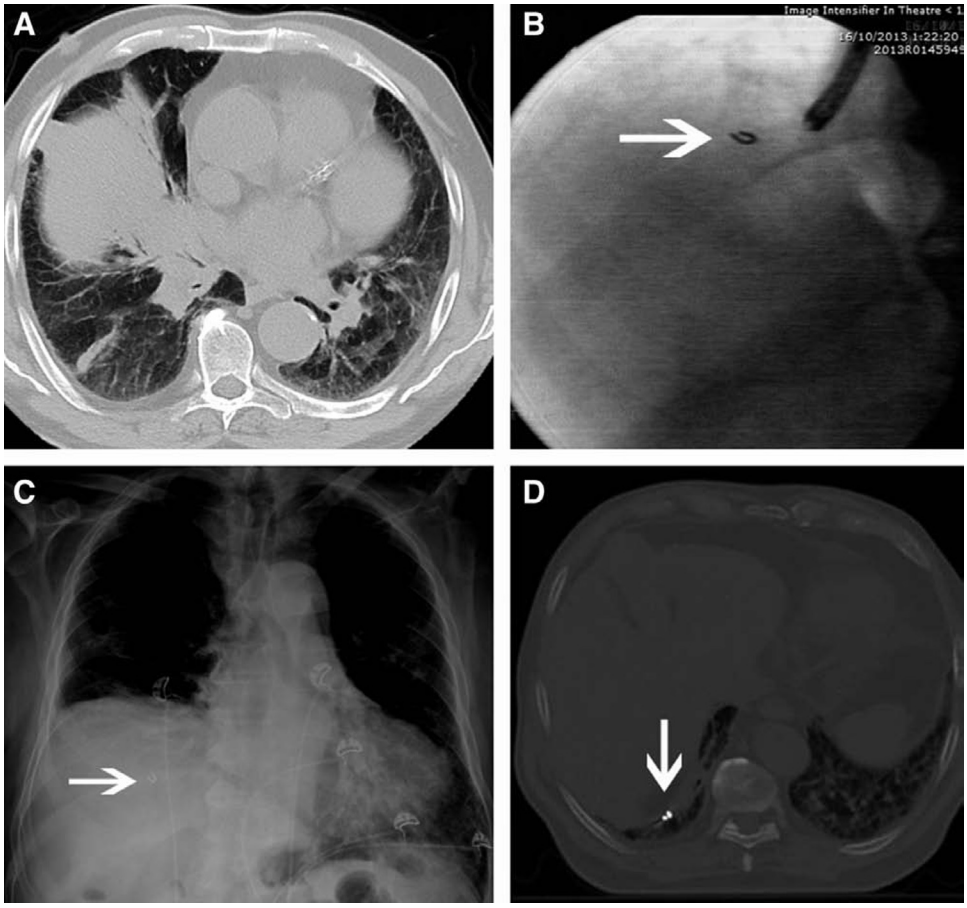

FIGURE 3. *A*, Fluoroscopic imaging demonstrating placement of fiducial marker targeting the (*B*) right mid-zone tumor seen on CT chest. *C*, CXR demonstrates apparent inferior migration of marker to lung base, confirmed on (*D*) postimplantation planning CT. CT, computed tomography; CXR, chest x-ray.

intimate relationship with the tumors *during* the procedure—all EBUS-located lesions had marker placed either within or in contact with the lesion. Close placement to target lesions is desirable as intra- and interfractional variations in geometric relationship between lung tumors and inserted markers is minimized by close positioning of markers and is abolished entirely by placement within tumors.[35] Misalignment during respiration is greater in cases where markers are placed at distances from the tumor greater than 2.5 cm.[36]

Whereas EBUS may be considered to be a *localization* tool, ENB should be considered a *navigation* tool. Previous studies have suggested that ENB may achieve successful localization in just 18% of peripheral lesions not detected by EBUS alone.[37] This is evident in the significantly greater marker–lesion distances reported by authors using ENB guidance without EBUS *localization* of the lesion.[11] Our results confirm this as, in contrast to EBUS-guided markers (where all markers were successfully placed *within* target lesions), cases where marker placement was ENB-directed were placed a mean 12 mm from the lesion. The bronchoscope and the stiff EWC can cause significant displacement of the bronchial tree and lung targets.[38] This can result in significant discrepancy

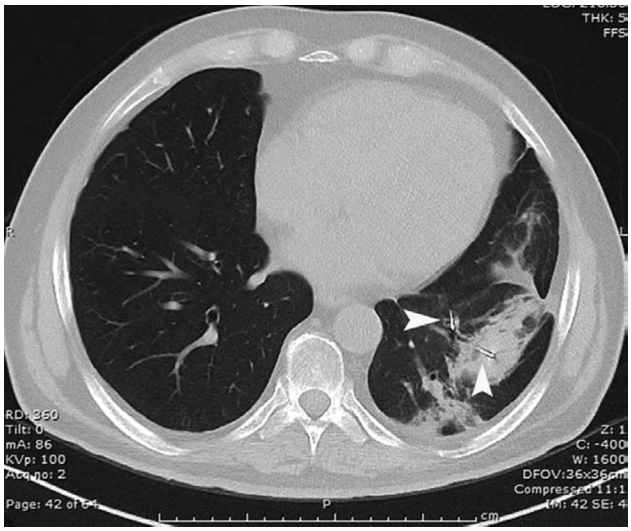

FIGURE 4. CT imaging of lesion #12 with fiducial implantation based on ENB. Initial marker placement was compromised by a significant discrepancy between intraprocedural AFTRE and final marker–tumor distance, which necessitated repeat marker implantation. The second marker was successfully sited much closer to the lesion (marker–lesion distance 4 mm *versus* 35 mm) (see also Supplementary Video file 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A730). AFTRE, average fiducial-target registration error; CT, computed tomography; ENB, electromagnetic navigation bronchoscopy.

between the passive position of pulmonary lesions (as measured during diagnostic CT) and their intraprocedural position. This is illustrated by the 24 mm discrepancy observed in lesion 12 between intraprocedural AFTRE (a "virtual" measurement) and the final CT-demonstrated postprocedure marker–lesion distance, and by Supplementary Video file 1 (Supplemental Digital Content 1, http://links.lww.com/JTO/A730), which demonstrates the marked transient distortion that may result from either deliberate or inadvertent bronchoscope manipulation. Perhaps reassuringly, the remaining four procedures all had variations of 4 mm or less between AFTRE and actual postprocedure marker–lesion distance.

The observed overall rate of marker migration (11.7%) was consistent with previously published data on both bronchoscopically inserted[5,12] and percutaneously inserted[8,39,40] markers. However, when analyzed by marker type, a significant difference in stability was observed. No migration was observed among the nine dumbbell-shaped two-band markers, whereas the smaller linear markers experienced a high rate of early migration (25%). Migration occurred between 1 and 10 days postinsertion, consistent with both clinical[34] and histopathologic[41] studies after fiducial insertion.

Migration of lung fiducials may be a significant safety concern.[42,43] Percutaneously inserted coils have previously been suggested to have a lower rate of migration than seed markers due to their ridged surface.[23] Schroeder et al. reported a high rate of migration of bronchoscopically inserted linear markers, though the authors observed stability of 99% of coil spring markers sited bronchoscopically.[10] We conclude from our findings, and from previous reports, that geometry of bronchoscopically inserted lung fiducials is important in their stability.

Future Directions

Future developments are required to achieve improvements in marker stability. Higher stability rates could allow lesions to be marked with a single marker, potentially reducing costs. High rates of marker migration[3,42] and potential major complications of this[42] have led to abandonment of solid markers into central airway malignancies. Even new technologies such as implantable transponders, used in preclinical/phase I studies to allow electromagnetic tracking of tumors,[44,45] have demonstrated significant challenges regarding transponder stability within the lung.[44,45]

Alternative marker types to gold markers may be attractive. Submucosal injectable markers have been described,[46] and such formulations require further research to examine their utility.

Studies are required to establish the optimal marker size and geometry and the geographic relationship between fiducial and tumor. Increased marker size affords easier visibility during in-treatment imaging and placement within the tumor may most accurately allow real-time tumor tracking. It remains to be established that such enhancements to tumor tracking do not come at the cost of visualization during radiotherapy planning studies.

CONCLUSION

Fiducial marker placement can be easily and safely performed bronchoscopically, including at the time of diagnostic bronchoscopy. Marker geometry appears important in stability of bronchoscopically inserted fiducials. Use of radial EBUS allows confirmation of marker placement within the tumor at the time of placement. In lesions not accessible to EBUS, ENB allows marker placement within acceptable proximity of the lesion. Future studies are required to confirm the optimal marker size, geometry and spatial relationship with the target lesion.

ACKNOWLEDGMENT

The authors thank Robertson Medical for provision of Visicoil markers.

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