Bronchoscopic Techniques for Surgical Marking and Fiducial Placement

Arianna Michaels, Martin L. Mayse, and Jason Akulian

Contents

Abstract

The treatment of early-stage lung cancer or solitary-/oligometastatic thoracic malignancy includes minimally invasive thoracic surgical resection (MITS) or stereotactic body radiotherapy (SBRT). These treatments are delivered with curative intent and aim to minimize effects on the surrounding tissues. Technologic advances have enhanced the precision of these interventions; however, with these advances have come new challenges in particular the challenge of target localization to deliver therapy. Attempts to overcome this challenge have centered on the placement of fiducial markers (FM) to act as visible surrogates of tumor location.

FM can provide accurate localization and tracking of tumors, even when the tumor is difficult to see on fluoroscopy or CT scan in the case of SBRT and/or when there is a loss of tactile feedback during MITS. A variety of FM are currently available for use. Some basic guidelines to follow when implanting FM for SBRT include the following: 3–6 should be implanted to so that three remain in place, they should be placed in and around the tumor at a distance of at least 2–5 cm from each other and such that the bulk of the tumor is bracketed by the fiducials, those placed outside the tumor should be placed as close to the edge of the tumor as possible, and they should not be placed collinearly. When placing FM for MITS, preoperative discussion with the surgical team is important if the markers are to be implanted by a separate team. In addition, the marker(s) should be placed such that they are visible from the visceral pleura and should include the whole of the target volume to ensure complete resection without margin involvement of tumor.

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1 Introduction

Lung cancer represents the number one cause of cancer-related mortality in the United States and abroad. Over the last several decades, there has been a rise in the number of CT scans performed for diagnostic purposes [1] as well as a rise in low-dose chest computed tomography (LDCT) scans performed specifically for lung cancer screening (LCS). LDCT utility in LCS was demonstrated to provide significant reduction in mortality from lung cancer screening a 'high-risk' population [2, 3]. With these findings, the US Preventative Services Task Force (USPSTF) now recommends that high-risk individuals, aged 50–80 with a 20 or more-pack year smoking history who are currently smoking or quit within the last 15 years, undergo LDCT LCS [4]. Recommendations for the management of incidentally found pulmonary nodules (IPN) are outlined in the Fleischner Society and National Comprehensive Cancer Network guidelines [5], while recommendations for the management of those found via LCS have been developed by the American College of Radiology [6]. Common to all of these management strategies is the concept that those nodules with a moderate- to high-risk pretest probability for malignancy should be considered for surgical resection or biopsy in conjunction with patient-provider shared decision-making.

For nodules with a high pretest probability of malignancy or those that are biopsy-proven as localized disease, resection remains the gold standard for both definitive diagnosis and treatment among those patients suitable for and/or willing to undergo surgery [7]. With the introduction of minimally invasive thoracic surgery (MITS) including video-assisted thoracic surgery (VATS) and robotic-assisted thoracic surgery (RATS), surgical morbidity has been reduced from when compared to open thoracotomy [8, 9], allowing for the ability to consider the resection of nodules in patients previously deemed too ill for surgery. Despite these advances, nearly a quarter of patients are still not candidates for lobectomy, owing to severe medical comorbidities [10]. For these patients, sublobar (wedge or segment) resection has been recommended. Recently several studies have demonstrated sublobar resection to be either noninferior or superior to lobar resection for early-stage lung cancer [11, 12]. For patients unable to tolerate or unwilling to undergo resection, radiosurgery therapy remains a reasonable option for early-stage lung cancer, with stereotactic body radiotherapy (SBRT) preferred for tumors less than 5 cm where normal tissue dose constraints can be respected [10, 13].

While these therapeutic modalities have excellent track records, they share a unique challenge in localizing and accurately treating the target lesion. Different approaches to solving this challenge have centered around placement of a marker to aid in either surgical removal or radiosurgery.

Historically, thoracic surgeons have relied on digital palpation of lung parenchyma to identify/localize small lung nodules during resection. However, distance to the pleural surface, nodule size, and nodule consistency have been shown to be associated with difficulty in nodule localization, in particular for nodules greater than 5 mm from the pleura, less than 10 mm in size, and/or subsolid in consistency. While this problem is a known but less frequent challenge when employing an open thoracotomy, the move away from open cases to MITS, especially RATS, in which haptic feedback is impaired, has made localization more difficult with reports of conversion to open thoracotomy as high as 50% of cases [14].

SBRT for inoperable early-stage lung cancer or oligometastatic disease may be chosen for patients too frail to undergo surgery or due to patient preference and is preferred over conventional radiation with higher rates of local control and survival, as well as patient convenience [10, 15].

The cornerstone of SBRT is accuracy, with precise delivery of radiation to the planned target volume (PTV) [16, 17] while simultaneously accounting for respiratory variation, either through breathholding techniques, respiratory gating, or tracking of the nodule to account for respiratory variation. While some systems are able to visually track the target nodule, limitations similar to those encountered in surgical resection exist [16, 18]. In addition, the thoracic anatomy to target nodule relationship can result in difficulties in detecting and/or tracking of the target lesion during SBRT. Fiducial markers (FM) act as visible surrogates of tumor location and provide accurate localization and tracking of target nodules, overcoming difficulties when encountered in identifying targets on fluoroscopy or CT scan. With these challenges, a variety of marking techniques and technologies have been developed or adapted to aid in localizing nodules for surgery and SBRT. In this chapter, we will present the current state of target marking to aid in localizing lung nodules during MITS and SBRT.

2 Target Marking for Minimally Invasive Thoracic Surgical Resection

2.1 History

The introduction of MITS represented a significant advancement in the field of thoracic surgery. Despite the benefits associated with MITS, surgeons also encountered growth in the challenge of target localization, resulting in the need to develop methods to improve intraoperative target identification and surgical success. The first attempt at addressing this

challenge was adoption of hookwire localization of small lung nodules via CT guidance. After placement of the hook into the target, a wire extended out through the parenchyma then across the pleura to the skin where its track was easily identified by the surgeon. Despite this seemingly simple and effective approach, transcutaneous, transpleural hookwire placement was found to have some inherent complications including displacement of the hook during transportation from radiology to the OR and/or even intraoperatively hemorrhage (9–35%) and pneumothorax (32–68%). As a result, an alternative technique of CT placement of microcoils was pioneered; microcoils are thin, coiled wires that can be inserted percutaneously to localize target nodules. A needle is inserted percutaneously to transect the lesion, then part of the microcoil wire is inserted. The needle is then withdrawn through the target lesion with the remaining length and then either inserted on the opposite side of the lesion or at the pleural line. The insertion site of the needle into the lung also serves as a marker for the surgeon, and fluoroscopy is often used to assist in visualization and localization if the wire does not extend past the visceral pleura. Intraoperative localization rates using microcoils have been reported to be excellent (90–100% success) [19], and placement can occur well before the surgery. Despite this excellent performance profile, this technique still suffered from an elevated risk of pneumothorax, hemorrhage, displacement, and even embolization [20] and additionally often requires intraoperative integration of fluoroscopy for localization.

Further exploration into the optimization of small nodule marking for MITS includes the use of various dyes to visually mark lesions, via both percutaneous and bronchoscopic application methods. Several studies have been published evaluating the use of dye alone to aid in target nodule localization during MITS. These agents are associated with their own challenges, particularly spillage and diffusion, resulting in a narrow window of utility (about 3 hours), which can limit their usefulness [19]. Fluorescent and near-infrared fluorescent dye use has also been reported. Applied via both CT guidance and bronchoscopy, these dyes have been reported to have a greater visual penetration through tissues, allowing a surgeon to localize nodules buried in up to 2 cm of tissue [21–23]. In addition, these fluorescent dyes have been reported to have a slower rate of parenchymal diffusion than traditional dyes, retaining fluorescence in situ for at least 5 hours [22]. However, this extended time still does not obviate the need for same day surgery.

Seeking to remedy the issue of rapid diffusion, radiopaque liquids (barium, lipiodol) have been used in isolation or combined with various dyes (methylene blue or near infrared (NIR) or infrared (IR) dyes) for improved localization. A significant detractor in the use of barium has been its inflammatory effect observed on postoperative histology, limiting its use. Lipiodol (ethiodized oil, an iodinated derivative of poppyseed oil) was first developed in the early 1900s as a contrast medium for hysterosalpingography and lymphography and has been found to have therapeutic indications for chemoembolization for unresectable hepatocellular carcinoma. Lipiodol has been used as a radiopaque marker for target nodules to guide thoracoscopic surgery, though it is more commonly used in bladder cancer. It has the benefit of being relatively inexpensive and safe (rare cases of embolization as it is not water soluble), with several case studies reporting its use as a FM prior to radiotherapy given its long residency, as it is seen in situ up to 8 months postplacement [24]. Unlike barium, lipiodol does not cause inflammatory changes to the histopathology of the resection specimen and can even be used in combination with cyanoacrylates as it does not interfere with the polymerization process [25].

While fluoroscopic localization with radiopaque markers has been successful, the added equipment burden to VATS and especially RATS prompted research into radiotracers such as technicium99 that can be detected by a handheld gamma ray detector. Injected by either CT-guided percutaneous or bronchoscopic placement, with or without concomitant dye or acrylic, radiotracers have been shown to confer high rates of VATS localization (88–96%) [19]. No intraoperative fluoroscopy is required, but radiation protection for the surgical team, as well as the team placing the radiotracer, is required and resources are necessary to allow for proper radioactive material handling. With a half-life of about 6 hours, surgery must occur soon after marking but with more flexibility than traditional nonfluorescent dyes. When delivered via CT guidance, there remains a risk of pneumothorax of 7–30% [19], and pleural soiling is a rare but known complication that results in making localization impossible [25].

Various marking modalities with advantages and disadvantages are listed in Table 1.

2.2 Challenges and Overview

The delivery of a marking medium is dependent on institutional expertise, nodule location, and availability of technologies such as navigation bronchoscopy. However, challenges in delivering localization markers via bronchoscope for lung nodule resection remain. Small nodules within the peripheral lung are not typically visualizable by traditional white light flexible bronchoscopy, which historically has limited its diagnostic utility for small lung nodules. Several techniques have been developed for improving bronchoscopic localization, including fluoroscopy and endobronchial ultrasound which allow for real-time guidance of the bronchoscope to the peripheral lesion; however, they are hampered by their lack of navigated mapping of the airway tree. To improve intraprocedural navigation, several different systems were developed to create three-dimensional maps of the airways from CT scans to generate onscreen directions akin to GPS. These systems use electromagnetic navigation (ENB) or fiberoptic light shape sensing

Table 1 An overview of various marking mediums used for surgical resection

Marking medium/device	Advantages	Disadvantages	Notes
Hookwires	Easily located at pleural surface	High rates of bleeding, pneumothorax, pain, displacement during transfer, and need for same day surgery	
Microcoils	Less associated pain than hookwires	Risk of embolization, pneumothorax, and bleeding	Occasional need for fluoroscopy if unable to visualize at pleural surface
Methylene Blue	Does not impact pathology results, safe, and relatively inexpensive	Narrow window of utility (<3 hours) and risk of "spillage" contaminating pleural space	
NIR/IR/ indocyanine green (ICG)	Marking can be seen buried in a 1–2 cm tissue	Need for same day surgery and possibility of being unable to localize if marking too deep to see	
Barium		Needs to be tumor "adjacent" due to risk of inflammation impacting pathology result	Need for fluoroscopy
Lipiodol	Remains in situ for months and inexpensive	Rare risk of embolization	Need for fluoroscopy
Radiotracer—technicium^{99}	No fluoroscopy required	Radiation protection required, resources are necessary for proper radioactive materials handling, and need for same day surgery	

with three-dimensional maps to provide real-time guidance through the airways to a target lesion.

In the largest study of nodule marking via ENB, data from 258 patients reported accurate FM placement in 99.2% of patients with 94.1% of markers durably in place. A mean on 2.2 FMs were placed per case, and complication rates were low with a pneumothorax rate of 5.4% [26]. This study confirmed ENB's significantly lower pneumothorax (1–5%) and pulmonary hemorrhage rates compared to CT-guided percutaneous marking (10–20%). In addition, ENB offers the benefit of marking nodules in hard-to-reach locations and can be conducted during the same setting as resection. This "single-anesthesia" approach has been shown to reduce time to intervention by 51 days on average and should be considered where possible [27–29].

The ideal marker from the patient's perspective would be one that was placed with minimal complications and guaranteed avoidance of open thoracotomy. From the surgical team's perspective, it could be placed the same day or days before, never be dislodged, be easily identified during MITS, require minimal additional intraoperative equipment, and pose no threat to the surgical team. Thus, all the benefits of MITS over thoracotomy would be maintained while still guaranteeing a curative result.

2.3 Current Techniques and Procedural Considerations

The administration of the chosen marking medium is dependent on both procedure team preference and the mechanism by which the mark is delivered (bronchoscopy vs. transthoracic CT guidance). When localizing targets using a bronchoscopic approach, the most common technology employed is a peripheral lung navigation platform in which a preprocedural CT will be used to generate a map and pathway to guide the bronchoscope to the lesion planned for resection. If the lesion is not visible, the use of a radial endobronchial ultrasound (rEBUS) probe and/or integrated advanced imaging (conebeam CT or digital tomosynthesis) may be employed to assist in locating the nodule to allow for tool-to-target colocalization. Once the nodule is located and punctured by a transbronchial aspiration needle, the marking medium is delivered into or adjacent to the nodule and with the intent of tattooing the visceral pleura to allow for improved visualization by the surgical team. The combination of marking media is also possible with traditional and fluorescent dyes being mixed prior to injection to provide that advantage of visualization under white light, NIR, and/or fluoroscopy. The volume of marking media to be delivered varies; however, previously published data would suggest between 0.5 and 1 ml are needed [30–32].

2.4 Future Directions

A different approach to improving localization has been to further engineer the marking medium. For example, a desiccated polyethylene glycol hydrogel that deploys as a solid cylinder (2.5 cm in length by 0.1 cm in diameter), self-expands upon contact with lung tissue, and can be visually identified intraoperatively has been developed [33]. The advantage purported in early studies is that this self-expansion seals the CT access tract preventing pneumothorax. Going a step further, there is an implantable infrared reflector that has been in use in breast cancer for nodule

marking. It is placed under CT guidance and can remain in place indefinitely like a FM, detangling radiology and OR schedules. Intraoperatively, an audible radar rangefinder guides the surgeon to the nodule to a published 1 mm accuracy. Only one published study exists currently for lung nodule marking, but typical complications of pneumothorax and hemothorax were low (9.5% and 0%, respectively) [19], and no cases of displacement, localization failure, or conversion to open thoracotomy were reported. More research is needed, but this system should inspire further exploration of implantable technology. Similarly, "smart" FM designs are being explored which when implanted are then detected via an emitted electromagnetic signature enabling intraoperative localization. These devices have been used for localization of suspicious breast lesions and are currently in the process of being adapted for bronchoscopic delivery.

An additional novel technique still in early trials is intraoperative molecular imaging (IMI). This technology utilizes visible or near infrared dyes tied to molecules that that are injected intravenously, preferentially accumulate in malignant tissue, and are used to guide the surgeon to the nodule intraoperatively. One such example is folate receptor IMI. Folate receptors have been shown to be upregulated in adeno- and squamous cell carcinoma of the lung to the point paired folate receptor NIR markers have been reported to successfully identify 70–95% of intraoperative nodules [34]. In a phase 2 trial, Gangadharan found that folate receptor IMI influenced intraoperative decision-making by detecting additional nodules (nearly half of which were malignant), revealing positive margins, or localizing nodules that were difficult to find in 26% of patients [35]. From the patient and surgeon's perspectives, localization via a simple infusion would be highly desirable given lack of need for a second proceduralist or risk of localization complications, and the benefit of identifying occult nodules intraoperatively cannot be overstated. Ultimately, no marking tool will have a true zero percent thoracotomy rate as patient factors such as adhesions or intraoperative hemorrhage can occur, necessitating conversation to an open approach.

2.5 Summary

Marking nodules for MITS localization and resection remains particularly helpful for lung nodules that are subsolid, small, and deep to the pleura. This is influenced by the transition to minimally invasive resection techniques (RATS and VATS), during which surgeons may lose the ability to digitally palpate their targets. However as discussed, marking nodules for MITS remains challenging—be it radiation exposure, limited time from placement to surgery, fluoroscopy requirement, or systemic embolization, surgical teams must weigh the risks and benefits of each option based on the resources available in their hospital system.

3 Placing Fiducials for SBRT

3.1 History

Radiation therapy is a standard treatment for lung cancer. In years past, its use has been limited by high rates of local recurrence and significant side effects. In the case of early-stage nonsmall cell lung cancer, both recurrence and overall survival rates can be improved by the delivery of higher doses of radiation to the tumor. Furthermore, by focusing and confining the radiation volume to the actual volume of tumor, radiotherapy can achieve similar survival rates and decreased complication rates when compared to less focused and less confined treatment volumes.

A variety of techniques have also been developed to "conform" the delivered radiation dose to the actual shape and size of the tumor and to "focus" the delivered radiation on the tumor, thereby decreasing the dose delivered to surrounding tissues. One technique uses multiple radiation beams directed at the tumor from multiple different angles, thereby "focusing" the radiation beams on a small volume of tissue. The shape of each beam is also adjusted so that it "conforms" to the contour of the target. This allows the majority of the radiation dose to be delivered to a very focused volume of tissue that has a shape and size very similar to that of the tumor. This is commonly referred to as three-dimensional conformal radiation therapy (3D-CRT). A similar technique adjusts the intensity of the radiation beam as it is directed at the tumor from multiple directions to "conform" the radiation delivery to the tumor shape and "focus" in on a small volume of tissue. This is referred to as intensity-modulated radiation therapy (IMRT). A third technique uses a single precise beam of radiation that can be moved around the patient and directed at different parts of the target volume from many angles. This allows the radiation dose to be contoured to the shape of the tumor and to focus the radiation delivery again to a small volume of tissue. These techniques can collectively be referred to as stereotactic body radiotherapy (SBRT) or image-guided radiation therapy (IGRT). So long as this conformed and focused volume of radiation coincides with the location of the tumor and the tumor does not move, then the tumor receives the vast majority of the radiation dose, and the surrounding tissue receives very little.

Unfortunately, these sophisticated but static methods that shape and focus the volume of delivered radiation to correspond to the known shape and position of the tumor do not account for microscopic tumor extension beyond the radiographic borders of the tumor, errors that occur in daily patient positioning relative to the linear accelerator (linac), and tumor movement secondary to respiratory motion. To overcome these problems and ensure that the entire tumor is located within the treatment volume, static conventional radiation delivery expands the size of the planned treatment

volume to include margins of error corresponding to these unknowns. Such a generic expansion of the treatment zone is shown graphically in Fig. 1. While this can help ensure that the entire tumor volume is adequately treated, it diminishes much of benefit possible by shaping and focusing the delivered radiation volume. Additionally, this generic expansion is not one size fits all: apical tumors typically move less than basilar tumors, central tumors move less than peripheral tumors, larger tumors move less than smaller tumors, and the lung does not follow the same trajectory during every breath in a given patient.

To take full advantage of the tightly focused and conformed radiation delivery volume, it is necessary to know where the tumor is located day to day and breath to breath. Since direct visualization of the tumor is not possible while the X-ray beam is actually on, and even when the beam is off, it is often difficult to visualize the tumor on fluoroscopy; FM that can be easily seen and continuously tracked can be placed in or near the tumor target.

The ability to place FM with accuracy is important to ensure targeting of the appropriate PTV to minimize effects of radiation to healthy tissues and maximize the therapeutic effect of SBRT. The PTV should account for microscopic tumor extension beyond the radiographic borders of the tumor, errors that occur in daily patient positioning relative to the linac, and tumor movement secondary to respiratory motion. To overcome these problems and ensure that the entire tumor is located within the treatment volume, static conventional radiation delivery expands the size of the planned treatment volume to include margins of error corresponding to these unknowns. While this can help ensure that the entire tumor volume is adequately treated, it diminishes much of the benefit possible by shaping and focusing the delivered radiation volume. Additionally, this generic expansion is not one size fits all: apical tumors typically move less than basilar tumors, central tumors move less than peripheral tumors, larger tumors move less than smaller tumors, and the lung does not follow the same trajectory during every breath in each patient.

While some systems have been developed to work without the use of FMs, they require nodules to be larger than 15 mm, denser than the surrounding parenchymal tissue, and be far

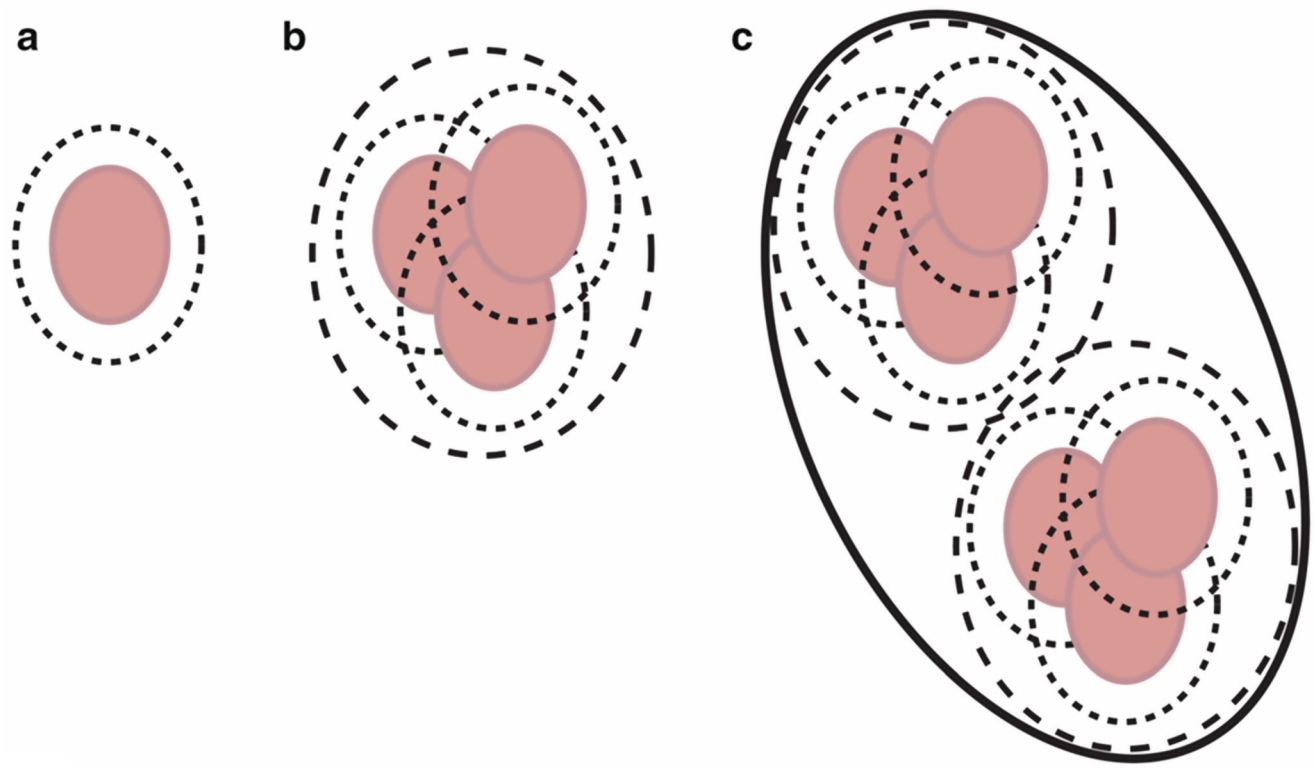

Fig. 1 Generic margin expansion to accommodate microscopic tumor extension beyond the radiographic borders of the tumor, errors that occur in daily patient positioning, and tumor movement secondary to respiratory motion. (**a**) Shows a generic tumor. The lightly *dashed line* represents the margin expansion added to increase the volume of planned radiation delivery to accommodate microscopic tumor extension beyond the radiographic borders of the tumor. (**b**) Shows the same generic tumor with its expanded margin as it might appear on three separate days. The variability in position is related to errors in daily patient positioning. The heavy *dashed line* represents the margin expansion performed to accommodate both microscopic tumor and daily patient positioning errors. (**c**) Shows the same generic tumor with its expanded margins as it might move during respiration. The solid line represents the margin expansion performed to accommodate microscopic tumor, daily patient positioning, and respiratory motion. As can be seen, the volume of tissue treated has the potential to be significantly larger than the actual volume of the tumor

enough away from the mediastinum for the system to detect. Thus, the need for FMs for accurate tracking has remained an important part of SBRT planning and execution as they provide the ability to track and respiratory gate the target tumor in real time. Real-time tumor tracking is a method of dynamically moving the focal point of the radiation mean so that this focal point always corresponds with the position of the tumor target. Respiratory gating is a method of turning the radiation beam on when the tumor target is located at the focal point of the radiation beam, and it is turned off as soon as the target moves outside of the beam. The patient is typically aligned so that the beam is on during expiration. Such gating also allows the margin expansion to accommodate respiratory motion (the margin expansion from B to C in Fig. 1) to be decreased. Real-time tumor tracking is a method of dynamically moving the focal point of the radiation energy mean dose so that this focal point always corresponds with the position of the tumor target. Such gating allows the margin expansion to accommodate respiratory motion (the margin expansion from B to C in Fig. 1) to be decreased.

A variety of radiation therapy systems are capable of real-time tumor tracking, based on the published literature; the system most widely used in conjunction with FM consists of a small 6-MV linac mounted on a computer-controlled robotic arm capable of moving with 6° of freedom, two orthogonally placed X-rays, two optical cameras, and an optic-radiographic motion monitoring system for real-time tumor tracking (Fig. 2). Radiopaque FMs implanted in or near the tumor and light-emitting diodes placed on the patient's chest are used for target tracking. Prior to radiation treatment and while the X-ray beam is off, a series of X-ray images are taken by the two orthogonal cameras at various times during the respiratory cycle, and the system develops a mathematical model relating the locations of the light-emitting diodes on the chest with those of the fiducials near the tumor in the lung. Continuous tracking of the light-emitting diodes combined with this mathematical model allows the robotic arm to be moved in real time such that the radiation beam tracks the moving tumor target. At regular intervals during treatment, additional orthogonal X-ray images are taken to allow the model to be validated and updated with small changes in breathing patterns. The total system accuracy of the device and the respiratory motion tracking has been reported as <1 mm.

3.2 Challenges

The challenges associated with localization of target nodules for fiducial placement are very similar to the challenges associated with localization for surgical marking, apart from the need to mark near the pleura (to guide surgical resection once the thorax has been entered for VATS or RATS). The ideal FM itself shares some of the same properties as one for surgical marking—it should be easy to place, safe, not pose a threat to the medical team, and be trackable without the need for palpation or direct visualization. Additionally, the ideal FM does not migrate after placement and remains in situ for SBRT therapy or could be used for localization should surgery be pursued down the road.

Placement via percutaneous methods conveys a risk of pneumothorax similar to or higher than percutaneous lung biopsy (13–48%) [36, 37] and is relatively more challenging for central nodules, which are often adjacent to vascular structures within the mediastinum. Percutaneous placement usually requires two punctures, with two markers placed along one tract and the third placed with a second puncture. With percutaneous CT-guided placement, there is also an increased risk of colinear placement, which makes tracking FMs for SBRT less accurate.

Placement via bronchoscopy helps mitigate risk to the patient and is a viable and safe alternative for placing FMs. This approach also allows for optimal distribution of FMs so are to avoid colinear placement [38, 39]. Retrospective review of the NAVIGATE cohort, which utilized EMN bronchoscopy for FM delivery, reported a 94.1% rate of successful FM placement based on postplacement imaging (most imaging performed same day as procedure) with a 5.4% pneumothorax rate [26]. Despite these reported successes, FM placement via the bronchoscopic approach faces its own challenges including difficult-to-reach targets, pneumothorax, FM misplacement/migration, and bleeding. FMs themselves are at risk for migration (up to 12%), and embolization and placement should be confirmed 1–2 weeks post-placement with a CT, as migration typically occurs within the first 10 days of placement [39, 40].

3.3 Current Techniques/Procedural Considerations

FMs are typically placed under bronchoscopic guidance on an outpatient basis and are deployed via peripheral navigation bronchoscopy using such techniques as rEBUS, ENB, and robotic bronchoscopy. As one example, CT-body anatomic mapping was used by bronchoscopists to traverse the lung to the target lesion where upon reaching the target the rEBUS probe and guide sheath were inserted through the working channel of the bronchoscope. Upon identification of the target nodule on radial EBUS, the probe was removed and the sheath left in place. An FM loaded into a brush was then inserted into the sheath and the FM was deployed at the level of the target. More recently, ENB or shape sensing robotic bronchoscopy has been used in peripheral lung navigation and with a similar workflow for FM placement (Fig. 3). Once the navigation and biopsy phase of the procedure is complete, an FM delivery catheter or FM loaded into a brush are used to deliver the FM as the level of the target

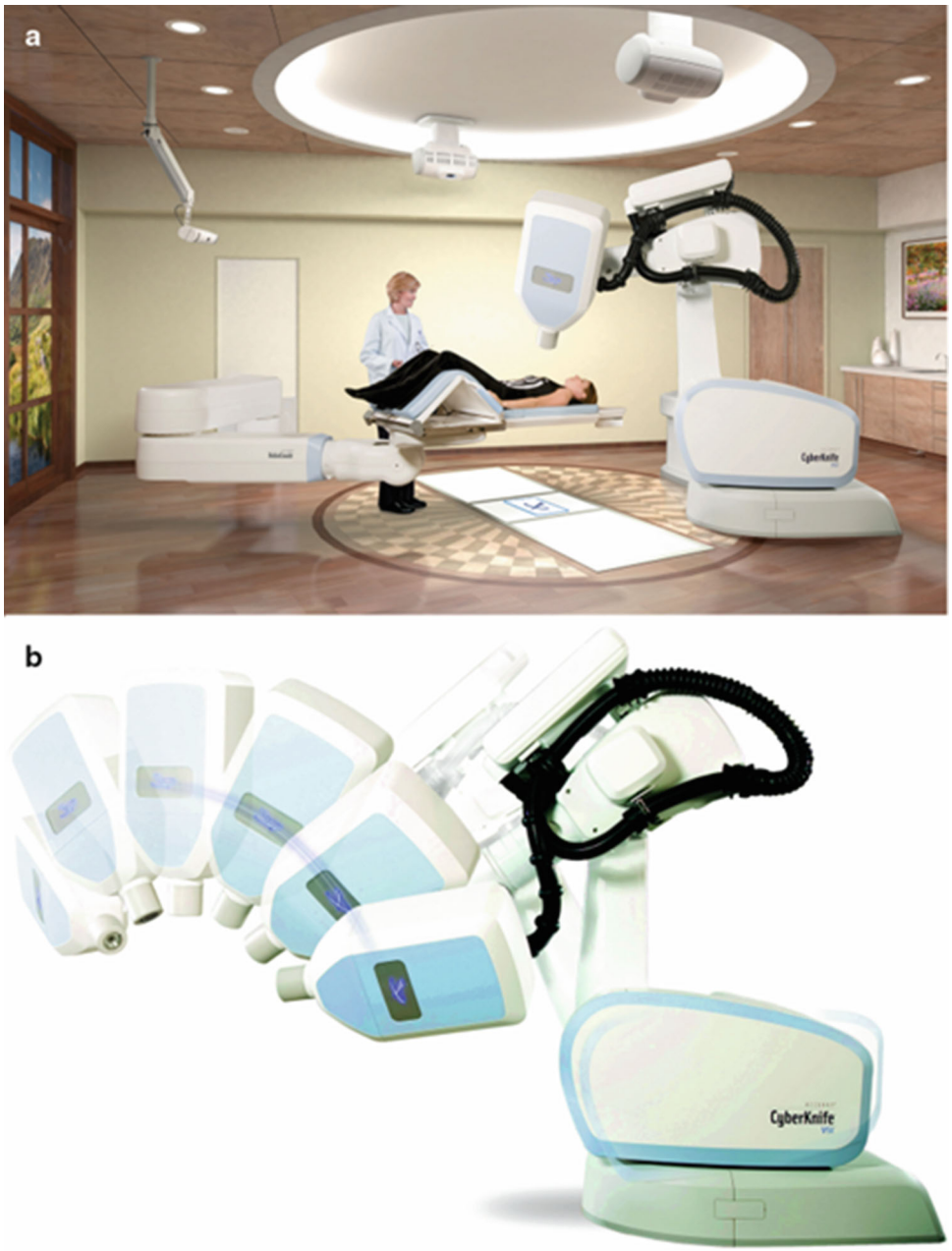

Fig. 2 A small 6-MV linac mounted on a computer-controlled robotic arm capable of moving with 6° of freedom, two orthogonally placed X-rays, two optical cameras, and an optic-radiographic motion monitoring system for real-time tumor tracking. Radio-opaque fiducial markers implanted in or near the tumor and light-emitting diodes placed on the patient's chest are used for target tracking. Prior to radiation treatment and while the X-ray beam is off, a series of X-ray images are taken by the two orthogonal cameras at various times during the respiratory cycle, and the system develops a mathematical model relating the locations of the light-emitting diodes on the chest with those of the fiducials near the tumor in the lung. Continuous tracking of the light-emitting diodes combined with this mathematical model allows the robotic arm to be moved in real time such that the radiation beam tracks the moving tumor target. At regular intervals during treatment, additional orthogonal X-ray images are taken to allow the model to be validated and updated with small changes in breathing patterns. The current system allows for a dozen different beam directions from over a hundred different robot arm locations, providing more than 1200 possible beam paths. (**a**) Shows an overview of the SBRT system with a patient positioned on the couch. (**b**) Demonstrates the motion capabilities of the linac system. (Images used by permission of Accuray Incorporated)

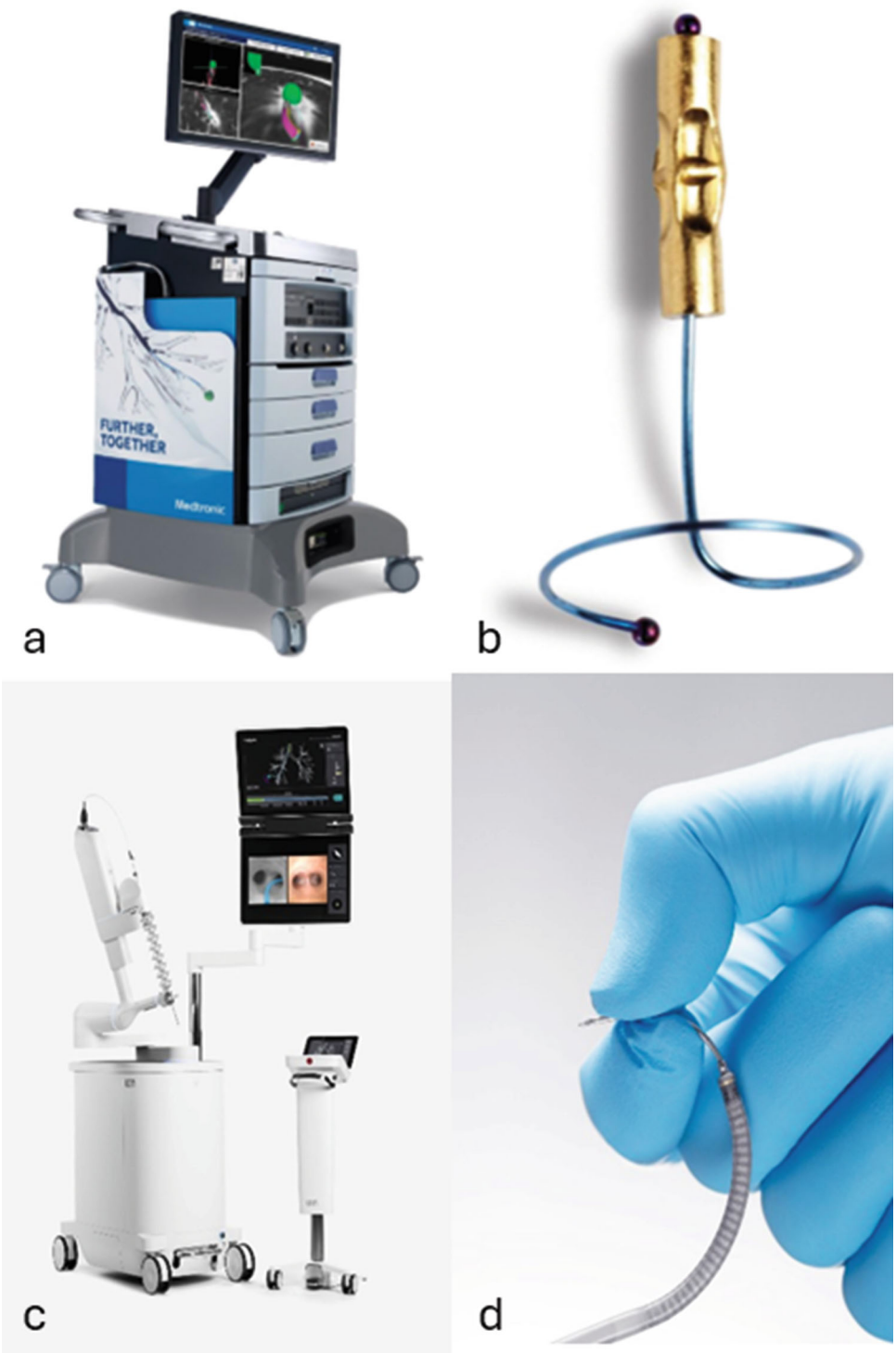

Fig. 3 (**a**) Representative image of an electromagnetic navigation bronchoscopy platform. (**b**) Nitinol coil with gold bead fiducial marker. All rights reserved. Used with the permission of Medtronic. (**c**) Representative image of a shape sensing robotic navigation bronchoscopy platform. (**d**) Proprietary flexible needle technology allowing negotiation of tight endoluminal angles for nodule biopsy, implantation of fiducial markers, and injection of dye for surgical marking. (Image courtesy of the Intuitive Surgical, Inc.)

nodule. Subsequent FMs are then placed with the intent that they be at least 1.5 cm but not more than 5 cm from each other. Advanced perioperative imaging (integrated or not) can be used to help confirm the spatial relationships between the FMs as they are being placed.

In the case of FM placement into a target nodule or lymph node, a needle is used to first puncture the target, and then the FM is delivered by pushing the marker out of the barrel of the needle using a stylet or if no stylet is available flushing the needle with sterile saline. Before this, the FM is carefully "musket" loaded into the needle's

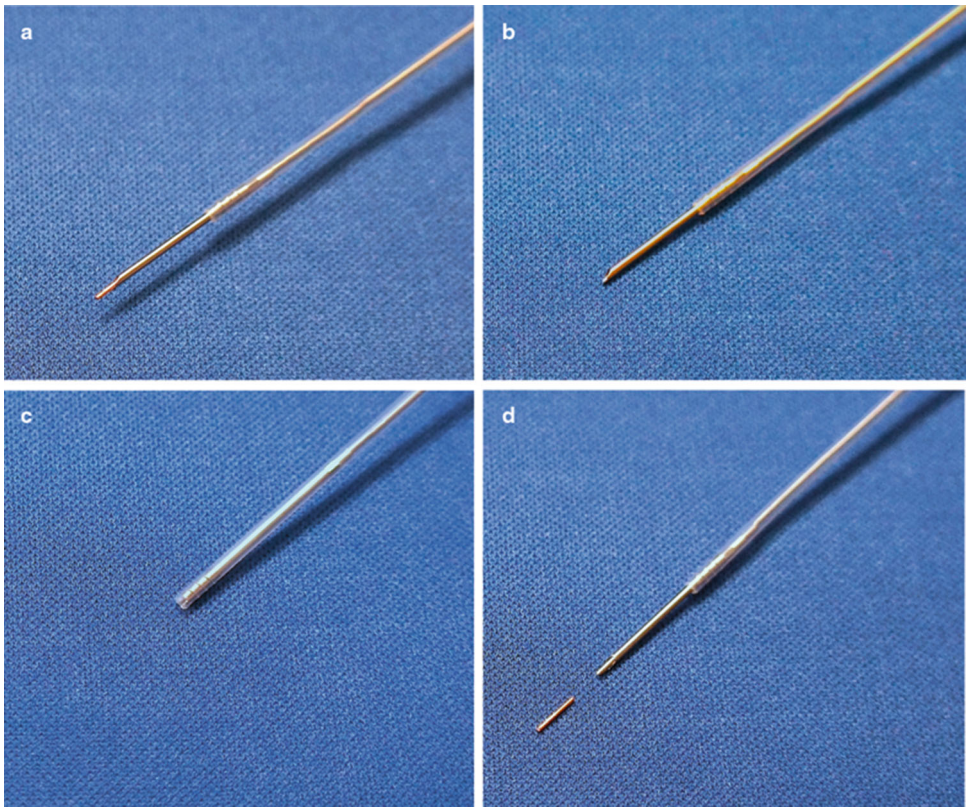

Fig. 4 This figure demonstrates loading of a fiducial marker into a bronchoscopy needle. (**a**) Shows the needle fully extended and a cylindrical fiducial with a 0.5 mm diameter and a length of 5.0 mm partially loaded in the tip of the outer needle. (**b**) Shows the fully extended needle after the fiducial has been completely inserted into the bore of the needle and sealed into place using bone wax. The bone wax prevents loss of the marker while it is being passed through the bronchoscope. (**c**) Shows the tip of the transbronchial histology needle catheter ready for insertion. In use, the needle catheter is then passed through the bronchoscope, or the extended working channel or guide sheath, and advanced until the tip of the catheter clears the end of the instrument and is approximately 2 cm proximal to the desired implantation site. The needle is then extended and the needle catheter advanced until the tip of the needle is located immediately proximal to the desired implantation site. The fiducial marker is then deployed out of the bore needle by either advancing the inner stylet or using saline, depositing it in the desired implantation site. (**d**) Shows the needle fully extended and the fiducial ejected from the needle

bore and may be sealed using bone wax (Fig. 4). The bone wax prevents loss of the marker while it is being passed through the bronchoscope.

The needle catheter is then passed through the bronchoscope, or the extended working channel or guide sheath if these are being used, and advanced until the tip of the catheter clears the end of the instrument and is approximately 1–2 cm proximal to the desired implantation site. The needle is then extended and the needle catheter advanced until the tip of the needle is located immediately proximal to the desired implantation site. The needle stylet is then advanced pushing the fiducial out of the bore of the needle and depositing it in the desired implantation site. Once implanted, the needle should be withdrawn slowly to ensure that the fiducial has cleared the outer barrel of needle. Deployment is performed under either convex EBUS or fluoroscopic guidance (Fig. 5) [41].

The number of FM needed is not universally agreed upon and is dependent on the type of marker. When considering the number of FM to implant, enough should be placed to provide accurate positional information and ideal rotational information as well. Two FM located in and around the tumor such that they bracket the bulk of the tumor can provide translational information about the tumor target. Three FMs located in and around the tumor such that they bracket the bulk of the tumor and do not overlap on the fluoroscopic tracking system provide both translational and rotational information. Enough FM should be placed so that it is possible to tell if a marker has migrated out of position and ideally enough so that it is easy to pinpoint which has migrated. Migration can be detected by measuring the distance between pairs of FM at the same phase of respiration. When only two FMs have been implanted, it is possible to tell that one of the fiducials has moved but not which one. When three or more FMs have been implanted, by measuring the distance between each marker and the others, it is possible to tell not only that one has migrated but which one. Knowing this allows the radiation oncologist to ignore the migrated FM with positional and tracking information obtained from the remaining markers.

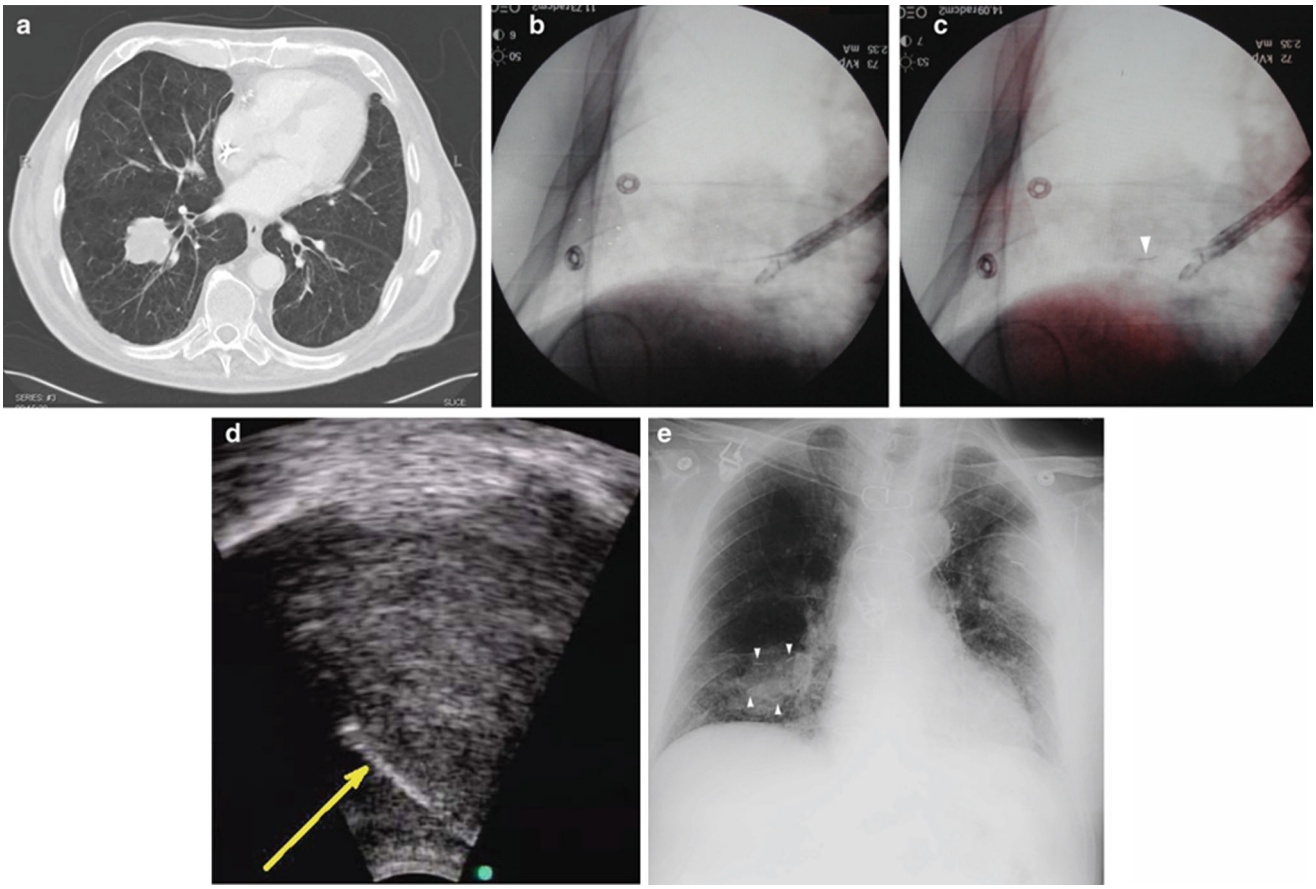

Fig. 5 Representative figure demonstrating implantation of a fiducial in a central tumor using endobronchial ultrasound guidance. (**a**) Shows cross-sectional CT image of the tumor target. (**b**) Shows a posterior-anterior fluoroscopic image of a standard 22-gauge TBNA needle preloaded with a 0.35 mm coiled wire fiducial being passed through an endobronchial ultrasound scope and into the tumor target. (**c**) Shows a posterior-anterior fluoroscopic image of the fiducial (indicated by the white arrowhead) being deployed from the needle. (**d**) Shows a near simultaneous ultrasound image of the same fiducial being deployed. (**e**) Shows an anterior-posterior chest X-ray following deployment of four fiducials around the periphery of this tumor target

When considering where to implant the FM, they should be close enough to the tumor target so that they move with the tumor and provide accurate information about the tumor's location and motion but far enough away from each other so that each fiducial provides independent information as fiducials implanted very close to one another look like a single fiducial on fluoroscopy. Other considerations include ensuring the markers are not so far apart that they are outside the field of the view of the tracking system and that they are not positioned such that a straight line can be drawn between any three of the fiducials; such collinear fiducials may appear superimposed on fluoroscopy and will not provide useful information. In total, FMs should be a minimum of 1.5 cm apart and should be no more than 5–6 cm from the lesion and be oriented differently in the x, y, and z planes to allow for optimal targeting. Representative positioning of a group of FMs is shown in Fig. 4.

The shape of FM may be selected due to concern for marker migration, ability for the surgeon to palpate should the nodule be resected surgically, or both. Coil-shaped fiducials are thought to retain their positioning better than seed- or dumbbell-shaped FMs but must fit through the working channel of the bronchoscope/catheter [42, 43]. Several different types of fiducials are pictured in Fig. 5. Recent publications have reported that the use of coil FMs soaked in ICG to help with localization should surgery be required for resection [27]. Postplacement imaging should be obtained immediately after placement to rule out pneumothorax and 1–2 weeks after placement of FMs to confirm appropriate placement.

3.4 Future Directions

Newer systems have attempted to apply SBRT without the need for FMs; however, limitations exist for nodules less than 15 mm, ground glass nodules, or those near the mediastinum or spine. In 2016, a nonmetallic liquid FM that forms a

sticky-soft adherent substance in vivo and is visible under relevant imaging modalities was introduced (Fig. 6). This has led to the development of other nonmetallic FMs that have been developed designed to produce less artifact on imaging.

3.5 Summary

FMs act as visible surrogates of tumor location and can provide accurate localization and tracking of tumors, particularly when the tumor is difficult to see on fluoroscopy or CT scan. A wide variety of FMs with an equally wide range of shapes, sizes, and surface treatments are currently available for use in the body. Some basic guidelines to follow when implanting fiducials include the following:

- 3–6 FMs should be implanted to so that at least three remain in place.
- FMs should not be placed collinearly.
- FMs should be placed in and around the tumor such that the bulk of the tumor is bracketed by the fiducials.
- FMs should be placed such that they are at least 1.5 cm but not more than 5 cm from each other.

Overall, bronchoscopic FM placement appears to be quite safe, with a low incidence of complications. This method offers distinct advantages, especially when using advanced integrated imaging systems like ENB or robotic bronchoscopy. These technologies allow for more precise placement of FMs in areas that might otherwise be inaccessible or unsuitable for traditional percutaneous techniques, particularly when nodules are located deep within the lung parenchyma or adjacent to critical structures (Figs. 7 and 8).

4 Conclusion

Lung cancer remains a leading cause of cancer-related mortality worldwide, with screening advancements such as LDCT offering a significant reduction in mortality for high-risk individuals. The use of LDCT in lung cancer screening has shifted the paradigm toward early detection and intervention, while guidelines from organizations like the NCCN and ACR have refined management strategies for pulmonary nodules, particularly through patient-provider shared decision-making. The integration of minimally invasive surgical techniques, such as VATS and RATS, alongside radiotherapeutic options like SBRT, has broadened the scope of

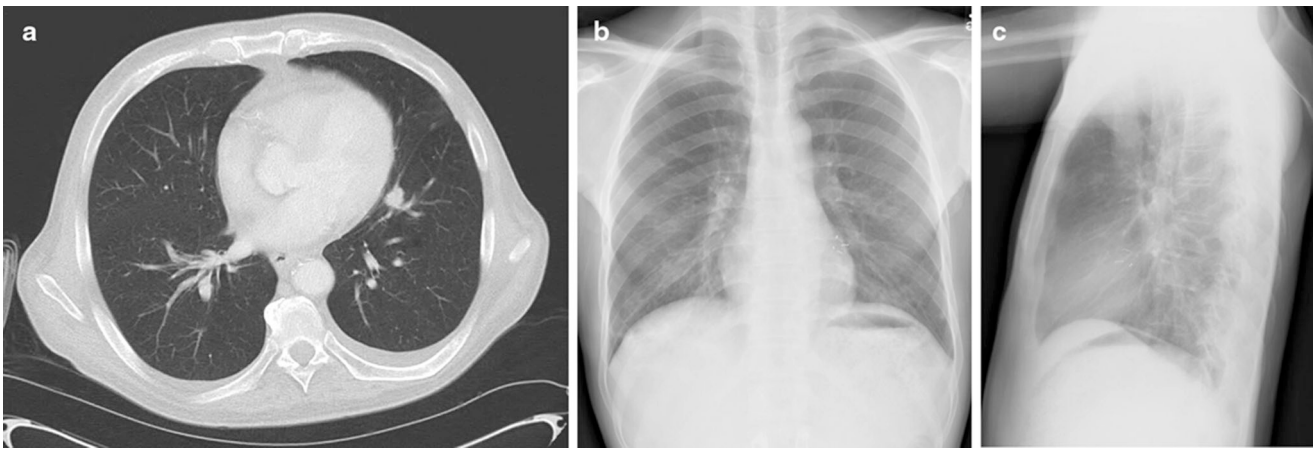

Fig. 6 Representative positioning of FMs in different x, y, and z planes

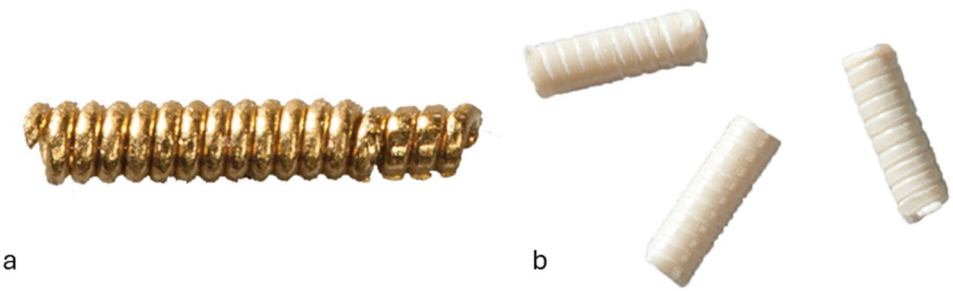

Fig. 7 (**a**) 5 mm helical gold fiducial marker with a solid central nodule that provides a single imaging point for radiation therapy targeting. (**b**) Polymer-based marker, designed to minimize artifact on imaging, implantable using an 18G needle. (Images courtesy of the CQ Medical)

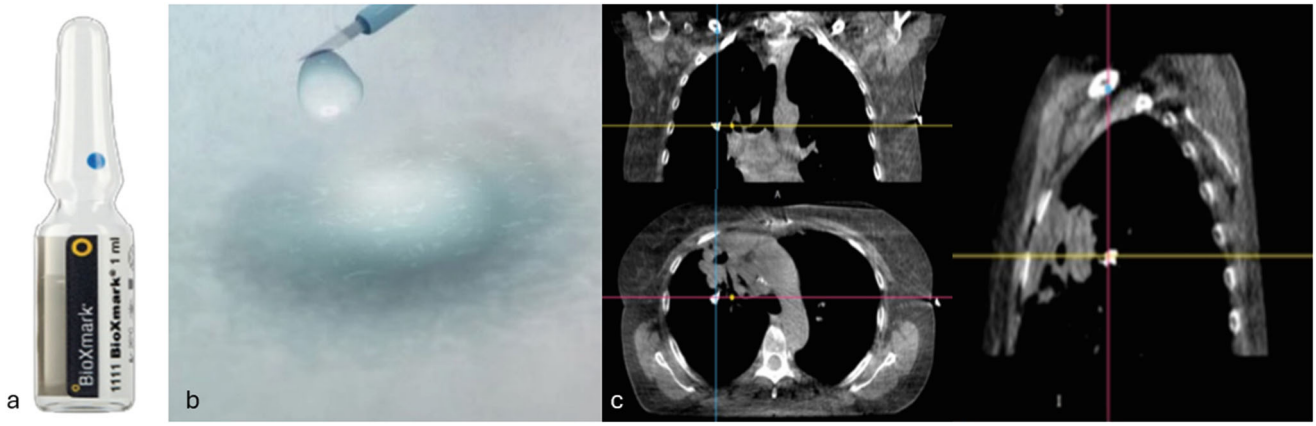

Fig. 8 (**a**) Iodine-based liquid fiducial marker can be implanted bronchoscopically. (**b**) Following implantation, the compound forms a sticky-soft marker in vivo (center). FDA approved for radiographic marking of lung cancer for radiation therapy for at least 3 months following implantation. (**c**) CT planning images showing the implanted compound in and adjacent to a lung tumor. (Images courtesy of the CQ Medical)

treatment for patients with early-stage lung cancer or those unsuitable for traditional surgery. As treatments become increasingly precise, accurate nodule localization and FM placement for SBRT remain a critical factor in ensuring successful outcomes. Techniques for marking for surgery and FM placement have improved the ability of surgeons and radiation oncologists to localize and treat lung nodules effectively. However, challenges such as marker displacement, pneumothorax, and FM migration remain areas of ongoing research. The evolution of these techniques is essential to further improve the success rates of surgical and radiotherapeutic interventions, ultimately leading to better patient outcomes and advancements in lung cancer care.

Competing Interest Declaration The author(s) has no competing interests to declare that are relevant to the content of this manuscript.

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