EUS-Guided Fiducial Placement

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Introduction

Image-guided radiation therapy (IGRT) uses real-time imaging to precisely localize tumors and deliver focused high-dose beams of radiotherapy [1]. Fiducials are radiopaque markers implanted at the site of a tumor or a lymph node that enhance lesion localization, and serve as reference points for targeting radiation therapy [2]. Historically, fiducial markers were placed surgically or percutaneously using ultrasound or CT guidance [3]. In the past decade, an endoscopic ultrasound (EUS)-guided approach has evolved and shown to be a safe method for fiducial marker placement.

Fiducial Types

Many types of fiducial markers have been developed and described in the literature. Table 10.1 outlines various fiducial types that have been placed using EUS. In early published studies, traditional cylindrical gold seeds were investigated. These gold seeds measured approximately 2.5–5 mm in length, ranged from 0.8 to 1.2 mm in diameter, and required a 19-gauge needle to deploy them [12, 15, 16]. Visicoil (Radio Med Corporation, Tyngsboro, MA, Core Oncology, Santa Barbara, CA) fiducials were subsequently introduced into the market and unlike traditional fiducials, they are flexible and have a coiled design to theoretically reduce risk of migration (Fig. 10.1). Visicoil fiducials are longer in length (10 mm) and produced in two different diameters (0.35 mm, 0.75 mm). The smaller diameter coiled fiducials can be used with a 22-gauge needle, providing more flexibility in anatomic areas requiring increased angulation or torque [4, 5, 8, 9]. This contrasts with the larger 0.75-mm fiducial which requires a 19-gauge needle for deployment. In addition, Visicoil fiducials utilize a specific needle-carrier delivery system to facilitate their insertion into the tip of the EUS needle (Fig. 10.2).

A retrospective study comparing traditional fiducials (0.8 mm × 5 mm) to the flexible Visicoil fiducials (0.35 mm × 10 mm) in patients with advanced pancreatic cancer demonstrated comparable technical success with no difference in migration or complication rates when fiducials were placed into tumors via EUS guidance. However, the visibility of traditional fiducials was significantly better than the Visicoil fiducials on CT scans and during subsequent IGRT, possibly related to their larger diameter [10]. In contrast, Machiels et al. reported higher rates of visibility in esophageal cancer with the newer

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Table 10.1 Summary of studies describing different gold fiducial types used with EUS

Fiducial type (Trademark)	Size (Diameter × Length)[a]	Needle gauge[a]
Visicoil flexible gold coiled fiducial (Radio Med Inc., Tyngsboro, MA) [4–7]	0.75 mm × 10 mm 0.35 mm × 10 mm	19G (Cook Endoscopy, Winston Salem, NC) 22G (Cook Endoscopy, Winston Salem, NC)
Visicoil flexible gold linear fiducial (Core Oncology, Santa Barbara, CA) [8–11]	0.35 mm × 10 mm 0.35 mm × 2–20 mm	22G (Cook Endoscopy, Winston Salem, NC)
Gold cylindrical fiducial (Best Medical International, Springfield, VA) [12–14]	0.8 mm × 3 or 5 mm	19G (MEDI-Globe, Achenmuhle, Germany, or Cook Endoscopy, Winston Salem, NC)
Gold cylindrical fiducial (Alpha Omega Services Inc, Bellflower, CA) [15, 16]	0.8 mm × 2.5 or 5 mm	19G (Cook Endoscopy, Winston Salem, NC)
Gold cylindrical fiducial (Northwest Medical Physics Equipment Inc., Lynwood, WA) [17]	0.8 mm × 3 mm	19G (Cook Endoscopy, Winston Salem, NC)
Gold cylindrical fiducial (CIVCO Medical Solutions, Orange County, IA) [18]	0.8 mm × 3 mm	19G (Cook Endoscopy, Winston Salem, NC)
Gold anchor ball shaped or line shaped fiducial (Naslund Medical AB, Huddinge, Sweden) [8]	0.28 mm × 10 mm	22G (Cook Endoscopy, Winston Salem, NC)
X-MARK gold fiducial (IZI Medical Products, Owings Mills, MA, ONC Solutions Inc., Acton, MA) [14]	0.85 mm × 1, 2, or 3 cm	19G

[a]Sizes of fiducials and needle gauge listed are limited to the ones used in the studies

Fig. 10.1 Visicoil gold fiducial marker

flexible Visicoil markers that were ≥5 mm in length when compared to the solid gold and liquid hydrogel fiducials markers. The authors suggested that length may play a critical role in improved visibility [11]. Fernandez et al. found no significant difference in visibility between the 0.35 mm × 10 mm and 0.75 mm × 10 mm diameter Visicoil fiducial markers in patients with esophageal cancer, except in patients with larger body habitus where the larger diameter fiducials were easier to see radiographically [6]. Given the limitations due to study design and sample size in many studies, firm conclusions cannot be made regarding the optimal type of fiducial to be placed by EUS guidance. Based on retrospective and limited prospective data, fiducials with increased length and diameter appear to have im proved visibility and may be preferable if the positioning of the echoendoscope allows their use.

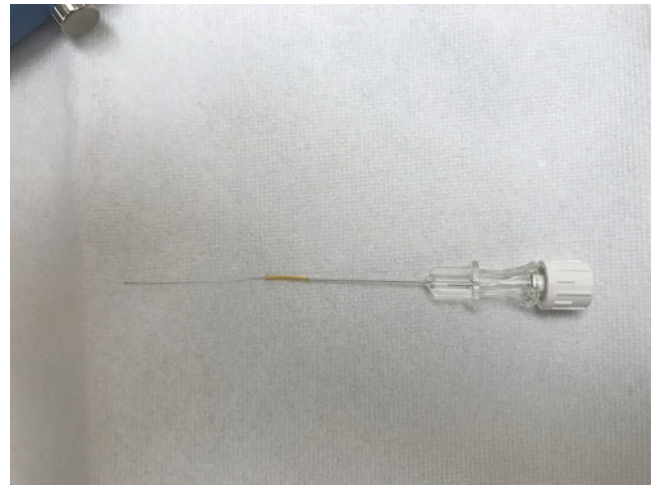

Fig. 10.2 Visicoil fiducial preloaded on a needle-carrier device

Fiducial Set Up and Deployment Techniques

Most studies have had successful outcomes with regard to delivery of fiducials into the target lesion (Table 10.2). Different techniques have been described with slight variations in technique with regard to loading of the fiducial marker into the needle and deployment into the target tissue.

An antegrade method for loading fiducials was first described in two case series [5, 12]. Ammar et al. preferred this approach because it prevented handling of the sharp end of the needle and minimized the risk of fiducial loss while accessing the lesion [4]. In this method, the needle is inserted into the target lesion and the stylet is withdrawn. Next, the fiducial is manually loaded into the needle lumen and the stylet is reinserted to push the fiducial forward into the target lesion. Another more commonly used method involves a back-loading technique using a 19- or 22-gauge EUS-FNA needle that has been described in numerous studies [6–10, 13, 15–18]. First, the stylet is withdrawn from the needle approximately 7–8 mm, and a fiducial marker is back-loaded into the needle tip in a retrograde manner using sterile forceps or using the needle-carrier delivery device (Fig. 10.3). Once the fiducial itself is within the lumen of the needle, the needle tip is sealed with sterile bone wax to prevent loss of the fiducial in the echoendoscope or in the patient before the target tissue has been reached. The needle is inserted into the operating channel of the echoendoscope and advanced into the target lesion using Doppler ultrasound to avoid intervening blood vessels. A small "track" is made in the target tissue to facilitate insertion and the fiducial is deployed by advancing the stylet completely while simultaneously retracting the needle an equal distance. The fiducial can be seen to deploy endosonographically and via fluoroscopy, if utilized. The needle is removed and reloaded with a new fiducial and the method is repeated until the desired number of fiducials have been placed. In both of these techniques, the stylet is used to deploy the fiducial. The back-loading technique and intra-tumoral deployment is demonstrated in Video 10.1.

An alternative to the stylet-push method has been developed. This technique uses a hydrostatic technique to deploy the fiducial into the target lesion. In this method, the stylet is removed, the needle is first flushed with sterile water or normal saline, and the fiducial is back-loaded into the needle. Then, the needle is inserted into the tumor and 1–2 mL of sterile water or normal saline is instilled into the needle to deploy the fiducial [13, 15]. The advantages reported include reducing air artifact and aiding delivery during difficult scope positions.

To improve efficiency, other specialists have described preloading two fiducials into the tip of the needle with the ability of placing multiple

Table 10.2 Summary of efficacy and safety of EUS-guided fiducial placement

Study	Design	Location of malignant lesion	Needle gauge (G)	Fiducial type (mm)	Technical success	Adverse events
Pishvaian et al. [12]	PS ($n = 13$)	Mediastinum Esophagus Pancreas Metastatic lesions in abdomen	19G	Gold (0.8 × 3 or 5)	11/13 (85%)	Cholangitis (1)
Sanders et al. [16]	PS ($n = 51$)	Pancreas	19G	Gold (0.8 × 5)	46/51 (90%)	Mild pancreatitis (1)
Park et al. [15]	PS ($n = 57$)	Pancreas	19G	Gold (0.8 × 2.5)	50/53 (94%)	Minor bleeding (1)
Ammar et al. [4]	RS ($n = 13$)	Pancreas Abdominal lymph node Liver lesion Adrenal gland Bile duct (CCA)	22G	VC (0.35 × 10)	13/13 (100%)	None
DiMaio et al. [9]	RS ($n = 30$)	Esophagus Pancreas Gastric Bile duct (CCA) Metastatic liver lesion	22G	VC (0.35 × 10)	29/30 (97%)	Fever (1)
Varadarajulu et al. [13]	RS ($n = 9$)	Pancreas	19G	Gold (0.8 × 3)	9/9 (100%)	None
Khashab et al. [10]	RS (n = 39)	Pancreas	19G 22G	Gold (0.8 × 5) VC (0.35 × 10)	39/39 (100%)	None
Fernandez et al. [6]	RS ($n = 60$)	Esophagus	19G 22G	VC (0.75 × 10) VC (0.5 × 10) VC (0.35 × 10)	60/60 (100%)	Abdominal pain (1)
Majumder et al. [19]	RS ($n = 77$)	Pancreas	19G	Gold (0.8 × 5)	35/39 (90%)	Abdominal pain (3) Mild pancreatitis (1)
Choi et al. [18]	RS ($n = 32$)	Pancreas Liver lesion Metastatic lymph node	19G	Gold (0.8 × 3)	32/32 (100%)	Mild pancreatitis (1)
Chandran et al. [20]	PS ($n = 8$)	Gastric	19G	VC (0.35 × 10)	7/8 (88%)	None
Davila Fajardo et al. [8]	PS ($n = 23$)	Pancreas	22G	VC (0.35 × 5–20) Gold anchor (0.28 × 10)	23/23 (100%)	Minor bleeding (1)
Moningi et al. [14]	RS ($n = 11$)	Rectum	19G	Gold (0.8 × 5) X-mark fiducial (0.85 × 10–30)	11/11 (100%)	None
Machiels et al. [11]	PS ($n = 32$)	Esophagus	22G	Gold (0.43–0.64 × 5) Visicoil (0.35 × 2–10) Hydrogel marker	30/30 (100%)	Pneumothorax (1) Mediastinitis (2)

(continued)

Table 10.2 (continued)

Study	Design	Location of malignant lesion	Needle gauge (G)	Fiducial type (mm)	Technical success	Adverse events
Dhadham et al. [7]	RS (n = 514)	Mediastinum Esophagus Pancreas Rectum/anal canal Metastatic lesions in abdomen and liver	19G 22G	VC (0.75 × 10) VC (0.35 × 10)	513/514 (99.8%)	Minor bleeding (9)

PS prospective study, *RS* retrospective study, *VC* Visicoil, *CCA* cholangiocarcinoma

markers at the same time [15]. Currently, preloaded needles are commercially available for use. The Beacon FNF needle (Medtronic, Minneapolis, MN) is available in two sizes and preloaded with two solid gold fiducial markers—22-gauge (0.43 mm × 5 mm) and 19-gauge (0.75 mm × 5 mm). In addition, the 22-gauge EchoTip Ultra preloaded needle (Cook Medical, Bloomington, IN) has been developed and been shown to be effective in a live porcine models [21]. The Cook needle system comes preloaded with four gold fiducials that are each 5 mm in length and 0.43 mm in diameter. A current randomized controlled trial is underway comparing overall efficiency and technical success between the 22-gauge EchoTip Ultra preloaded fiducial needle versus the traditional back-loading technique in patients with pancreatic cancer.

The optimal number of fiducials to be placed into a lesion has not been well established. In the literature, most studies have placed between 2 and 5 fiducials for each tumor/lymph node/target lesion. In our experience, we attempt to place at least three fiducials in different locations within pancreatic lesions and one fiducial marker at both the proximal and distal margins of luminal tumors if feasible, although practice in this regard varies between centers.

Technical difficulties that have been encountered include resistance while pushing the fiducial with the stylet [8, 12, 15], and the presence of intervening vasculature [7, 16] which makes safe deployment challenging. As described above, to overcome difficult anatomic positions, techniques that have been successfully reported include repositioning the scope, using a smaller size fiducial/needle or trying a different deployment technique such as the hydrostatic technique.

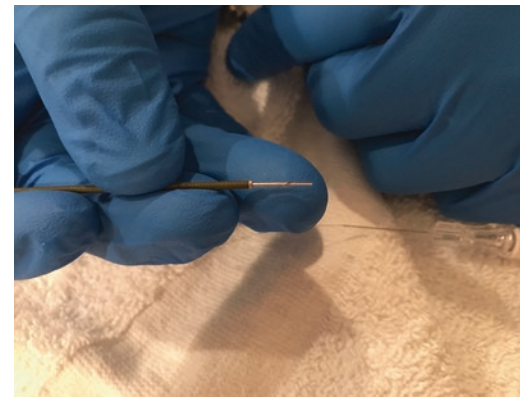

Fig. 10.3 Visicoil fiducial loaded on the distal tip of EUS needle

Fiducial Tumor Targets

Pancreatic Cancer

Pancreatic cancer has recently become the third most common cause of cancer-related deaths, and only 20% of patients are surgically resectable at the time of diagnosis [22, 23]. For patients with borderline resectable or locally advanced disease, neoadjuvant chemotherapy and radiation play an important role in controlling tumor growth and influencing overall survival [24–26]. While EUS has traditionally aided in the diagnosis and staging of pancreatic cancer, more therapeutic options have emerged including celiac plexus neurolysis, EUS-guided biliary access and drainage, fine needle injection, and fiducial placement (Fig. 10.4) [27]. In 2006, Pishvaian et al. performed the first case series evaluating EUS-guided gold fiducial placement in mediastinal and abdominal malignancies which included five patients with advanced pancreatic cancer and

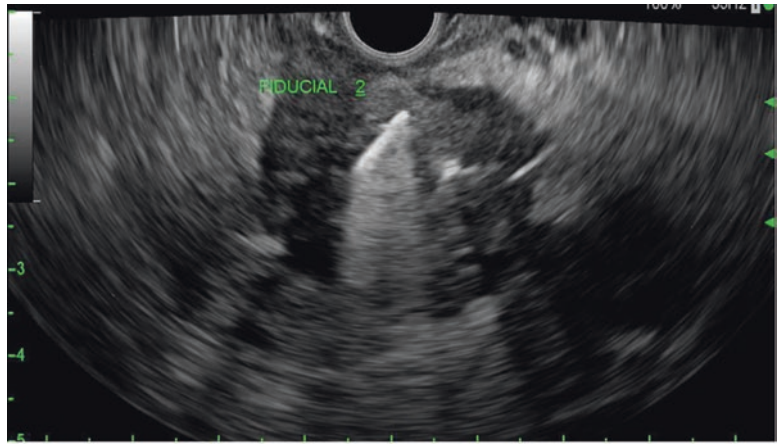

Fig. 10.4 Endosonographic image of a hyperechoic fiducial placed within the pancreatic body mass

one with recurrent cancer post-Whipple. The technique followed the same principle of EUS-guided FNA and delivered an average of 3–4 fiducials in each of the five patients using a 19-gauge needle. One failure occurred secondary to gastric outlet obstruction in a patient with a tumor in the pancreatic head. The study showed an overall technical success rate of 85% and was the first to demonstrate the safety and feasibility of EUS-guided fiducial placement for tumor marking to guide radiotherapy [12]. Since that report, multiple prospective and retrospective case series have described the feasibility of fiducial placement, specifically in pancreatic cancer, with high success rates ranging from 88 to 100% [10, 13, 15, 16, 18]. Four studies demonstrated success with the use of a 22-gauge needle to place smaller diameter Visicoil fiducial markers in patients with pancreatic cancer [4, 8–10]. There are no prospective data comparing the 19- and 22-gauge needles for fiducial placement, but experts report that the 22-gauge needle may help overcome issues of angulation in pancreatic lesions in the head and uncinate process [8, 9].

In the largest retrospective series involving 188 patients with pancreatic cancer, a 22-gauge needle was used to place 414 Visicoil fiducials (0.35 mm × 10 mm) in 80% of patients, and a 19-gauge needle was used to place 93 Visicoil fiducials (0.75 mm × 10 mm) in 20% of patients. Technical difficulty occurred in 16 patients (3.1%) mainly involving intervening blood vessels, and minor bleeding that resolved spontaneously in seven patients (1.3%) [7].

In early studies, fluoroscopy was used in conjunction with EUS to help achieve appropriate angulation and distance between fiducial markers (Fig. 10.5). More recent studies have shown successful placement of EUS-guided fiducial markers without the use of fluoroscopy, suggesting that fluoroscopy can be used if available but is not considered essential for safe and successful EUS-guided fiducial placement [6, 7, 9, 18]. In addition, a recent retrospective study by Majumder et al. found that achieving ideal fiducial geometry may be unnecessary for successful tracking and delivery of radiation in patients with pancreatic cancer [19].

Esophageal Cancer

Radiotherapy plays an important role in esophageal cancer as many patients also present with advanced stage disease [28]. Several studies have specifically evaluated EUS-guided fiducial placement in patients with esophageal cancer and have shown favorable results with high technical success [6, 7, 9, 11].

Fiducials can be placed proximal and distal to the tumor and provide accurate delineation of the extent of the lesion (Fig. 10.6) [6, 7, 11].

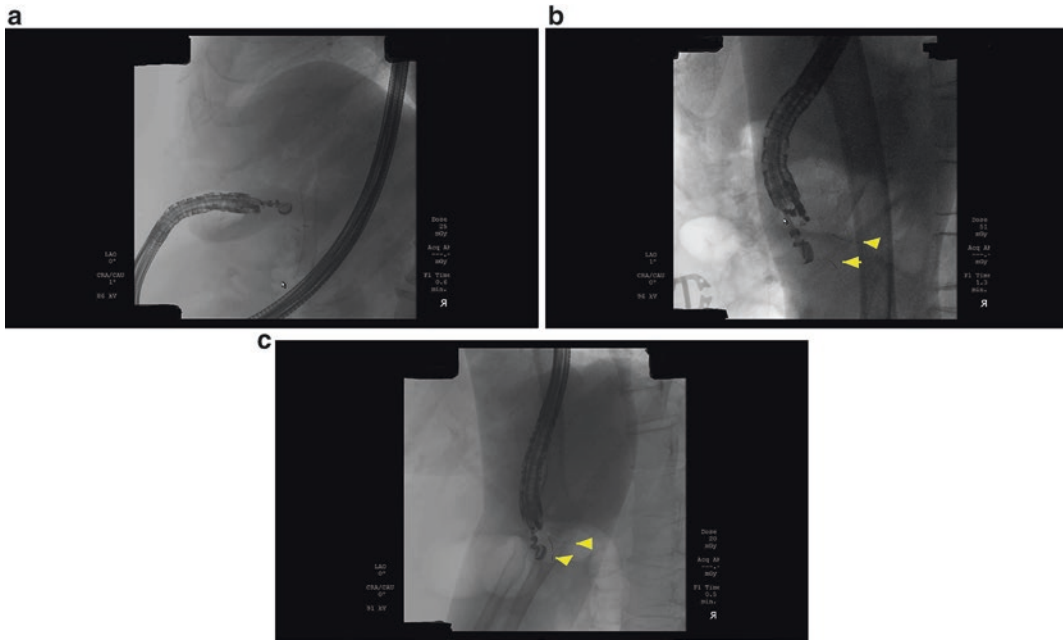

Fig. 10.5 Fluoroscopic image of fiducials placed within the: (**a**) pancreatic head, (**b**) uncinate process of the pancreas, and (**c**) pancreatic body

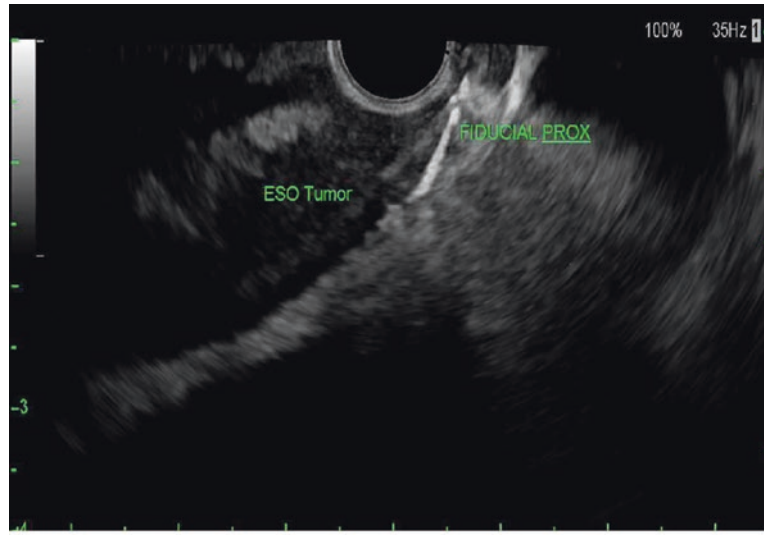

Fig. 10.6 Endosonographic imaging of a hyperechoic fiducial placed just proximal to an esophageal mass

In approximately one-third of cases, a single fiducial marker was placed given that the tumor was obstructing and prevented passage of the echoendoscope [6, 7]. Most studies have described securing the fiducial into the submucosa or muscularis propria adjacent to the tumor, instead of into the tumor itself, to theoretically reduce migration rates especially after tumor regression from treatment (Fig. 10.7) [6, 7, 11].

DiMaio et al. assessed EUS-guided fiducial placement (Visicoil 0.35 mm × 10 mm) using a 22-gauge needle in 12 patients with esophageal tumors; all were technically feasible except for one in which the lesion could not be identified

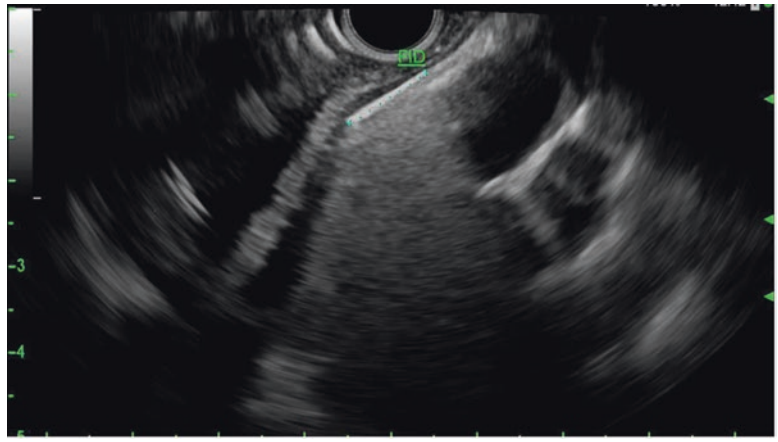

Fig. 10.7 Endosonographic image of a hyperechoic fiducial clearly placed within the muscularis propria proximal to a distal esophageal mass

[9]. Fernandez and colleagues reported a retrospective series of 60 patients with esophageal cancer who underwent EUS-guided fiducials. In the majority of patients, Visicoil fiducial markers (0.75 mm × 10 mm) were placed with a 19-gauge needle, and in a few patients, the smaller diameter (0.35 mm × 10 mm) fiducials were used. A total of 105 markers were placed, 33% had a single fiducial marker, 58% had two fiducial markers, and 8% had three fiducial markers inserted proximal and distal to the lesion if possible. The investigators concluded that implantation of fiducials for esophageal cancer was feasible, allowed for more confident target delineation, and improved assessment of respiratory tumor motion on CT simulation [6]. Another retrospective study involved 207 patients with esophageal cancer in which 348 fiducials were inserted. The 0.75 mm × 10 mm Visicoil fiducial marker was used in 91% of patients using a 19-gauge needle. In addition, there were 33 patients with gastroesophageal junction tumors, of which 64% had two fiducials placed and 36.4% of patients had one fiducial placed. These patients successfully underwent radiation therapy with no significant complications related to fiducial placement [7]. A recent retrospective analysis showed the placement of fiducial markers coupled with 3D PET/CT aided in planning tumor volume, specifically along the inferior border of the tumor, and offered more accurate radiation treatment delivery for locally advanced esophageal cancer [29].

Rectal Cancer

Two studies have evaluated the role of EUS-guided fiducial placement in rectal cancer. The first report described EUS-guided fiducial placement used in the management of rectal cancer with high-dose rate endorectal brachytherapy. In this study, 11 patients underwent EUS-guided placement of two different types of gold fiducials. All fiducials were placed at the superior and inferior extents as well as in the center of the tumor, and the mean number of fiducials placed per patient was 3.6. All fiducials, regardless of type, were clearly visible, and all 11 patients underwent IGRT with subsequent successful resection [14]. In a subsequent study, 54 patients with rectal cancer had 103 fiducials inserted, 70% fiducials were placed at both the proximal and distal margins, 16.6% at the proximal margin only, and 13.1% at the distal margin only. Minimal complications were reported with mild bleeding occurring in one patient [7]. Figure 10.8 demonstrates an endoscopic image of a rectal cancer and CT performed 1 month later with fiducials remaining visible at site of rectal tumor.

Other Sites

Several studies have described the feasibility and technical success of EUS-guided fiducial placement in a variety of other malignancies including prostate cancer [30], gastric cancer [20], anal

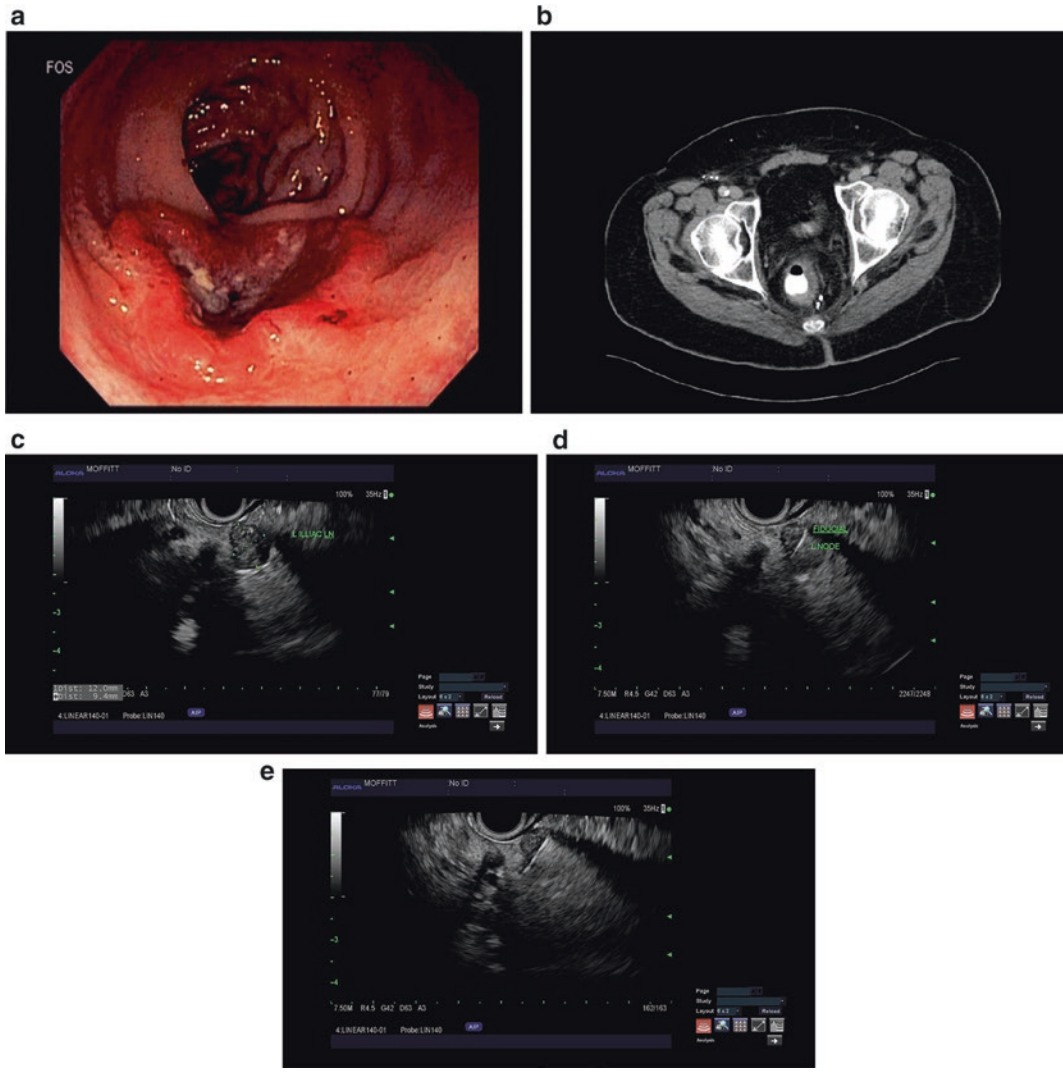

Fig. 10.8 (**a**) Endoscopic image of rectal cancer along the posterior wall of the rectum, (**b**) CT scan confirming the placement of multiple fiducial at the proximal margin of the rectal tumor. (**c**) EUS image of a peritumoral malignant left iliac lymph node near known rectal cancer. (**d**) Fiducial needle inserted in a transrectal manner into the malignant node. (**e**) Fiducials after deployment into the malignant node

cancer [7], cholangiocarcinoma [4, 9], and metastatic lesions in the abdomen, liver, or mediastinum (Fig. 10.9) [4, 7, 12, 18].

Durability of Fiducial Placement

In regard to fiducial placement and feasibility as stated above, high rates of technical success ranging from 85 to 100% have been reported. In addition, most studies have reported that over 90% of patients with successfully placed EUS-guided fiducials completed radiation therapy [6–8, 13, 16, 18]. However, data on long-term outcomes in fiducial placement are limited and have not been clearly defined. In addition, studies assessing improved overall survival with fiducials are lacking. Various endpoints that have been evaluated include the presence of markers at simulation CT scan, visibility during treatment period, and

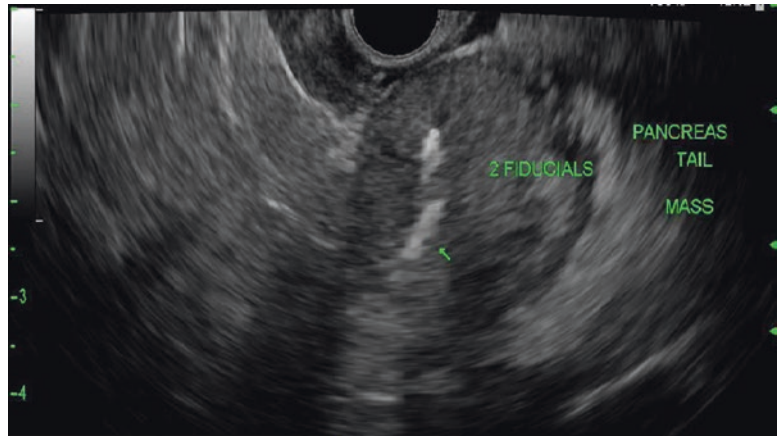

Fig. 10.9 Endosonographic image of two hyperechoic fiducials placed within a metastatic pancreatic tail mass

migration rates. Figure 10.10 demonstrates visibility of fiducials on CT scan and PET-CT.

DiMaio et al. evaluated fiducial placement in 30 patients with various GI malignancies and fiducials were identified in 83% of patients at the time of CT simulation for radiation therapy [9]. Fernandez and colleagues investigated long-term stability of fiducial placement in the setting of esophageal cancer. In their study, 105 Visicoil markers were placed; 94% of markers were still present at CT simulation, and 88% were still present in their initial position at a median time of 107 days. In patients who did not undergo surgery, 90% of fiducials were visible at a median time of 165 days following implantation [6]. Machiels et al. reported in a small prospective study that 63% of solid gold markers and 80% of Visicoil markers placed in esophageal tumors remained visible during the treatment period. In a subgroup analysis, 91% of Visicoil markers ≥5 mm in length were visible at the end of their treatment period. Most markers that lost visibility were related to detachment and small size, and rarely related to migration [11]. Dhadham et al. also reported a low fiducial migration rate of 0.4% evaluated during IGRT in 207 patients with locally advanced esophageal cancer [7].

Adverse Events

EUS-guided fiducial placement is safe with a low reported adverse event rate between 1 and 5%. Common adverse events were self-limited and include fever, cholangitis, mild acute pancreatitis, minor bleeding, and post procedure abdominal pain. Rare cases of pneumothorax, mediastinitis, and intramural duodenal hematoma have also been reported [11, 31].

Fiducial migration rates have been measured on simulation exams and during therapy and have ranged from 0.4 to 9.5%. There was one report of migration of a fiducial into the lung in a patient with esophageal cancer, although the patient remained asymptomatic [11].

The use of prophylactic antibiotics for EUS-guided fiducial placement is debatable and multiple studies have used them in their protocol [4, 10, 13, 15, 16]. Infectious complications rates were not increased in other studies that did not routinely give antibiotics [7, 8]. There are no prospective data on this topic, and based on the current literature, there is no firm evidence to support the routine use of antibiotics during EUS-guided fiducial placement.

Conclusion

EUS-guided fiducial placement is a safe, effective technique to enhance IGRT and provides precise targeted radiation while limiting dosage to normal surrounding tissue. EUS may be the preferred approach as diagnosis, staging, and therapeutic interventions can be performed in the same session and expedite treatment. Many studies have investigated EUS-guided fiducial placement in pancreatic tumors, but there is

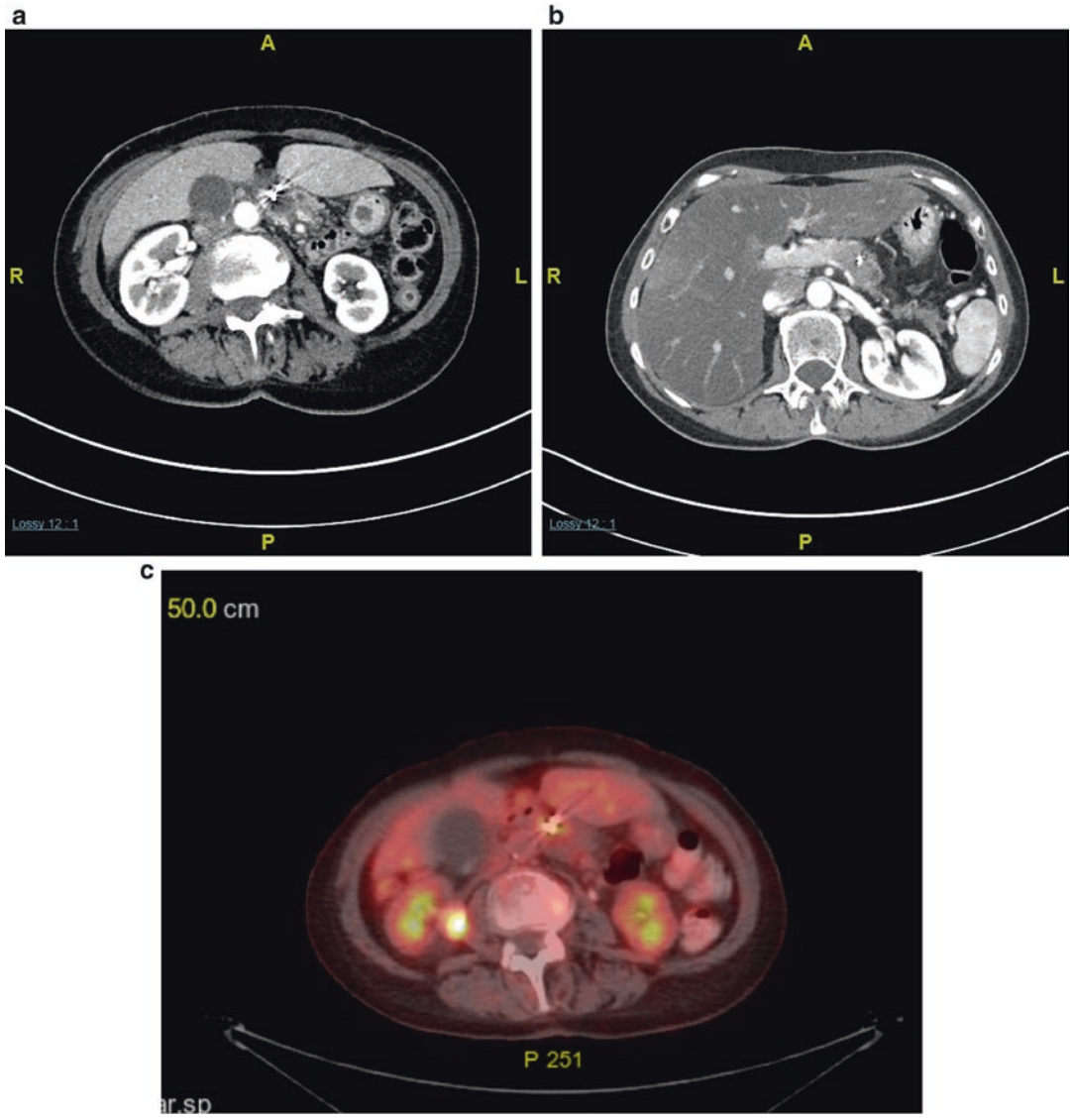

Fig. 10.10 Fiducial markers seen on: (**a**) CT scan within the pancreatic head, (**b**) CT scan within the pancreatic body, and (**c**) PET-CT within the pancreatic head

increasing evidence for its use in other GI malignancies including esophageal, gastric, rectal, anal, and hepatobiliary cancers. As described in this chapter, the technique and feasibility for EUS-guided fiducial placement has been well delineated in the current literature with high technical success. More prospective studies are needed to assess the short- and long-term clinical impact of fiducial placement on IGRT, and to help further guide the endoscopist in choosing the correct size, number, and type of fiducial/needle to use in specific malignancies.

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