Background and study aims: Endoscopic ultrasound (EUS)-guided fiducial marker placement for image-guided radiation treatment (IGRT) is becoming more widespread. Most case series report the procedure performed using fluoroscopy for spatial geometry although the benefits of this are unclear. The aim of our study is to report the technical feasibility, safety, and migration rate of fiducial marker placement in a large cohort of patients with gastrointestinal malignancies who underwent EUS-guided fiducial marker placement for IGRT without fluoroscopy.

Patients and methods: A retrospective chart review was performed on all patients referred for EUS-guided fiducial marker placement from 08/1/07 to 7/31/14 at Moffitt Cancer Center.

Results: During the study period, 514 patients underwent placement of 1093 fiducial markers under EUS-guidance. Two hundred and forty patients with esophageal/gastro-esophageal junction cancer had 405 fiducials placed. In 188 patients with pancreatic ancer, 510 fiducials were placed. In 54 patients with rectal cancer, 103 fiducials were placed and 32 patients had 75 fiducials placed into other gastrointestinal tract lesions. Minor bleeding, which resolved spontaneously, occurred in two patients. Technical difficulty in placing fiducials was noted in 18 patients. Intraprocedural fiducial migration was noted in two patients and only 2/1093 fiducials (.002%) in two esophageal patients migrated as noted on simulation computed tomography scan.

Conclusions: EUS-guided fiducial marker placement without fluoroscopy is technically feasible and safe. There were minimal intraprocedure/post-procedure complications. Imaging at the time of simulation also revealed the migration rate to be extremely low. These results may allow for more widespread adoption of EUS-guided fiducial marker placement.

Introduction

Image-guided radiation therapy (IGRT) for the treatment of gastrointestinal cancers is enhanced by fiducial markers placed for tumor localization, which allows for precise targeting of the tumor, taking into account the respiratory motion of the target lesion during radiation therapy [1]. This technique minimizes toxicity to adjacent organs. Until recently, fiducial marker placement was performed either intraoperatively, percutaneously or via the computed tomography (CT)-guided approach [2]. With the evolution of intervention-al EUS, EUS-guided placement of fiducial markers for esophageal, pancreatic, and rectal malignancies is increasing in popularity [1,3]. Most of the current published literature on this technique describes performing the procedure with the aid of fluoroscopy to improve the spatial geometry of fiducials placed but the benefits of this are unclear. At our center we routinely place EUS-guided fiducials without the aid of fluoroscopy. There are also limited published data on the technical feasibility, safety, and migration rate of EUS-guided fiducial placement. Studies have addressed the placement of fiducials using different size needles and in different abdominal and mediastinal locations in a limited number of patients [3–6]. Only one recent study has reported on the technical feasibility and stability of fiducial markers that were placed under EUS guidance alone for pancreatic and hepatic malignancies, but in a limited number of patients [3]. Assessment of the feasibility and complications using this technique is limited in the literature. With increasing demand for this procedure, further knowledge is needed on different techniques for performing the procedure and their associated adverse event and migration rates. We thus set out to review and report our center’s experience with EUS-guided fiducial marker placement without the aid of fluoroscopy.
Patients and methods

Patients
We retrospectively reviewed an institutional review board (IRB)-approved database (University of South Florida IRB #Pro00019208) of all patients who had undergone EUS-guided fiducials for gastrointestinal malignancies. Patient characteristics, including, age, gender, date of fiducial placement, number and size of fiducials placed, size of needle used, technical feasibility in placing fiducials, type of gastrointestinal malignancy, complications, and stability of EUS-guided fiducial placement for IGRT in the last 7 years (August 1, 2007 – July 31, 2014) were obtained. Baseline patient characteristics are summarized in Table 1.

EUS-guided fiducial placement
All patients underwent EUS with a linear-array echoendoscope (GF-UC140P-ALS; Olympus America, Center Valley, PA) under propofol-administered monitored anesthesia. For the majority of patients, a 19-gauge or 22-gauge EUS-FNA needle (Cook Endoscopy, Winston Salem, NC) was used for fiducial placement. After withdrawing the stylet, 7 to 8 mm from the needle, a gold cylindrical fiducial marker measuring 0.75 × 10 mm or 0.35 × 10 mm (Visicoil, RadioMed, Inc, Tingsboro, MA) was back loaded into the 19-gauge or 22-gauge needle tip, respectively, by using sterile forceps and then sealed into place with sterile bone wax. The needle was then advanced via the operating channel of the echoendoscope without losing the fiducial. Once a safe insertion window away from blood vessels was identified on doppler echoendoscopy, the needle was then inserted into the target area under EUS guidance. Upon needle insertion into or adjacent to the target lesion, the fiducial was deployed by simultaneously retracting the needle while advancing the tool. The needle was then withdrawn from the echoendoscope and reloaded with a new fiducial, and the technique repeated until the desired number of markers had been placed. All fiducials were inserted under EUS guidance alone; fluoroscopy was not used. All endoscopy procedure reports, post-procedure orders, 24-hour post-procedure telephone notes, and all electronic medical record entries occurring in the 4 weeks after fiducial placement were reviewed to determine if any early (defined as within 72 hours) or late (72 hours to 30 days post-procedure) complications related to fiducial placement occurred.

Timing of fiducial marker placement
For patients with esophageal and rectal cancers, fiducial markers were placed at the time of initial EUS staging. For pancreatic cancer, all patients at our institution were treated initially with systemic chemotherapy. We did not place the fiducial markers upfront at the time of initial staging and fine-needle aspiration because not all of those patients were candidates for local therapy after chemotherapy. If, after systemic chemotherapy, there was no evidence of progression, the patients were considered for radiation. We performed endoscopic ultrasound evaluation at that time point to reassess the response to therapy and to place fiducial markers. We believe that this strategy prevents unnecessary fiducial marker placement in patients who have evidence of disease progression and will not receive local radiation therapy.

Results
A total of 514 patients underwent placement of 1093 fiducials under EUS guidance during the study period. Fiducial placement was unsuccessful in only a single patient with pancreatic cancer because intervening blood vessels precluded safe advancement of the fiducials into the mass. In subgroup analysis there was no statistical difference between the 19-gauge and 22-gauge needle placement of fiducials with respect to adverse events or fiducial migration. The location, number of fiducials placed, technical difficulty, and rates of migration and adverse events are summarized in Table 2.

Esophageal cancer
Two hundred and seven patients with esophageal cancer had a total of 348 fiducials inserted. A 19-gauge needle back loaded with a 0.75 × 10 mm Visicoil gold fiducial marker was used in the majority of patients (n=188 [90.8%]); while a 22-gauge needle back loaded with a 0.35 × 10 mm fiducial was used in 11 patients (5.3%). In a small number of patients (5), a 25-gauge needle back loaded with a 0.35 × 10 mm fiducial was used. Both a 19- and 22-gauge needle were used in one (0.5%) and the gauge was unknown in two (1%). Fiducials could be inserted proximal and distal to the tumor in 112 patients, whereas only proximal fiducials could be placed in 82 patients (due to luminal obstruction) and only distal fiducial placement was possible in one patient. In a small subset of patients (12), the fiducial was placed into the bulk of the tumor due to inability to place a marker at the proximal or distal margin of the tumor. Eight fiducials in eight patients were inserted in the superficial muscularis layer as noted endoscopically, necessitating repeat placement of fiducials into the muscularis propria layer during the same procedure. Only two fiducials in two patients migrated as noted during IGRT. One patient had post-procedure bleeding which was not related to fiducial placement but was due to migration of an esophageal stent that was placed at the time of fiducial placement.

Gastroesophageal junction cancer
Thirty-three patients with gastroesophageal junction (GEJ) tumors had 57 (5.2%) fiducials placed. Fiducials were placed at both the proximal and distal margins of the tumor in 21 patients (63.6%) and in 12 patients (36.4%) only one fiducial was directly placed proximal to the tumor due to inability to traverse the tumor with the echoendoscope.
Table 2  Results.

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Patients</th>
<th>No. fiducials placed</th>
<th>Technical difficulty (no. of cases)</th>
<th>Technical success (%)</th>
<th>Fiducial migration (no. of cases)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal</td>
<td>207</td>
<td>348 (32 %)</td>
<td>8 (1.5%) placed into superficial layers repeated to place into muscularis layer</td>
<td>207 (100 %)</td>
<td>2 (0.4%) noted during planning CT scan.</td>
<td>0</td>
</tr>
<tr>
<td>GE junction</td>
<td>33</td>
<td>57 (5.3 %)</td>
<td>0</td>
<td>33 (100 %)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>188</td>
<td>510 (46.7 %)</td>
<td>16 (3 %) due to intervening vessels</td>
<td>187 (99.5 %)</td>
<td>No fiducials placed due to intervening blood vessels in one.</td>
<td>1 minor^ bleeding</td>
</tr>
<tr>
<td>Rectal</td>
<td>54</td>
<td>103 (9.3 %)</td>
<td>1 (0.2 %)</td>
<td>54 (100 %)</td>
<td>0</td>
<td>1 minor^ bleeding</td>
</tr>
<tr>
<td>Others</td>
<td>32</td>
<td>75 (6.7 %)</td>
<td>2 (0.4 %) fiducials slipped out 1 (0.2 %) needle changed from 19 to 22 gauge</td>
<td>32 (100 %)</td>
<td>2 (0.4 %) needle changed from 22 to 19 gauge</td>
<td>1 minor^ bleeding</td>
</tr>
<tr>
<td>Total</td>
<td>514</td>
<td>1093</td>
<td>29 (5.6 %)</td>
<td>513 (99.8 %)</td>
<td>7 (1.4 %)</td>
<td>9 (1.8 %)</td>
</tr>
</tbody>
</table>

No., number CT, computed tomography

^ Spontaneously resolved bleeding

Pancreatic cancer

One hundred and eighty-eight patients with pancreatic cancer had 510 (46.7 %) fiducials placed. A 22-gauge needle was used to place 414 (81.2 %) 0.35 × 10 mm fiducials in 150 patients (80 %), a 19-gauge needle was used to place 93 (18.2 %) 0.75 × 10 mm fiducials in 37 patients (19.7 %), and 3 (0.6 %) fiducials, size unknown, were placed in one patient (0.3 %). Technical difficulty due to intervening blood vessels was noted in 16 patients (3.1 %). Minor bleeding that resolved spontaneously was noted in seven patients (1.3 %). Intraprocedural fiducial migration was noted in two patients (0.4 %). The EUS needle was changed from 22- to 19-gauge in two patients (0.4 %). Unraveling of the fiducial occurred after deployment into the lesion in one patient (0.1 %).

Rectal cancer

Fifty-four patients with rectal cancer had 103 (9.3 %) fiducials inserted. In 38 patients (70.3 %), fiducials were placed at both the proximal and distal margins of the lesion, nine (16.6 %) at the proximal margin only, and seven (13.1 %) at the distal margin only. A small amount of bleeding was noted which resolved spontaneously in one patient (0.2 %). Technical difficulty was also noted only in one patient (0.1 %).

Other lesions

In 32 patients, 75 fiducials were put into a variety of targets including peripancreatic and pancreatic metastatic lesions (8), mediastinal lymph nodes (6), metastatic liver lesions (6), anal canal cancers (3) and porta hepatitis lymph nodes (2). Technical difficulty was noted in placing fiducials into a liver lesion in one patient (0.1 %). Two fiducials slipped while they during placement into the gastrohepatic ligament and porta hepatitis lymph node. There was small self-limited bleeding noted in one patient (0.1 %) in which a fiducial was placed into a subcarinal lymph node.

Discussion

EUS-guided fiducial marker placement is becoming more widespread as more radiation oncologists are requesting placement prior to initiating IGRT. This large retrospective series clearly demonstrates that EUS-guided fiducial marker placement is safe, technically feasible, and, in addition, does not require the use of fluoroscopy. Several other groups have reported on techniques and success rates for EUS-guided fiducial marker implantation for various malignancies including pancreatic cancers [2, 3, 5–8], mediastinal cancers [4, 9], prostate cancer [10], cholangiocarcinoma [4], esophageal cancers [6, 11], gastric cancers [12] and metastases from a variety of primary cancers [4, 10]. Few of these reports, though, have focused on the technical aspects of EUS-guided fiducial implantation using different size needles and techniques of EUS-guided fiducial placement [13–16], and all the prior studies had fewer than 100 study patients (Table 3).

In our study, we describe fiducial marker placement in many different targets using different gauge needles and fiducial marker sizes. Minimal data or only case reports have been published regarding some of these target areas. As mentioned earlier, EUS-guided fiducial placement was possible in both proximal and distal aspects of rectal tumors in 70.3 % of cases. Our study is only the second one to report EUS-guided fiducial placement in rectal tumors, the first being reported by Moningi et al [17] albeit with only 11 patients. We also noted that in the majority of our esophageal malignancies (90.8 %), a 19-gauge needle was used for placing the 0.75 × 10 mm fiducials, which was in accordance with the study by Kashab et al [16]. However, a 22-gauge needle back loaded with 0.35 × 10 mm fiducials was used in the majority of primary pancreatic lesions (80 %) at our center. This was the preference of the endoscopists because of our experience with technical difficulty in using the 19-gauge needle in the duodenal bulb and second portion of the duodenum. This is in contrast to the majority of the prior studies published where a 19-gauge needle was used for pancreatic lesions [3, 5, 7–9, 16].

With regard to technical success rates, in current published series they have varied between 85 % to 100 % [4–9, 14, 16]. In our series of 514 patients, our success rate was 99.8 %, suggesting that EUS-guided fiducial placement in various gastrointestinal malignancies can be performed routinely with a high success rate. Although many centers and most published series report the use of fluoroscopy to aid in EUS-guided fiducial marker placement to improve the spatial geometry of the fiducials being placed, it is unclear whether using fluoroscopy for this purpose has any impact on the clinical success rate of IGRT in these patients. In a study by Majumder et al [18] they found that achieving Ideal Fi-
findings. We also note our center number of patients and longer-term follow-up to confirm these associated higher toxicity. Whether this translates into im-
the 28 patients who received 56Gy using fiducial markers with-
patients who received 50.4 Gy compared with a 60.7% pCR rate in city. In this retrospective study, the pCR rate was 30.2% in the 43
ducial markers to 56 Gy doubles the pCR without increasing toxi-
tion at the national ASTRO meeting in 2012 [19], we demonstrat-
personalized motion management and daily IGRT. In a presenta-
study, we do have some data on esophageal cancer fiducial reten-
occurred within 48 hours after placement. Although we do not
only 0.4 % and in the majority of patients in this series, migrate occurred within 48 hours after placement. Although we do not
have long-term fiducial retention rates on all the patients in this study, we do have some data on esophageal cancer fiducial reten-
tion that our group reported in 2013 [23]. We published our ex-
perience in 60 patients with 105 fiducials for esophageal/GEJ cancers and confirmed stability, with 88% still present on the post-treatment imaging films at a median of 107 days. This high retention rate, we feel, is mainly due to the placement of the fiducials into the muscularis propria next to the tumor instead of into the tumor itself. This avoids the potential for migration if the tu-
our center defines the gross tumor volume (GTV) and then an elective clinical target volume (CTV) [21]. Placement of the fiducial marker in the center of the tumor allowed us to correlate the length of the tumor with the endoscopic report and then measure the respiratory-associated target motion and ensure that the fiducial was encompassed in the region of interest every day as part of the IGRT. There would not be any difference in dose because the inferior CTV expansion is 3 to 5cm below the inferior extent of GTV. Our radiation oncologists correlate the EUS report with the positron emission tomography/CT report and any intra-
venous contrast CT scan to ensure that all sites of disease (including lymph nodes) are encompassed within the target volume. For patients with esophageal cancer who receive only one fiducial, this is helpful for identification of motion management strategies to personalize the simulation parameters and for daily IGRT if we are dose-escalating the primary tumor. For example, at our insti-
tution, we dose-escalate the region demarcated as the gross tumor volume by the fiducial markers to 56 Gy in 28 fractions while the remainder of the elective adjacent volume receives 50.4 in 28 fractions. Aligning the image generated on the treat-
ment machine to the fiducial marker allows us to reliably treat the highest risk area every day and avoids potential underdosage issues [22].

Table 3 Summary of all studies on Endoscopic Ultrasonography-Guided Fiducial Placement in Gastrointestinal Malignancies including the current study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>No. of cases</th>
<th>Needle used, gauge</th>
<th>Type of fiducials (length, diameter, mm)</th>
<th>Technical success (%)</th>
<th>Adverse events related to fiducial placement (no. of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pishvaian et al (2006)</td>
<td>P</td>
<td>13</td>
<td>19</td>
<td>Gold (3 or 5 × 0.8)</td>
<td>11 (85)</td>
<td>Cholangitis (1)</td>
</tr>
<tr>
<td>Varadaraju et al (2010)</td>
<td>R</td>
<td>9</td>
<td>19</td>
<td>Gold (5 × 0.8)</td>
<td>9 (100)</td>
<td>None</td>
</tr>
<tr>
<td>Park et al (2010)</td>
<td>P</td>
<td>57</td>
<td>19</td>
<td>Visicoil (2.5 × 0.8)</td>
<td>56 (98)</td>
<td>Minor bleeding (1)</td>
</tr>
<tr>
<td>Sanders et al (2010)</td>
<td>P</td>
<td>51</td>
<td>19</td>
<td>Gold (5 × 0.8)</td>
<td>46 (90)</td>
<td>Mild pancreatitis (1)</td>
</tr>
<tr>
<td>DiMaio et al (2010)</td>
<td>R</td>
<td>30</td>
<td>22</td>
<td>Visicoil (10 × 0.35)</td>
<td>29 (97)</td>
<td>Fever (1)</td>
</tr>
<tr>
<td>Ammar et al (2010)</td>
<td>C</td>
<td>13</td>
<td>22</td>
<td>Visicoil (10 × 0.35)</td>
<td>13 (100)</td>
<td>None</td>
</tr>
<tr>
<td>Khasab et al (2012)</td>
<td>R</td>
<td>29</td>
<td>19</td>
<td>Gold (5 × 0.8)</td>
<td>39 (100)</td>
<td>None</td>
</tr>
<tr>
<td>Fernandez et al (2013)</td>
<td>R</td>
<td>60</td>
<td>19</td>
<td>Visicoil (10 × 0.75)</td>
<td>60 (100)</td>
<td>None</td>
</tr>
<tr>
<td>Choi et al (2014)</td>
<td>R</td>
<td>32</td>
<td>19</td>
<td>Gold (3 × 0.8)</td>
<td>32 (100)</td>
<td>Mild pancreatitis (1)</td>
</tr>
<tr>
<td>Chandran et al (2014)</td>
<td>P</td>
<td>8</td>
<td>19</td>
<td>Visicoil (10 × 0.35)</td>
<td>7 (88)</td>
<td>None</td>
</tr>
<tr>
<td>Moningi et al (2015)</td>
<td>P</td>
<td>11</td>
<td>19</td>
<td>Gold (5 × 0.8) and X-mark fiducials (10, 20, or 30 × 0.85)</td>
<td>11 (100)</td>
<td>None</td>
</tr>
<tr>
<td>Machiels et al (2015)</td>
<td>P</td>
<td>30</td>
<td>22</td>
<td>Visicoil (10 × 0.35)</td>
<td>30 (100%)</td>
<td>Pneumothorax (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cook Preloaded-Fiducial needle Hydrogel Marker</td>
<td></td>
<td>Mediastinitis (2)</td>
</tr>
<tr>
<td>Current study</td>
<td>R</td>
<td>514</td>
<td>19,22</td>
<td>Visicoil (10 × 0.35 or 0.75)</td>
<td>513 (99.8)</td>
<td>Minor bleeding (9)</td>
</tr>
</tbody>
</table>

P, prospective; R, retrospective; C, case series; No., number

mor shrinks or completely resolves and thus, the fiducial would just pass luminally. Although no major AE such as life-threatening bleeding or death were noted in any of the prior studies or in the current study, care must be employed when performing EUS-guided fiducial placement to avoid intervening blood vessels and to ensure placement into the proper target tissue. Limitations of this study include the retrospective nature. In addition, all procedures were performed by expert interventional endoscopists with a high volume of fiducial cases. Thus, our success rate and low AE rate may not be reproducible in the community setting.

**Conclusions**

This large retrospective study demonstrates that EUS-guided fiducial marker placement without the aid of fluoroscopy is technically safe and feasible in patients undergoing IGRT for various gastrointestinal malignancies. We expect that the indications and requests for EUS-guided fiducial marker placement will continue to increase in the future as fiducial markers allow radiation oncologists to more confidently demarcate the local extent of disease and to quantify the location of a tumor as it moves with respiration, thereby allowing dose escalation to the tumor. This improves the therapeutic ratio of higher dose to the target while not compromising normal tissue morbidity. The added knowledge that fiducials can be placed without fluoroscopy may allow for more widespread adoption of this technique in endoscopy settings where simultaneous EUS and fluoroscopy are not readily available.

**Competing interests:** None

**References**