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Endoscopic ultrasound-guided fiducial placement in pancreatic tumors: safety and technical feasibility

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ABSTRACT

Background and aims: stereotactic body radiation therapy (SBRT) for pancreatic malignancies requires the placement of fiducials to guide treatment delivery. The aim of this study was to assess the safety and feasibility of endoscopic ultrasound (EUS) guided fiducial placement using a 22-gauge needle, in patients with pancreatic cancer undergoing SBRT.

Methods: this single-center retrospective study included 47 patients with biopsy-proven advanced pancreatic cancer who underwent EUS-guided fiducial placement between February 2014 and February 2018. Primary outcome measurements included technical success, fiducial migration rate and procedural complications.

Results: all 47 patients received a sufficient number of fiducials and could therefore undergo a successful SBRT. The mean number of fiducials inserted per case was 2 ± 1 (range 1-3) and no fiducial migration was noted. The adverse event rate was 4.2%, as one patient developed mild pancreatitis and another patient required one week of
hospitalization one month after fiducial placement due to a duodenal abscess.

**Conclusions:** EUS-guided fiducial placement is a safe and technically feasible procedure in centers with endosonographers that are well trained in EUS with FNA.

**Key words:** Fiducial markers. Endoscopic ultrasound. Pancreatic tumors.

**INTRODUCTION**

Pancreatic cancer has a poor prognosis, with postoperative five-year survival rates ranging from 3% to 25%. Local recurrence develops within two years of surgery in two-thirds of patients with resectable tumors (1). The disease is often advanced at presentation and nearly 90% of patients have inoperable disease at the time of diagnosis. Chemotherapy, conventional radiation therapy (RT) or a combination of both may positively influence overall survival and quality of life in patients with locally advanced pancreatic adenocarcinoma (2). These treatments aim to downstage the tumor, improve local control and offer palliation. However, these treatment modalities have had a modest impact on the overall prognosis. Improvements in RT in recent years, such as stereotactic body RT (SBRT), have become possible due to advances in computed tomography (CT), magnetic resonance imaging and positron emission tomography. SBRT delivers multiple beams of radiation with extreme accuracy, allowing the safe and effective delivery of RT to target sites (3). SBRT allows for the delivery of high radiation doses while minimizing toxicity to normal adjacent tissues (4).

However, pancreatic cancer treatment with SBRT requires the placement of intratumoral radiographic markers (fiducials) to allow image-guided RT, considering respiratory and other involuntary movements of the target lesion. SBRT requires the presence of multiple reference points or markers through which the tumor can be identified and tracked. Recent publications support the use of intratumoral pancreatic markers for improved targeting in IGRT for pancreatic cancer (5,6). Fiducial markers serve as reference points for the simultaneous correction of target motion. Fiducial markers are radiopaque spheres, coils or cylindricals that are implanted inside or adjacent to the tumor. Before the development of endoscopic ultrasound (EUS)
interventional procedures, fiducial pancreatic markers were placed either intraoperatively or percutaneously under ultrasound or CT guidance (7). With the development of the linear array echoendoscope and EUS fine-needle aspiration (FNA), EUS has become not only a diagnostic procedure but also an important interventional procedure. The aim of this study was to assess the safety and feasibility of EUS-guided fiducial placement using a 22-gauge needle in patients with pancreatic cancer undergoing SBRT.

METHODS
Patients
This was a single-center retrospective study of 47 patients referred for EUS-guided fiducial placement, between February 2014 and February 2018. The patients had biopsy-confirmed malignant tumors of the pancreas. All the tumors were locally advanced and unresectable and thus, were appropriate candidates for SBRT. Patient characteristics, including age, gender, needle size, number of fiducials placed, technical feasibility, migration of the fiducial and other complications were collected. This study was approved by the Ethics Committee of the Hospital HM Sanchinarro and informed patient consent was obtained before each procedure.

Materials
Gold fiducial markers (Visicoil™ gold fiducial marker, IBA) measuring 10 mm in length and 0.35 mm in diameter were implanted in all patients. Unlike traditional cylindrical gold seed fiducials, the gold coil fiducials are flexible and their coil design may reduce the incidence of fiducial migration. The gold coil fiducial comes preloaded on a needle carrier delivery device that allows direct insertion into the tip of the needle (Fig. 1).

EUS technique
Patients underwent EUS with a linear-array echoendoscope (Pentax EG3870), under deep sedation by an anesthesiologist. A 22-gauge needle (Boston Expect) was back-loaded with one fiducial marker, using a sterile technique. The stylet of the EUS needle was withdrawn by around 2-3 cm. The fiducial-loaded needle carrier device was
inserted into the tip of the EUS needle. The needle carrier was withdrawn from the device while holding the other trocar of the delivery device, which effectively deploys the fiducial into the distal tip of the EUS needle. Finally, the needle tip was sealed with sterile bone wax to prevent loosening of the fiducial during the advancement of the needle down the accessory channel of the scope. Once the target lesion was localized, color Doppler imaging was performed to identify any intervening vascular structures. When a safe window was identified, the EUS needle was inserted into the target lesion under EUS guidance. The fiducial was deployed by the simultaneous retraction of the needle and advancement of the stylet. The EUS needle was then withdrawn from the echoendoscope and reloaded with a new fiducial. The technique was repeated until the desired number of markers were placed. All fiducials were implanted under EUS guidance alone, without fluoroscopy (Fig. 2). The preferred target location for fiducial placement was inside the tumor and the fiducial was only delivered near to the neoplasm in the case of an unsafe window. The optimal number of fiducials for adequate IGRT is still unclear. However, based on the experience of our radiotherapeutic oncologists, we agreed to place two fiducials in each patient.

**Periprocedural care**

Patients were monitored in a recovery area for approximately 30 minutes after the procedure and were assessed by a physician for pain and fever. All patients received prophylactic antibiotics before the procedure and oral prophylaxis for five days after the EUS. Complications within 30 days of the procedure were assessed via a review of the medical record. In addition to clinical complications, any technical complications related to the procedure were also reported.

**Outcome measures**

Technical success was defined as the ability to implant one or more fiducials in the tumor area. Technical difficulty was defined as cumbersome loading or unloading of a fiducial. Clinical success was defined as the possibility of SBRT using the fiducials. Complete migration was defined as non-visualization of the fiducial on the reference scan or the disappearance of a previously visualized fiducial on any of the subsequent
CT scans. The following adverse events were considered to be procedure-related: pancreatitis, clinically relevant upper gastrointestinal bleeding, abscesses in the area of the fiducials and bacteremia or sepsis.

RESULTS
Forty-seven patients with locally advanced biopsy-proven malignant tumors of the pancreas were referred for EUS-guided gold fiducial insertion. Patient and tumor characteristics are summarized in table 1. Twenty patients were male (43%) and 27 were female (59%) and the mean age was 66.8 (range 47-87) years. Twenty-nine (61%) tumors were located in the head and neck of the pancreas, which represented the most common location for fiducial insertion. This was followed by eleven (24%) tumors in the body of the pancreas, five in the uncinate process (11%) and two (4%) in the tail. The mean size of the tumors was 2.7 (range 1.3-6.2) cm.

EUS technique
All procedures were performed by two expert endoscopists, who perform 600 EUS per year. A total of 3,186 EUS were performed between 2014 and 2018, including upper and lower EUS (Table 2). The total EUS per year and the number of fiducial placements are summarized in figure 3, showing how both procedures have been increasingly used over time.

Outcome measures
Technical success
A total of 92 fiducials were placed and one or more fiducials were implanted in the tumor area. The mean number of gold fiducials inserted by EUS per case was 2 ± 1 (range 1-3). Almost all of the patients (46 of 47) had two fiducials implanted and only one patient had three fiducials due to an elongated tumor shape, which was a concern for the radiation oncologists.

Technical difficulty
The second case had only one fiducial placed due to the inability to load the needle twice. Technical difficulty was encountered in nine patients, although successful fiducial placement was still achieved in all of these cases. The difficulty was related to changes in tumor endosonographic characteristics after chemotherapy in three patients, where a solid lesion changed to a cystic appearance. Thus, fiducials could not be implanted inside the tumor and were placed in the pancreatic parenchyma next to the lesion. Similarly, the target lesion in the pancreatic head could not be satisfactorily visualized in three patients after chemotherapy, due to a significant improvement after systemic chemotherapy. Thus, the two fiducials where the tumor was described previously remained. Finally, technical difficulty due to intervening blood vessels was noted in three patients. Thus, fiducials were placed in the pancreatic parenchyma near to the target lesion. The duration of the procedure was similar to an average EUS procedure with FNA.

**Adverse events**

No intra-procedural or delayed complications were encountered, except in two patients. The first presented with fever and abdominal pain one month after fiducial placement. A duodenal abscess was noted on CT scan and the patient was admitted for one week. No drainage was required as it was a small fluid collection and the patient responded well to intravenous antibiotic therapy. The SBRT was completed a few days before this complication. Thus, it was unclear whether this complication was related to RT or the endoscopic procedure that was performed four weeks earlier. The second patient had epigastric pain that lasted 24 hours, with a mild elevation of pancreatic enzymes related to mild pancreatitis the day after EUS was performed.

**Clinical success**

Fiducials were used for SBRT in all patients and no fiducial migration was noted during the procedure (Fig. 4).

**DISCUSSION**
SBRT is a novel technique (4) that takes advantage of the technological advances in image guidance and direct high dose radiation delivery to pancreatic tumors with an acceptable toxicity, which cannot be achieved with conventional RT techniques. Pancreatic cancer SBRT requires a high degree of confidence regarding tumor location, which can be provided by EUS-guided fiducial placement. Our study showed the technical feasibility and safety of EUS-guided fiducial placement in patients with malignant pancreatic tumors using a 22-gauge needle. To our knowledge, this is the first study published in our country focusing on this subject. All patients received a sufficient number of fiducials and could therefore undergo a successful SBRT. The technical success rate of 100% demonstrates the feasibility of this technique for endosonographers who perform FNA. This is in accordance with the literature, where technical success rates between 85% and 100% have been reported (8-12). As the study was retrospective, it should be noted that preferential candidates for EUS-guided fiducial placement may have been included, resulting in a high success rate.

The tumor was located at the head of the pancreas in most cases (61%), which is known to be more difficult to puncture, especially with a 19-gauge needle. Our technical success rate of 100% indicates an important advantage of the 22-gauge needle. Several published studies have studied the feasibility of EUS-guided fiducial placement using 19-gauge and 22-gauge needles. Five studies investigated the feasibility of EUS-guided fiducial placement using a 19-gauge FNA needle to deploy cylindrical gold seeds of 2.5 to 5 mm in length with a 0.8-mm diameter and reported a high success rate (8-10,13,14). Three studies showed the feasibility of EUS-guided fiducial placement using a 22-gauge FNA needle to deploy gold coil fiducials of 10 mm in length with a 0.35-mm diameter, offering potential advantages over the 19-gauge needle (11,12,15). Further prospective randomized studies are needed to evaluate the technical success and complication rates of EUS-guided fiducial placement using 19-gauge and 22-gauge needles. Based on the currently available evidence and our own experience, the 22-gauge needle seems to be the best choice for fiducial placement.

Different types of fiducials are available. These include traditional fiducials (TFs) of 5-mm length and 0.8-mm diameter, as well as Visicoil™ fiducials (VFs) of 10-mm length
by 0.35-mm diameter and 10-mm length by 0.75-mm diameter. TFs need a 19-gauge needle and VFVs can be used inside a 22-gauge needle. Unlike TFs, VFVs are flexible and have a coiled design, which theoretically reduces the incidence of fiducial migration. In addition, VFVs are preloaded on a needle carrier delivery device that allows the direct insertion of the fiducial into the EUS needle. Recently, a retrospective study compared TF (5-mm length, 0.8-mm diameter) and VF (10-mm length, 0.35-mm diameter) and there was no significant difference between the two types in terms of technical success, complications and migration (18). Our experience with the 22-gauge needle was satisfactory as no fiducial migration was noted. Furthermore, the tracking of the fiducials by the SBRT system was correct.

Procedure-related complications associated with fiducial placement include cholangitis, mild pancreatitis, fever or minor bleeding (4-8,13). Based on previous studies, the overall complication rate of EUS-guided fiducial placement in gastrointestinal malignancy ranges between 2 and 3% (Table 3). Therefore, our adverse event rate of 4.2% is similar to previously published reports. However, the relationship between fiducial placement and deferred duodenal abscess remains uncertain.

The optimal number of gold fiducials that should be inserted into the tumor by EUS for adequate SBRT is unclear. A recent study shows that ideal geometry might not be as important as previously assumed. Thus at least three fiducials with a minimum interfiducial distance of greater than 2 cm and a greater minimum inter-fiducial angle is needed (19). In practice, the precision of angulation and distance is not critical and measurement is not required, as long as the endoscopist places the fiducials in grossly disparate locations in the tumor or even adjacent to the target lesion. This is in agreement with the study by Fuccio et al. (20). The inter-fiducial distance was less than 2 cm and SBRT was still possible in most patients in the current study.

We did not encounter severe resistance while deploying the VFVs. Most difficulties were related to changes in tumor endosonographic characteristics after chemotherapy, which turned from a solid to a cystic appearance. It is important to remember that metallic stents placed in the common bile duct for tumors in the pancreatic head always make the procedure more challenging. In our experience, fluoroscopic
assistance was not necessary during fiducial placement. Fiducials placed were identified by EUS alone, thus allowing the immediate verification of proper placement. In conclusion, fiducial placement is a safe and technically feasible procedure in centers with endosonographers well trained in EUS with FNA. Fluoroscopy was unnecessary, a 22-gauge needle was used in all cases and complications rates were similar to those previously reported. However, technical aspects such as the appropriate number of fiducials and timing of the procedure require prospective studies for their clarification.

REFERENCES


Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>47</td>
</tr>
<tr>
<td>Number of fiducials</td>
<td>92</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>66.8 (43-87)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (43%)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (57%)</td>
</tr>
<tr>
<td>Pancreatic tumor location, n (%)</td>
<td></td>
</tr>
<tr>
<td>Uncinate process</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Head/neck</td>
<td>29 (61%)</td>
</tr>
<tr>
<td>Body</td>
<td>11 (24%)</td>
</tr>
<tr>
<td>Tail</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>
Table 2. Number of EUS and fiducials performed

<table>
<thead>
<tr>
<th>Year</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total EUS</td>
<td>862</td>
<td>697</td>
<td>798</td>
<td>829</td>
</tr>
<tr>
<td>Upper EUS</td>
<td>590</td>
<td>499</td>
<td>581</td>
<td>633</td>
</tr>
<tr>
<td>Upper with FNA</td>
<td>204</td>
<td>160</td>
<td>206</td>
<td>230</td>
</tr>
<tr>
<td>Fiducials</td>
<td>9</td>
<td>4</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>% Fiducials/FNA</td>
<td>4.4</td>
<td>2.5</td>
<td>4.3</td>
<td>6</td>
</tr>
<tr>
<td>Lower EUS</td>
<td>272</td>
<td>198</td>
<td>217</td>
<td>196</td>
</tr>
<tr>
<td>Lower with FNA</td>
<td>6</td>
<td>13</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

EUS: endoscopic ultrasound; FNA: fine-needle aspiration.
### Table 3. Summary of all studies on endoscopic ultrasonography-guided fiducial placement in gastrointestinal malignancies, including the current study

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Type of study</th>
<th>No. of cases</th>
<th>Needle gauge used</th>
<th>Type of fiducial (length x diameter, mm)</th>
<th>Technical success (%)</th>
<th>Adverse events (no. of patients)</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 x 0.8)</td>
<td>11 (85)</td>
<td>Cholangitis (1)</td>
</tr>
<tr>
<td>Varadarajulu et al. (2010)</td>
<td>R</td>
<td>9</td>
<td>19</td>
<td>Gold (5 x 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 x 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 x 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 x 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 x 0.35)</td>
<td>13 (100)</td>
<td>None</td>
</tr>
<tr>
<td>Khashab et al. (2012)</td>
<td>R</td>
<td>29</td>
<td>19</td>
<td>Gold (5 x 0.8)</td>
<td>39 (100)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>22</td>
<td>Visicoil (10 x 0.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernández et al. (2013) (16)</td>
<td>R</td>
<td>60</td>
<td>19</td>
<td>Visicoil (10 x 0.75)</td>
<td>60 (100)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td></td>
<td>Visicoil (10 x 0.35 or 10 x 0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choi et al. (2014)</td>
<td>R</td>
<td>32</td>
<td>19</td>
<td>Gold (3 x 0.8)</td>
<td>32 (100)</td>
<td>Mild pancreatitis</td>
</tr>
<tr>
<td>Davila Fajardo et al. (2014)</td>
<td></td>
<td>23</td>
<td>22</td>
<td>Visicoil (10 x 0.35)</td>
<td>23 (100)</td>
<td>Minor bleeding</td>
</tr>
<tr>
<td>Dhadham et al. (2016)</td>
<td>R</td>
<td>188</td>
<td>19</td>
<td>Visicoil (10 x 0.75)</td>
<td>187</td>
<td>Minor bleeding (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td></td>
<td>Visicoil (10 x 0.35)</td>
<td>(99.5)</td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td>R</td>
<td>47</td>
<td>22</td>
<td>Visicoil (10 x 0.35)</td>
<td>47 (100)</td>
<td>Duodenal abscess (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild pancreatitis (1)</td>
</tr>
</tbody>
</table>

P: prospective; R: retrospective; C: case series.
Fig. 1. Visicoil™ fiducial marker.
Fig. 2. Visicoil™ fiducial markers inside a pancreatic tumor.
Fig. 3. Endoscopic ultrasound procedures and fiducial placements performed per year in our institution.
Fig. 4. SBRT image. Visicoils inside the green circle.