Improvement of diagnosis and treatment of pancreatic diseases
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CHAPTER 8

EUS-GUIDED FIDUCIAL MARKERS PLACEMENT WITH A 22-GAUGE NEEDLE FOR IMAGE-GUIDED RADIATION THERAPY IN PANCREATIC CANCER

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INTRODUCTION

The prognosis of patients with pancreatic carcinoma is extremely poor, with an overall 5-year survival of 6%. Surgery is the only treatment option with curative intent, but less than 20% of patients are eligible at diagnosis and even after complete resection, the 5-year survival is only 20%. Neo-adjuvant radiochemotherapy (RChT) may increase the resection rate and the number of microscopically complete (R0) resections, decrease the local recurrence rate and hence improve survival.

Delivering an adequate radiation dose is challenged by position changes of the pancreas within one fraction, due to respiration-induced motion, and between subsequent fractions, due to differences in gastrointestinal filling. Therefore, large treatment margins around the tumor are applied. Image-guided radiation therapy (IGRT) is used to improve targeting. Since pancreatic tumors are poorly visible on cone-beam CT (CBCT) due to low soft tissue contrast, radiographically visible gold markers (fiducials) are placed in the pancreatic tumor and used for localization.

Although the safety and feasibility of this EUS-guided placement of fiducials has been assessed in several studies, there are no prospective studies evaluating the 22-gauge needle. This needle may be easier to use compared to the stiffer 19-gauge needle, especially when the tumor is located in the pancreatic head or uncinate process. The aim of this study is to assess the safety and feasibility of EUS-guided fiducial placement using a 22-gauge needle in patients with pancreatic cancer undergoing IGRT.

METHODS

Patient population
From October 2010 to August 2013, all consecutive patients with resectable, borderline resectable or locally advanced pancreatic cancer in which RChT was planned were included. Patients were planned to undergo EUS-guided insertion of fiducial markers at the Academic Medical Center (AMC). The ethics committee of the AMC approved the protocol and all patients gave informed consent.

EUS-guided fiducial placement
Procedures were performed by 3 experienced endosonographers. All patients were sedated using midazolam and fentanyl or propofol, with continuous monitoring of vital signs. The tumor was localized using a curvilinear-array echoendoscope and color-Doppler imaging was used to ascertain any intervening vascular structure. If the diagnosis of adenocarcinoma had not been previously confirmed, fine needle aspiration (FNA) was performed. Fiducials were only placed after conformation of malignancy.

Two types of fiducials were used: Visicoil (Core Oncology, Santa Barbara, CA), a flexible gold coiled fiducial with a diameter of 0.35 mm, hand-cut in length, and the Gold Anchor...
fiducial (Naslund Medical AB, Huddinge, Sweden) with a diameter of 0.28 mm and a length of 10 mm. Fiducials were back-loaded into the distal tip of a 22-gauge needle and the tip was sealed with sterile bone wax to prevent inadvertent loss of the fiducial while advancing the needle. After placement of a fiducial, the procedure was repeated until at least two fiducials were placed. When available, fluoroscopy was used to confirm the location of the fiducials.

**Periprocedural care**
Prophylactic antibiotics were not routinely administered. All patients were monitored for 1 to 2 hours in a recovery area. Upon discharge, patients were instructed to notify the nurse and/or physician of any symptoms of procedure-related adverse events. Weekly follow-up on adverse events was performed during RChT.

**Radiochemotherapy**
The dose of radiotherapy varied between 36Gy in 15 fractions and 50.4Gy in 28 fractions depending on the tumor stage and the clinical study protocols. IGRT was combined with weekly gemcitabine in all patients. Patients with locally advanced disease were included in the phase I/II study evaluating the addition of panitumumab to gemcitabine and radiotherapy (trial ID NTR2441). IGRT treatment planning was based on a reference scan. Position verification consisted of daily CBCT, enabling patient positioning based on the position of the fiducials.

**Outcome measures**
Technical success was defined as the ability to implant at least two fiducials in the tumor area. Cumbersome loading or unloading of a fiducial was defined as technical difficulty. 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. Nausea/vomiting, diarrhea, weight loss and asthenia were considered to be related to RChT. Migration was defined as a change in interfiducial distance. The coordinates of the fiducials were determined by manually selecting the center of each fiducial on the reference scan. From these 3D coordinates, the interfiducial distance was calculated. This distance was preferably 2 cm, to achieve an ideal geometry daily identifiable on CBCT during the course of RChT. 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 following CBCT scans. Clinical success was defined as the possibility to apply IGRT using the fiducials.

**RESULTS**
A total of 23 consecutive patients underwent EUS-guided fiducial placement (JB 2, JH 17 and PF 4). The patient and tumor characteristics are described in Table 1.
Technical success
Visicoil fiducials were hand-cut in length between 5 and 20 mm, with 3 exceptions: fiducials of 2 mm, 3 mm and 4 mm. In 21 patients fiducials were inserted transduodenally, in 2 patients the transgastric approach was used. Fluoroscopy was used in 9 patients. In all patients at least two fiducials could be placed in the tumor, leading to a technical success rate of 100%.

In the first 15 patients, only Visicoil fiducials were used. Afterwards Gold Anchors were temporary used, because they were expected to be easier to load, due to the smaller diameter, and because of their fixed length. Seventeen patients received Visicoil fiducials (73.9%), 4 patients Gold Anchor fiducials (17.4%), and 2 patients received both fiducial types (8.7%), see Figure 1. In total, 63 fiducials were placed; 11 Gold Anchor and 52 Visicoil fiducials. Eight patients received 2 fiducials, in 13 patients 3 fiducials were inserted and 2 patients received 4 fiducials. Technical difficulty occurred in 8 (11.3%) out of 71 attempts of fiducial placement; placement failed due to inability to load the needle twice and in 6 attempts the fiducials could not be pushed out of the needle. In 5 of these 6 attempts a Gold Anchor was used.

Figure 1. Periprocedural X-ray of a patient with a Visicoil (below) and Gold Anchor fiducial inserted.
Table 1. Patient, tumor and procedure characteristics.

<table>
<thead>
<tr>
<th>n</th>
<th>Age/sex</th>
<th>Tumor</th>
<th>Tumor size (cm)</th>
<th>Fiducials placed</th>
<th>Fiducials visible</th>
<th>Technical difficulties</th>
<th>Adverse events</th>
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<tbody>
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<td>3, Visicoil</td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
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<tr>
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<td></td>
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<tr>
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<td>2, Gold Anchor</td>
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<tr>
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<td>Unloading Gold Anchor</td>
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<tr>
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<td>2.5</td>
<td>4, Visicoil</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

R = resectable, BR = borderline resectable, LA = locally advance.

Adverse events
One periprocedural adverse event occurred (4.3%): a minor bleeding at the site of needle insertion. Because of the bleeding this procedure was terminated after successful insertion.
of 2 fiducials. The patient was hemodynamically stable and neither re-intervention nor transfusion was necessary. One patient presented with cholangitis due to obstruction of his percutaneous transhepatic cholangiography (PTC) drain 6 days after EUS-guided fiducial placement. This PTC drain had been placed one day after the fiducial insertion.

**Clinical success**

Median time between fiducial placement and the reference scan was 4 days (range 0 to 45 days, SD 10.5). Complete fiducial migration occurred in 5 patients. In total, 57 of the 63 initially placed fiducials were visible on both the reference scan and the subsequent CBCT scans, leading to a complete migration rate of 9.5%. In one patient, insertion of two fiducials was confirmed with fluoroscopy during the procedure, but no fiducials were visible on the reference scan. For 3 patients who each had 3 fiducials inserted, only 2 fiducials were visible on imaging. One patient received 4 fiducials and 3 fiducials were visible. The fiducial that could not be visualized in this patient measured 2 mm. Two patients did not receive RT, due to disease progression prior to the start of RChT. Fiducials could be used for applying IGRT in 20/21 patients (95.2%).

**DISCUSSION**

This is the first study that prospectively evaluates EUS-guided pancreatic fiducial placement with a 22-gauge needle. All patients received a sufficient number of fiducials. This is in accordance with the literature reporting a technical success rate varying between 85 and 100%. In most of our patients the tumor was accessed using the transduodenal approach. This is known to be more difficult compared to the transgastric approach, especially with a 19-gauge needle. Our technical success rate of 100% indicates an important advantage of the 22-gauge needle.

Technical difficulties occurred in 11.3% (8 out of 71) of the attempts to insert a fiducial. Insertion of a Gold Anchor fiducial was difficult in 5/16 (31.3%) attempts, probably due to kinking of the fiducial inside the needle because of the design and the limited diameter of the fiducial (0.28 mm) in relation to the inner diameter of the needle (0.41 mm). Insertion of a Visicoil fiducial was challenging in 1/53 attempts (1.9%). Although we expected the Gold Anchor fiducials to be easier to use compared to the Visicoil fiducials, more technical difficulties occurred. In our cohort, the mean interfiducial distance was 16.6 mm (range 3.5-37.9 mm), close to the aspired distance of 2 cm. In 2 patients, 2 fiducials were used as one during CBCT image registration, because the interfiducial distance was too small to consider them separately. A recent study shows that ideal geometry might not be as important as previously assumed: in most patients the interfiducial distance was less than 2 cm and IGRT was still possible.13

No severe adverse events occurred. One patient had a minor bleeding during the procedure (4.3%), but no intervention was needed and the patient remained
hemodynamically stable. No other procedure-related adverse events occurred. One patient presented with cholangitis 6 days after fiducial insertion, most probably related to PTC drain obstruction. Whether or not prophylactic antibiotics should be administered during EUS-guided fiducial insertion is debatable. In most previous studies prophylactic antibiotics were used, because increased risk for infection was expected.\(^7,8,10,12,13,15\) In our study, prophylactic antibiotics were not routinely given. Two patients received prophylaxis as preferred by the treating physician. One patient had cholecystitis at the time of the procedure and was therefore treated with antibiotics. Twenty of our patients did not receive antibiotics. In previous studies 33 patients underwent fiducial insertion without the use of prophylactic antibiotics.\(^8,11\) One of those 33 patients developed a fever, which was successfully treated with an outpatient course of antibiotics.\(^11\) Including our study, a total of 53 patients underwent fiducial placement without prophylactic antibiotics and one (1.9%) patient developed a fever. The American Society for Gastrointestinal Endoscopy gives no recommendation for the use of prophylactic antibiotics during EUS-guided fiducial placement. Although there are no prospective randomized studies focusing on this subject, we believe that, based on the current available literature and our own experience, prophylactic antibiotics during EUS-guided fiducial placement might not be required.

Positional stability of the fiducials is of great importance for successful delivery of IGRT. We previously reported on fiducial migration in 13 of the first 14 patients of this cohort (the patient with complete fiducial migration was excluded).\(^6\) In these subjects fiducial migration was minimal. Therefore, in the subsequent cases only the complete migration rate and the clinical success rate were analyzed. In total, 9.5% (6 out of 63) of the initially placed fiducials had completely migrated (Table 1). The 2 mm fiducial could not be visualized with fluoroscopy during the procedure and therefore it is likely that this fiducial was not migrated, but that it was too small to be visualized.

In 20/21 (95.2%) of the patients who received RT, IGRT could be successfully applied. Not all previous studies confirm whether IGRT was feasible. The reported success rates vary from 84 to 100%.\(^7,9,12,13\) In some centers the CBD stent is used as a fiducial during IGRT, but the use of this stent as a surrogate for tumor motion has never been validated. Goldstein et al.\(^5\) compared gross tumor volume (GTV) movement with biliary stent movement during respiration in patients with locally advanced pancreatic carcinoma. The average movement of the stent was significantly greater than movement of the GTV, with a difference up to 9 mm. Also, they found that GTV and biliary stent motion correlate poorly (\(R^2 = 0.23\)). Therefore, we did not use the CBD stent for applying IGRT.

Our results show that EUS-guided fiducial insertion with a 22-gauge needle is a safe and feasible procedure in patients with pancreatic carcinoma. Although more research is needed, the clinical impact of IGRT in these patients is promising and the use of fiducials makes high-accuracy IGRT possible.
REFERENCES