*JOP. J Pancreas (Online) 2011 Mar 9; 12(2):86-91.*

HIGHLIGHT ARTICLE

# EUS-Guided Pancreatic Diagnosis and Beyond

***Highlights from the "2011 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 20-22, 2011***

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**Summary**

The therapeutic ability of endoscopic ultrasound has expanded, especially in assisting with radiation planning for image guided radiation techniques such as stereotactic body radiation therapy. Endoscopic ultrasound enables precise placement of fiducial markers into pancreatic cancers to accurately delineate the position of the target lesion as it moves with respiration. The authors summarize the data presented at the 2011 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, including Abstracts #302, #327, #176, #182, and #349.

## What We Knew Before 2011 ASCO GI Cancer Symposium

Endoscopic ultrasound (EUS) is established as an accurate diagnostic and staging modality for pancreatic tumors [1]. Contrast agents may improve the accuracy of EUS [2]. The linear echo-endoscope facilitates EUS-guided interventions such as fiducial placement. Fiducial markers are radiopaque spheres, coils, or seeds that are implanted in or near the tumor. The objective is to demarcate the extent of tumors to facilitate image guided radiation therapy (IGRT) [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13].

Stereotactic body radiation therapy (SBRT) techniques rely on IGRT to permit escalation of radiation dose to tumors while simultaneously minimizing dose to normal tissues. Implantation of fiducials into the region of interest facilitates quantification of respiratory associated tumor motion as well as delineation of the local extent of malignant disease. In addition, fiducial markers enable reproducible daily treatment delivery. There are several studies on the feasibility of EUS guided fiducial placement for a variety of tumors [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. Two publications discuss the feasibility of EUS guided fiducial placement for locally advanced and recurrent pancreatic cancer [4, 9]. SBRT has been introduced into the locally advanced pancreatic cancer armamentarium by investigators at Stanford University [14]. Recent evidence has also suggested the feasibility of 5 high dose fractions of radiation prior to pancreatic cancer resection [15]. However, there is no published evidence regarding the utility of EUS implanted markers for SBRT as part of a neoadjuvant regimen for the subset of patients specifically designated to have “borderline resectable” pancreatic cancer [16, 17].

Prior studies on EUS-guided fiducial placement using the 19G FNA (large bore) needle reported technical failures associated with pancreatic head tumors and with altered anatomy. Pancreatic EUS-guided fiducial placement is reported to be successful in about 88-97% of patients, with minor complications related to needle malfunction [4, 5, 6, 7, 8, 9]. There are recent reports using a 22G FNA needle for fiducial placement for multiple sites but it is unclear if these small caliber needles are consistently successful for EUS-fiducial placement for pancreatic head tumors [5, 6, 13]. It has been suggested that the 0.35 mm diameter fiducials deployed using the 22G FNA needle may improve the success of EUS-fiducial placement in pancreatic tumors [5, 6]. Different techniques of EUS-fiducial placement are described in prior studies and involve using the stylet within the needle to deploy the marker [4, 5] or injecting sterile water into the needle using hydrostatic pressure to deploy the marker [9]. However, there is little data on the migration rate and utility of the smaller diameter (0.35 mm) fiducials for SBRT planning in borderline resectable pancreatic cancer.

**Key words** Endosonography; Fiducial Markers; Pancreatic Neoplasms

**Abbreviations** IGRT: image guided radiation therapy; NCCN: National Comprehensive Cancer Network; SBRT: stereotactic body radiation therapy

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**URL** http://www.serena.unina.it/index.php/jop/article/view/3329/3576

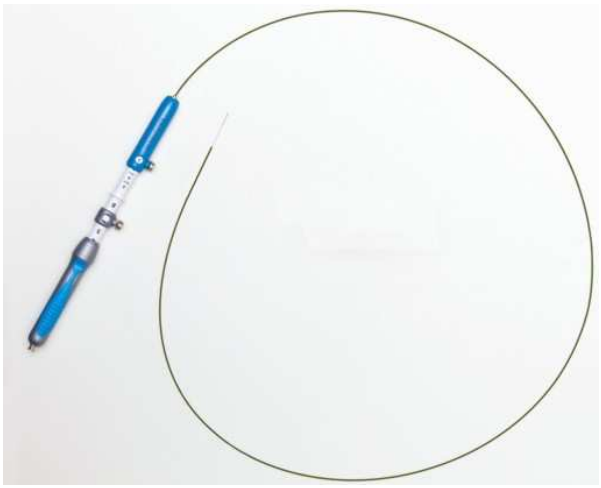

**Figure 1.** ECHO TIP® (3-22) needle for small caliber fiducial placement.

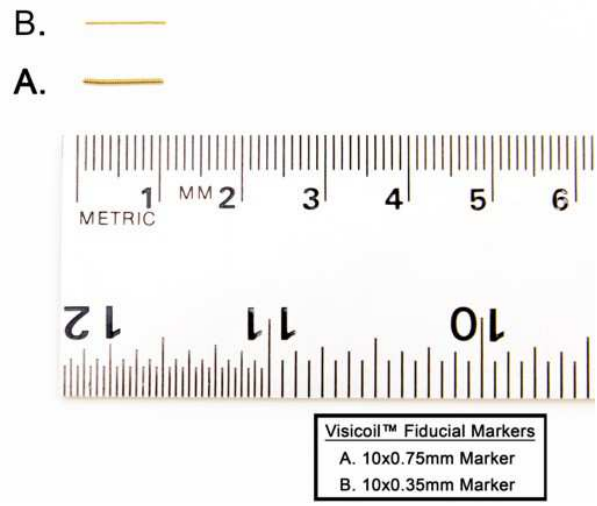


**Figure 2.** Visicoil™ fiducial markers of different caliber: A. 10x0.75 mm; B. 10x0.35 mm.

Fluoroscopy is frequently used to confirm location of fiducials but was not used in all the studies. Migration has been reported in about 7% of patients undergoing EUS-guided fiducial placement [4]. This resulted in repeat EUS for fiducial placement. Despite limitations such as previous pancreaticoduodenectomy, EUS-fiducial placement is less invasive than surgical or percutaneous approaches.

## What We Learnt at 2011 ASCO GI Cancer Symposium

*EUS-Guided Pancreatic Fiducial Placement*

Vignesh *et al*. reported the technical feasibility and migration rate of EUS-fiducial placement in 25 patients with pancreatic cancer with a specific type of 22G needle (ECHO TIP® 3-22 needle; COOK®, Winston-Salem, NC, USA; Figure 1) to assist with planning SBRT (Abstract #327) [18]. Apparent *versus* true migration rate and utility of the smaller caliber fiducial markers for SBRT planning is discussed. The pancreatic cancers were classified as borderline resectable (National Comprehensive Cancer Network (NCCN) criteria) based on careful assessment of the vasculature by EUS and CT (thin slice, triphasic) scan. Twenty two of the 25 patients were classified as "borderline resectable" by the NCCN criteria [16, 17] and 3 were staged as locally advanced disease. Two of the 25 patients had pancreatic neuroendocrine carcinoma (PNET) and the rest had adenocarcinoma. Gold cylindrical fiducials (0.35x10 mm or 0.75x10 mm; Visicoil™, RadioMed, Inc., Tingsboro, MA, USA; (Figure 2)) were loaded into a 22G or 19G EUS needle. With the needle in the target, the fiducial was deployed by simultaneously retracting the needle and advancing the stylet. Fifteen of 25 patients received the smaller (0.35x10 mm) fiducials, using the ECHO TIP® (3-22) FNA needle equipped with a "ball tip" stylet that facilitated deployment in pancreatic head lesions. This specific needle was selected based on prior experience using different types of 22G FNA needles for EUS-fiducial placement in the pancreatic head. A mean of 3 fiducials were placed (range 1-6) per patient. Fluoroscopy was not used to confirm placement as EUS confirmed fiducial position after deployment (Figure 3). Technical success was defined as placement of at least one fiducial marker.

Fiducial placement was successful in 24/25 patients (96.0%). Most tumors were of the pancreatic head (n=18) *vs*. body/tail (n=7). A total of 72 fiducials were placed and 38 of these were the smaller caliber (0.35x10 mm) markers. Technical difficulty (not failure) was encountered in 4 patients secondary to retained food in stomach, altered anatomy and uncinate tumors. However, smaller (0.35x10 mm) fiducials were successfully placed in these 4 patients using the ECHO

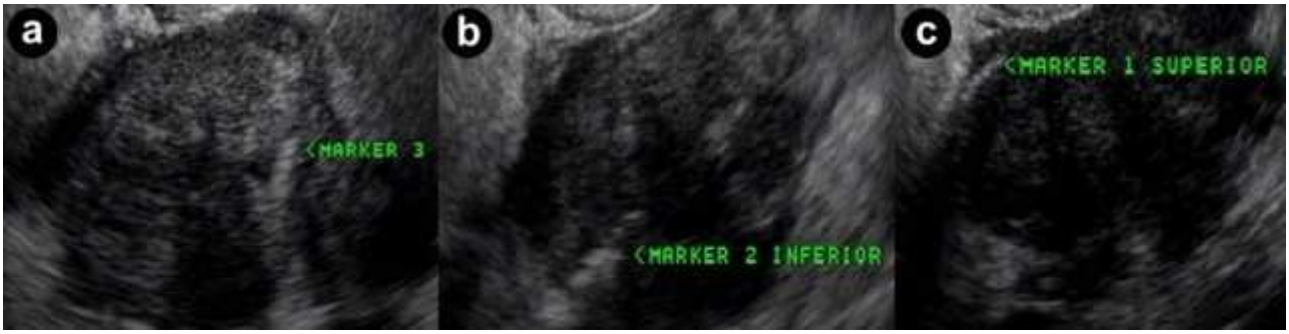


**Figure 3.** EUS image of 0.75x10 mm Visicoil™ markers in a pancreatic mass.

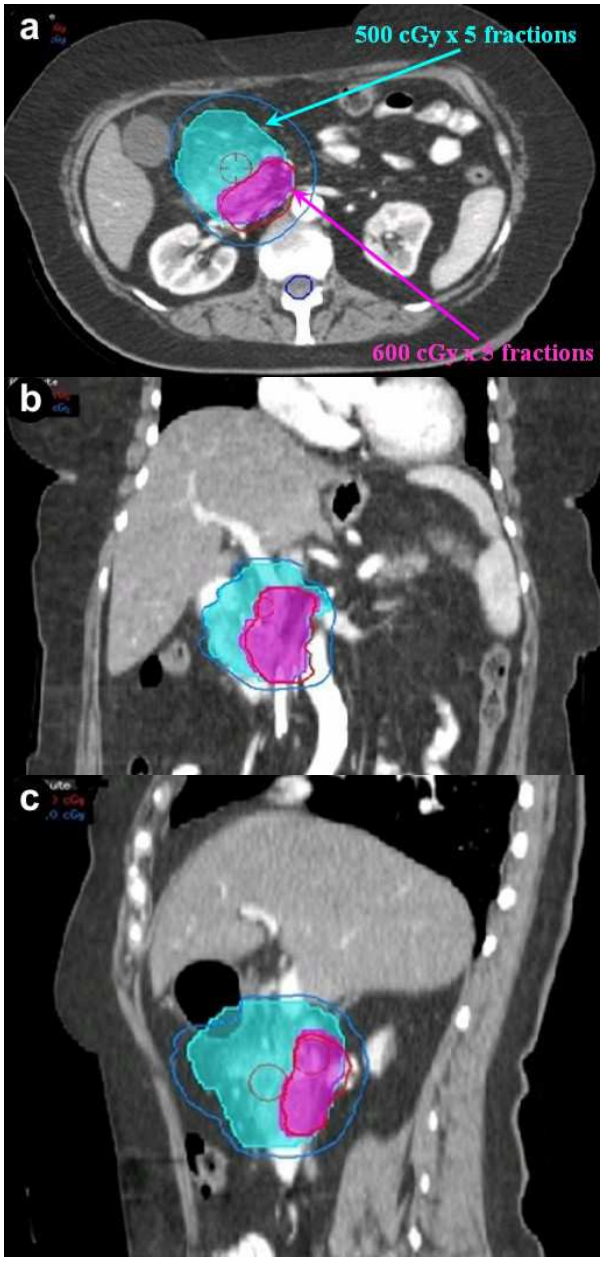


**Figure 4.** Pancreas protocol CT scan (dose painting).

TIP® (3-22) FNA needle. Three patients had abdominal pain lasting less than 12 hours after fiducial placement but none had documented pancreatitis. No other complications occurred at the end of the follow-up period of 190 days. In 3 patients, change in fiducial position was noted on follow-up cone beam CT. This apparent change in position was related to biliary drainage, gastric distension and a pre-existing pseudocyst. Though this was not indicative of fiducial migration, it impacted radiation planning and delivery. These patients underwent repeat planning with a new 4D CT in the treatment position.

Patients with adenocarcinoma were treated with 3 cycles of induction gemcitabine based chemotherapy. Daily SBRT began at least 1 week following completion of chemotherapy. Fiducial position was analyzed at 4D CT simulation and fluoroscopy/cone beam CT prior to SBRT. Treatment was delivered with dose painting (Figure 4) over 5 fractions on a Trilogy® unit (Varian Medical Systems, Inc., Palo Alto, CA, USA). Treatment was delivered with either respiratory gating or abdominal compression to decrease respiratory associated tumor motion. Restaging PET/CT (Figure 5) and pancreas protocol CT were performed 3-4 weeks after completing SBRT for consideration for surgical exploration.

Chuong *et al*. have reported the initial Moffitt clinical outcomes with this technique for borderline resectable pancreatic adenocarcinomas, noting a 61% rate of conversion to R0 resection (Abstract #302; Figure 5b) [19]. For the patients with PNETs, fiducials were used for planning only since a fractionated course of radiation was delivered along with continuous infusion 5-flourouracil. Conventionally fractionated treatment was delivered with an intensity-modulated radiation therapy compensator based technique. PNETs were reimaged in 4-6 weeks with pancreas protocol CT. Radiation was well-tolerated in both patient populations. No complications were reported [19].

## Highlights of Additional Abstracts Related to EUS and Pancreatic Tumors

*Diagnosis of PNET*

Strosberg *et al*. presented the outcome of 4 patients with stage I nonfunctioning PNETs (size less than, or equal to, 15mm) diagnosed via EUS-FNA (Abstract

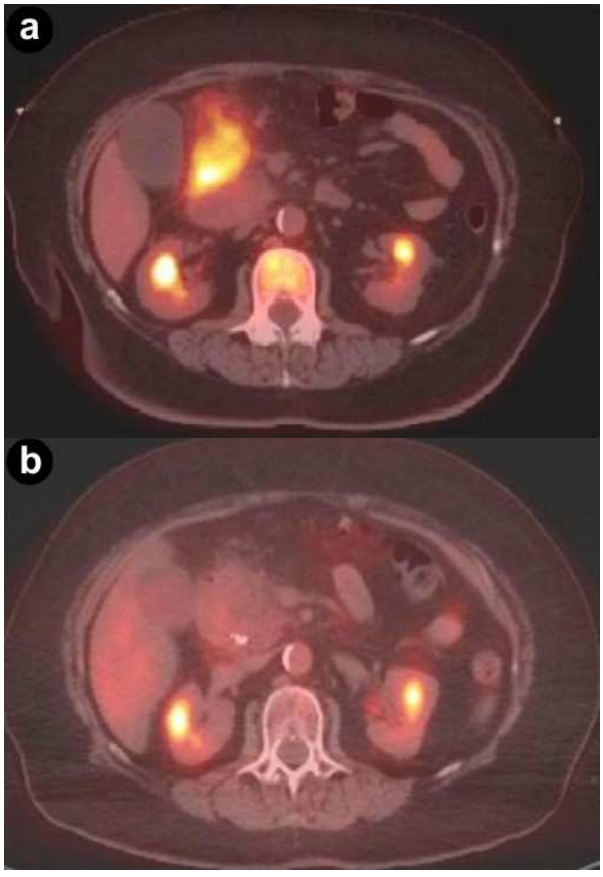


**Figure 5.** Fused PET-CT showing pre- and post-stereotactic body radiation therapy images.

#349) [20]. At 2-year follow-up all tumors were unchanged. They concluded that surveillance may be a strategy for incidental stage I PNETs [20].
This study highlights the accuracy of EUS-FNA for small pancreatic tumors.

*EUS to Predict Malignancy in Branch-Duct IPMN*

Lee and Cho evaluated a EUS based scoring system in predicting malignancy in branch-duct type IPMN. Of 32 patients who underwent diagnostic EUS, 12 underwent surgical resection (Abstract #182) [21]. Cyst size, mural nodule, main pancreatic duct dilation and patulous pancreatic duct opening were significantly associated with malignancy. Mean score for benign cases was 2.47, and 6.33 for malignant cases (P=0.001). They recommended surgical resection for patients score greater than 7, to consider surgery for score between 4 and 6, and careful follow-up for score less than 3.
This study quantifies EUS morphology based risk assessment and needs to be validated using a larger sample [21].

*Cytology Yield from Pancreatic EUS-FNA*

Nguyen *et al*. compared the diagnostic yield of cell block alone against smear technique in pancreatic mass EUS-FNA (Abstract #176) [22]. Of 96 patients, 66 had cell block alone and 30 had smear plus/minus cell block preparation. In the absence of onsite cytology, the diagnostic yield from cell block alone was 80% and was superior to smear technique. The addition of cell block after smearing did not improve the diagnostic yield [22].
Onsite cytopathological assessment is accepted as a quality control measure for EUS and is the standard of care at most academic EUS centers. Therefore, this study is unlikely to impact the practice of EUS in the USA.

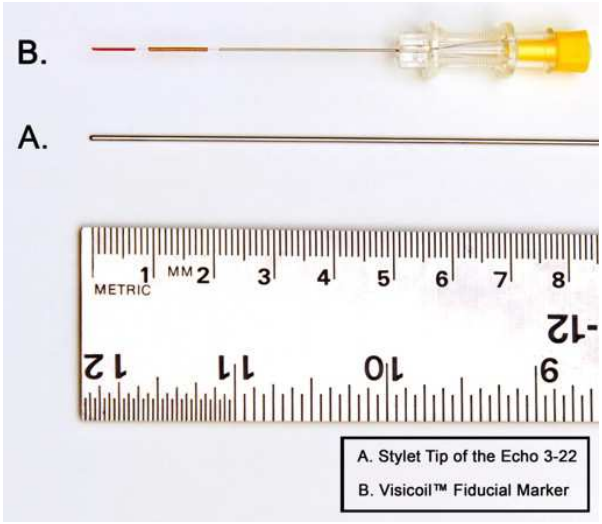


**Figure 6.** Visicoil$^{TM}$ marker and EUS needle stylet tip.

**Discussion**

EUS guided fine needle aspiration (EUS-FNA) is an integral part of the diagnosis and staging of pancreatic tumors. The accuracy of EUS in the detection of pancreatic tumors smaller than 3 cm and in assessment of portal vein and superior mesenteric vein involvement in pancreatic cancer is established. EUS guided core biopsy and brush cytology of pancreatic cysts has expanded its role and provides tissue for histology and additional molecular studies. EUS guided therapeutic interventions include celiac plexus neurolysis, pancreatic and biliary drainage [3] and more recently EUS guided fiducial marker placement for IGRT [4, 5, 6, 7, 8, 9]. Studies have reported the feasibility and safety of EUS guided fiducial placement. Previous studies on EUS-guided fiducial placement have reported the difficulty placing markers with the standard 19G needle in the pancreatic head tumors. The curvature of the endoscope tip when positioned in the duodenum results in difficulty deploying the maker into pancreatic head lesions. DiMaio *et al*. used a 22G needle with smaller diameter fiducials for a variety of tumors but only 5 patients in that study had pancreatic head tumors [5]. We reported our experience [18] with different EUS needles and a specific type of 22G FNA needle (ECHO TIP® (3-22)) with a design suited for fiducial placement in pancreatic head tumors as it is a small caliber (flexible) needle with a “ball tip” stylet (Figure 6). The design of this stylet tip (component of the ECHO TIP® (3-22) needle) facilitates deployment of the fiducial despite the curvature of the endoscope tip that occurs when positioned in the duodenum to visualize pancreatic head tumors. The design of this needle makes EUS guided fiducial placement significantly easier and successful in most cases. Though this was not measured, we observed that EUS guided fiducial placement is usually of shorter duration than the initial EUS-FNA performed for diagnosis and staging. Also, the smaller caliber fiducials are visible on CT scan and helpful in radiation planning. Fluoroscopy is conventionally used to confirm marker placement in many of the published studies. Like Park *et al*. [9], we did not require fluoroscopy to confirm marker placement as the EUS exam confirmed accurate placement immediately after fiducial deployment.
Prior studies reported on a migration rate of about 7% using a marker with a solid cylindrical design [4]. The type of fiducial marker used is not the same in all studies and true migration did not occur in our study in any of the 24 patients. Though the causes of fiducial migration are unclear it may be associated with the “solid” fiducial design and possibly related to the exact location of deployment in relation to the tumor. The coil structure of the marker we used (Visicoil$^{TM}$) is the likely reason for stability of the marker over time. The other reason may have been our practice of ensuring that the marker was placed within the margins of the lesion rather than at or outside the tumor margin. Pancreatic tumors with their desmoplastic stroma and

the "coil" structure of the marker both resulted in a zero migration rate.

We also reported on apparent *versus* true migration and the reasons for the apparent migration [18]. Apparent migrations seen on CT scan were explained by an enlarging pseudocyst in one patient and a large meal causing gastric distension prior to the planning CT in another patient. In 2 other patients biliary decompression for worsening biliary obstruction resulted in "apparent migration" of the marker by a few centimeters. On careful study of the CT images it was clear than none of the 4 cases represented true migration. The review of the fiducial marker position on the pre-treatment images immediately detected the altered position, allowing replacement of the biliary stent and replanning. Also, issues such as impending biliary obstruction should be addressed prior to fiducial placement. Several techniques have been reported for EUS guided fiducial placement; based on our experience, the easiest technique is simultaneous withdrawal of the needle while pushing the stylet forward under EUS-guidance. Though not a part of this study, we have not had consistent success with the sterile water injection technique.

The accuracy of EUS in the diagnosis of PNETs smaller than 2 cm and utility of EUS based scoring system in predicting malignancy in branch-duct IPMNs highlight the diagnostic ability of EUS. EUS serves three critical roles in pancreatic cancer. It establishes a diagnosis, confirms the stage (borderline resectable status) and guides fiducial placement to plan SBRT. Fiducial assisted SBRT planning may improve the outcome after neoadjuvant chemotherapy in this setting. The study by Vignesh *et al*. addresses the reported technical issues using a specifically designed EUS needle and confirms the stability of the Visicoil$^{TM}$ fiducial marker [18]. EUS guided fiducial placement is a minimally invasive procedure that highlights the therapeutic role of EUS and collaboration between endoscopic oncologists and radiation oncologists. The future role of EUS is likely to evolve in this direction.

**Conflict of interest** The authors have no potential conflict of interest

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