EUS-guided placement of fiducial markers for image-guided radiotherapy in gastrointestinal tumors: A critical appraisal

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ABSTRACT

We present here a new chapter of the series of papers on how to perform specific EUS techniques. In this manuscript, we discuss on how to perform EUS-guided placement of fiducial markers in gastrointestinal tumors. The aim is to present the scientific evidence of fiducials placement before radiation therapy, including an accurate revision of the literature, to give some advices on the technical approach, and to discuss Pros and Cons from the point of view of gastroenterologists and radiation oncologist.

Key words: fiducial markers, EUS, radiotherapy, tumors, guideline

INTRODUCTION

We included this paper in the series of manuscripts that constructively present a practical approach to some of the most current EUS topics.[1-3] Although not intended as a guideline, it presents a comprehensive revision of the literature and it summarizes the techniques and the products available, with the aim to be a useful tool for endosonographers who have the opportunity or the need to introduce this technique into their clinical practice.

Apart from the purely technical endosonographic aspect, radiation therapy is still a controversial issue, especially for its application in pancreaticobiliary cancer. In this paper, we included the opinion of the

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radiation oncologists in order to give the readers the widest possible view of the topic, keeping in mind that the purpose of placing fiducial markers is to support the radiation oncologist to perform a specific kind of radiation therapy as treatment. In this context, the role of the multidisciplinary team is of paramount importance because every patient has his/her own diagnostic and therapeutic path in which the utility and the timing of the fiducial placement has to be discussed and approved by all the specialists involved in the treatment of the patient.

THE ROLE OF RADIATION THERAPY IN GASTROINTESTINAL MALIGNANCIES

Radiation therapy remains an important oncologic tool for local tumor control or neoadjuvant treatment in various gastrointestinal (GI) tumors, particularly in esophageal, pancreatic, hepatobiliary, rectal, and anal cancers. Controversies still exist especially about its specific role for treatment of pancreatico-biliary tumors, since there is a tremendous lack of large-scale randomized controlled trials (RCTs) that demonstrate its efficacy in such cancers when compared with other treatment modalities such as systemic chemotherapy alone. However, new concepts that assess optimal treatment of locally advanced pancreatico-biliary malignancies are evolving rapidly. Ongoing clinical trials and investigations on the basis of previous clinical studies[4] focus on the role of systemic chemotherapy alone *versus* chemo-radiation treatment protocols incorporating different types of radiotherapy (e.g., conventional *vs.* cyberknife techniques including stereotactic body radiation therapy (SBRT).[5,6] Most oncology practices first offer chemotherapy for the treatment of locally advanced pancreatic cancer, either in the form of FOLFIRINOX or gemcitabine/nab-paclitaxel. Radiotherapy is often used for consolidation for patients that either do not tolerate chemotherapy or who have not progressed after 2–6 months of chemotherapy.

There is no consensus with regards to the best chemotherapy regimen or type of radiotherapy to offer, but SBRT is an emerging technique. SBRT has the main advantage of delivering high ablative doses/fraction in a short overall treatment time (typically around 1–5 fractions), without the need to interrupt systemic therapy for a prolonged period of time.[7] In addition, the high doses achieved using SBRT have shown remarkable local control and survival rates in previous phase I/II studies, while maintaining acceptable toxicity.[8-11]

On the other hand, a major challenge for SBRT delivery is respiratory organ motion management, since the pancreas can move 2–3 cm.[12-14] Without ways to account for this with breath hold or image guidance, the margins for treatment become quite large to ensure that tumors are not missed. This is compounded by the fact that pancreatic tumors are radiation resistant, but have close proximity to other organs that are very sensitive to radiation, most notably, the duodenum. Early SBRT studies that used large treatment margins showed unacceptably high GI toxicity.[15]

In this context, placement of "fiducial markers" within/around the tumor appears to be an attractive tool since it is relatively simple to apply, has been studied for many years (particularly in prostate cancer), and has an affordable cost compared to more recent image-guided therapies like MR-Linac. Taking into account the respiratory motion of the target mass during radiation therapy, the placement of fiducials has been related to better targeting compared with localization using adjacent bony anatomy.[16,17]

During radiation therapy, the position of the pancreatic tumor is first localized by aligning to bony anatomy using standard kV imaging. The accuracy of the tumor targeting is then confirmed by doing a secondary alignment to fiducial markers. Sometimes treatment is performed while the patient performs a breath hold technique, while other prefer treating using respiratory gating, where the radiation is delivered only during certain phases of the respiratory cycle (usually expiration). Fiducials allow significant flexibility for radiation oncologists since they can be used with almost any machine regardless of the patient's ability to breathe or body habitus.

Many patients with pancreaticobiliary tumors often have biliary stents, which are also easily seen on imaging systems used to guide radiation. However, several studies have demonstrated that fiducial markers derived from metals such as gold or platinum act as better surrogate markers than other materials such as endoscopic stents, since stents can sometimes migrate and vary in position to an unacceptable degree.[18] At the beginning, fiducials had been placed mainly during surgery or

percutaneously, for instance under ultrasound or computed tomography (CT) guidance.[19-21] More recently, EUS – guided marker application by means of needle-guided placement has emerged as first-line tool to facilitate fiducial marker placement into pancreatico-biliary tumors under direct visualization from close proximity of the target lesion. Compared with percutaneous techniques, EUS offers a greatly improved access to the pancreas from the stomach or duodenal bulb and avoids needle passage through sensitive structures, particularly surrounding blood vessels.[22]

Patients may still experience long-term side effects following neo-adjuvant chemo-radiation for treatment of esophageal, pancreatic or rectal cancers including swallowing disorders, duodenal perforation, fecal incontinence, and/or impaired urinary and sexual functions. Hence, any technique allowing an effective reduction of target volume of radiation is greatly appreciated. In this context, some investigators were keen on use of fiducial markers for improved organ-sparing radiation or chemo-radiation treatments in other GI tumors such as esophageal and rectal cancers.[23-27] Theoretically, fiducial markers offer the option to improve radiotherapy verification in these settings despite tumor movements for both external beam treatment and brachytherapy. Up to the current date, EUS-guided fiducial placement has been reported for treatment of esophageal, gastric, rectal and pancreatic cancer (GI tumors); other studies focused on the treatment of prostate cancer and mediastinal masses. Most of these studies suggest an extremely high success rate without severe adverse events (AE).[28,29] Novel applications include pancreatic neuroendocrine tumors.[30] and metastatic lymph nodes.[31] The Current National Comprehensive Cancer Network guidelines[32] indicate that EUS-guided fiducial placement is preferred over CT-guided placement.

The decision to include fiducial marker placement in the treatment plan of a patient has to be discussed by a multidisciplinary team that includes the gastroenterologist, the radiation oncologist, the medical oncologist, the surgeon, and the patient.[33] Therefore, in this article, we shall review the current literature and the technical aspects of EUS-guided fiducial marker techniques as an international group of experienced Endosonographers who have used such tools for years.

REVIEW OF THE LITERATURE ON EUS-GUIDED PLACEMENT OF FIDUCIAL MARKERS

In general, the technique of EUS-guided fiducial marker placement is characterized by a high technical success rate in the clinical setting that ranges somewhere between 85% and 100%[25] in previous studies. Furthermore, the procedure is relatively safe with an AE rate ranging between 1.7% and 7.6%.[25] Most of the reported AE consist of minor complications with spontaneous resolution. The migration rate is relative low (reported in up to 7%) and the procedure could be repeated, if needed. A systematic review and meta-analysis on 9 full manuscripts and 5 abstracts including 1155 patients reported a technical success rate of 98% (95% CI, 96–99) and pooled rates for migration of fiducials and AE of 3% and 4%, respectively.[34]

EUS-guided fiducial marker placement in pancreato-biliary malignancies

Previous data on safety and efficacy of pancreato-biliary fiducial marker techniques for guidance of chemoradiation in cancer patients remain fairly limited. Previous studies[35-37] suggested that the technical feasibility and safety of this route look favorable. However, prospective data on clinical efficacy, safety of the procedure, optimal fiducial marker equipment, and the role of peri-interventional antibiotic treatment are still relatively sparse. Recently, a retrospective, single-center study was published.[38] In a retrospective setting, a total of 355 consecutive patients who had undergone EUS-guided fiducial marker placement prior to SBRT for pancreatico-biliary malignancies (mostly pancreatic cancer), were assessed in one large U.S. Center (Boston). Out of these 87% finally received SBRT. EUS-guided fiducial marker placement was carried out under antibiotic prophylaxis in 86% of patients and markers could be successfully deployed in virtually all patients. Side effects were noted in 6% of patients (n = 21) after EUS intervention and ranged from mild to severe (serious adverse event [SAE]), but no statistical difference was observed between groups with regard to prophylactic antibiotic treatment prior to EUS interventions. SAEs included three cases of acute pancreatitis, of whom two had also undergone endoscopic retrograde cholangiopancreatography and stent placement in the same session. One patient developed significant hemorrhage after EUS-puncture

requiring administration of blood transfusion, while other three patients developed either acute cholangitis or bacteremia/septic shock of an unknown source. Infectious SAEs occurred only rarely and in both groups of patients, *i.e.*, with and without antibiotic prophylaxis. However, the mix of patients with simultaneous endoscopic interventions and presence of biliary stents makes interpretation of safety data of EUS-fiducial application rather difficult in this setting. In conclusion, this comprehensive but retrospective study demonstrates an impressive and high rate of technical success of EUS-guided marker placement in pancreatico-biliary cancers. The clinical efficacy - and possible superiority above existing protocols - of this technique prior to cyberknife radiotherapy, however, remains to be shown by subsequent RCTs. Particularly, subsequent studies should focus on patient comfort and clinical advantages, for example, due to lesser doses of radiotherapy, less side effects, and other parameters that favor the use of fiducials in this patient group. Table 1 presents the efficacy and safety of EUS-guided fiducial markers placement in patients with pancreatic tumors.

EUS-guided fiducial marker placement in rectal cancer

One recent prospective multicenter "pilot" study[49] assessed the feasibility of EUS-guided fiducial marker placement prior to radiotherapy of rectal cancers. Clinical endpoints of this study included technical success rate and safety profile of EUS-guided marker placement in 20 patients with rectal cancer who were scheduled for subsequent neoadjuvant chemoradiation. Two different placement strategies and four different company-fabricated types of fiducial markers were compared within this study setting. Markers were either deposited directly in the tumor mass and within the surrounding mesorectal fat, or only at the tumor site. The assessment of the number of retained markers (despite patient movements and passing of stools) was

Table 1. Efficacy and safety of EUS-guided fiducial markers placement for pancreatic tumors

Study (1st author, year)	Number of patients	Needle used (gauge)	Type of fiducials (length × diameter, mm)	Technical success (%)	Adverse events (*n*)
Pishvaian, 2006[39]	7	19	Gold (3 or 5×0.8)	86	None
Ammar, 2010[40]	7	22	Visicoil (10×0.35)	100	None
Varadarajulu, 2010[41]	9	19	Gold (3×0.8)	100	None
Park, 2010[42]	53	19	Visicoil (2.5×0.8)	94	Minor bleeding (1)
Sanders, 2010[36]	51	19	Gold (5×0.8)	90	Mild pancreatitis (1)
DiMaio, 2010[43]	9	22	Visicoil (10×0.35)	100	Cholangitis (1)
Khashab, 2012[44]	39	19 22	Gold (5×0.8) Visicoil (10×0.35)	100	None
Majumder, 2013[37]	39	19	Gold (5×0.8)	90	Abdominal pain (3); vomiting (1); mild pancreatitis (1)
Law, 2013[30]$	2	22	Visicoil (10×0.35)	100	None
Choi, 2014[45]	29	19	Gold (3×0.8)	100	Mild pancreatitis (1)
Davila Fajardo, 2014[23]	23	22 22	Visicoil (2-20×0.35) Gold (10×0.28)	100	Minor bleeding (1)
Packard, 2015[16]	12	19	Gold (2.5×0.8)	100	None
Dhadham, 2016[25]	188	22 19	Visicoil (10×0.35) Visicoil (10×0.75)	100	Minor bleeding (7)
Phan, 2018[46]	28	22 19	Gold (5×0.43) Visicoil (NR)	100	None
Ussui, 2018[47]	2	19	Hydrogel marker	100	None
Machicado, 2019[48]	44	22	Gold (10×0.35 or 5×0.43)	95.5%	Pain (10); nausea and/or vomiting (2); other (5)*
Chandnani, 2020[38]	355€	19 or 22	Gold (3×0.8 or 5×0.43)	NR¥	Acute pancreatitis (3)£; bleeding (2, one major); acute cholangitis, bacteremia or septic shock (3)¤; pain (11); fever (5)

$Fiducials were placed inside small pancreatic NETs for echografic identification during parenchymal-sparing resection surgery, successfully performed in both cases; *Reported at 24-48 h; €Of the total no. of patients, 37 (10.4%) had tumors located outside of the pancreas: 16 of these patients had cholangiocarcinoma, seven hepatocellular carcinoma, four esophageal carcinoma, three ampullary carcinoma, three gallbladder carcinoma, two gastric adenocarcinoma, one metastatic peripancreatic mass and one colon cancer with liver metastases; ¥Of the 355 patients, 308 (86.8%) underwent SBRT successfully; only one patient could not undergo SBRT due to the inability of the cyberknife system to properly track the fiducials; the rest of the patients were either lost to follow-up, had interval disease progression, died before or denied SBRT, or were eventually diagnosed with benign disease; this would translate into a technical success rate of 308 from 309 patients (99.7%); £Two of them had same session ERCP performed; ¤All these three infectious AEs had other causes more likely than fiducials placement. NR: Not reported; NET: Neuroendocrine tumor; SBRT: Stereotactic body radiation therapy; AE: Adverse events

carried out by measuring cone-beam CT scans during the first five radiotherapy fractions. As results, 64 fiducials could be deployed in 20 patients without any serious adverse effects despite accidental misplacement of one marker into the peritoneal cavity and two markers within the prostate gland. Deposition of an average of 3 markers (mean value) was achieved per patient. Some minor technical failures were also observed: in two cases fiducial markers were blocked within the deploying needle and had to be subsequently replaced, while in four patients two markers were ejected simultaneously, but caused no impediment for further treatment. However, during the observation period of 17 days after deployment, a marker retention rate of only 55% was noticed for those applied only into the tumor site, as compared to 90% of those that had been applied mesorectally. In conclusion, this small study suggests a high technical success rate and safety profile of EUS-guided fiducial marker placement over time, when markers are deployed in the mesorectum and deep within the tumor. Since different types of fiducials were used in this small patient series, no firm conclusions about superiority/inferiority of any equipment can be drawn from the sparse data set. Finally, the clinical significance of this technique remains to be shown in further studies. This is of particular importance since other cheaper and less invasive techniques (*i.e.*, endoscopic clip placement) may well compete with such fiducial techniques, which makes a comparative prospective and randomized clinical study almost mandatory.

EUS-guided fiducial marker placement in esophageal cancer

The multimodality approach to esophageal cancer treatment recognizes radiation therapy as an important tool together with chemotherapy. Although the presence of markers at the margins of the tumors may theoretically facilitate the target visualization and may guide the radiation therapy, only few reports of very small series described the role of EUS in the fiducials placement in esophageal cancer, most of them in series that included different kinds of GI malignancies.[43] Fernandez *et al.* placed a total of 105 fiducial markers under EUS-guidance at the margins of 60 esophageal cancers and they evaluate the stability of the fiducials during and after the treatment.[50] One of the important messages of this study is that all the patients underwent fiducial placement on an outpatient basis and all were discharged to home. In times in which health-care costs have a strong impact on the society, the possibility to demonstrate the safety of an interventional technique in outpatient modality is very important. At time of CT simulation, 99 markers were visualized and 57 patients had post-treatment imaging available: in these 57 patients, 94 markers (94%) were visible at time of RT simulation and 88% of fiducials were still present posttreatment imaging at a median of 107 days after implantation.

The placement of mucosal clips at the superior and inferior tumor margin has also been described with standard endoscopy.[51] This technique is easy to perform but has some limitations like the limited ability to define the precise extension of the tumor in the submucosa and usually clips are temporary markers that may dislodge during the treatment or during the follow-up.

Other applications of EUS-guided fiducial marker placement

Previously, the technique has been used for more than a decade for radiotherapy of prostate cancer and mediastinal masses with an extremely high success rate and without reports of severe AE.[28,29] Novel indications include fiducial placement to allow localization of small pancreatic neuroendocrine tumors,[30] metastatic liver lesions, cholangiocarcinomas,[25,43] or metastatic lymph nodes[31] during surgery in order to guide the surgeons' hands in parenchymal sparing resections. The Current National Comprehensive Cancer Network guidelines[32] indicate that EUS-guided fiducial placement is the preferred method and superior to CT-guided placement.

TOOLS AND TECHNIQUE OF FIDUCIAL MARKER APPLICATION

Types of fiducials available

The markers are made of gold or platinum which are inert metals with good radiological visibility and low CT and magnetic resonance artifacts. Fiducial markers can be placed under surgical, percutaneous, or EUS-guidance. EUS-guided fiducial placement has been reported in GI tract cancers including esophageal, gastric, rectal, and pancreatic cancers.

Different types of fiducial markers are currently available with various shapes, lengths, and diameters. In terms of shape, they can be classified as traditional or coiled. The last are more flexible and are thought to reduce the risk of migration. The two types of fiducials

were compared in a retrospective study.[44] which enrolled 39 patients with locally advanced pancreatic cancer. No intra- or post-procedural complications were encountered. The visibility was significantly better for the traditional fiducials while the migration was not different in comparison to Visicoil fiducials (Visicoil, RadioMed, Inc, Tingsboro, MA, USA).

The "Gold Anchor markers" (manufactured by Naslund Medical AB, Huddinge, Sweden) were initially made for percutaneous implantation. The Gold Anchor needle (GA150), preloaded with a 25G marker (0.28 mm × 20 mm), can be inserted into the needle tip of a standard 22G EUS-*fine needle aspiration* (FNA) needle and the marker is left in place to be released under EUS guidance. These markers are unique in that they can be released as completely folded or straight.[31]

A new product has been developed by Cook Medical (Bloomington, Indiana, USA), the "EchoTip Ultra Fiducial Needle." Based on the flexible sheath design of the EchoTip Ultra 22G needle, it is a preloaded EUS-guided fiducial needle and it allows implicit placement of up to four gold fiducials. Being pre-loaded, it has the potential advantage of saving valuable procedure time when compared to traditional methods of manually loading fiducials. A recent randomized control trial investigated this aspect, comparing the procedure duration of EUS-guided fiducial insertion between the traditional back-loaded needle (Visicoil) and preloaded needles (EchoTip Ultra Fiducial Needle) in patients with pancreatic cancer. The study demonstrated a shorter time using preloaded needles, with no differences in feasibility, technical success, or AE.[48]

The «Beacon FNF needle» (Medtronic, Dublin, Ireland) is pre-loaded with two gold fiducial markers available in two sizes: 22G and 19G. Each fiducial marker features a knurled (ridged) exterior design that may help reduce migration. The needle has a deployment indicator that provides visual and tactile feedback for the deployment of each fiducial marker. These fiducials, available in the US, have now been approved for clinical practice also in Europe.

The latest tool available on the market is "LumiCoil Platinum Fiducial Marker" from Boston Scientific (Marlborough, Massachusetts, USA) which is manually backloaded on a standard 22G EUS needle. There are two marker options: straight or with the shape of an 8.

Recently, a new injectable hydrogel made of iodinated polyethylene glycol particles ("TraceIT Fiducial Marker," Augmenix Inc., Waltham, MA, USA) has been approved and used as a liquid fiducial on solid tumors. One prospective non-randomized study compared 3 types of fiducial markers in 30 patients with esophageal cancer who were referred for RT.[26] Different kinds of fiducials were used: a solid gold marker (Cook Medical, Limerick, Ireland), a flexible coil-shaped gold Visicoil marker (Visicoil; Core Oncology, Santa Barbara, Calif, USA) and a radiopaque polyethylene glycol-based hydrogel marker (TraceIT Tissue Marker; AugmenixInc, Waltham, Mass). The procedure was feasible and safe for all fiducial types, and all of them could be used on CT for target volume delineation. Flexible coil-shaped gold marker had a better visibility than the others.

Slagowski *et al.*[52] built a phantom to quantitatively evaluate the visibility and artifacts of commercially available fiducial markers to optimize their selection for image guided SBRT. They placed various fiducials within the phantom that can be delivered under EUS guidance, pre- or backloaded, from various manufacturers of various materials, sizes, and shapes. A survey between radiation oncologists ranked each fiducial in terms of clinical usefulness and the conclusion was that a balance of artifacts and visibility has to be found for the best treatment.[52]

Technical approach

The EUS-guided fiducial marker placement is technically similar to the EUS-guided biopsy, but it may be some more challenging especially in case of pancreatic cancer after chemotherapy. The tumor is hard because of the desmoplastic reaction, the borders are sometimes less clear to be recognized in detail and advancing and deploying of the marker into different areas of the target lesion may be difficult. Video 1 shows EUS-guided fiducials placement after first line chemotherapy in a patient with locally advanced pancreatic cancer.

Loading of fiducial markers into the needle can be performed by using a "front-loading" (anterior) technique, or a "backloading" (retrograde) approach.[53] When the first modality is used, the needle first punctures the target area, then the stylet is removed and the marker is advanced into the needle lumen reinserting the stylet until the deployment is reached.[40] Most previous studies used a backloading approach, in

which the fiducials were back-loaded into the tip of the needle and the stylet slightly withdrawn, followed by sterile bone wax sealing of the needle tip. When the needle enters into the tumor, the stylet is advanced and thus deploying the marker by pushing them forward into the lesion.[54] A variation of backloading modality has been developed to reduce air introduction in the tumor, because that effect hampers EUS visualization.

Coronel *et al.* explained the technique in a dedicated "tools and techniques" section with a video where both backloaded and preloaded fiducials needles were used to target a pancreatic cancer before SBRT.[55]

In the hydrostatic technique[42] the stylet is completely removed and the needle channel is then flushed with sterile water. The fiducials are back-loaded into needle tip and, after the puncture of the tumor, the markers are subsequently deployed by using 1–2 mL of sterile water injected into the needle channel. This technique has the potential to overcome difficulties regarding angulations of the endoscope which is frequently encountered during push-stylet technique. The number of fiducials placed depends on the endoscopists' preference, the indications given by the radiation oncologists, as well as the size and location of the tumor. In general, 2–6 markers are placed at the margins and center of the tumor. Finally, another variation is the use of fluoroscopy during needle insertion, which can confirm proper fiducial placement. However, it is not mandatory, and in a recent large case series,[25,42,45] the authors reported the feasibility and the safety of EUS-guided fiducial marker placement without the aid of fluoroscopy.

Figures 1-3 demonstrate the results of EUS-guided fiducial placement in a patient with a small pancreatic tumor. After 2–3 days from the placement (the settling time to avoid target changes during the treatment), a simulation CT scan is performed and a map of the area to be treated is drawn. Figure 4 describes how the target area is defined during the simulation CT scan.

DISCUSSION

Pros

As reviewed above, EUS-guided fiducial marker placement is characterized by a high technical success rate ranging between 85% and 100% in different clinical settings. When carried out by experienced teams the procedure is relatively safe showing favorable AE rates that range between 1.7% and 7.6%. Most of the reported AE are minor complications with spontaneous resolution that do not require interventional measures. Depending on the location of placements the migration rate ranges from relatively low (7%) in pancreatic cancers and lymph nodes, up to significant rates (30%), for example in rectal cancers, and the procedure could be repeated if needed.

One of the major benefits of fiducials is that they can be placed without fluoroscopy and this may allow for more widespread adoption of this technique in Endoscopic Units where EUS and fluoroscopy are not simultaneously available.

Ideally, well-placed fiducial markers allow the focal dose escalation toward higher targeted radiation doses similar to those typically used in radiotherapy modalities

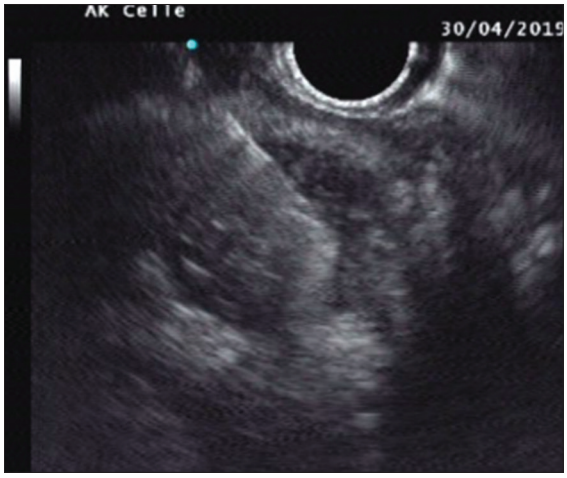

Figure 1. Fiducial needle is seen as an hyperechoic line, just like the FNA needle

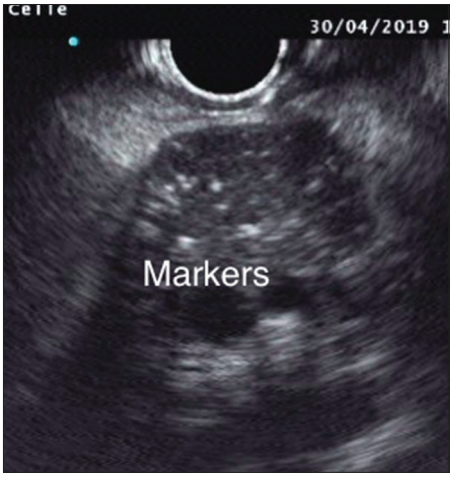

Figure 2. At the end of the placement, the fiducials are seen as small hyperechoic segments within the tumor

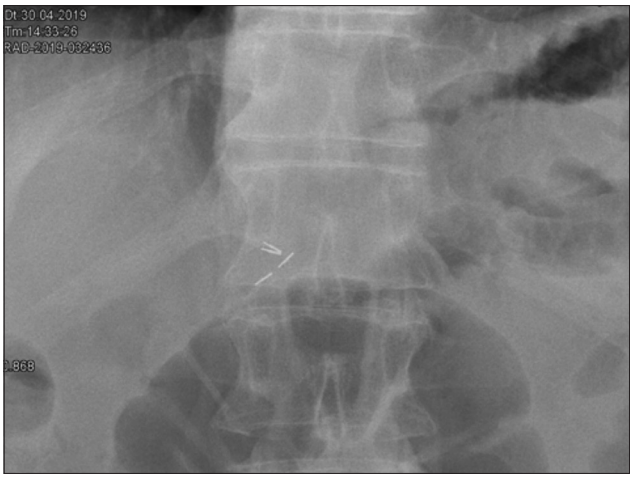

Figure 3. The fluoroscopic scan confirms the right placement with good visibility at Rx

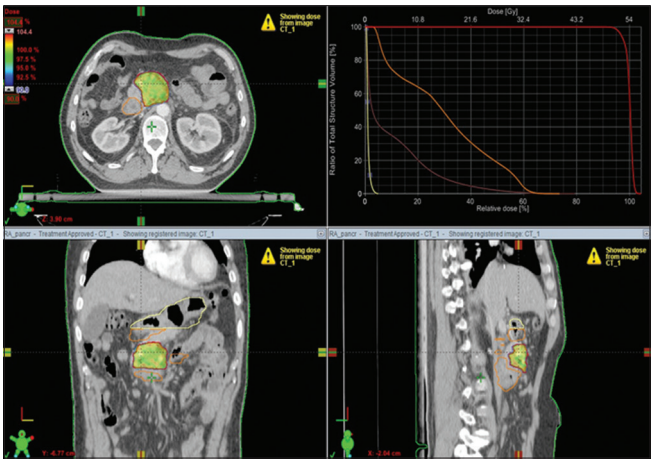

Figure 4. The target area is defined during the simulation computed tomography scan

like SBRT (typically 35–40Gy in 3–6 fractions, but also up to 55 Gy in 5 fractions; NCT03340974). As such, fiducial markers allow proper respiratory motion management and adequate tumor visualization to spare neighboring organs at risk, most notably the duodenum from the high radiation doses of SBRT. The following would allow the delivery of high radiation doses specifically to the pancreatic tumor, with the potential for better local control. Thus, fiducial markers also have the potential to eventually facilitate margin-negative tumor resection for patients that undergo surgery, while ensuring that the adjacent organs of the GI tract do not receive high radiation doses and remain relatively spared of severe radiation-induced lesions.

Cons

However, some caveats have to be considered prior to wide-spread use of fiducial marker placement techniques in various cancer patients: the oncologic benefits of fiducials are unclear since there is a tremendous lack of randomized prospective comparative studies. Hence, this interventional EUS-technique needs to be standardized, refined, and eventually assessed for its clinical efficacy by scientific evaluation.

Following neoadjuvant multidrug chemotherapeutic schemes, the response of the tumor may lead to a dramatic decrease of tumor volume. In these cases of small masses still attached to the vessels, the goal would be to standardize how many fiducials have to be placed and where. Would it be enough to insert one fiducial in the middle of the tumor? This would reduce interferences due to scatter effect during simulation CT. Moreover, the portal hypertension, which often accompanies pancreatic cancer with gastric and duodenal varices and collateral venous vessels, could make the placement of many fiducials more difficult and with a higher risk of bleeding.[56]

In some cases, there is a question of whether the introduction of a fiducial may inadvertently seed tumor along the needle track. For example, this phenomenon has been published as case reports resulting from EUS-FNA of the pancreas, but has been observed infrequently during the clinical practice of SBRT for pancreatic cancer, and therefore is considered to be a minimal risk. However, the fact that the phenomenon is rarely observed does not mean it is not important. The potential for needle track seeding in pancreatic cancer from a fiducial placement would be more relevant in patients who are borderline resectable and undergoing SBRT with the intention of surgery in the future with a curative intent and less so in advanced or unresectable cases. Fortunately, in pancreatic head cancers who would have undergone trans-duodenal fiducial placement, the needle track would be included in the surgical specimen but in pancreatic body/tail cancers who undergo transgastric fiducial placement, and eventually get a curative resection, the potential of a recurrence in the needle track along with gastric wall is there.[57]

Specific limitations of EUS-guided fiducial placement may include a relatively small window of accessibility for the marker needle which may be caused by factors such as surgically altered anatomy, spread of cancer near major vessels, or difficult position of the echoendoscope hampering needle placement and movements. Failure of marker deployment is frequently

related to mechanical and technical factors such as angled endoscope or needle malfunction, or they are caused by characteristics of the individual tumor, for example, calcified tissue. Particularly factors such as tumor hardness due to desmoplastic reaction may deviate the needle and may alter the feeling of the fiducials release in a hard tissue. Other factors such as inadequate tumor visualization due to post-surgical anatomy and the interposition of vessels could further hamper the placement of fiducials.

CONCLUSIONS

EUS-guided placement of fiducial markers to facilitate image-guided radiotherapy in selected cancer patients has become a new tool in clinical oncology and it may be part of the multidisciplinary approach to a patient with a cancer. The technique appears to be safe and easy to handle, at least in hands of experienced endosononographers. The placement of tiny metal fiducials is generally safe and can be successfully applied in most patients. It resembles a technique that could increase the success of local radiotherapy and minimize side effects of targeted radiation therapy. However, data on its oncologic efficacy are sparse, particularly when compared with other competing techniques such as endoscopic clips or CT-guided marker insertion of lesions. In the future, the clinical indications for the optimal use of fiducials need to be elucidated further and the technique should be standardized, thus facilitating further research about its oncologic efficacy.

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Conflicts of interest
Christoph F. Dietrich is a Co-Editor-in-Chief of the journal, Manoop S. Bhutani is a Senoir Associate Editor, and Alberto Larghi is an Editorial Board Member. The article was subject to the journal's standard procedures, with peer review handled independently of the editors and their research groups.

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