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EUS-guided hydrogel injection to separate pancreatic head carcinoma from duodenum for enhanced radiotherapy: Multi-site feasibility study

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ABSTRACT

Background and study aims The proximity of a pancreas head tumor to the duodenum often limits delivery of an ablative dose of radiation therapy. This study evaluated the feasibility and safety of using an injectable polyethylene glycol (PEG) hydrogel between the head of the pancreas and duodenum.

Patients and methods In a multi-site feasibility cohort study of patients with localized pancreatic cancer, PEG hydrogel was injected under endoscopic ultrasound guidance to temporarily position the duodenum away from the pancreas. Procedure characteristics were recorded, including hydrogel volume and space created. Patients were monitored for adverse events (AEs) and radiotherapy toxicity.

Results In all six intent-to-treat patients (four with borderline resectable, two with locally advanced disease), the ability to place and visualize PEG hydrogel and create space between the duodenum and the head of the pancreas was successful. There were no procedure-related AEs resulting in radiotherapy delay. There were no device-related AEs and no reports of pancreatitis.

Conclusions PEG hydrogel was successfully placed, created space between the duodenum and the head of the pancreas, and was not associated with major toxicity. Enhancing radiotherapy for pancreatic cancer by using PEG hydrogel to create peri-duodenal space could have beneficial implications for treatment and warrants more exploration.

Introduction

Pancreatic cancer has a poor prognosis, with over half of cases diagnosed at distant stage [1]. Fewer than 20% of patients have resectable disease [2]. Delivery of high-dose ablative radiation therapy (RT) is effective for some cancers, but for the pancreas, the amount of radiation possible is limited by surrounding anatomy and the risk for significant duodenal toxicity [3].

The concept of creating space proximal to a primary tumor has shown promise in prostate cancer populations undergoing RT [4, 5], prompting an interest in its application for other cancers. Polyethylene glycol hydrogel [6, 7, 8] addresses some limitations of previously tested biomaterials used for spacing [9]. Hydrogel can be distributed evenly for precise and durable spacing, and the water-soluble molecules reliably degrade and excrete through renal filtration months after application [10].

There is evidence from porcine and cadaver studies of the feasibility of endoscopic ultrasound (EUS)-guided injection of PEG hydrogel into the space between the head of the pancreas (HOP) and the duodenum, increasing space for RT administration [6, 11]. A first-in-human single-site pilot study showed feasibility of administering PEG hydrogel and creating space in patients with pancreatic cancer undergoing ultra-hypofractionated stereotactic body radiotherapy (SBRT) [7]. In this multi-site study of a similar population, we sought to evaluate with greater generalizability the feasibility, RT benefits, and safety of using an injectable PEG hydrogel to create space between the pancreas and duodenum. Here we report on technical and safety outcomes of PEG hydrogel administration; RT findings have been reported separately [12].

Patients and methods

Study design

This was a multicenter prospective, single-arm early feasibility study (April 24, 2019-May 1, 2021) of a PEG hydrogel used as a spacer in six patients with localized (resectable, borderline resectable or locally advanced) pancreatic cancer for whom a course of RT was indicated. The trial was registered at ClinicalTrials.gov (NCT03998566).

Patients

Inclusion criteria were: age ≥ 18 years; biopsy-confirmed localized pancreatic cancer in the head or neck of the pancreas visualized via CT or other imaging modality with no evidence of distant metastasis as defined by National Comprehensive Cancer Network guidelines; tumor clearly delineable from duodenum and no clear evidence of invasion of the duodenum; RT was indicated; medically fit to undergo endoscopy; screening/baseline laboratory testing met established laboratory value criteria; and life expectancy of at least 9 months.

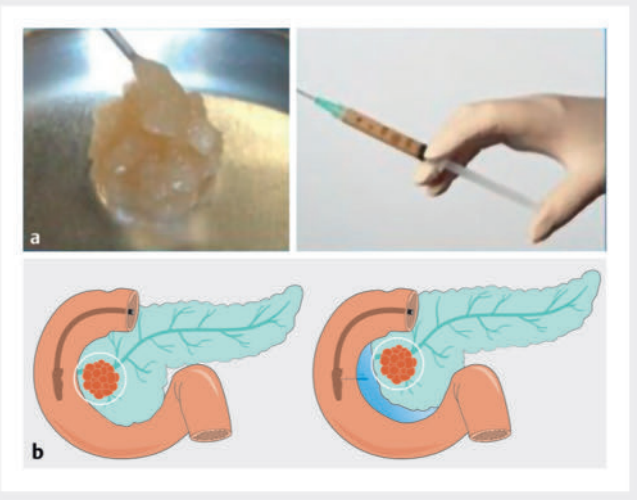
Patients were excluded for any of the following: RT was contraindicated; history of previous thoracic or abdominal RT; presence of tumor invasion of the duodenum detected on EUS at time of biopsy; previous Whipple procedure or other resection of pancreatic tumor prior to screening; active gastroduodenal ulcer or uncontrolled watery diarrhea; history of chronic renal failure; history of uncontrolled diabetes; enrolled in another investigational drug or device trial that would clinically interfere with this study; or unable to comply with the study requirements or follow-up schedule.

Patients provided written consent before study-specific procedures were performed. The study was approved by the Institutional Review Board of the respective clinical sites (July 3–31, 2018).

Index procedure

TraceIT Tissue marker ("TraceIT," Augmenix, Waltham, Massachusetts, United States) is an absorbable radiopaque PEG hydrogel material, currently FDA-cleared to radiographically mark soft tissue during a surgical procedure or for future surgical procedures for at least three months after injection. In this study, TraceIT was administered for an off-label use, soft tissue spacing in the duodenal pancreatic groove, to temporarily position the duodenum away from the pancreas in patients undergoing RT for treatment of pancreatic cancer.

Enrolled patients underwent placement of fiducial markers into the pancreatic head tumor and peri-duodenal administration of PEG hydrogel within the same EUS procedure. Patients were positioned in the left lateral position and a linear EUS was used to identify the duodenal wall, pancreas head tumor, and HOP interface. Under EUS guidance, a 22G fine needle aspiration was advanced into the potential space between the duodenum and pancreas. PEG hydrogel was prepared per the instructions for use. The single-use kit consists of a pre-filled glass syringe containing the absorbable radiopaque cross-linked PEG hydrogel spacer and a delivery system (syringe and needle) (▶ **Fig. 1a**). Immediately before injection, the PEG hydrogel was mixed five times between the two syringes and placed in a plastic receiving syringe. Once the needle was confirmed to be in the proper position, hydrogel was injected in 1- to 2-mL increments. This process was repeated as the needle was repositioned around the target (▶ **Fig. 1b**).



▶ **Fig. 1** PEG hydrogel. **a** Injectable PEG hydrogel used in the study. **b** PEG hydrogel injection (blue) into the peri-duodenal space (white outline) between the duodenum and pancreas tumor using endoscopic ultrasound guidance.

After each procedure, the following was collected: ability to access injection site and inject PEG hydrogel; average duodenal space measurements on CT measured at three points along the HOP; injection procedure duration; ease of device use; device malfunctions; and adverse events (AEs) per NCI Common Terminology Criteria for Adverse Events (CTCAE v4). Any event precipitating an intestinal acute CTCAE score of 2 or higher was documented as an AE.

RT simulation planning was performed prior to and following PEG hydrogel placement for evaluation and comparison of duodenal dose/dose distribution and to assess differences in RT dosing parameters. RT was to be initiated no later than 28 days following PEG hydrogel administration.

Within 2 to 6 weeks after RT completion, patients were restaged to determine whether they could progress to surgery. If surgical resection was successful, pathological data were recorded. All patients were evaluated at minimum 3 and 6 months post-index procedure. MRI was performed at the six-month visit to evaluate for PEG hydrogel presence in unresected patients. Throughout the study, patients were assessed for duodenal AEs. Additional follow-up clinic visits were performed per standard care at 12 and 18 months at minimum.

Study endpoints

Feasibility was defined as technical success, i.e., the ability to administer and visualize PEG hydrogel and create space between the duodenum and HOP; the technical success rate was calculated as the proportion of patients who achieved technical success in the intention-to-treat (ITT) population. RT benefits were assessed via comparison of pre- and post-administration RT plans and have been reported separately [12].

Patients were monitored for AEs and RT toxicity (using CTCAE v4) and in particular, for PEG hydrogel administration procedure-related events resulting in a delay in initiation of RT, as reviewed and adjudicated by a Clinical Events Committee.

Additional data collection included: incidence of resection; histology of duodenal tissues when resection was performed; incidence of acute (≤ 3 months) and late (> 3 months) duodenal toxicity for unresected patients; theoretical dose escalation from post-injection treatment plan (reported separately); PEG hydrogel persistence (6 months post-treatment in unresected patients); and progression-free and overall survival through follow-up. Histology of the duodenal tissues was assessed when resection was performed. The pathological duodenum damage score was rated by a local board-certified gastrointestinal surgical pathologist using the methods outlined by Verma et al. (1 = no/minimal signs of mucosal damage, 2 = moderate damage, 3 = severe damage) [13]. Pathologic response was graded according to the College of American Pathologists (CAP) Protocol for pancreatic cancer [14].

Table 1 Patient characteristics.

Baseline demographics and clinical characteristics		
		Patients (N = 6)
Age (n = 6 patients)	Mean ± SD	69.5 ± 7.4
	Median	69.5
	Range	60.0 – 80.0
Sex	Male	4 (66.7%)
	Female	2 (33.3%)
Ethnicity	Hispanic or Latino	1 (16.7%)
	Not Hispanic or Latino	5 (83.3%)
Race	White	3 (50.0%)
	Black/African American	2 (33.3%)
	Asian	1 (16.7%)
	American Indian/Alaska Native	0 (0.0%)
	Native Hawaiian/Pacific Islander	0 (0.0%)
Smoking history	Current smoker	0 (0.0%)
	Past smoker	2 (33.3%)
	Never smoked	4 (66.7%)
BMI (n = 4 patients)	Mean ± SD	29.9 ± 5.4
	Median	32.1
	Min, max	22.0 – 33.5
Pancreatic cancer medical history		
Neoadjuvant therapy for pancreatic cancer	No	0 (0.0%)
	Yes	6 (100.0%)
Largest pretreatment dimension of tumor (cm) (n = 6 patients)	Mean (SD)	3.0 ± 0.6
	Median	3.2
	Min, max	2.2–3.5
Initial resection status	Borderline resectable	4 (66.7%)
	Locally advanced	2 (33.3%)
Initial tumor anatomic stage	Stage 0	0 (0.0%)
	Stage IA	0 (0.0%)
	Stage IB	3 (50.0%)
	Stage IIA	1 (16.7%)

SD, standard deviation; BMI, body mass index.

Screening/baseline data collection

Information collected at screening and baseline included: demographics; disease documentation (tumor location, initial resectability status, tumor staging, pretreatment tumor dimension); medical/surgical history and status (concomitant medical conditions, prior surgeries, prior therapies); physical examination; assessment of baseline duodenal symptoms; and baseline concomitant medications.

▶ **Table 2** Injection characteristics by patient.

Patient	22 gauge dilution ratio	Number of injections	Total volume	Pre-injection space (mm)	Post-injection space 1 (mm)	Post-injection space 2 (mm)	Post-injection space 3 (mm)
1	1:1	3	3 mL	1	6.84	3.96	8.95
2	3:1	3	2.5 mL	1	5.56	7.89	5.73
3	3:1	4	3.75 mL	1	10.78	7.99	6.76
4	3:1	3	3 mL	1	5.85	3.19	3.89
5	No dilution	12	10 mL	1	12.35	10.52	9.16
6	No dilution	6	6 mL	1	10.16	8.78	10.83

Results

Enrollment in analysis population

A total of eight patients were consented. One was consented but did not meet the eligibility criteria and was deemed a screen failure. Another was consented but withdrew consent before eligibility criteria was verified. This left six patients in the ITT population. There were no major protocol deviations with the potential to affect the study.

Baseline characteristics

The median and age range of the patients enrolled were 69.5 and 60 to 80 years, respectively (▶ **Table 1**). The majority were male (66.7%) and 50.0% were White. All subjects received neoadjuvant therapy for pancreatic cancer. There were four patients (66.7%) who were in borderline resectable stage while two patients (33.3%) were in the locally advanced stage. RT planning and treatment characteristics have been reported separately; briefly, five of six patients were treated with SBRT and one with intensity-modulated RT.

Feasibility/technical success

The ability to place and visualize PEG hydrogel, creating space between the duodenum and the HOP was successful in all patients (100%, N = 6).

PEG hydrogel administration and space created

The median time between hydrogel injection and initiation of RT was 18 days (range: 9–19 days). PEG hydrogel was distributed in small volumes (approximately 1 to 2 mL per injection for up to a total of 10 mL) at several areas along the proximal portion of the duodenum in the areas closest to the HOP. The precise location of each injection varied according the anatomy and tumor characteristics of each case. ▶ **Table 2** presents injection characteristics by patient. ▶ **Fig. 2** shows the space created in two patients on EUS. ▶ **Fig. 3** shows the hydrogel between the duodenum and pancreatic head tumor on CT scan.

Of the three unresected patients able to be assessed for persistence at two to six weeks post-RT, PEG hydrogel was still present in all. At 6 months post-RT, in the two patients who received imaging and were assessed for persistence, PEG hydrogel was not detected. Stability was similar from the time of placement to 2 to 6 weeks afterward, based on the distance from a fiducial marker (8.2 ± 5.9 mm vs 8.5 ± 10.2 mm, N = 3).

Safety/adverse events

No procedure-related AEs resulting in a delay in RT initiation were reported. Two patients (33.3%) had procedure-related AEs; these took place at two sites. One of these patients was reported to have sinus bradycardia; the other had nausea, chills, dehydration, and stomach pain. All of these AEs were noted as resolved. There were no device-related AEs. There were no reports of pancreatitis, perforation, bleeding, or infection.

Progression-free and overall survival

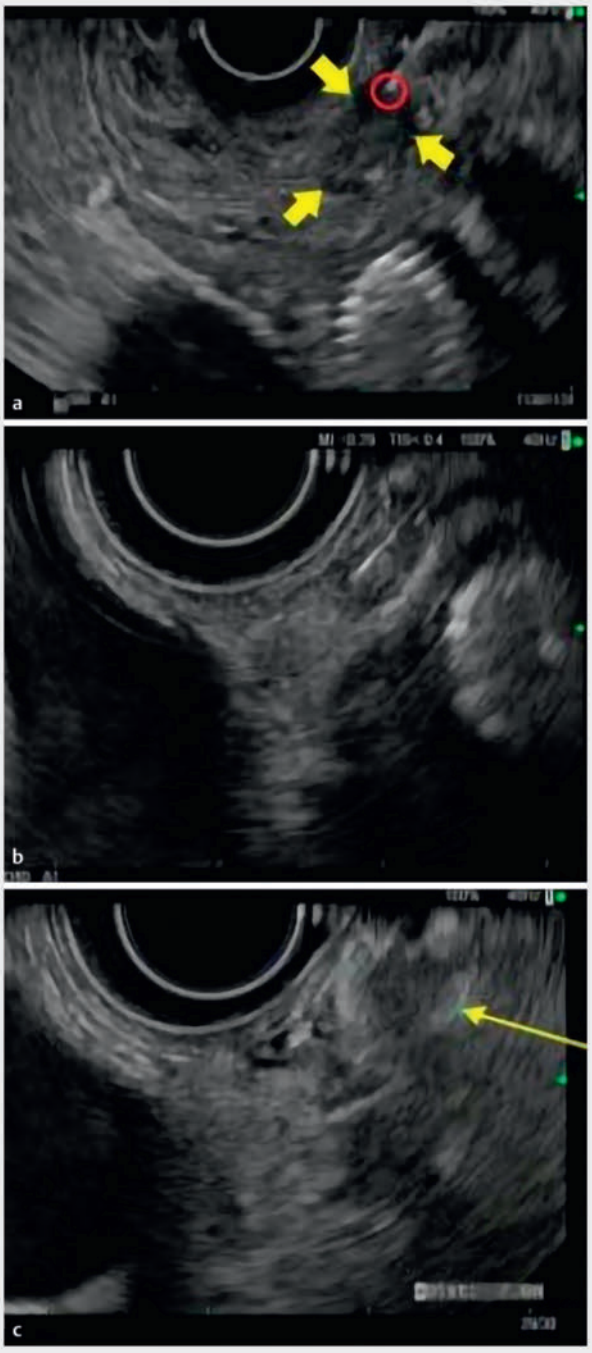
Mean progression-free survival for all patients was 17.6 ± 4.7 months, ranging from 8.5 to 21.2 months (▶ **Table 3**). Progression-free survival was longer for the three patients with resected tumors compared to the three who did not undergo resection (18.9 ± 2.3 months vs 16.2 ± 6.8 months). Overall mean survival (to death or end of study) was 21.6 ± 6.9 months (12.0 to 31.3 months).

Acute and late duodenal toxicity

All six patients had one or more grade 1 duodenal AEs, with 100% (6/6) having acute and 66.7% (4/6) having late duodenal AEs. Four patients (66.7%) had grade 2 duodenal AEs. Of these four patients, three had acute and three had late duodenal AEs. Two patients (33.3%) had grade 3 duodenal AEs occurring after three months. No patients had grade 4 or 5 duodenal AEs. (See Supplementary Material for tabular summary.)

Pathology

Of the three patients that qualified for tumor resection, 100% showed no/minimal signs of mucosal damage. One subject (33%) had complete pathologic response (no cancer cells detected on pathology specimen), and two (66.7%) had near complete response. Pathology is included in tables in the **Supplementary Material**.



▶ **Fig. 2** Injection and post-injection EUS images. **a** Transduodenal PEG hydrogel injection with a 22 G EUS FNA needle (needle tip circled in red) with a hypoechoic nodule (margins indicated by arrows) developing around the needle tip after the injection. **b** Injection of PEG hydrogel with 22 G EUS FNA needle between the duodenum and the pancreatic head mass with a hypoechoic nodule forming around the tip of the needle. **c** After injection of PEG hydrogel in the same patient as in **Fig. 2b**, there is a hypoechoic nodule (arrow) separating the pancreatic head tumor from the duodenal wall by 7.6 mm.

Discussion

High-dose ablative radiation is an important advancement in RT, enabling precise delivery of high-dose radiation to a small tumor volume [15, 16]. SBRT (the approach used in the majority of patients in this study) has shown promise for use in pancreatic cancer [17, 18], but the tissues adjacent to the pancreas raise substantial concerns about late gastrointestinal toxicity [19, 20]. The duodenum, a radiosensitive organ, limits RT dosing of the HOP [15, 21].

This study adds to findings from animal and cadaver studies and a single-site pilot study [6, 7, 11], all of which showed the feasibility of administering and creating space with PEG hydrogel between the HOP and the duodenum. The current study provides evidence for a lack of AEs that would delay RT.

A leading concern following injection of a spacing agent would be causing acute pancreatitis. In this study, there were no reports of pancreatitis following the index procedure. Another potential concern is injection into the duodenal wall and resulting toxicity. The patients in this study who were resected did not have any significant toxicity to the duodenal wall. In the previous porcine study, the same PEG hydrogel was injected directly into duodenal wall and no necrosis was observed [11].

Conclusions

Although the multi-site design of this study builds on the previous evidence of feasibility, conclusions about the clinical relevance of PEG hydrogel for use in borderline resectable or locally advanced pancreatic cancer are limited by small sample size and the high morbidity and mortality rate. Poor survival outcomes are typical of a pancreatic cancer population, but none of the serious AEs that led to death were attributed to PEG hydrogel or RT. The concept of enhancing RT for pancreatic cancer by using PEG hydrogel to create peri-duodenal space warrants further investigation.

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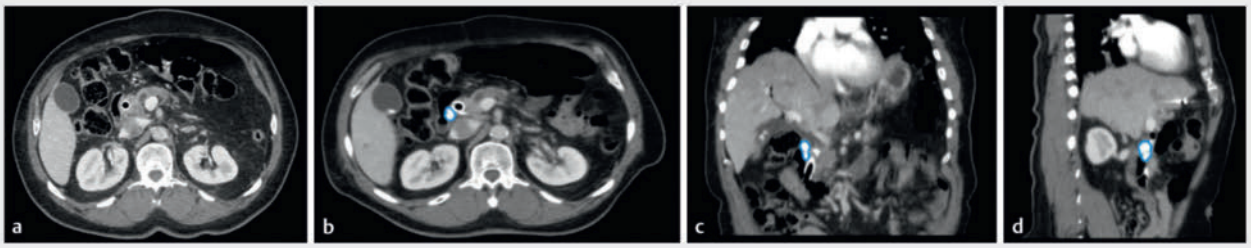

▶ **Fig. 3** PEG hydrogel between the duodenum and pancreatic head tumor on CT scan. **a** Contrast-enhanced CT scan showing pancreatic head tumor and metal biliary stent prior to PEG hydrogel injection. **b**, **c**, **d** Contrast-enhanced CT scan post-injection showing the PEG hydrogel (in blue outline) clearly visible and separating the duodenal wall from the pancreatic head for stereotactic radiation therapy (axial, coronal, and sagittal planes in same patient as shown in **Fig. 3a**).

▶ **Table 3** Progression-free and overall survival.

		Total (N = 6)	Resected (N = 3)	Not Resected (N = 3)
Progression-free survival (months) (in patients with tumor progression event)	Mean ± SD	17.6 ± 4.7	18.9 ± 2.3	16.2 ± 6.8
	Median	18.9	18.8	19.0
	Min-max	8.5–21.2	16.7–21.2	8.5–21.1
Overall survival (months)	Mean ± SD	21.6 ± 6.9	20.0 ± 3.4	23.3 ± 10.0
	Median	21.7	20.0	26.5
	Min-max	12.0–31.3	16.7–23.4	12.0–31.3

SD, standard deviation.

Conflict of Interest

Manoop S. Bhutani: Nanobiotix, Trisalis, Oncosil, Starpax Medical, Augmenix/Boston Scientific. Amol K. Narang: Boston Scientific, Flavocure, Nanocan Therapeutics Corporation. Kai Ding: Boston Scientific. Brenna Casey: no COI to declare. Kumar Krishnan: Boston Scientific, Olympus. Eugene J. Koay: AstraZeneca, RenovoRx, Quantum Aurea Capital, Kallisio, International Cholangiocarcinoma Research Network. Theodore S. Hong: Synthetic Biologics, Novocure, Boston Scientific, Inivata, Merck, GSK, PanTher Therapeutics, Lustgarten, Taiho, AstraZeneca, BMS, IntraOp, Ipsen. Joseph M. Herman: Histosonics, Boston Scientific, Canopy Cancer Collective, 1440 Foundation, BTG. Kristen H. Griffin: Boston Scientific (employee). Eun Ji Shin: Boston Scientific.

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Clinical trial

ClinicalTrials.gov (http://www.clinicaltrials.gov/)
Registration number (trial ID): NCT03998566
Type of Study: Multi-Center Feasibility Study

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