Demonstration of Safety and Feasibility of Hydrogel Marking of the Pancreas—Duodenum Interface for Image Guided Radiation Therapy (IGRT) in a Porcine Model: Implications in IGRT for Pancreatic Cancer Patients

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Abstract

Purpose: To test the feasibility and safety of injecting a high-contrast hydrogel marker at the head of the pancreas (HOP) and duodenum interface and assesses the marker visibility on cone beam computed tomography (CBCT) to localize this important boundary during image guided radiation therapy in a porcine model.

Methods and Materials: This was a 2-stage study. The feasibility/visibility stage evaluated the ability to place the hydrogel using endoscopic ultrasound guidance on 8 swine (4 euthanized at post-injection day 8, 4 euthanized at post-injection day 22) and assessed the quality of visibility of the marked location on CBCT in the longer-surviving group. The risk assessment stage evaluated the toxicity of targeted intrapancreatic injections (3 swine) and intramural duodenal wall injections (3 swine) to assess toxicity of a misplaced hydrogel injection. All swine underwent postmortem examination and histopathologic studies.

Results: The HOP—duodenum interface was successfully marked using hydrogel in 6 of the 8 swine. Histopathologic examination of the 6 successful hydrogel injections showed mild/minimal (4 cases) or moderate (2 cases) reactive inflammation isolated to the injection site. Of the 4 swine survived to 22 days, 3 demonstrated successful hydrogel placement at the HOP—duodenum interface, and this marked location was clearly visible for positional guidance on CBCT. There was no evidence of pancreatitis or duodenal toxicity in the swine undergoing targeted intrapancreatic or intramural duodenum injections for the risk assessment stage.

Conclusions—We demonstrate the feasibility and safety of injecting a hydrogel marker to highlight the HOP—duodenum interface that has acceptable visibility on CBCT. This technique, translated to humans, enables on-board visualization of this important boundary between the radiation target and dose-limiting, radiosensitive duodenum, facilitating efforts to safely deliver dose-escalated radiation therapy. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Summary

This study presents the feasibility and safety of marking the pancreas and duodenum interface with a high-contrast hydrogel and demonstrates acceptable visibility of the marked location on cone beam computed tomography using a porcine model. Translation of this technique to the radiation therapy treatment of pancreatic cancer patients would enable on-board visualization of this important boundary between the radiation target and the dose- limiting duodenum, facilitating future efforts toward safe dose escalation.

Introduction

Dose escalation with image guided intensity modulated radiation therapy (RT) and stereotactic body RT (SBRT) are potential strategies to improve local control and possibly overall survival in unresectable pancreatic cancer (1–5). Challenges to dose escalation include both the radiosensitivity of the surrounding gastrointestinal organs, particularly the duodenum directly adjacent to the head of the pancreas (HOP), and limitations in soft-tissue contrast of on-board cone beam computed tomography (CBCT) prohibiting clinicians from being able to visualize this boundary (6, 7).

TraceIT (Augmenix, Bedford, MA) is a high-contrast hydrogel made of iodinated polyethylene glycol and water (approximately 90% water, 9.25% polyethylene glycol, and 0.75% iodine). The hydrogel paste creates a bleb of particles at the needle tip on injection. This bleb remains dimensionally stable for 3 months and is fully absorbed after 7 months. The hydrogel has a specific gravity of 1.02 and, in planning, can be treated as water. Several existing reports demonstrate its stability for marking purposes in the esophagus, bladder, and cervix (8–10).

The aim of the present study was to use a porcine model to assess the feasibility and visibility of using this hydrogel, placed via endoscopic ultrasound (EUS) guidance, to mark the HOP—duodenum interface and assess its visibility on CBCT to aid in image guided RT. Our results will set the stage for future investigations using the technique to mark the HOP

—duodenum interface in pancreatic cancer patients, to enable more accurate image guidance to facilitate dose escalation with intensity modulated radiation therapy or SBRT in patients with unresectable pancreatic cancer.

Methods and Materials

Study design

Following approval from the Johns Hopkins University Animal Care and Use Committee, 2 stages of studies using Yorkshire swine were conducted.

The first stage tested the feasibility of the hydrogel (TraceIT) placement using EUS at the HOP—duodenum interface, as previously described (11), followed by assessment of visibility of the hydrogel on on-board CBCT. Eight swine were treated with prophylactic antibiotics and anesthetized, and each swine underwent EUS to guide 2 consecutive injections of the hydrogel along the interface of the HOP and duodenum using either a 19-gauge or 21-gauge endoscopic needle. Each injection consisted of 1 mL of the hydrogel. If a 21-gauge needle was used, the hydrogel was diluted 1:1 with sterile saline to reduce viscosity for injection, and 2 mL (4 mL of 1:1 dilute TraceIT) was injected at each site. Four swine underwent contrast-enhanced computed tomography (CT) on post-injection days 1 and 7 and were euthanized on day 8 (group 1). The remaining 4 swine underwent contrast-enhanced CT on post-injection days 1, 7, and 21 and were euthanized on day 22 (group 2). Cone beam CT was performed on the swine in group 2 with successful hydrogel placement to test the visibility of the hydrogel at the longest surviving time point, simulating the anticipated time frame for completing the process of hydrogel placement to delivery of the final fraction of a course of hypofractionated SBRT in a pancreatic cancer patient. All swine underwent postmortem gross examination and histopathologic studies as described below. The procedure was deemed successful if at least 1 injection site was retained in the intended region between the duodenum and HOP.

Visibility of the hydrogel on CBCT was assessed by the radiation oncologist as follows: 0 = not visible; 1 = low visibility, unacceptable for positional guidance; 2 = visible, unacceptable for positional guidance owing to portions of the hydrogel volume with hazy appearance; and 3 = visible, acceptable for positional guidance owing to clear demarcation of full hydrogel volume.

The second stage was performed to understand the most adverse risks of the procedure, particularly misinjection of the hydrogel into the pancreas parenchyma or duodenal wall, in preparation for a future in-human clinical trial. Six pigs were dosed with prophylactic antibiotics, anesthetized, and underwent laparotomy by a veterinarian. Three milliliters of hydrogel was injected directly into the pancreas in 3 swine. Although data are lacking on the sensitivity and specificity of biochemical markers on detection of pancreatitis in swine, for completeness, blood draws were performed to assess for possibility of pancreatitis at day 0 (before injection) and at 1, 3, 5, 14, and 21 days, with killing on day 31 (12). Intramural injections within the duodenal wall were attempted in 3 swine, followed by killing on day 21. All swine were monitored clinically for changes in vitality and feeding habits by a

veterinary technician and underwent postmortem gross examination and histopathologic studies as described below.

Histopathologic assessments

All 14 swine (8 from the feasibility/imaging study and 6 from the risk assessment study) underwent necropsy with complete external and internal gross examination and histopathologic evaluation by a veterinary pathologist. Representative sections of the lungs and spleen, as well as en bloc resection of the distal pylorus, duodenum, midjejunum, pancreas, and injection sites, were collected. Tissues were fixed in formalin, hematoxylin and eosin stained, and sectioned for analysis.

Results

Feasibility and visibility study of hydrogel placement

Three of 4 swine in group 1 and 3 of 4 swine in group 2, totaling 6 of 8 swine, underwent successful hydrogel placement in the feasibility study. Table 1 summarizes the feasibility results of each injection attempt. Gross images representing both a successful injection at the interface of the HOP and duodenum and an unsuccessful injection within the wall of the duodenum are shown in Figure 1.

The hydrogel was clearly visible on all swine with successful injections on cross-sectional CT at each time point, specifically post-injection days 1 and 7 in the 3 swine in group 1 swine and post-injection days 1, 7, and 21 in the 3 swine in group 2. The mean change in volume of the hydrogel from post-injection day 1 to day 7 was –0.1 cm^3 (range, –0.3 to 0.0 cm^3) and from day 1 to day 21 was –0.1 cm^3 (range, –1.0 to 0.0 cm^3) as measured on CT. A representative CT demonstrating the hydrogel placement is shown in Figure 2.

Of the 3 swine with successful hydrogel placement in group 2, the hydrogel was visible on CBCT and graded as a 3 out of 3 (visible, acceptable for positional guidance) by the radiation oncologist in all 3 swine. The CBCT images in Figure 3 (Videos E1-E3; available online at www.redjournal.org) demonstrate visibility of the hydrogel at the longest surviving time point to simulate the anticipated time frame for completing the process of hydrogel placement to delivery of the final fraction of a course of hypo- fractionated SBRT in a pancreatic cancer patient.

Histopathologic examination of the 6 successful hydrogel injections showed mild/minimal (4 cases) or moderate (2 cases) reactive inflammation isolated to the injection site. In the 1 unsuccessful case of injection into the duodenal wall, there was no inflammation surrounding the hydrogel, which was splitting the muscularis mucosa and muscularis propia (Fig. 4).

Risk assessment study of hydrogel placement

To understand the toxicity of a direct intrapancreatic hydrogel injection, 3 swine underwent targeted intrapancreatic hydrogel injections. Compared with baseline, serum lipase and triglycerides were slightly elevated at post-injection day 5, with return to baseline levels at the subsequent blood collection performed on day 14 (Fig. 5). Consultation with a

veterinarian confirmed that the relative increase was not indicative of pancreatitis. This was supported by lack of change in appetite or animal behavior on daily checks or evidence of pancreatitis on histopathology.

To understand the toxicity of an injection within the duodenal wall, 3 swine underwent targeted intramural injections. However, on histopathologic investigation, only 1 of the 3 injections was retained intramurally. There was no clinical evidence of an adverse reaction to this intramural injection, and there was no associated inflammation, necrosis, or ulceration within the duodenum surrounding the hydrogel on histopathology.

Discussion

Existing preliminary data support optimism for the possibility of improving outcomes for patients with unresectable pancreatic cancer with dose-escalated RT (13–15). The opportunity to deliver a higher prescription dose, however, has largely been restricted to only those with >1 cm of separation between the pancreas and the closest gastrointestinal mucosa (<25% of patients in the published series) (13) or to centers with a magnetic resonance imaging—guided linear accelerator (14, 15).

The technique of HOP—duodenum marking to visualize the interface on CBCT demonstrated in this study will enable more patients to benefit from the possible survival advantages of dose escalation, owing to more reliable patient setup using improved image guidance, potentially obviating the need for such a generous minimum separation or magnetic resonance imaging guidance to visualize the anatomy. Given the promising data presented here highlighting in vivo feasibility and safety of hydrogel placement and its visibility on CBCT, an in-human clinical trial is currently being deployed at our institution in which patients with unresectable pancreatic cancer will undergo placement of both a traditional high-Z fiducial marker and the hydrogel marker before SBRT to verify a stable relationship between the 2 markers. If stability is verified, then future clinical trials will investigate the possibility of using this hydrogel as a spacer to distance the duodenum from the pancreas, further facilitating the possibility of dose-escalated RT for patients with unresectable pancreatic cancer.

Acknowledgments—

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A

B
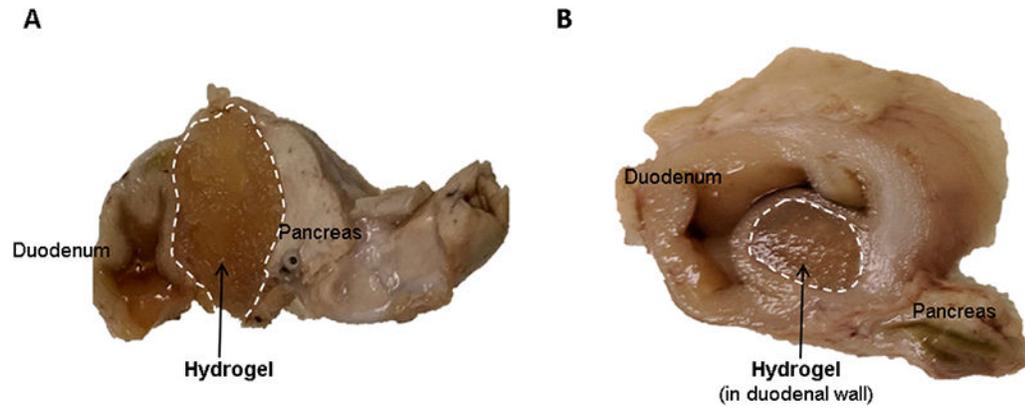
Fig. 1.
Gross pathology images representing both (A) a successful injection at the interface of the head of the pancreas and duodenum and (B) an unsuccessful injection within the wall of the duodenum.
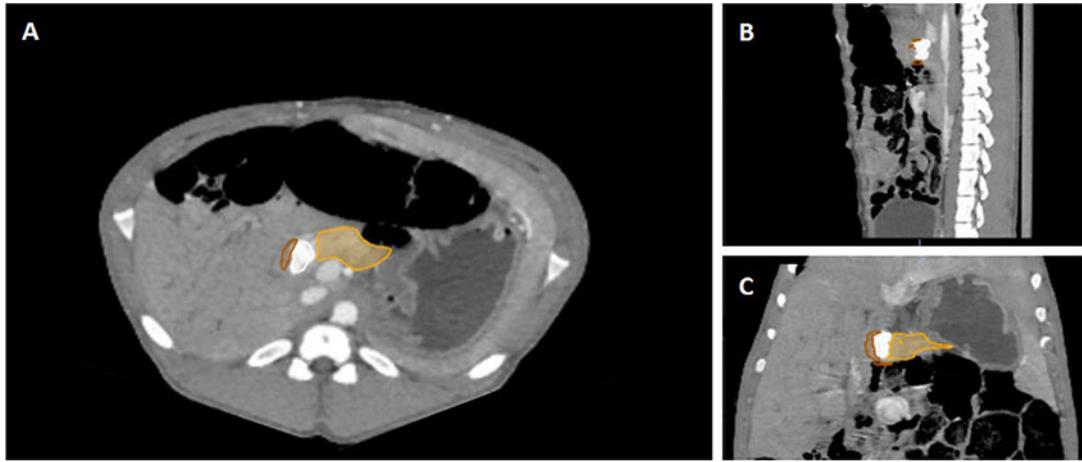
Fig. 2.
Representative computed tomography scan demonstrating successful hydrogel marker placement (high contrast, white contour) between the duodenum (brown contour) and head of the pancreas (orange contour), with clear visibility on (A) axial, (B) sagittal, and (C) coronal views. (A color version of this figure is available at www.redjournal.org.)
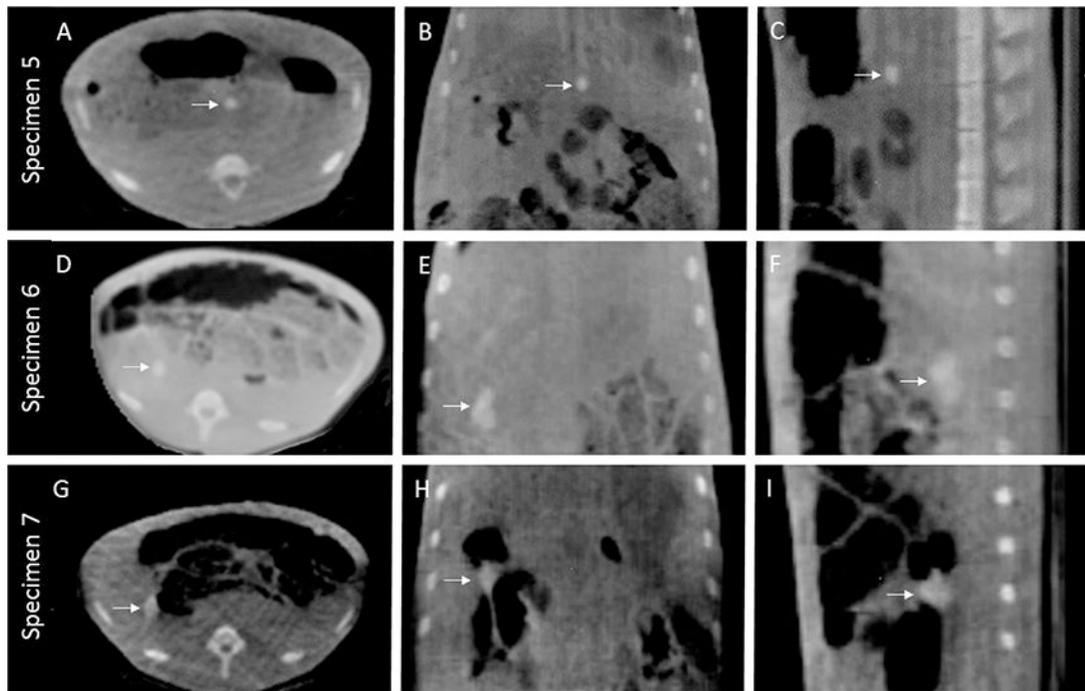
Fig. 3.
Hydrogel marker (white arrow) clearly visible and acceptable for positional guidance using cone beam computed tomography in specimen 5 (A-C), specimen 6 (D-F), and specimen 7 (G-I).
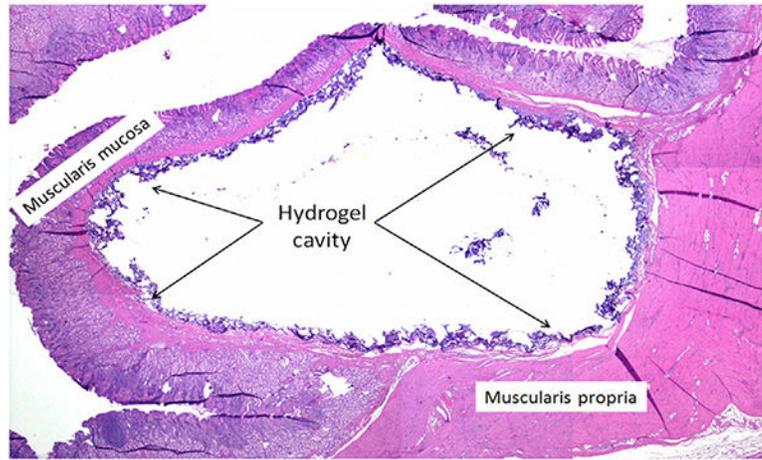
Fig. 4.
Histopathologic examination with hematoxylin and eosin staining of an injection classified as unsuccessful. Hydrogel was injected intramurally into the duodenal wall; however, there was no inflammation surrounding the hydrogel, which was splitting the muscularis mucosa and muscularis propia. Magnification, $\times 20$.
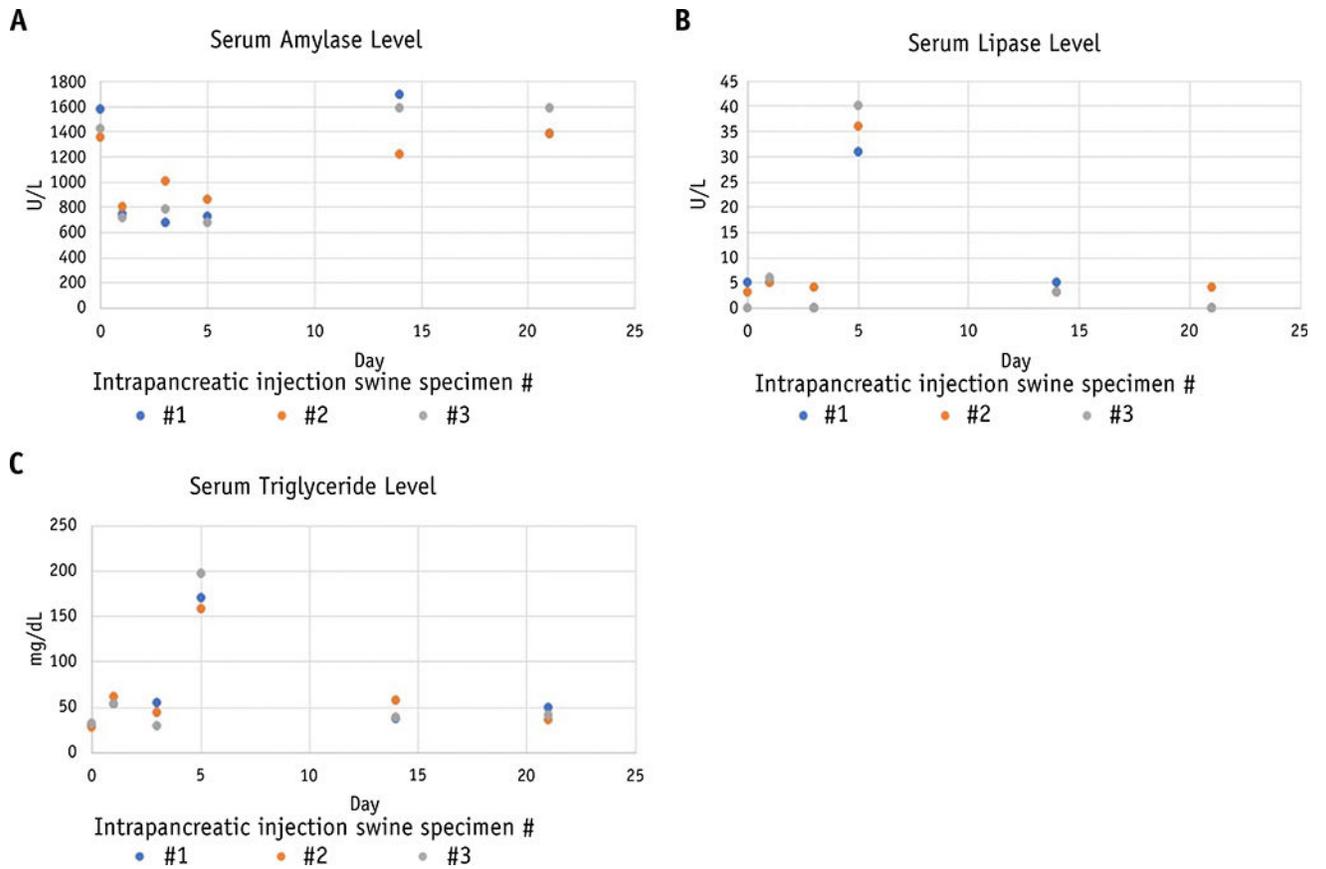
Fig. 5.
Plots of baseline and post-injection days 1, 3, 5, 14, and 21 serum (A) amylase, (B) lipase, and (C) triglyceride levels from 3 swine undergoing intrapancreatic injections.

Table 1

Summary of the feasibility of markint the HOP—duodenum interface

Specimen no.	Overall impression	Retained sites
Group 1		
1	Success	2
2	Success	2
3	Success	2
4	Failure	1 (duodenal wall)
Group 2		
5	Success	2
6	Success	2
7	Success	1
8	Failure	0

Abbreviation: HOP = head of the pancreas.