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Evaluation of a Novel Absorbable Radiopaque Hydrogel in Patients Undergoing Image Guided Radiation Therapy for Borderline Resectable and Locally Advanced Pancreatic Adenocarcinoma

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Abstract

Purpose—We assessed the feasibility and safety of placing a radiopaque hydrogel in the pancreaticoduodenal groove via endoscopic ultrasound guidance in patients with borderline resectable/locally advanced pancreatic cancer (BR/LAPC).

Methods and Materials—Hydrogel injections were done at time of fiducial placement to form blebs in the pancreaticoduodenal groove. Patients subsequently underwent simulation computed tomography (sim-CT) followed by hypofractionated stereotactic body radiotherapy (SBRT; 33 Gy in 5 fractions). Four to 8 weeks after SBRT, patients underwent CT re-evaluation for surgical candidacy and assessment of hydrogel location and size. Hydrogel placement was considered successful if identified in the pancreaticoduodenal groove on sim-CT scan. Stability was evaluated using equivalence testing analyses, with a null hypothesis of the presence of a 20% mean percentage change in volume and change in the median and mean interbleb surface distance with a P value $<.05$ required to reject the null hypothesis and conclude equivalence. For patients undergoing pancreaticoduodenectomy, hydrogel sites were histologically examined for location and local inflammatory reactions.

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Results—Hydrogel placement was successful in 6 of the 6 evaluable patients. The average changes in median and mean interbleb distances were -0.43 mm and -0.35 mm, respectively, with $P < .05$. The average change in volume from sim-CT to post-SBRT CT was -1.0% , with $P < .05$. One patient experienced grade 3 nausea after fiducial/hydrogel placement, with no other adverse events to date.

Conclusions—These data demonstrate feasibility and safety of injecting a hydrogel marker in the pancreaticoduodenal groove in patients with BR/LAPC and set the stage for a follow-up clinical trial to place hydrogel as a spacer between the pancreatic tumor and dose-limiting, radiosensitive duodenum.

Introduction

For patients with borderline resectable and locally advanced pancreatic cancer (BR/LAPC), the main challenges to the delivery of dose-escalated radiation therapy (RT) include proximity of the radiosensitive duodenum adjacent to the head of the pancreas (HOP) and limitations in soft tissue contrast of on-board cone beam computed tomography, prohibiting clinicians from being able to visualize this boundary during treatment.¹

Our group has previously reported the feasibility of placing a radiopaque hydrogel (TraceIT, Augmenix, Bedford, MA) between the HOP and duodenum to function as a marker and spacer in both in human cadaveric,² porcine,³ and patient simulation⁴ studies, with additional support for safety in the porcine studies.³ TraceIT is a high-contrast hydrogel made of iodinated polyethylene glycol and water ($\sim 90\%$ 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 the treatment planning process can be treated as water.

We report the experience of a clinical trial ([NCT03307564](#)) to assess the feasibility and safety of placing hydrogel between the HOP-duodenum interface via endoscopic ultrasound (EUS) guidance for the first time in patients with BR/LAPC. As this is the first in-human experience to attempt to use the hydrogel tissue marker to localize this important boundary, hydrogel injection was restricted to a small volume (<1 mL per injection).

Methods and Materials

Study design

After approval from the Johns Hopkins Institutional Review Boards Institutional Review Board, patients were enrolled on this prospective, single institution, single arm pilot study ([NCT03307564](#)) to evaluate the feasibility of injecting TraceIT Tissue Marker to mark the interface between the pancreas and duodenum. Six patients with pathologically confirmed BR/LAPC pancreatic adenocarcinoma delineable >1 mm from the duodenal wall planned for stereotactic body radiotherapy (SBRT) based on multidisciplinary consensus were enrolled.

Enrolled subjects were scheduled for TraceIT placement at the time of fiducial procedure. Fiducials were implanted as previously described using an EUS-guided transduodenal

approach.⁵ After fiducial placement, the pancreaticoduodenal groove was identified using a linear echoendoscope. The hydrogel was diluted with saline (3:1, 2:1, 1:1, TraceIT:Saline) to reduce viscosity for injection, with dilution concentration determined at time of injection attempt based on perceived resistance to injection at the HOP-duodenum interface. A 22-gauge EUS needle was used to inject a total of 3 to 4 hydrogel blebs, formed by 1 mL of TraceIT (or dilute TraceIT solution) along the HOP-duodenum interface. After fiducial and hydrogel placement, patients underwent computed tomography simulation (median 1 day postfiducial and hydrogel placement), followed by hypofractionated SBRT (33 Gy in 5 fractions) within 1 month from simulation as previously described.^{6,7} After SBRT, patients proceeded with standard of care follow-up, which included CT scan at 4 to 8 weeks after SBRT to determine resectability. Patients were assessed for side effects from hydrogel placement at the time of the placement procedure, simulation, and surgical re-evaluation visit.

If a patient on study proceeded to pancreaticoduodenectomy, the hydrogel injection sites between pancreas and duodenum were examined in the surgical specimen for implant location and local inflammatory reactions, scored on a scale of 1 (none or minimal signs of mucosal damage) to 3 (severe damage) using methods outlined by Verma et al.⁸ Tissues were fixed in formalin, hematoxylin and eosin stained, and sectioned for analysis.

Statistical analysis

Data were collected using Velocity software (Varian Medical Systems, Palo Alto, CA) and analyzed in R version 3.5.3 (R Core Team, 2019). The placement procedure was determined successful if the hydrogel was identified between the region of the pancreatic tumor and the duodenum on axial cross-sectional planning CT scan. To assess stability, individual bleb volume and the surface distances of points on one bleb surface to the nearest point on the second bleb were calculated. The median and mean of the surface distances between any pair of blebs were used allowing for consistent assessment of spatial relationship among blebs on simulation and post-SBRT CT. Stability was evaluated using equivalence testing analyses, with a null hypothesis of the presence of a 20% mean percentage change in volume and 2 mm change in the median and mean interbleb distance with a P value $< .05$ required to reject the null hypothesis and conclude equivalence. Equivalence testing thresholds were selected to reflect the estimated uncertainty in measurement of scans that were performed using a 2-mm slice thickness for blebs that were generated using sequential 1-mL injections.

Results

Hydrogel placement procedure

All patients ($n = 6$) underwent successful hydrogel placement (Table 1) with appropriate position confirmed on cross-sectional CT as shown in a representative case in Figure 1. Only one adverse event was deemed potentially attributable to the EUS-guided hydrogel placement. Patient 2 experienced grade 3 nausea after recovery from anesthesia; however, in addition to hydrogel placement, the patient had undergone anesthesia and several research biopsies, which may have contributed to these symptoms.

Hydrogel stability

The median and mean interbleb distances were measured on SBRT simulation CT and compared with the interbleb distances at 4 to 8 weeks post-SBRT CT are shown in Table 2. The average of the changes (post-minus pre-SBRT) in median and mean interbleb distances were -0.43 mm (standard error, 0.95 mm) and -0.35 mm (standard error, 0.95 mm), respectively, with $P < .05$ supporting equivalence of distance measurements with equivalence margin of 2 mm. The average of the changes in hydrogel bleb volume from simulation CT to post-SBRT CT was -1.0% (range, -16.3% to 17.1%), with $P < .05$ supporting the equivalence of the volumes across the cohort (Table 3).

Histopathologic assessment

Five patients underwent subsequent resection of their pancreatic primary, with 4 patients undergoing pancreaticoduodenectomy and 1 patient undergoing distal pancreatectomy (Table 1). In the 4 patients undergoing pancreaticoduodenectomy allowing for resection of hydrogel blebs in the surgical specimen, placement in the pancreaticoduodenal groove was confirmed, but hydrogel was also noted in regions within the duodenal submucosa with giant cell and granulomatous reaction as shown in Figure 2. There was no evidence of microscopic (score of 1 = no/minimal signs of damage) or gross duodenal ulceration in the evaluable patients.

Discussion

We demonstrate the feasibility and safety of placing hydrogel in the pancreaticoduodenal groove in this first in-human trial exploring this technique of hydrogel injection via EUS guidance in patients with BR/LAPC. We further demonstrate the stability of the relationship of the hydrogel blebs and bleb volume.

Existing preliminary data support optimism for the possibility of improving outcomes for patients with unresectable pancreatic cancer with dose-escalated RT.^{9–11} Having developed this technique of hydrogel placement in the pancreaticoduodenal groove presented here, we are now enrolling patients with BR/LAPC on a study to inject a larger volume of hydrogel with the ultimate goal of serving as a spacer to reduce risk of duodenal toxicity and provide the opportunity for dose-escalated radiation therapy for patients with BR/LAPC.

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Figure 1.

Hydrogel placement confirmation on computed tomography and visibility on cone beam computed tomography. Hydrogel blebs between the pancreatic mass (green arrow) and duodenum (blue arrow) are clearly visible on coronal and axial computed tomographic views (A, B), 3-dimensional reconstruction (C), and cone beam computed tomography (D) in a representative case of patient 4.

Figure 2.

Histopathologic analysis of hydrogel placement. Gross examination (A) of hydrogel placement in the pancreaticoduodenal groove. Histopathologic examination shows hydrogel placement in the pancreaticoduodenal groove (B) and regions within the duodenal submucosa with giant cell and granulomatous reaction without evidence of microscopic or gross ulceration (C). Original magnification (B, C) $\times 20$ (2×10).

Patient, hydrogel, and treatment details

Table 1

Patient	Hydrogel concentration	Stage	Pre-SBRT chemotherapy	Hydrogel bleb	Adverse event*	Resection	Path
1	50%	BL	6 cycles FOLFIRINOX	4		PD	Complete path response
2	50%	BL	4 cycles FOLFIRINOX	3	Grade 3 nausea	None	n/a
3	67%	BL	6 cycles gemcitabine + abraxane	3		DP	Moderate treatment effect
4	100%; 67%	BL	6 cycles FOLFIRINOX + GVAX pancreas vaccine w/ cyclophosphamide, nivolumab	3		PD	Complete path response
5	67%	BL	4 cycles FOLFIRINOX	3		PD	Marked treatment effect
6	75%	BL	2 cycles FOLFIRINOX and 4 cycles gemcitabine + abraxane	3		PD	Moderate treatment effect, R0, N0

Abbreviations: BL = borderline resectable/locally advanced; DP = distal pancreatectomy; PD = pancreaticoduodenectomy.

* Adverse event listed if thought to be potentially related to endoscopic ultrasound-guided placement of hydrogel.

Table 2

Bleb position analysis pre and post treatment

Patient	Bleb pair	Sim CT median (mm)	Post-SBRT CT median (mm)	Average change $\pm$ standard error (mm) (post/pre)	P value for equivalence	Sim CT mean (mm)	Post-SBRT CT mean (mm)	Average change $\pm$ standard error (mm) (post/pre)	P value for equivalence*
1	1→2	8	8.21	-0.43 $\pm$ 0.95	.0498		7.65	-0.35 $\pm$ 0.95	.0406
1	1→3	12.71	14.71				12.81	14.72	
1	1→4	18	18.93				17.69	19.03	
1	2→3	3.65	4.55				3.37	4.58	
1	2→4	8.56	9.42				8.54	9.16	
1	3→4	4.85	4.07				4.75	4.02	
2	1→2	16.43	13.59				16.49	13.98	
2	1→3	16.14	9.94				16.37	10.00	
2	2→3	9.62	9.65				9.84	10.33	
3	1→2	27.04	26.58				26.77	26.50	
3	1→3	28.24	28.84				28.61	29.42	
3	2→3	11.52	11.42				11.32	11.23	
4	1→2	7.70	6.46				7.40	6.66	
4	1→3	18.08	18.00				17.69	16.62	
4	2→3	8.00	9.00				7.28	7.81	
5	1→2	14.68	15.00				14.69	15.12	
5	1→3	20.36	23.52				20.59	23.75	
5	2→3	15.31	21.93				15.37	22.51	
6	1→2	20.35	15.97				21.11	17.24	
6	1→3	44.08	39.97				44.67	40.42	
6	2→3	24.70	19.14				24.37	19.00	

Abbreviation: CT = computed tomography.

* To evaluate stability of in the median and mean before and after stereotactic body radiotherapy (SBRT) interbleb distances, a P value $< .05$ was required to reject the null hypothesis that there was a 2 mm change distance and conclude equivalence.

Table 3

Bleb volume analysis pre and post treatment

Patient	Bleb	Time pre/post Tx, d	Simulation CT volume (cm ³)	Post-SBRT CT volume (cm ³)	Mean percent change across all blebs	P value for equivalence *
1	1	53	0.45	0.40	-1.0% (-16.3%, +17.1%)	.0125
	2		0.62	0.71		
	3		0.21	0.19		
	4		0.16	0.16		
2	1	31	0.40	0.25		
	2		0.14	0.07		
	3		0.21	0.18		
3	1	43	0.42	0.48		
	2		0.53	0.61		
	3		0.50	0.54		
4	1	41	0.57	0.67		
	2		0.39	0.46		
	3		0.54	0.68		
5	1	34	0.13	0.18		
	2		0.45	0.70		
	3		0.68	0.62		
6	1	50	1.53	1.08		
	2		1.51	1.59		
	3		1.29	1.11		

Abbreviation: Tx = treatment.

* To evaluate equivalence of the bleb volumes on simulation computed tomography (CT) and after stereotactic body radiotherapy (SBRT) CT, the null hypothesis was that there was a >20% mean percent change in volume with a Pvalue <.05 required to reject the null hypothesis and conclude equivalence.