HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2020 October 01.

Published in final edited form as:

Gastroenterology. 2019 October ; 157(4): 933–935. doi:10.1053/j.gastro.2019.07.012.

Feasibility of Using Hydrogel Spacers for Borderline-Resectable and Locally Advanced Pancreatic Tumors

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Abstract

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e14 (https://www.gastrojournal.org/cme/home). Learning Objective: Upon completion of this CME activity, successful learners will be able to describe the pharmacokinetics of hydrogel, identify appropriate candidates for hydrogel injection among patients with pancreatic cancer, and describe key techniques to successfully inject hydrogel as well as the histopathologic findings associated with hydrogel.

Pancreatic ductal adenocarcinoma has a dismal prognosis with a 5-year survival rate of 9%.[1] Although surgical resection offers the only chance for long-term survival, vascular involvement often precludes surgical resection or places the patient at high risk for margin-positive resection or local recurrence after resection. Radiation may improve survival outcomes after surgery or serve as definitive therapy for patients with unresectable disease, particularly if able to administered in a dose-escalated fashion, but radiation doses are typically limited by proximity of the radiosensitive duodenum.[2,3] In prostate cancer, the use of a hydrogel to space the nearby rectum away from prostate tumors has proved successful in a large randomized controlled trial, a strategy that may be extrapolated to the pancreatic cancer setting.[4] Our recent study in cadaveric and swine models demonstrated the feasibility, safety, and acceptable visibility of endoscopically placed hydrogel on a cone-beam computed tomography.[5,6] Herein, we aim to demonstrate the feasibility of hydrogel spacer to separate the head of the pancreas and the duodenum by first testing small volume injections

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.07.012.

Conflicts of interest

The authors have made the following disclosures: Amol Narang, Kai Ding, and Eun Ji Shin received research grant support from Augmenix. Tossapol Kerdsirichairat, Elizabeth Thompson, Seong-Hun Kim, and Avani Rao declare no conflict of interest.

in vivo for patients with borderline resectable/locally advanced pancreatic ductal adenocarcinoma.

Description of Technology

In prostate cancer, a traditional hydrodissection technique is used via a transperitoneal approach to separate the plane between Denonvillers' fascia and the anterior rectal wall. The hydrogel spacer used in prostate cancer has 2 components of solution, the precursor and the accelerator. By mixing the solution, it initiates a cross-link reaction that results the formation of a soft polyethylene glycol-based gel within 10 seconds, without a measurable increase in temperature. The hydrogel is radiopaque and remains in the body for 12 weeks, after which hydrolysis occurs, resulting in complete absorption after 7 months and excretion via the renal system.[7] Using a hydrogel spacer to separate the rectal wall from the prostate in prostate cancer resulted in significant radiation dose reduction to the rectal wall.[7]

TraceIT (Augmenix, Bedford, MA) is a modified solution of 90% water, 9.25% polyethylene glycol, and 0.75% iodine. This solution has been only used for fiducial marking purpose in management of esophageal, gynecologic, and bladder malignancies.[8] To accomplish endoscopic ultrasound-guided spacer injection, we used a curvilinear-arrayed GF-UCT180 echoendoscope (Olympus, Center Valley, PA) coupled to an ultrasound workstation (ProSound F75, Hitachi-Aloka, Twinsburg, OH). Unlike the pre-rectal space, which could be easily separated by a hydrodissection technique, injection to the interface between the serosa of the duodenal wall and the head of the pancreas (the pancreaticoduodenal interface [PDI]) requires multiple injections marching along the C-loop of the duodenum owing to its dense connective tissue in the interface.

Video Description

This is an institutional review board-approved prospective study. The distance from borderline resectable/locally advanced pancreatic ductal adenocarcinoma has to be delineable from the duodenal wall of >1 mm. An advanced endoscopist (E.J.S.) underwent training of endoscopic ultrasound-guided hydrogel placement using cadaveric and porcine models before this study. Under sterile technique, the prefilled hydrogel syringe is connected to a receiving syringe via a Luer-Luer connector and hydrogel is mixed for activation. Subsequently, hydrogel is diluted with sterile water to 50% dilution per the study protocol. Using a linear echoendoscope, the PDI was identified. A 22-G needle is used and a syringe with diluted hydrogel is attached. Diluted hydrogel is delivered to the targeted PDI, approximately 1 mL for each bleb, 3–5 blebs along the C loop of the duodenum. At simulation CT, hydrogel blebs are identified and later contoured for stereotactic body radiation therapy. All patients received stereotactic body radiation therapy over 5 consecutive days (33 Gray, 6.6 Gray/d in 5 fractions). Patient demographics, procedure details, and outcomes after spacer placement are shown in Tables 1 and 2. One patient developed interval hepatic metastasis and succumbed to disease at 161 days after spacer placement, and the other 3 patients underwent a successful Whipple operation. All 3 patients had macroscopic findings of implanted hydrogel at the time of the Whipple operation. Microscopic findings showed hydrogel in the PDI associated with foreign body-type giant

cell reaction and granulomatous inflammation, without pathologic changes to the duodenal mucosa. All patients were prospectively followed (median, 342 days). There has been no duodenal toxicity to date.

Take Home Message

Hydrogel injection for spacing organs at risk from the radiation target to increase the deliverable dose or improve the safety of radiation therapy has proven successful in other tumor sites. We report the first feasibility study of endoscopic injection of hydrogel into the pancreaticoduodenal groove for patients with pancreatic cancer undergoing radiation therapy. Future studies to assess whether larger volumes can be injected to create clinically significant space are planned.

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Table 1.

Patient Demographics and Procedure Details

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Age (years), gender	68, female	54, female	74, female	65, male
Size of tumor (cm)	4.9	3.5	1.5	3
NCCN stage before treatment[a]	Locally advanced	Borderline resectable	Borderline resectable with indeterminate liver lesion	Locally advanced
AJCC stage before treatment[b]	T3N0M0, stage IIA	T2N0M0, stage IB	T1N0M0, stage IA	T2N1M0, stage IIB
Hydrogel volume (mL)	1.75	2	1.75	1.75
Procedure time (minutes)[c]	49	55	63	45

[a] National Comprehensive Cancer Network (NCCN) version 1.2019.

[b] American Joint Committee on Cancer (AJCC) 8th edition.

[c] Procedure time including hydrogel injection and placement of three fiducials for stereotactic body radiation therapy.

Table 2.

Outcomes after Spacer Placement

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Chemo/immunotherapy regimen	FOLFIRINOX	FOLFIRINOX, nivolumab	FOLFIRINOX, nivolumab	FOLFIRINOX
Disease progression	None	Liver metastasis	None	None
Time from hydrogel to resection	78	-	60	60
AJCC stage at resection	ypT0N0, R0	-	ypT0N0, R0	ypT1aN1, R0
Follow-up time (days)	366	161, deceased	352	331, liver metastasis at day 248 after resection

AJCC, American Joint Committee on Cancer.

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