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IS ALCOHOL FREE ABLATION EFFECTIVE AND SAFE FOR TREATMENT OF PRE-CANCEROUS PANCREATIC CYSTS?

A Thesis in

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by

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ABSTRACT

Background: Approximately 15% of precancerous pancreatic cysts will develop into pancreatic cancer. Endoscopic Ultrasound (EUS)-fine needle infusion is a new technique to deliver drugs and ablate these pre-cancerous pancreatic cysts. EUS ablation is typically followed with ethanol lavage followed by infusion of the chemotherapeutic agent, paclitaxel, and has been shown to be an effective treatment for ablation of mucinous precancerous cysts. This procedure is associated with 3–10% adverse events after treatment, and it has been hypothesized that these adverse events are linked to the inflammatory effects of alcohol. Our research focused on elucidating whether alcohol is required for effective ablation, whether removing alcohol from the ablation decreases the rate of adverse events, and whether this novel multi-drug chemotherapeutic mixture of Paclitaxel and Gemcitabine (Drug cocktail) is more effective and can increase the rate of ablation compared to paclitaxel alone.

Method: Between November 2011 and December 2016, we conducted a single-center, prospective, randomized, and double-blinded study. Forty-six patients with pre- cancerous cysts were randomized into this study and 39 underwent treatment. All patients were randomized to either the control arm which included EUS-guided pancreatic cyst lavage with an 80% ethanol lavage followed by a drug cocktail (or to the experimental arm, namely normal saline lavage followed by the same chemotherapeutic cocktail. The primary outcomes were the rates of complete ablation 12 months after the procedure and rate of serious and minor adverse events within 30 days after the procedure.

Results: Of the 39 patients who received treatment, 23 (59%) were male and 16 (41%) were female. The majority of cysts were located in the head and body of the pancreas (48.7% of the cysts for both locations) and the mean cyst diameter was 2.5 cm. Fourteen (67%) patients underwent EUS ablation in the saline lavage arm had a complete response, defined as ≥ 95% reduction in cyst volume, after 12 months. In the alcohol arm, eleven (64%) of patients had a complete response after 12 months (CI= -0.38-0.24, p=0.01). Serious adverse events occurred in 6% of patients in the alcohol arm and 0% in the trial group. Minor adverse events occurred in 22% of patients in the control group and 0% in the alcohol-free group. The overall rate of complete ablation in both groups was 64% after 12 months.

Conclusion: In this prospective, randomized study we demonstrated that alcohol is not required for effective ablation. Moreover, removing alcohol from the EUS ablation of a pancreatic cyst significantly reduced the number of adverse events in patients who underwent this procedure. A multi-agent chemotherapeutic ablation admixture did not appear to significantly improve the rate of complete ablation compared to previous studies which used alcohol followed by paclitaxel alone.

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INTRODUCTION

Pancreatic cancer (PC) is the fourth leading cause of cancer death in the United States (US), has a median survival measured in months and a 5-year survival of < 5%. In the US, it is expected that there will be 46,000 people diagnosed with this cancer and 40,000 will die from it during this year. While 85% of pancreatic cancers are ductal carcinomas, a significant portion of such cancers develop from pancreatic cyst lesions.[1-2] Pancreatic cyst lesions, including intraductal papillary mucinous neoplasia (IPMN) and mucinous cystic neoplasms (MCNs) have been diagnosed with an increasing prevalence (2–14%), particularly in elderly asymptomatic patients.[3] These pancreatic cystic neoplasms are becoming a more frequently detected disease because of the advances in imaging technologies, and increased use of cross-sectional imaging such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). Endoscopic ultrasound (EUS) is a safe, accurate and critically valuable procedure in this regard at it usually allows complete evaluation of pancreatic lesions.[4-6] Moreover, EUS-guided fine needle aspiration (EUS_FNA) allows for accurate diagnosis of a pancreatic cyst via analysis of the cystic fluid for markers such as carcinoembryonic antigen (CEA) and amylase to discriminate mucinous from non-mucinous lesions. Serous adenomas are characterized by low amylase and CEA levels, while MCN typically show low amylase and high levels of CEA. Both pseudocysts and IMPNs contain high levels of amylase, although an IMPN cyst has a high level of CEA, versus a pseudocyst having a low level of CEA. [7-9] Early detection and treatment of these lesions are critical. However, despite advances in diagnostic technology, proper management has remained a challenging clinical problem.[10-11]

Although several clinical guidelines have been developed to help manage the care of patients diagnosed with pancreatic cyst lesions, management of these patients is still complicated given uncertainty at the time of diagnosis. Specific treatment plans include surveillance with MRI or CT imaging or surgical resection, both which have significant limitations. Surveillance involves significant economic costs for monitoring and there are possible psychological burdens while waiting for signs of malignancy to develop, as well as radiation exposure with repeated CT scans.

On the other hand, surgical resection possesses a significant risk of serious adverse events (approximately 20–40% of patients) and a possible mortality rate of 1–5%.[12-14]

These clinical issues challenge clinicians to develop effective, but more minimally invasive and less stressful treatments for patients with pancreatic lesions. EUS_FNI ablation has emerged as an innovative and promising approach.[14, 15]

This novel technique provides a new and valuable mode of drug delivery that allows for injection directly into pancreatic cysts. [16] Ethanol has been used historically as it is economic and reasonably effective. It is hypothesized to induce cell death by membrane breakdown, rapid protein degradation, and vascular occlusion.[17,18] This technique was introduced by Gan et al. followed by Oh et al. The initial pilot study included 25 patients who had an asymptomatic pancreatic cyst, undergoing EUS examination for pancreatic cysts followed by ethanol lavage with 5–80% ethanol. In this study, the cyst was aspirated with a 22-gauge needle and evacuated until it collapsed. With the cyst collapsed, ethanol was then injected into the cyst and lavaged for 3–5 minutes. At the end of the procedure, all of the fluid was completely drained from the cyst. In follow-up, 35% of patients had complete resolution of their cyst and no patients had any adverse events during short or long term follow up.[19]

Following this investigation, a randomized double-blinded study was conducted to evaluate the efficacy of ethanol lavage for resolution of a pancreatic cyst. There were 42 patients who underwent initial ethanol or saline lavage. Ethanol lavage resulted in a greater mean decrease of cyst surface area compared to saline. Subsequently 33 of these patients, in both groups, underwent a second lavage with 80% ethanol, after which one patient (randomized to ethanol) developed pancreatitis. At the time of follow up with CT scan, 33% of patients had a decrease in the mean surface area of their cysts.[20]

Compared with earlier studies that focused on ethanol alone, in a new prospective trial, the addition of paclitaxel seemed to significantly improve cyst resolution while limiting low risk complications. Paclitaxel is a widely used chemotherapy drug for the treatment of ovarian cancer, breast cancer, and lung cancer. Where it inhibits cell processes that are dependent on microtubule turnover. It causes the disassembly of the microtubules during cell division and

leads to cell death.[18, 21] The hydrophobicity and viscosity of paclitaxel reduce the possibility of leaking through the puncture site and therefore decreases complications.

In the study performed by Oh et al., 14 patients underwent EUS- guided ethanol lavage with paclitaxel injection. Complete resolution was observed in 11 patients, two patients had partial resolution of their cysts, and one patient developed acute pancreatitis, which was believed to be the result of extravasation of ethanol.[21]

Previous studies have shown the safety and efficacy of EUS-guided injection for pancreatic cyst ablation, as well as the beneficial infusion of a chemotherapy agent for ablation of pancreatic cysts. However, it is unknown if alcohol is required for the ablation of pancreatic cysts. Moreover, while the rate of complication was low in the trials, it was believed that the complications were caused by the extravasation of alcohol.

The use of multidrug therapies has become the standard care in a variety of cancers using increasingly effective chemotherapy protocols that target multiple cellular mechanisms and receptor pathways. For this reason, we designed a multi-agent chemotherapeutic cocktail. We choose paclitaxel as the first chemo drug, as it has been used in previous studies with proven efficacy. Due to the high viscosity of paclitaxel, it is diluted 1:1 with 0.9% normal saline and prepared in a final dose concentration of 3mg/ml for needle infusion. Further, we replaced normal saline with gemcitabine. Gemcitabine is a cytotoxic chemical approved to be a first-line treatment of pancreatic cancer since 1997. Gemcitabine is a pyrimidine analog that is phosphorylated to diphosphate and triphosphate to inhibit both ribonucleotide reductase and DNA polymerase, leading to cell death. When reconstructed with normal saline, it has low viscosity, making it an ideal second agent to dilute paclitaxel and add as a second cellular treatment pathway.[14,18,22]

Therefore, our study has three aims:

We hypothesize:

1) Alcohol is not required for effective ablation of a pancreatic cyst prior to infusion of the chemotherapeutic cocktail ablation

2) The removal of alcohol from the procedure will decrease the rate of adverse events associated with the ablation
3) Compared to the historical controls, the efficacy of pancreatic cyst ablation can be improved with the infusion of multi-agent chemotherapeutic drug that has been specifically designed for the treatment of pancreatic cyst lesions

METHODS:

Preclinical Drug Evaluation

As per a Food and Drug Administration (FDA) request, in bench-top testing we demonstrated that combining of paclitaxel and gemcitabine does not change the viscosity, color or form, and also that 2 ml of this mixture can be injected n less than two minutes through a 22-gauge needle with a High-pressure chemotherapy syringe (aka "gun") as shown in Figure 3. To confirm stability and compatibility, we did a high-performance liquid chromatography test of the two agents (3 mg/ml paclitaxel and 19 mg/ml gemcitabine) separately and then in a mixture. The volume of drug cocktail used is well within the FDA approved limit of 8 ml. The analysis showed that the amount of gemcitabine in a mixture of paclitaxel/gemcitabine is not significantly different from the original formulation (percent of gemcitabine in mix 100.79% p=0.92). Similarly, the amount of paclitaxel in the paclitaxel/gemcitabine mixture was not significantly different from the original formulation (percent of paclitaxel 103.85%, p=0.77) (Figure 1).

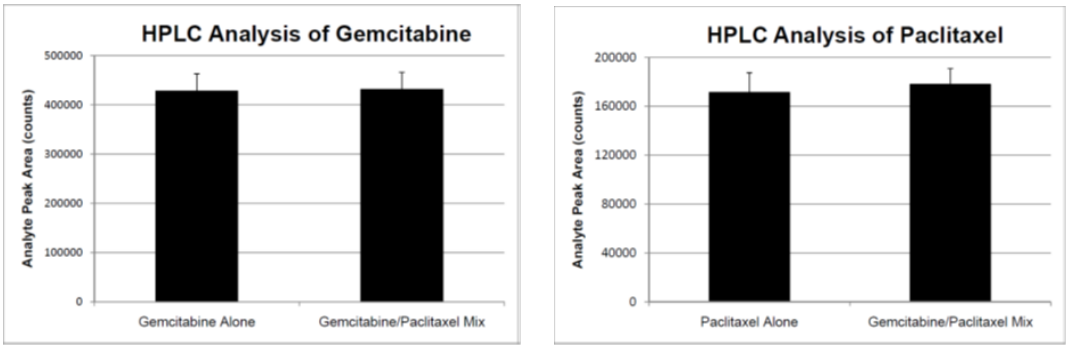

FIGURE 1: In-use compatibility and stability testing of paclitaxel/gemcitabine, as measured by HPLC analysis. Gemcitabine (Gemzar, Eli Lilly, 38 mg/ml) and paclitaxel (Hospira, 6 mg/ml) were mixed 1:1 in a syringe and stored at room temperature for 24 hours. Analyze peak area was measured to indicate the amount of paclitaxel and gemcitabine in the original formulations compared to the 1:1 mixture.

Study Design

This is an investigator-initiated prospective, randomized double-blinded study. Patients previously identified as having one or more pancreatic cysts through EUS or cross-sectional analysis were referred to the Penn State Hershey Medical Center. All medical records and imaging results were reviewed to assess the eligibility of subjects. All patients had to agree to have a prior EUS-FNA to be a part of the study. The type of cyst was diagnosed based on the combination of clinical, radiographic, cytological and chemical (carcinoembryonic antigen (CEA) and amylase) results as outlined in published guidelines.

These characteristics were used to classify a cyst as mucinous (precancerous), indeterminate or benign. Patients with a benign cyst (pseudocyst or serous cystadenoma) were excluded from enrollment. Candidates with a mucinous or indeterminate cyst were seen in the clinic for evaluation, consultation, and the consenting process. If a patient did not have a surgery consult before, they were offered an appointment with the surgical oncology team to discuss all of their surgery options.

Inclusion Criteria:

All subjects 18 years and older, of any gender, race, and ethnicity, who had at least one 1.5–5 cm pancreatic cyst, which had less than five septum separated compartments (septations) and were classified as a precancerous or indeterminate cyst, and were able to give voluntary written informed consent, and undergo a safe endoscopy with deep sedation or general anesthesia.

Exclusion criteria included the following:

Presence of known or suspected pancreatic cancer or lymphadenopathy, main pancreatic duct dilation of > 5 mm, high grade communication with main pancreatic duct, as determined either prior EUS or magnetic resonance cholangiopancreatography, pregnancy, evidence of active pancreatitis or pancreatic infection, white blood cells > 14 K/ul or <2 K/ul, hematocrit < 30%, platelets < 30 k/ul, INR >1.6, Cancer Antigen 19–9 > 40 U/ml or lipase > 3 times of upper normal

level. Patients were excluded if they had a benign cyst (pseudocyst or serous cystadenoma) or for concomitant disease, which would preclude a reasonable 5-year life expectancy post-treatment.

Patients were placed into the treatment plan following a predetermined 1:1 ratio randomization, blinded to the endoscopists and patients, with study drugs managed by the Investigational Drug Pharmacy. Of all patients screened and enrolled in the study, 46 were randomized and 39 underwent the study treatment (Figure 2).

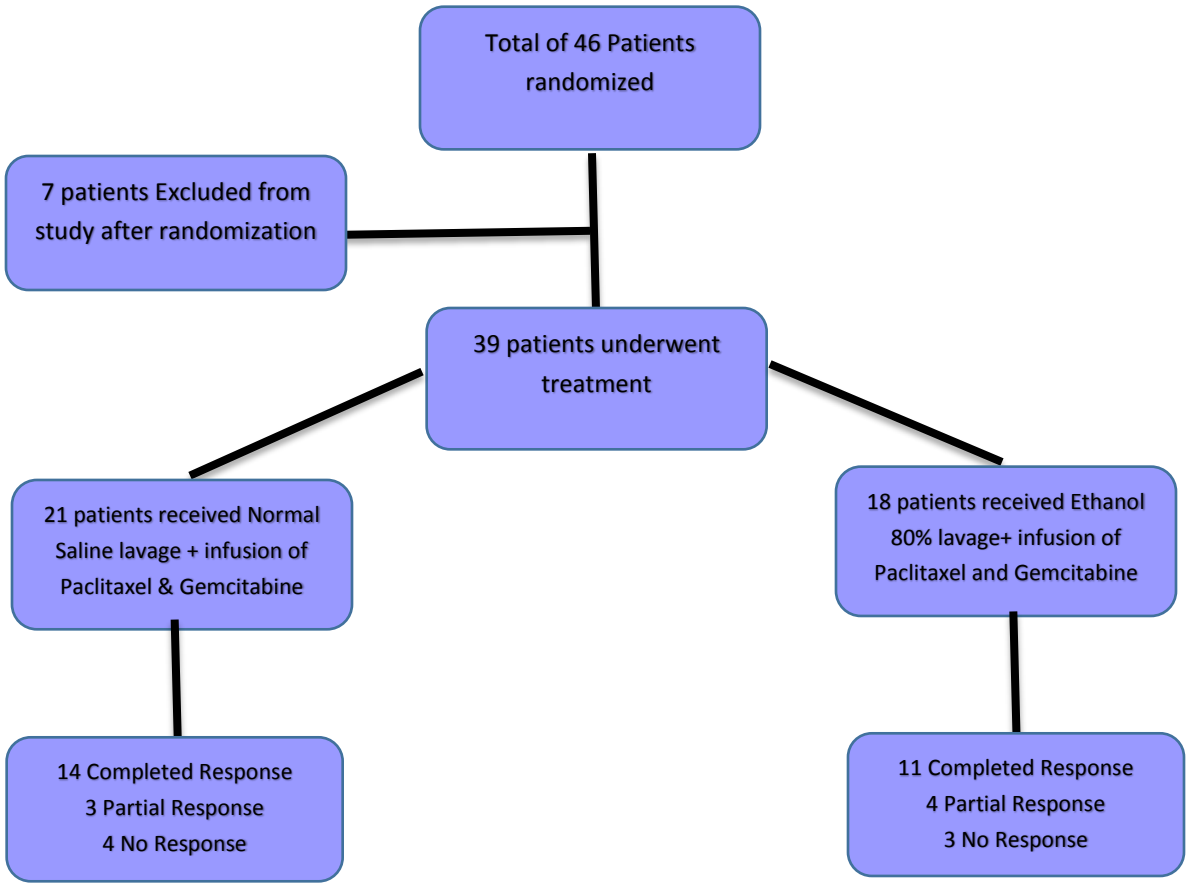

Figure 2: Study flow diagram. Details of study are discussed in study design and results section.

Interventional Procedure:

All EUS procedures were performed by one of three experienced endoscopists. Either propofol sedation or general anesthesia were used for all patients with a complete pancreatic examination performed using a curvilinear endoscope. The cyst lesion was identified and characterized based on its diameter, number of septations, location and high-risk features per

2012 consensus criteria[24]. The cyst was aspirated (EUS-FNA) preformed, and the fluid from the cyst was sent to obtain CEA and lipase levels as well as cytology (if the retrieved fluid was greater than 1 ml). The procedure was aborted if the cyst re-accumulated fluid immediately (suggesting high-grade communication with the pancreatic duct). A 22- or 19-gauge needle was used for 1.5–2.5 cm, and 2.6–5 cm cysts, respectively. Then, with the tip of the needle in the center of the cyst, lavage was performed using a 10-ml syringe filled with the study agent, either 80% ethanol or normal saline, alternating aspirating and infusion of the cyst via the same amount of lavage for three minutes. Complete aspiration of the lavage was followed by infusion of the paclitaxel/gemcitabine cocktail using a 30 ml syringe custom fitted to a high-pressure gun to allow infusion of the mixture in the allotted time.

Those patients who were randomized to the control group underwent the EUS procedure with cyst lavage using 80% ethanol after the cyst was completely aspirated, followed by infusion of 3 mg/ml paclitaxel and 19 mg/ml gemcitabine, (drug cocktail). The amount of cocktail infused was equal to the original amount of fluid that was aspirated from the cyst to re-establish the original size cyst size and volume. Patients randomized to the study group had their cyst aspirated and lavaged with normal saline followed by infusion of 3 mg/ml paclitaxel and 19 mg/ml gemcitabine in the same manner of the control group.

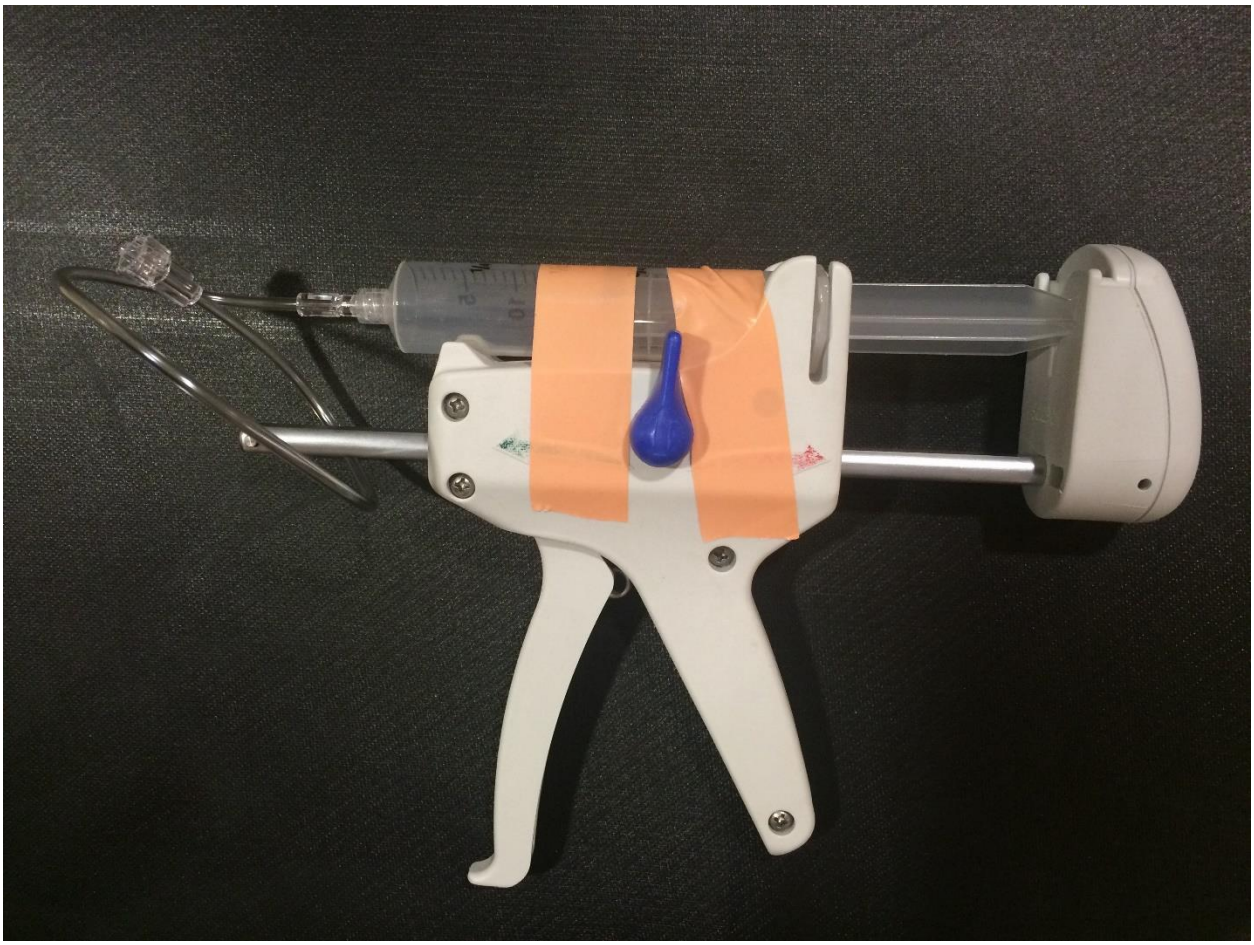

Figure 3. High-pressure chemotherapy syringe ("gun") setup that was required to infuse the viscous ablation cocktail in a timely fashion

Post-Treatment follow-up:

Post EUS-guided fine needle infusion care was same as the EUS FNA; however, patients were monitored for two hours post-procedure followed by telephone interview 72 hours after the treatment by the study coordinator who was blinded to the subject's treatment arm. All patients had a comprehensive lab test two weeks post-procedure. To evaluate and measure the response to treatment, a CT or MRI/magnetic resonance cholangiopancreatography was obtained at six and 12 months after the procedure for all patients.

Study Definitions:

Pancreatic cysts classified based on clinical, radiographic, chemical analysis and the following table:

Table 1. Schema for the classification of cystic lesions.

	Serous	**MCN**	**IPMN**	**Inflammatory**
Cytology	Epithelial	Epithelial	Epithelial	Inflammatory cells
CEA, ng/mL	< 200	> 200	> 200	< 200
Amylase, U/L	< 800	< 800	> 800	> 800
Viscosity	Thin	Mucoid	Mucoid	Thin

MCN, Mucinous cystic neoplasm; *IPMN,* intraductal papillary mucinous neoplasm; *CEA,* carcinoembryonic antigen.[19]

Cyst size was calculated by measuring x and y dimeters and calculating the cyst volume per the formula below:

$4/3x\ \mu\ x\ r^3$

Where r was the average of the radius. It was measured three times (at the initial visit and six and 12 months after the procedure) using a CT scan or MRI. Response was defined as complete response if there is ≥ 95% reduction in cyst volume, partial response if there was 75–95% reduction in cyst volume and no response if there was < 75% reduction in cyst volume. The overall ablation rates were also compared to historical controls to assess the efficacy of the chemotherapeutic cocktail.

Safety Monitoring:

The clinical study was monitored by Penn State Cancer Institute Board every six months during the study. This board also reviewed any study-related adverse events in patients. Adverse events were documented using the standardized definition and lexicon recommended by the FDA.

Statistical Analysis:

This was a non-inferiority study to evaluate the efficacy of chemotherapy with or without ethanol for ablation of a pancreatic cyst. After reviewing the previous studies, we proposed that a reduction > 38% in the rate of complete ablation in the study arm, relative to the control arm, would be considered as inferior. [14,17,20,21] The null hypothesis was the study group is inferior to control group and the alternative was the study group is not inferior to control group. The sample size calculation was based on 0.05 statistical significance 38% expected difference in both groups and 80% power. Using an online statistical calculator[23], 46 patients (23 patients in each arm) were estimated as needed for the sample size. The efficacy of the multi-agent drug was compared to previous data.[14,17,20,21]

The x^2 test and Fisher's exact test were used to compare categorical variables and to evaluate ablation performance characteristics (complete resolution versus non-complete resolution). Variables that were evaluated included patient sex, cyst location (head, body, or tail), mean cyst diameter, effect of cyst septation, effect of cyst viscosity, type of cyst (MCN, IPMN, or indeterminate), CEA, and amylase level. Quantitative data were presented as mean (range) with a p value < 0.05 considered significant. A post-study statistical analysis was performed using SAS version 9 (SAS Institute, Carry NC) and SPSS, version 23 (IBM Corp, Armonk, NY).

RESULTS:

There were 46 patients enrolled and randomized in this study between November 2011 and December 2016. Of this group, 39 patients underwent the procedure and received the treatment. There were seven patients excluded from the study. The reasons for excluding patients included signs of malignancy during the procedure (two patients), cyst was too small (one patient), excessive main duct communication (two patients), losing the needle position due to patient coughing (one patient) and osteophyte obstruction of the proximal esophageal prevented the procedure (one patient).

From these 39 patients, 23 were female and 16 were male. The majority of cysts were located in the body and head of the pancreas. Most cysts were unilocular with no septation. The mean diameter of the cysts was 25mm. The mean for CEA and amylase were 4728.6 ng/ml and 3385.6 U/L respectively. Analysis found that 27 lesions were determined to be intraductal papillary

mucinous neoplasms, nine were mucinous neoplasms and three were indeterminate. Patient characteristics are shown in Table 2.

Table 2. Preoperative patient characteristics and presumed diagnosis of cystic tumors (n=39)

Sex, no. (%)	
Male	16 (41)
Female	23 (59)
Location, no. (%)	
Head/uncinate	19 (48.7)
Body	19 (48.7)
Tail	1 (2.6)
Mean diameter (range), in cm	2.5 (1.55–4.2)
Locularity, no. (%)	
Unilocular	28 (72)
Oligolocular	11 (28)
CEA Median (range), ng/ml **CEA Mean (range), ng/ml**	489.2 4728.6 (1.4–83,224)
Amylase, U/L, mean (range)	3,385.6 (15–12,000)
Presumed diagnosis prior to treatment, no. (%)	
MCN	9 (23.1)
IPMN	27 (69.2)
Indeterminate	3 (7.7)
Mean amount of fluid aspirated (range), cc	4.1 (0.5–23)
Color of aspirated cyst fluid, no. (%) **Clear** **Cloudy** **N/A**	 33 (84.6) 5 (12.8) 1 (2.5)
Viscosity of aspirated cyst fluid, no. (%) **Thick** **Thin**	 16 (41) 23 (59)

Patients in the alcohol arm had an average of 78% volume reduction and patients in the alcohol-free arm had an 84% volume reduction after six months. At 12 months, the average reduction in alcohol and alcohol-free arms were 85% and 84%, respectively. Complete ablation was achieved in 61% of patients in the alcohol arm and 64% of patients in the alcohol-free arm. These results rejected the null hypothesis that the experimental group (alcohol-free arm) is not inferior to control group (95% confidence Interval -0.38 to 0.24, p=0.01) (Table 3).

Table 3: Results at 6 and 12 months post-procedure.

	No.	% reduction in cyst size after 12m	Complete response after 6 m No. (%)	Complete response after 12 m No. (%)	Major Adverse Events No. (%)	Minor Adverse Events No. (%)
Alcohol arm	***18***	**85**	**6 (35)***	**11 (61)**	**1 (6)**	**4 (22)**
Saline arm	***21***	**84**	**12 (57)**	**14 (67)**	**0 (0)**	**0 (0)**
Total	***39***	**84.5**	**18 (47)**	**25 (64)**	**1 (3)**	**4 (10)**

* Six-month imaging not available for one patient.

The full year of surveillance was required for complete cyst ablation in several cases (Figure 5). The overall complete response rate with the multi-drug ablation (both arms combined) was 64%, which was within the average response reported in previous ablation studies (50–79%).

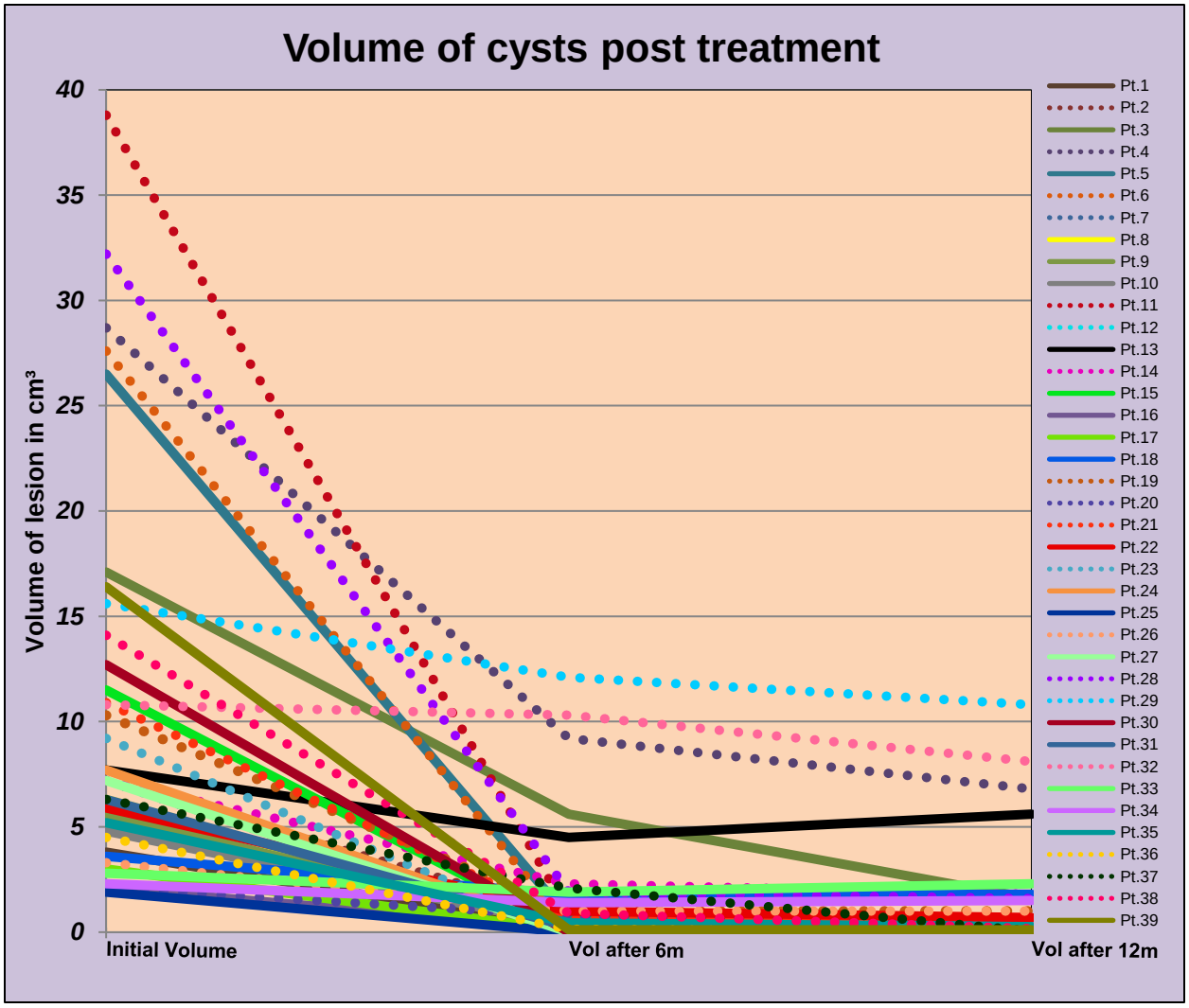

Figure 5: Clinical response of all ablated cysts when measured as cyst volume in cm^3 over a 12-month period. Although not every cyst completely responded, most lesions underwent a dramatic reduction in size by six months. Note that a full 12 months was required to achieve complete ablation in several cases**.** (…….. alcohol arm, _____alcohol-free arm)

There was a statistically significant difference between adverse events in the alcohol versus alcohol-free arms (p=0.01) with all adverse events occurring in the alcohol arm. One patient had a serious adverse event (acute pancreatitis after ablation of a 20 mm cyst) in the control arm (6%) and there were no serious adverse events in the experimental arm. Minor adverse events occurred in four patients (abdominal pain requiring unscheduled clinical evaluation and

treatment for pain control) in the alcohol arm (22%) and no minor adverse events occurred in the alcohol-free arm (Table 3).

Serum level drugs were measured 3- and 24-hours post procedure in seven patients and there were no significant drug levels in patients. In the univariate analysis, the percent of patients with complete ablation were evaluated for having either a unilocular versus septated cyst (57% versus 82%), mucinous cystic neoplasm versus intraductal papillary mucinous versus indeterminate (44% versus 70% versus 67%), CEA level and initial lesion diameter. There was no statistically significant association between any variables compared (Table 4).

Table 4: Univariate analysis: baseline characteristics of pancreatic cystic lesions with associated rate of complete ablation.

Variables	Complete response (No.)	Non-complete response (No.)	*p*-value
Initial Diameter (cm)			0.8
< 2.5	15	9	
≥ 2.5	10	5	
Locularity			0.3
Unilocular	16	12	
Oligolocular	9	2	
Fluid cyst CEA Level ng/ml*			0.4
< 50	3	0	
50–500	8	7	
> 500	11	6	
Presumed diagnosis prior to treatment			0.4
MCN	4	5	
IMPN	19	8	
Indeterminate	2	1	

*CEA Level not available for 4 patients

Discussion:

Any pre-cancerous pancreatic cyst, including mucinous cystic neoplasms and intraductal papillary mucinous neoplasms, has significant potential for progressing to invasive cancer (2–14%).[3] The specific rate of pancreatic cyst processing to cancer is thought to be linked to a number of its high-risk features, as per the 2012 consensus criteria. [24] However, the ability of these cysts to progress to cancer is still unknown. Molecular testing has been shown to have some benefit to determine the risk of these changes, although these tests are usually very expensive and need further validation.[25]

EUS ablation seems to be a safe and effective technique to treat these cysts and a way to decrease the need for additional extensive predictive tests or invasive surgery. EUS ablation can prevent pre-cancerous cysts from developing into cancer. For all the above reasons, improving this technique to be safe and more effective would be necessary.

Previous studies have shown that the use of alcohol lavage, followed by paclitaxel, has an efficacy rate of 50–79% in selected lesions and demonstrates long-term durability of resolution of a pancreatic cyst. The majority of patients undergoing effective ablation show elimination of the KRAS mutation.[14,17,21,26] However, with a rate of up to 10% adverse events, some have questioned the safety of this technique.[14,17] Notably, most of the reported adverse events (pancreatitis, adjacent vein thrombosis, or peritonitis) have been thought to be caused by the extravasation of alcohol. Moreover, the efficacy of alcohol when used alone is weak and its role in the ablative process is unknown.[15,19,20,27]

In our study, the prospective, randomized, double-blinded clinical trial, compared an alcohol-free chemo-ablation approach with the standard alcohol arm, followed by infusion of a chemotherapeutic cocktail (paclitaxel + gemcitabine) in both arms. This study reveals two important findings.

There was no statistically significant difference in terms of ablation of cysts between control and experimental arms. In the alcohol free arm, there was a 67% complete response versus 61% complete response in the alcohol arm. The second finding was that the rate of serious and minor adverse events was 6% and 22%, respectively, in the alcohol arm and 0% for both types of adverse events in the alcohol-free arm. This result is important because the alcohol-free arm

can increase the safety of the procedure while preserving its efficacy. Recent guidelines do not recommend EUS ablation due to the adverse events. By removing alcohol from the EUS ablation process and presenting a safer procedure, it raises a need for reevaluating this approach in appropriately selected patients.

The third hypothesis for the study was that the special mixture (paclitaxel and gemcitabine) designed for pancreatic cyst ablation will increase the rate of complete ablation when compared to paclitaxel alone. The results from this study at this time do not support this because the overall complete ablation in both arms was 64%, which is within the range of complete ablation (50–79%) reported from previous studies.[17,20,21]

This study has three limitations:

1) In this trial, there was a one-time ablation of the cyst only; when referenced to other ablation techniques in gastroenterology, there is a chance of missing the opportunity for subsequent treatment (if needed) to achieve complete ablation.
2) The maximum amount of chemotherapy was limited to 8 ml by the FDA. However, the maximum toxicity dose of IV infusion for gemcitabine is 1000 mg/m^2 and 125 mg/m^2 and thus the dose that we used in this study is much lower that this amount.[28] This may limit the efficiency with some larger cystic tumors. For example, a 5-cm cyst has a volume of 65 ml so that the infusion of 8 ml of chemotherapy may not be efficient enough.
3) Although our clinical trial was the second-largest randomized trial using a chemotherapeutic agent for the ablation of a pancreatic cyst, it is still weakly powered to show these differences with high levels of scientific certainly.

These issues should be addressed with further studies, as we plan to do in a follow-up multi-center trial.

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