Author Manuscript

HHS Public Access

Author manuscript

Gastrointest Endosc. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

Gastrointest Endosc. 2024 August ; 100(2): 262–272.e1. doi:10.1016/j.gie.2024.04.002.

Use of pancreatic endotherapy in patients with chronic pancreatitis: results from a multicenter cohort study in the United States

Samuel Han, MD, MS[1], Darwin L. Conwell, MD, MS[2], Jeffrey J. Easler, MD[3], Yunlong Yang, PhD[4], Dana K. Andersen, MD[5], William E. Fisher, MD[6], Evan L. Fogel, MD[3], Chris Forsmark, MD[7], Phil A. Hart, MD[1], Steven J. Hughes, MD[8], Liang Li, PhD[4], Stephen J. Pandol, MD[9], Walter G. Park, MD, MS[10], Jose Serrano, MD, PhD[5], Stephen K. Van Den Eeden, PhD[11], Santhi Swaroop Vege, MD[12], Dhiraj Yadav, MD, MPH[13] on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

[1]Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

[2]Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, Kentucky, USA

[3]Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, Indiana, USA

[4]Department of Biostatistics, MD Anderson Cancer Center, Houston, Texas, USA

[5]Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

[6]Department of Surgery, Baylor College of Medicine, Houston, Texas, USA

[7]Division of Gastroenterology, University of Florida, Gainesville, Florida, USA

[8]Department of Surgery, University of Florida College of Medicine, Gainesville, Florida, USA

[9]Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, California, USA

[10]Division of Gastroenterology & Hepatology, Stanford University, Stanford, California, USA

[11]Division of Research, Kaiser Permanente Northern California, Oakland, California, USA

[12]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

[13]Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Abstract

This is an open access article under the CC BY-NC-ND license (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Reprint requests: Samuel Han, MD, MS, Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, 395 W 12th Ave, Doan Office 2nd Tower, Columbus, OH 43210.

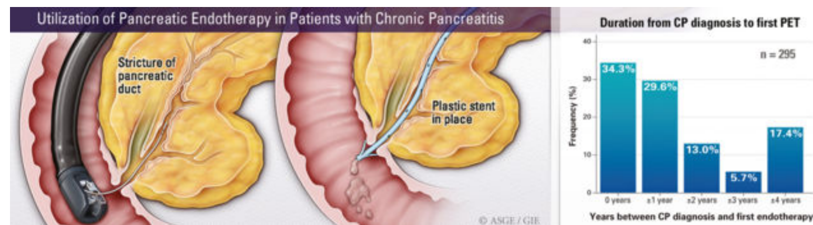
Background and Aims: Although pancreatic endotherapy (PET) is commonly used for treating adverse events of chronic pancreatitis, data on the frequency and factors associated with the use of PET are limited. Our aim was to define the use of and factors predictive for receiving PET in a well-characterized chronic pancreatitis cohort.

Methods: This is a cross-sectional analysis of data from PROCEED, a multicenter U.S. cohort study of chronic pancreatitis. PET modalities primarily consisted of ERCP. A treatment course was defined as the number of sessions performed for a specific indication. A repeat course was defined as PET >1 year after completion of the last course. Multivariable logistic regression identified predictive factors for receiving PET, and proportional rates model assessed risk factors for repeat PET.

Results: Of 681 subjects, 238 (34.9%) received PET. Factors associated with receiving PET included female sex (odds ratio [OR], 1.26; 95% confidence interval [CI], 1.03–1.53), lower education (OR, 1.30; 95% CI, 1.04–1.62), income $50,000 per year (OR, 1.35; 95% CI, 1.07–1.71), and prior acute pancreatitis (OR, 1.74; 95% CI, 1.31–2.32). Of 238 subjects, 103 (43.3%) underwent repeat PET at a median duration of 2 years, with 23.1% receiving 2 courses, 9.7% receiving 3 courses, and 10.4% receiving 4 courses.

Conclusions: Nearly half of patients with chronic pancreatitis who undergo PET received 1 or more repeat courses within 2 to 3 years. In addition to a prior history of acute pancreatitis, demographic and socioeconomic factors were associated with receiving PET.

Graphical Abstract



Chronic pancreatitis is a fibroinflammatory condition of the pancreas characterized by irreversible damage stemming from parenchymal injury and stress.[1] Chronic inflammation resulting in fibrosis can lead to pancreatic duct (PD) strictures, whereas PD stones are believed to form from the combination of ductal stasis and protein plug formation.[2] Ductal obstruction, in turn from PD strictures and stones, is postulated to contribute to the pain experienced by patients with chronic pancreatitis and can also lead to atrophy of the upstream pancreas.[2,3]

Pancreatic endotherapy (PET) offers a treatment option for these disease adverse events with ERCP, representing a standard approach for the treatment of PD stones and strictures in conjunction with extracorporeal shock-wave lithotripsy (ESWL) for larger PD stones.[4,5] Additionally, EUS-guided transmural drainage has emerged as a primary treatment modality for symptomatic pancreatic fluid collections, and EUS-guided celiac plexus block offers a potential treatment for pain.[5,6] Furthermore, advances in peroral pancreatoscopy and the development of lumen-apposing metal stents in the last decade have greatly facilitated performing endotherapy for cases that were previously not amenable to endoscopic therapy.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The proportion of patients with chronic pancreatitis who receive PET differs based on the clinical setting. Studies from tertiary referral centers report that between 40% and 60% of patients receive PET at some time during their clinical course.[7–9] Data from the North American Pancreatitis Study-2 reported that 35.9% of patients who received care between 2000 and 2006 received PET. In contrast, in a population-based evaluation of patients in Olmsted county (Minnesota) treated between 1977 and 2006, only 23% received PET.[10,11]

The current literature is limited in terms of understanding patient- and disease-related factors associated with the use of PET and the durability of PET (ie, how often patients need a repeat course of PET). Although prior studies demonstrate high success rates in stricture resolution and stone clearance, data on recurrence rates for PD strictures and/or stones, timing of recurrence, and risk factors for recurrence are limited.[12–16] Similarly, data on the number of PET courses a patient undergoes during long-term follow-up are often lacking.

The PROCEED (Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies) is an ongoing, multi-institutional, longitudinal cohort study of chronic pancreatitis in the United States (NCT3099850). The study collects information on prior or ongoing PET at the time of enrollment.[17] Thus, the PROCEED provides a unique opportunity to characterize the use and predictors of PET in patients with chronic pancreatitis treated at referral centers in the United States. In this study, our aim was to use baseline data in the PROCEED to define the patterns of use of PET and the patient- and disease-related factors associated with performance and access to PET in patients with chronic pancreatitis.

METHODS

This study involves a cross-sectional analysis of data collected at baseline for adult subjects with definite chronic pancreatitis enrolled in the PROCEED from June 2017 to December 2021. Institutional review board approval was obtained at each participating site.

Study setting and chronic pancreatitis definition

This study included subjects with definite chronic pancreatitis enrolled from 9 clinical centers across the United States who are part of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer.[18] Definite chronic pancreatitis was defined by the presence of pancreatic parenchymal or ductal calcifications, a Cambridge classification of 3 or 4 on CT and/or MRCP, or histology.[17,18] Structured case reports were completed by study subjects, study coordinators, and enrolling physicians as described previously.[17] Information collected included demographic data, socioeconomic status, environmental risk factors (smoking status, alcohol use), and disease-related data such as the age at diagnosis, disease duration, etiology, disease manifestations (eg, acute pancreatitis attack[s], abdominal pain in the year before enrollment, diabetes, exocrine pancreatic dysfunction, bone health, etc), quality of life, imaging findings, treatment, hospitalizations, and emergency department visits. Although follow-up questionnaires assessing the similar information are currently being administered yearly for each subject, analyses for this study reflect data collected for each subject at the time of enrollment.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Pancreatic endotherapy

In attempting to describe the practical use of endoscopic therapy in subjects with chronic pancreatitis, we identified all subjects who received endotherapy before or were undergoing endotherapy at the time of enrollment. Because our aim was to analyze PET, we excluded subjects who received ERCP for biliary indications (eg, chronic pancreatitis–related biliary stricture or choledocholithiasis) or endotherapy performed for treatment because of other reasons (eg, gastric outlet obstruction) from the analysis. We also excluded subjects who had pancreatic surgery before undergoing PET (Fig. 1). We defined PET when endotherapy was performed primarily for a pancreatic indication (eg, abdominal pain, recurrent acute pancreatitis, or PD stricture and/or stones). PET treatment modalities included any combination of therapeutic EUS (eg, celiac plexus block), ERCP, and ESWL (Fig. 1). In the treatment of PD stones, performance of ERCP with or without ESWL was based on the discretion of the treating physician or endoscopist.

A treatment course was defined as any number of PET procedures performed for treatment of a specific indication (eg, PD stone clearance or stricture resolution). A treatment session was defined as each individual PET procedure performed as part of a treatment course, including preplanned procedures (eg, stent removal or assessment of stricture). A repeat treatment course was defined when PET was performed at least 1 year after completion of a prior treatment course.

For this analysis, treatment response was defined as either complete or partial improvement of pain as documented in medical records with discontinuation of opiates (if applicable) or of the indication for the procedure (eg, no further acute pancreatitis attacks, etc).[19] No response was defined as no improvement in symptoms.

Variables of interest

Demographic and behavioral risk factors included age, sex, race, ethnicity, body mass index, and tobacco and alcohol use. Socioeconomic risk factors included education, income level, employment, and marital status. Disease-related variables included etiology; history of acute pancreatitis or recurrent acute pancreatitis; presence, severity, and temporal nature of abdominal pain in the year preceding enrollment; medication use (pancreatic enzyme replacement therapy, opioids, nonsteroidal anti-inflammatory drugs, neuromodulators); and morphologic changes on the most recent imaging study (calcifications, pancreas size, PD dilation, PD stricture). Diabetes was defined based on blood glucose and hemoglobin A_{1c} levels according to the American Diabetes Association criteria or by the use of medications to treat diabetes. Exocrine pancreatic dysfunction was defined by a known history before enrollment (clinical steatorrhea, fecal elastase of <100 μg/g stool, or quantitative stool fat excretion of >7 g/24 hours) or a fecal elastase of <100 μg/g stool on a per-protocol analysis after enrollment. Subjects with no known exocrine pancreatic dysfunction before enrollment who did not undergo a per-protocol assessment were categorized as “not tested.” Pancreatitis disease duration was defined as the time from the first episode of acute pancreatitis or chronic pancreatitis diagnosis (whichever was earliest) to the time of enrollment. Chronic pancreatitis duration was defined as the time from chronic pancreatitis diagnosis to the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

time of enrollment. Healthcare use variables included pancreatitis-related hospitalizations (lifetime, past 12 months) and emergency department visits (past 12 months).

Statistical analysis

Summary statistics were calculated and compared between subjects who received PET and those managed medically (ie, not receiving any endotherapy or surgery before PET) for all potential risk factors and healthcare use variables. Missing data were excluded from this descriptive analysis, although the missing data counts were reported. To determine treatment course characteristics among patients who received PET, we cross-tabulated PET courses together by treatment modality, indication, specific treatment done, treatment duration, and treatment outcomes. Repeat PET was evaluated using the reported years and frequencies of PET courses.

Multivariable logistic regression was used to determine patient- and disease-related factors associated with receiving PET. Multiple imputations using fully conditional specification were performed across all risk factors of interest. Backward variable selection ($P < .1$) was performed on 5 imputed datasets to develop a final parsimonious model. Variables selected in 1 of the imputed datasets were retained in the final model. The variance estimation and P value calculation in the final model were performed by combining all imputed datasets using the multiple imputation formula.

A proportional rates model was used to determine predictive factors associated with the number of PET courses over time (rate), defined as the average number of courses per year, among patients receiving PET. The proportional rates model is an analytical tool for modeling recurrent events data. Its regression parameters (proportional rate ratio) quantify the fold change in the rate with the presence of risk factors. It allows the rate to be time-varying rather than time-invariant, thus being more flexible than the Poisson regression model. Multiple imputations and backward variable selection procedures similar to logistic regression model noted above were used to develop a final parsimonious model from the aforementioned list of risk factors. All statistical analyses were performed in SAS (SAS Institute, Cary, NC, USA).

RESULTS

Study population

Of 681 subjects with definite chronic pancreatitis enrolled in the PROCEED, 295 had not received any form of endotherapy. These patients represented the medically managed group and served as control subjects for this analysis (Fig. 2). Of the 360 subjects who received endotherapy, after excluding those who either received surgery before PET (n = 10), received PET for a nonpancreatic indication (n = 90), and received EUS alone (n = 19), 238 subjects formed the PET group. On the most recent imaging before enrollment, the location of PD strictures (n = 130) was most common in the body (58%) and head (40%) and least common in the tail (16%). Among 113 subjects with intraductal stones, the most common location was in the body (72%), with 35% in the head and 22% in the tail.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Predictors of first PET

Univariate analyses.—When compared with the medically managed group, subjects who received PET were younger (median age, 53 vs 57 years) and were diagnosed with chronic pancreatitis at an earlier age (median, 48 vs 55 years). They were more likely to be women (53.8% vs 43.4%) and to have a lower income and education and higher rate of unemployment (Table 1). Although no difference in smoking was found, a lower proportion of subjects who received PET had ongoing alcohol use compared with the medically managed group. A significantly higher proportion of subjects who received PET had severe pain and constant pain compared with the non-PET group (Table 2). Concordantly, opiate use was greater in the PET group (50.9% vs 38.4%), as was pancreatic enzyme replacement therapy use. Subjects in the PET group had more hospitalizations in the year before enrollment (median, 1 vs 0) as well as over their lifetime (median, 6 vs 2). Among the 238 subjects in the PET group, 20 (8.4%) underwent surgery after the index or subsequent PET course, with 55% of those subjects undergoing surgery after 1 PET course.

Multivariable analyses.—In the multivariable logistic regression analysis (Table 3), the odds of receiving PET were significantly greater in women (OR, 1.255; 95% CI, 1.031–1.527) and in those with an education level of high school or general education development or less (odds ratio [OR], 1.3; 95% confidence interval [CI], 1.042–1.623) and lower income (<$50,000) (OR, 1.348; 95% CI, 1.066–1.706). Disease-related factors significantly associated with receiving PET included having prior acute pancreatitis (OR, 1.744; 95% CI, 1.313–2.316), a dilated pancreatic duct (OR, 1.942; 95% CI, 1.505–2.506), and longer duration of chronic pancreatitis (OR, 1.163; 95% CI, 1.104–1.224).

As a secondary analysis, 19 subjects (8.0%) who quit smoking within a year of receiving an index PET were included in the "current smoker" category. Multivariable regression analysis then found that current smoking was significantly associated (OR, 1.49; 95% CI, 1.09–2.03) with receiving PET, whereas female sex was no longer associated with receiving PET. Additionally, in this analysis, alcohol etiology of chronic pancreatitis was associated with not receiving PET (OR, .62; 95% CI, .46–2.49).

Endotherapy modalities

Most subjects in the PET group received ERCP alone (86.6%), whereas 13% of subjects had a combination of EUS and ERCP. A small number of subjects received ESWL in combination with ERCP (13.1%), with only 1 subject (.4%) receiving ESWL alone (Supplementary Table 1, available online at www.giejournal.org).

Specific endoscopic treatments performed during the index PET course included pancreatic sphincterotomy (60.7%), PD dilation (27.7%), therapeutic PD stent placement (51.8%), and PD stone removal (47.3%). Some cases involved pancreas divisum with interventions including minor papilla sphincterotomy (7.3%) and minor papilla stent placement (6.7%).

Timing, duration, and outcome of first PET course

The relationship between chronic pancreatitis diagnosis and performance of the first PET course is shown in Figure 3. About one-third of subjects (34.3%) received PET in the

Author Manuscript

same year of diagnosis and nearly another one-third (29.6%) within a year of diagnosis. Forty-three subjects (18.3%) were undergoing PET at the time of enrollment. The median duration of the first course of endotherapy was 2 months (interquartile range, 1–4), with a median of 2 treatment sessions (interquartile range, 1–3). For the first PET course, 62.7% of subjects receiving PET had a treatment response (Supplementary Table 2, available online at www.giejournal.org), whereas 54 subjects (22.9%) had no treatment response.

Repeat PET courses

Of the 238 subjects receiving PET, 103 (43.3%) received more than 1 treatment course. Of these, 55 (53.4%) received 2 PET courses, 23 (22.3%) received 3 courses, and 25 (24.3%) received 4 courses (Table 4). The median duration of the treatment course and number of treatment sessions were generally consistent across treatment courses (Table 5, Supplementary Tables 3 and 4, available online at www.giejournal.org). Between the first and second PET course, the median time interval was 2 years (mean, 3.0), and between the second and third PET course, the median time interval was 1 year (mean, 2.3). Similar to the index PET course, treatment response for subsequent course was observed in 60.4% and 65.2% of subjects after their second and third endotherapy course, respectively.

In the proportional rates model analysis, subjects who were unemployed (vs those who were employed) at the time of enrollment had a significantly lower rate of repeat PET during their clinical course until the time of enrollment (proportional rate ratio, .794; 95% CI, .649-.972). Subjects who received repeat PET had a higher proportion of PD stones in the head of the pancreas (43% vs 31%) compared with those who received a single course of PET. There was no difference in PD stricture location between those who received and did not receive repeat PET.

DISCUSSION

This large multicenter study provides an insight into how often patients with chronic pancreatitis managed at U.S. referral centers undergo PET and factors associated with performance of PET. We observed that a large proportion of subjects with chronic pancreatitis received PET during the course of their disease. PET was performed more frequently in women and in those with lower education and income levels. Nearly half of the subjects who underwent PET needed additional treatment courses within 2 to 3 years after the initial course.

In clinical practice, the most common scenario for performance of PET is abdominal pain or episodes of acute pancreatitis because of PD obstruction from PD stricture and/or stones. Not surprisingly, PD dilation and prior history of acute pancreatitis were among the strongest predictors for being offered and receiving PET in our study. Similarly, patients who received PET also reported higher levels of pain in the year preceding enrollment and were more likely to use opioids at the time of enrollment. The odds of receiving PET also increased with the duration of chronic pancreatitis, which is likely related to increased likelihood of developing obstructive adverse events such as PD strictures and/or stones because of ongoing inflammatory changes and progressive fibrosis.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

We also noted demographic and socioeconomic factors to be associated with receiving PET, such as in women and in those with lower education or income, which have not been reported in prior studies[10,12,13,19–21] The exact explanation for these observations is unclear. Lower socioeconomic status has been associated with reduced access to health care in conditions such as cerebrovascular disease and coronary artery disease where lower socioeconomic status is also associated with worse outcomes.[22,23] For subjects in our study, access to health care may not be necessarily reduced, but their socioeconomic status may affect their ability for self-care and to navigate the decision-making process for potential treatments. Nevertheless, because chronic pancreatitis can place a large financial burden on both patients and healthcare systems, further study is needed to understand the role of socioeconomic factors on the access to, use of, and response to different treatment strategies for chronic pancreatitis, including nonendoscopic options.[24,25]

In the secondary analysis, when including current smokers as those who quit smoking within 1 year of receiving PET to the "current smoker" category, smoking was found to be significantly associated with receiving PET. Smoking has been associated with the development of PD stones and strictures, which may explain this association.[26] Further, prior studies have demonstrated that smokers with chronic pancreatitis have higher levels of pain and worse quality of life, which may lead to increased referral for PET.[27–29] In the ongoing longitudinal phase of the PROCEED, we hope to evaluate whether smoking cessation reduces the need for PET.

Institutional practices and physician preference may bias the use of PET. In light of this, we performed a univariate analysis by center for the use of PET and included center as a covariate in the multivariable regression model. We found variability between centers in the use of PET (5%–71%). Importantly, on multivariable regression, although center was an independent predictor, inclusion of center as a covariate only had a modest effect on other covariates with independent association, and none of them lost significance because of confounding. Therefore, although institutional practices certainly affect PET patterns, the primary associations noted in the study are still relevant and important contributions of our analyses.

In the cohort of subjects who received PET, nearly two-thirds were found to have had a treatment response (complete or partial) after their first endotherapy course, which was similar with subsequent courses of endotherapy. A randomized study comparing ESWL with the combination of ESWL and ERCP had previously demonstrated a similar response rate for the treatment of PD stones, whereas randomized studies comparing surgery with endotherapy for PD strictures and stones found a lower (32%–39%) response rate than seen in this study.[12,19,30] Although the retrospective nature of data collection in our study limits the accuracy of treatment response, it is important to note that nearly one-third of subjects had no response to PET. This highlights a cohort of patients for whom endotherapy is not effective, and future studies should attempt to identify these patients before initiating endotherapy.

A small proportion of subjects (8.4%) in this study went on to receive surgery after PET. Furthermore, despite literature suggesting that surgery is effective for improving

pain when performed early in the course of the disease, few subjects underwent surgery before receiving any PET.[19,30,31] This highlights variability in practice patterns and patient preferences between the United States and other countries. Similarly, the use of ESWL was infrequent, likely related to challenges with access to ESWL in the United States because it is often performed by urologists and not endoscopists or pancreatologists.[32] For this reason, pancreatoscopy-guided lithotripsy is often chosen by some endoscopists in the United States. Although a head-to-head comparison of ESWL with pancreatoscopy is ongoing, early reports have found high (~90%) stone removal rates with pancreatoscopy compared with rates (~70%) typically seen with ESWL.[15,33–35] Importantly, however, the low number of subjects who elected for surgery before PET likely also reflects patient preference in the United States where patients would rather attempt endotherapy first before considering surgery as seen previously.[10] Finally, selection bias likely played a role in that the PROCEED initially avoided recruiting subjects who had already undergone surgery.

This study provides a glimpse into the timing of PET in relation to the diagnosis of chronic pancreatitis. For those who received PET, the first treatment course typically occurred within a year before or after (63.9%) the diagnosis of chronic pancreatitis, and only 17.4% received their index PET 4 years after diagnosis. This finding matches with the study population in the ESCAPE trial comparing early surgery with endoscopy in patients with chronic pancreatitis where the median duration of disease was 12 months.[19] Given that PD stones and strictures typically represent disease progression, however, this brings into question whether those who require PET have an accelerated disease progression when compared with the medically managed group; this in part is consistent with the younger age of patients who received PET when compared with the medically managed group. The median duration (2 months) and number of treatment sessions (n = 2) in our study for the index and subsequent courses are similar to data published from the North American Pancreatitis Study-2, which found a similar average treatment duration (4 months).[20] Randomized trials on PET have also shown treatment courses lasting 1 to 2 sessions on average, but the short duration of treatment in our study (among other studies) does raise the possibility of undertreatment.[12,20,30]

A unique aspect of this study relates to insights into the use and timing of repeat endotherapy. In a study examining refractory PD strictures treated with endoscopic stent placement, stricture recurrence was found in only 7% of patients during a mean follow-up duration of 9.5 years.[21] In a randomized trial comparing surgery (n = 20) with endoscopy (n = 19) in patients predominantly with PD stones, 5-year follow-up data revealed recurrent obstruction in 47% of patients treated endoscopically. In our study, we found that nearly 50% of patients who received PET underwent a second course and 20% at least 3 courses. This likely reflects the progressive nature of fibrosis in chronic pancreatitis. Although nearly 65% of subjects experienced treatment success, recurrence of PD strictures and/or stones occurred within 2 to 3 years as inferred from the interval between PET courses. Unemployment was associated with not receiving repeat endotherapy, which may speak to the financial burden of PET and the relationship of unemployment with health insurance coverage, but this association warrants further investigation. We anticipate that prospective follow-up data provided by this study will illuminate other risk factors for receiving repeat endotherapy and further clarify the durability of endotherapy.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Several limitations of this study warrant further discussion. Our results reflect a cross-sectional analysis, so a direct assessment of the effectiveness of PET is difficult to determine. We were thus unable to assess the effect of PET on outcomes such as pancreatic exocrine or endocrine function or opiate use. Patients were enrolled from tertiary medical centers, so the results may not be fully representative of a community practice. We focused primarily on the treatment of PD strictures and stones and did not include other treatment modalities such as EUS-guided celiac plexus block and EUS-guided drainage of pancreatic fluid collections because of their small number. Although the study collected data on different aspects of PET, it was not designed to examine specific endoscopic methods, such as details about stents (eg, number, diameter, etc), dilation techniques, or whether pancreatoscopy-guided lithotripsy was performed, the latter representing a more recent technologic breakthrough in PD stone treatment. Importantly, these data reflect the different practice patterns of many endoscopists from 9 different centers. The lack of standard endotherapy protocols makes it challenging to generalize endotherapy results and limits our analysis. Relatedly, the variable disease duration of subjects before enrollment limits analyses on the durability of PET. Finally, this study did not focus on the effects of PET on patient-centered outcomes such as improvement in quality of life.

In summary, data from this large multicenter cohort revealed that although PET is frequently performed in patients with chronic pancreatitis, demographic and socioeconomic factors play a role in patient selection for PET. Furthermore, after an index course of PET, nearly half of patients underwent a repeat course within 2 years, suggesting limitations of durable response for pain management in these patients. Continued prospective follow-up of this and other cohorts will help illuminate risk factors for receiving repeat endotherapy and the effect of endotherapy on patient-centered outcomes in chronic pancreatitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

Samuel Han was supported by the Path to K award from the Ohio State University College of Medicine Office of Research and the Center for Clinical and Translational Science through the Richard P. & Marie R. Bremer Medical Research Fund and William H. Davis Endowment for Basic Medical Research.

DISCLOSURE

The following authors disclosed financial relationships: S. Han, J. J. Easler: Consultant for Boston Scientific. W. G. Park: Research support from AbbVie; advisory board for Nestle, Pfizer, and Ariel Medicine; consultant for Arctx Medical, Olympus, and Capsovision. S. S. Vege: Royalties from UpToDate. D. Yadav: Research support from AbbVie; consultant for Pfizer. All other authors disclosed no financial relationships. Research support for this study was provided by the National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases under award numbers U01DK 108288 (Mayo Clinic), U01DK108320 (University of Florida), U01DK108323 (Indiana University), U01DK108326 (Baylor College of Medicine), U01DK108327 (The Ohio State University), U01DK108300 (Stanford University), U01DK108306 (University of Pittsburgh), U01DK108314 (Cedars-Sinai Medical Center), U01DK108328 (University of Texas–MD Anderson Cancer Center), and U01DK108332 (Kaiser Foundation Research Institute).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Abbreviations:

CI	confidence interval
ESWL	extracorporeal shockwave lithotripsy
OR	odds ratio
PET	pancreatic endotherapy
PD	pancreatic duct
PROCEED	Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies

REFERENCES

1. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. Pancreatology 2016;16:218–24. [PubMed: 26924663]
2. Singh VK, Yadav D, Garg PK. Diagnosis and management of chronic pancreatitis: a review. JAMA 2019;322:2422–34. [PubMed: 31860051]
3. Asaumi H, Watanabe S, Taguchi M, et al. Externally applied pressure activates pancreatic stellate cells through the generation of intracellular reactive oxygen species. Am J Physiol Gastrointest Liver Physiol 2007;293:G972–8. [PubMed: 17761838]
4. Chandrasekhara V, Chathadi KV, Acosta RD, et al. The role of endoscopy in benign pancreatic disease. Gastrointest Endosc 2015;82:203–14. [PubMed: 26077456]
5. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) guideline—updated August 2018. Endoscopy 2019;51:179–93. [PubMed: 30654394]
6. LeBlanc JK, DeWitt J, Johnson C, et al. A prospective randomized trial of 1 versus 2 injections during EUS-guided celiac plexus block for chronic pancreatitis pain. Gastrointest Endosc 2009;69:835–42. [PubMed: 19136101]
7. Ammann RW, Akovbiantz A, Largiader F, et al. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. Gastroenterology 1984;86:820–8. [PubMed: 6706066]
8. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Prognosis of chronic pancreatitis: an international multicenter study. International Pancreatitis Study Group. Am J Gastroenterol 1994;89:1467–71. [PubMed: 8079921]
9. Glass LM, Whitcomb DC, Yadav D, et al. Spectrum of use and effectiveness of endoscopic and surgical therapies for chronic pancreatitis in the United States. Pancreas 2014;43:539–43. [PubMed: 24717802]
10. Vipperla K, Kanakis A, Slivka A, et al. Natural course of pain in chronic pancreatitis is independent of disease duration. Pancreatology 2021;21:649–57. [PubMed: 33674197]
11. Machicado JD, Chari ST, Timmons L, et al. A population-based evaluation of the natural history of chronic pancreatitis. Pancreatology 2018;18:39–45. [PubMed: 29221631]
12. Dumonceau JM, Costamagna G, Tringali A, et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. Gut 2007;56:545–52. [PubMed: 17047101]
13. Costamagna G, Bulajic M, Tringali A, et al. Multiple stenting of refractory pancreatic duct strictures in severe chronic pancreatitis: long-term results. Endoscopy 2006;38:254–9. [PubMed: 16528652]
14. Attwell AR, Patel S, Kahaleh M, et al. ERCP with per-oral pancreatoscopy-guided laser lithotripsy for calcific chronic pancreatitis: a multi-center U.S. experience. Gastrointest Endosc 2015;82:311–8. [PubMed: 25841585]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

15. Brewer Gutierrez OI, Raijman I, Shah RJ, et al. Safety and efficacy of digital single-operator pancreatoscopy for obstructing pancreatic ductal stones. Endosc Int Open 2019;7:E896–903. [PubMed: 31281875]
16. Han S, Shah RJ, Brauer BC, et al. A comparison of endoscopic retrograde pancreatography with or without pancreatoscopy for removal of pancreatic duct stones. Pancreas 2019;48:690–7. [PubMed: 31091217]
17. Yadav D, Park WG, Fogel EL, et al. PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies: rationale and study design for PROCEED from the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Pancreas 2018;47:1229–38. [PubMed: 30325862]
18. Serrano J, Andersen DK, Forsmark CE, et al. Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer: from concept to reality. Pancreas 2018;47:1208–12. [PubMed: 30325859]
19. Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. JAMA 2020;323:237–47. [PubMed: 31961419]
20. Clarke B, Slivka A, Tomizawa Y, et al. Endoscopic therapy is effective for patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2012;10:795–802. [PubMed: 22245964]
21. Tringali A, Bove V, Vadalà di Prampero SF, et al. Long-term follow-up after multiple plastic stenting for refractory pancreatic duct strictures in chronic pancreatitis. Endoscopy 2019;51:930–5. [PubMed: 31378858]
22. Marshall IJ, Wang Y, Crichton S, et al. The effects of socioeconomic status on stroke risk and outcomes. Lancet Neurol 2015;14:1206–18. [PubMed: 26581971]
23. Schröder SL, Richter M, Schröder J, et al. Socioeconomic inequalities in access to treatment for coronary heart disease: a systematic review. Int J Cardiol 2016;219:70–8. [PubMed: 27288969]
24. Hall TC, Garcea G, Webb MA, et al. The socio-economic impact of chronic pancreatitis: a systematic review. J Eval Clin Pract 2014;20:203–7. [PubMed: 24661411]
25. Singh P, Chakraborty B, Sarkhel S, et al. Indian outpatients with idiopathic chronic pancreatitis have catastrophic healthcare expenditure, malnutrition, anxiety/depression and work-impairment. Dig Dis Sci 2022;67:3612–22. [PubMed: 34581905]
26. Olesen SS, Nojgaard C, Poulsen JL, et al. Chronic pancreatitis is characterized by distinct complication clusters that associate with etiological risk factors. Am J Gastroenterol 2019;114:656–64. [PubMed: 30741740]
27. Olesen SS, Kuhlmann L, Novovic S, et al. Association of multiple patient and disease characteristics with the presence and type of pain in chronic pancreatitis. J Gastroenterol Hepatol 2020;35:326–33. [PubMed: 31314128]
28. Machicado JD, Amann ST, Anderson MA, et al. Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities. Am J Gastroenterol 2017;112:633–42. [PubMed: 28244497]
29. Han S, Patel B, Min M, et al. Quality of life comparison between smokers and non-smokers with chronic pancreatitis. Pancreatology 2018;18:269–74. [PubMed: 29500114]
30. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med 2007;356:676–84. [PubMed: 17301298]
31. Bordacahar B, Couvelard A, Vullierme MP, et al. Predicting the efficacy of surgery for pain relief in patients with alcoholic chronic pancreatitis. Surgery 2018;164:1064–70. [PubMed: 30029988]
32. Bush N, Han S, Akshintala VS. Extra-corporeal shock wave lithotripsy for pancreatic duct calculi: a perspective from a practice in the United States. Pancreas 2024;53:e223–4. [PubMed: 38206656]
33. Han S, Miley A, Akshintala V, et al. Per-oral pancreatoscopy-guided lithotripsy vs. extracorporeal shock wave lithotripsy for treating refractory main pancreatic duct stones in chronic pancreatitis: protocol for an open-label multi-center randomized clinical trial. Pancreatology 2022;22:1120–5. [PubMed: 36273991]
34. Gerges C, Albers D, Schmitz L, et al. Digital single-operator pancreatoscopy for the treatment of symptomatic pancreatic duct stones: a prospective multicenter cohort trial. Endoscopy 2023;55:150–7. [PubMed: 35672016]

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

35. Moole H, Jaeger A, Bechtold ML, et al. Success of extracorporeal shock wave lithotripsy in chronic calcific pancreatitis management: a metaanalysis and systematic review. Pancreas 2016;45:651–8. [PubMed: 26580454]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

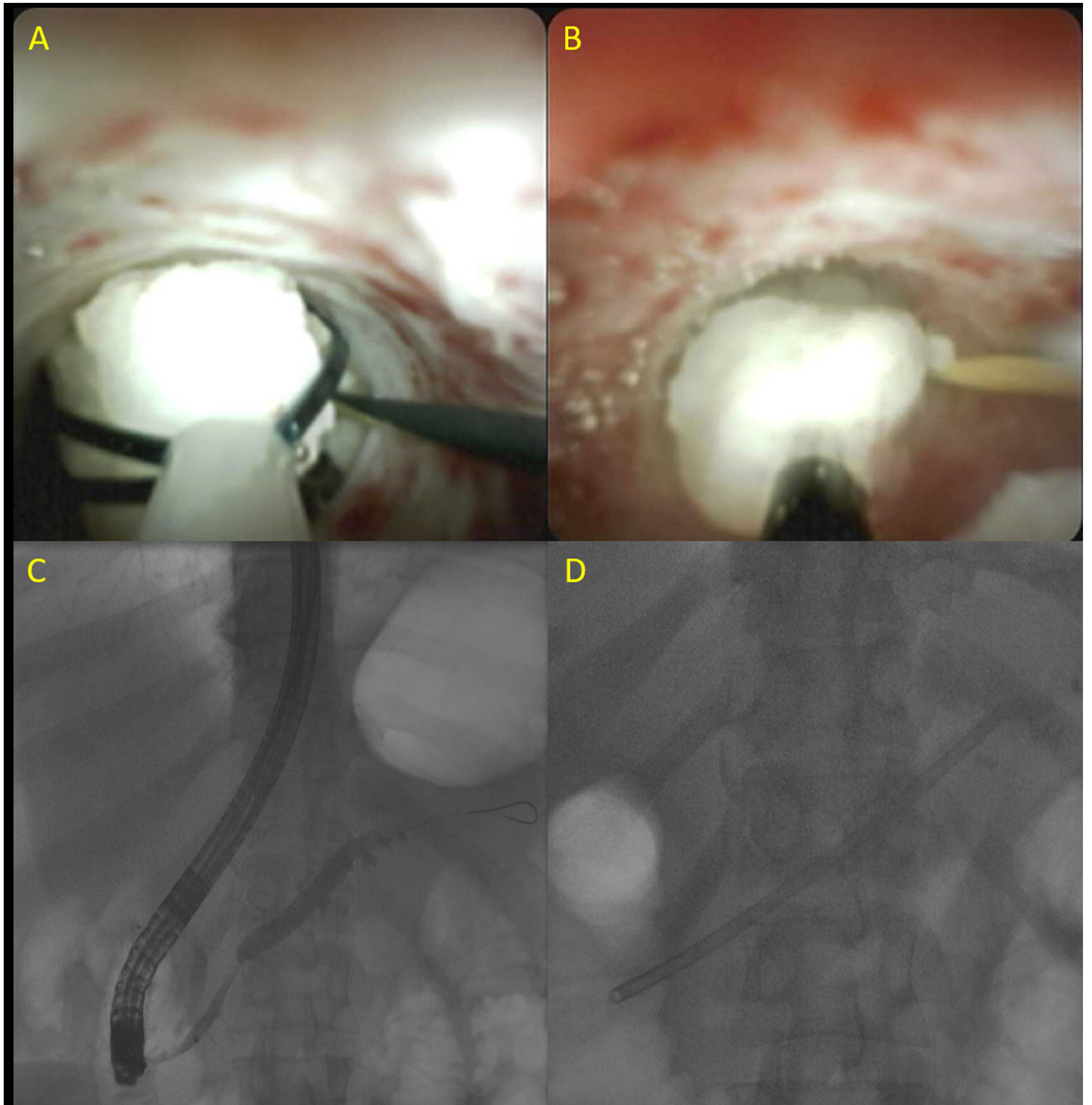


Figure 1.

Examples of pancreatic endotherapy. **A,** Basket removal of the pancreatic duct stone. **B,** Pancreatoscopy-guided electrohydraulic lithotripsy. **C,** Pancreatic duct stricture seen on pancreatogram. **D,** Pancreatic duct stricture treated with pancreatic duct stent placement.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

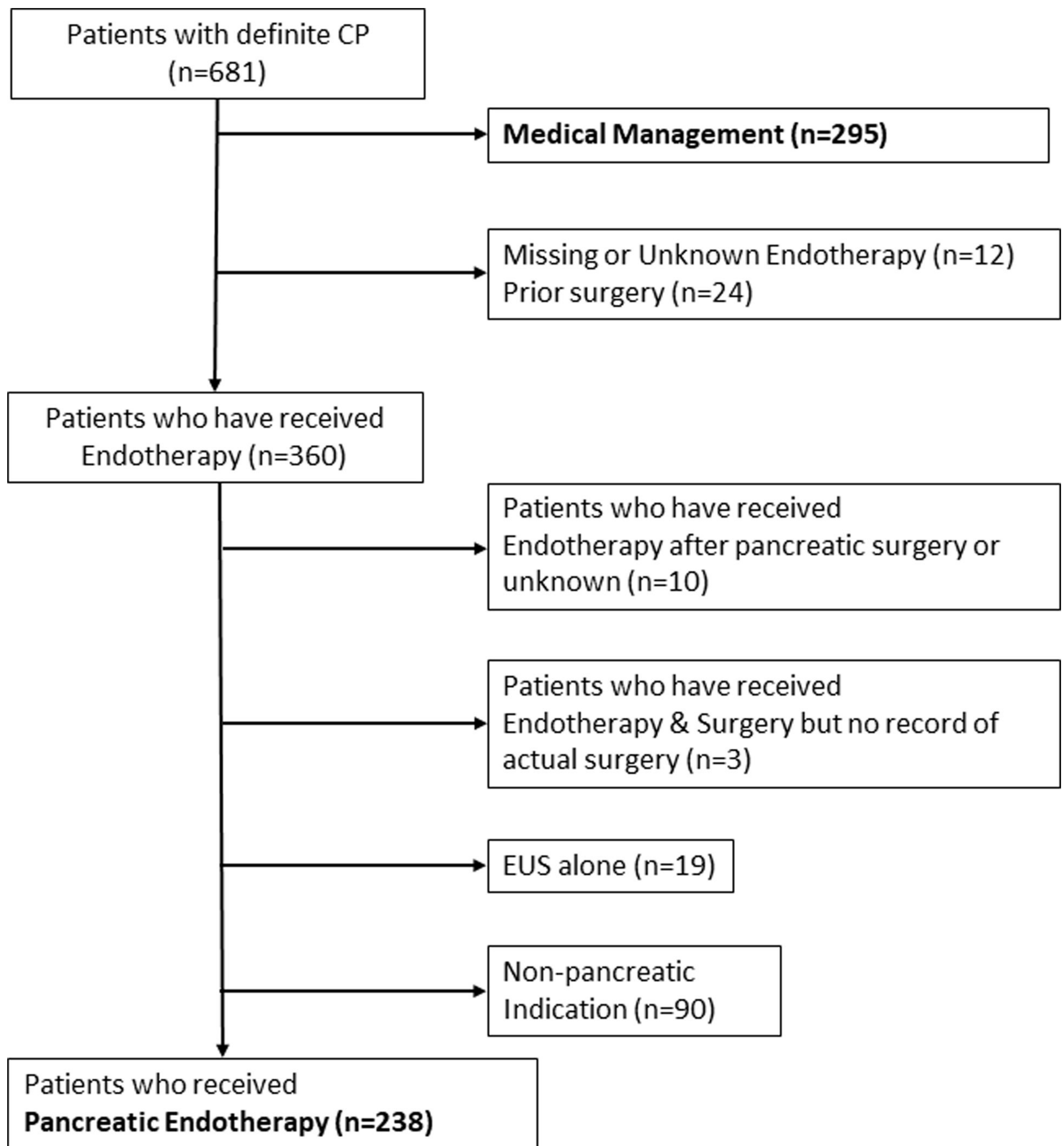


Figure 2.
Study flowchart. *CP*, Chronic pancreatitis.

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

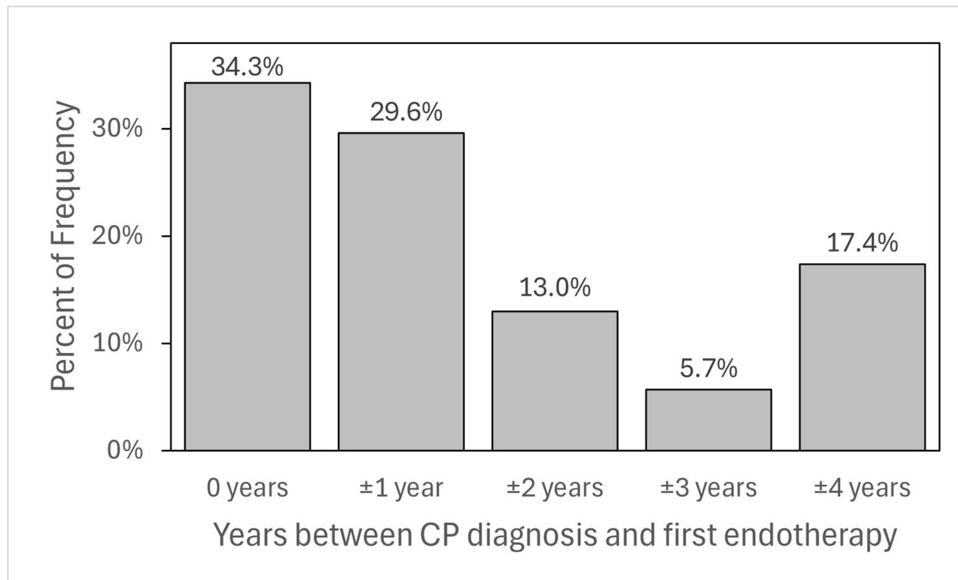


Figure 3.
Duration from chronic pancreatitis diagnosis to first pancreatic endotherapy (PET) among 295 subjects with chronic pancreatitis who had undergone PET at the time of baseline enrollment. *CP*, Chronic pancreatitis.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1:

Demographics, socioeconomic status and selected participant characteristics amongst participants with chronic pancreatitis (CP).

	Pancreatic endotherapy (n=238)	Medical management (n=295)	p-value
Age (years)	53 (43, 61)	57 (46, 65)	0.0011
BMI	24.4 (21.3, 28.3)	25.5 (22.1, 29.2)	0.041
Age at CP (years)	48 (38,57)	55 (44, 64)	<0.001
CP duration (years)	2 (1,7)	1 (0, 2)	<0.001
Duration of pancreatitis (total) (years)	7 (3, 14)	3 (1, 7)	<0.001
Sex			0.017
Male	110 (46.2)	167 (56.6)	
Female	128 (53.8)	128 (43.4)	
Race			0.087
White	206 (86.6)	234 (79.3)	
Black	15 (6.3)	26 (8.8)	
Other	17 (7.1)	35 (11.8)	
Education			<0.001
HS/GED or less	102 (44.0)	83 (29.1)	
Higher than HS	130 (56.0)	202 (70.9)	
Income Level			0.0012
50K or greater	91 (43.8)	153 (58.9)	
Less than 50k	117 (56.2)	107 (41.1)	
Employment Status			0.0023
Employed	90 (38.6)	125 (43.4)	
Unemployed	96 (41.2)	79 (27.4)	
Retired	47 (20.2)	84 (29.2)	
Marital Status			0.31
Married	131 (55.7)	177 (60.4)	
Divorced/Separated/Widowed	48 (20.4)	62 (21.2)	
Single	56 (23.8)	54 (18.4)	
Prior AP	203 (90.2)	219 (75.8)	<0.001
Etiology			0.0031
Alcohol	91 (38.2)	117 (39.7)	
Idiopathic	80 (33.6)	129 (43.7)	
Other	67 (28.2)	49 (16.6)	
Smoking Status			0.19
Never	74 (31.5)	109 (37.6)	
Past	67 (28.5)	86 (29.7)	
Current	94 (40.0)	95 (32.8)	
Drinking Status			0.036

	Pancreatic endotherapy (n=238)	Medical management (n=295)	p-value
Never	36 (15.3)	38 (13.2)	
Past	155 (66.0)	169 (58.5)	
Current	44 (18.7)	82 (28.4)	
Diabetes	91 (40.3)	123 (43.6)	0.45
Exocrine Pancreatic Dysfunction	90 (37.8)	106 (35.9)	0.16
Pancreatic calcifications on imaging	186 (78.2)	217 (73.6)	0.22
Pancreatic size on imaging			0.037
< 7mm	27 (11.3)	42 (14.4)	
7mm – 14mm	99 (41.6)	90 (30.9)	
>14mm	112 (47.0)	159 (54.6)	
Pancreatic duct dilation on imaging	210 (88.2)	195 (67.0)	<0.001

BMI: body mass index; CP: chronic pancreatitis; HS: high school; GED: general educational development; AP: acute pancreatitis; RAP: recurrent acute pancreatitis. Continuous variables described using median (IQR range); Categorical variables described using n (%).

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2:

Pain features, medication use and healthcare utilization at and prior to enrollment.

	Pancreatic endotherapy (n=238)	Medical management (n=295)	p-value
Pain Severity at enrollment			<0.001
Severe	155 (67.1)	138 (47.8)	
Mild-moderate	57 (24.7)	89 (30.8)	
No pain	19 (8.2)	62 (21.5)	
Pain Temporality			<0.001
Constant	127 (55.0)	94 (32.5)	
Intermittent	85 (36.8)	133 (46.0)	
No pain	19 (8.2)	62 (21.5)	
PERT	126 (54.3)	123 (41.8)	0.0043
Current narcotic use	118 (50.9)	112 (38.4)	0.0042
NSAID use	45 (19.4)	50 (17.1)	0.50
Neuromodulator use	73 (31.5)	91 (31.2)	0.94
Number of hospitalizations in last 12 months before enrollment	1 (0,3)	0 (0,2)	<0.001
Number of hospitalizations in lifetime	6 (2,15)	2 (0,5)	<0.001
Number of ER visits in last 12 months before enrollment	0 (0,2)	0 (0,1)	0.068
Surgery the same year as endotherapy	8	N/A	N/A
Surgery after endotherapy completed	12	N/A	N/A

PERT: pancreatic enzyme replacement therapy; NSAID: non-steroidal anti-inflammatory drug; ER: emergency room, N/A: not applicable

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3:

Multivariable logistic regression analysis of risk factors for receiving pancreatic endotherapy amongst 681 participants with chronic pancreatitis.

Variable (reference group)	Odds Ratio	95% Confidence Interval	p-value
Intercept	0.176	[0.110,0.284]	<0.001
Duration of CP in years	1.163	[1.104,1.224]	<0.001
Sex: Male (Female)	0.812	[0.668,0.987]	0.036
Race: Black (White)	0.697	[0.409,1.187]	0.184
Race: Other (White)	0.873	[0.527,1.446]	0.597
Education: Training past HS (HS/GED or less)	0.763	[0.611,0.952]	0.017
Income Level: >= 50k (<50k)	0.763	[0.600,0.971]	0.028
Prior AP: Yes (No)	1.744	[1.313,2.316]	<0.001
Pancreatic duct dilation: Yes (No)	1.942	[1.505,2.506]	<0.001

CP: chronic pancreatitis; HS: high school; GED: general education development; AP: acute pancreatitis. An odds ratio greater than 1 indicates that the risk factor is associated with a higher probability of receiving pancreatic endotherapy than the reference group (in parentheses).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 4:

Distribution of the number of treatment courses of pancreatic endotherapy (PET) amongst 238 participants with chronic pancreatitis who received PET.

Total Courses	Number of subjects	Percent
1	135	56.7
2	55	23.1
3	23	9.7
4	14	5.9
5	6	2.5
6	2	0.8
7	2	0.8
8	1	0.4

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 5:

Duration (years) between individual PET courses

Years between	N	25th Percentile	Median	Mean	75th Percentile
Course 1–2	103	1	2	3.0	4
Course 2–3	46	1	1	2.3	3
Course 3–4	23	1	2	3.0	3
Course 4–5	11	1	2	2.2	4
Course 5–6	5	1	1	1.0	1

N: Number of patients receiving endotherapy courses