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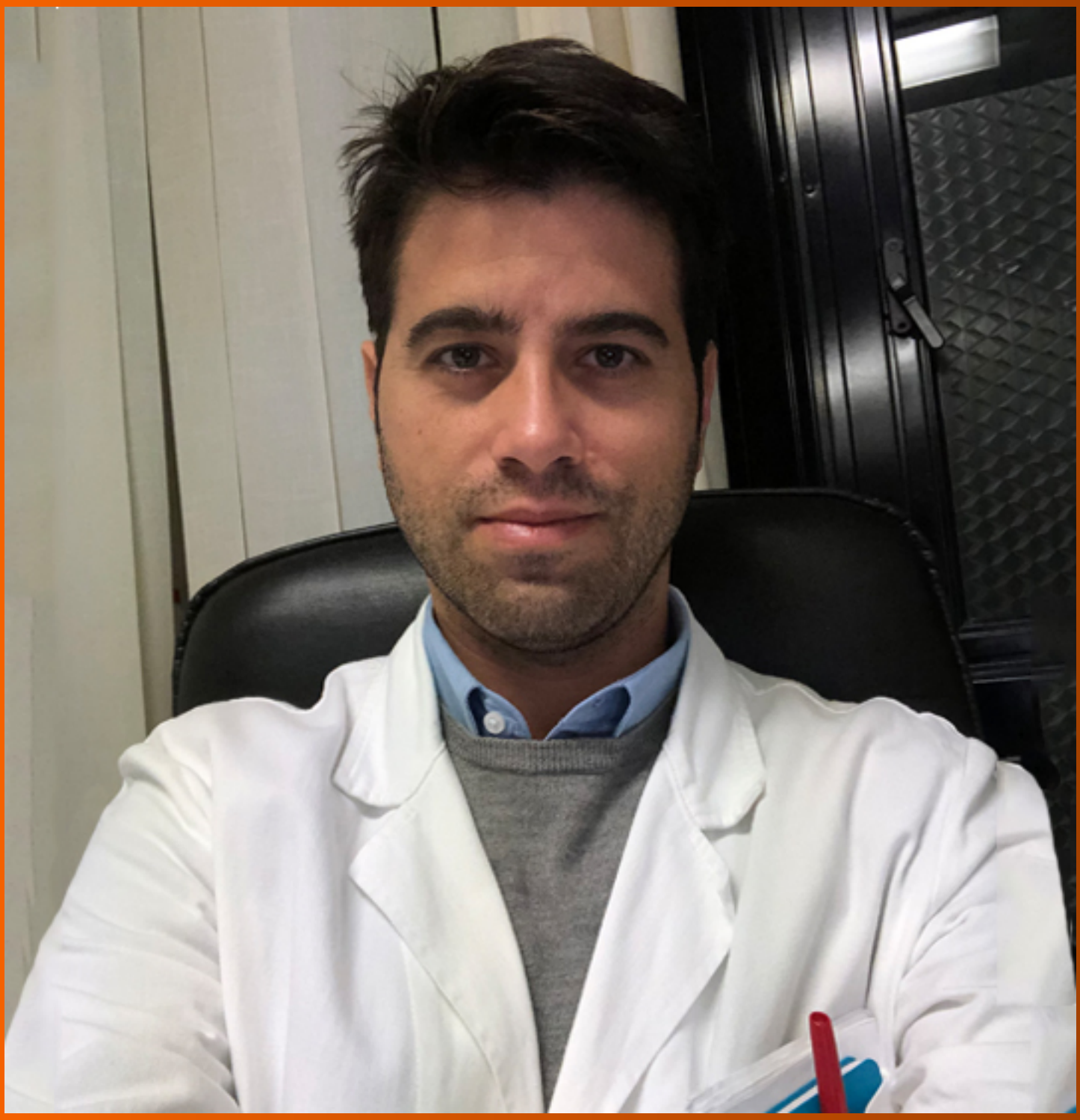

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ORIGINAL ARTICLE

Retrospective Study

Evaluating the risk of adverse events with interventional endoscopic retrograde cholangiopancreatography and endoscopic ultrasound procedures in cirrhotic patients

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Author contributions: Yoo T, Epistola R and Ku L assisted in data gathering; Yoo T contributed to data analysis; all authors contributed to writing/editing the paper; Epistola J performed the statistical analysis; Fleischman MW, Reicher S, Eysselein VE and Hou LA performed the procedures; Hou LA conceived and designed the study and supervised the entire project.

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Abstract

BACKGROUND

Hepatic cirrhosis is associated with greater adverse event rates following surgical procedures and is thought to have a higher risk of complications with interventional procedures in general. However, these same patients often require interventional gastrointestinal procedures such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). While studies examining this scenario exist, the overall body of evidence for adverse event rates associated with ERCP/EUS procedures is more limited. We sought add to the literature by examining the incidence of adverse events after ERCP/EUS procedures in our safety-net hospital population with the hypothesis that severity of cirrhosis correlates with higher adverse event rates.

AIM

To examine whether increasing severity of cirrhosis is associated with greater incidence of adverse events after interventional ERCP/EUS procedures.

METHODS

We performed a retrospective study of patients diagnosed with hepatic cirrhosis who underwent ERCP and/or EUS-guided fine needle aspirations/fine needle

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biopsies from January 1, 2016 to March 14, 2019 at our safety net hospital. We recorded Child-Pugh and Model for End-stage Liver Disease (MELD-Na) scores at time of procedure, interventions completed, and 30-day post-procedural adverse events. Statistical analyses were done to assess whether Child-Pugh class and MELD-Na score were associated with greater adverse event rates and whether advanced techniques (single-operator cholangioscopy, electrohydraulic lithotripsy/laser lithotripsy, or needle-knife techniques) were associated with higher complication rates.

RESULTS

77 procedures performed on 36 patients were included. The study population consisted primarily of middle-aged Hispanic males. 30-d procedure-related adverse events included gastrointestinal bleeding (7.8%), infection (6.5%), and bile leak (2%). The effect of Child-Pugh class C *vs* class A and B significantly predicted adverse events ($\beta = 0.55$, $P < 0.01$). MELD-Na scores also significantly predicted adverse events ($\beta = 0.037$, $P < 0.01$). Presence of advanced techniques was not associated with higher adverse events ($P > 0.05$). When MELD-Na scores were added as predictors with the effect of Child-Pugh class C, logistic regression showed MELD-Na scores were a significant predictor of adverse events ($P < 0.01$). The findings held after controlling for age, gender, ethnicity and repeat cases.

CONCLUSION

Increasing cirrhosis severity predicted adverse events while the presence of advanced techniques did not. MELD-Na score may be more useful in predicting adverse events than Child-Pugh class.

Key words: Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasound; Fine-needle aspiration; Fine-needle biopsy; Hepatic cirrhosis; Model for End-stage Liver Disease; Child-Pugh Class; Adverse events

Core tip: We performed a retrospective review of all patients with hepatic cirrhosis who underwent interventional endoscopic retrograde cholangiopancreatography/ endoscopic ultrasound procedures over a 3 years span at our safety-net hospital and evaluated outcomes within a 30-d period. 77 cases were included. Both Model for End-stage Liver Disease (MELD-Na) score and Child-Pugh class C predicted adverse events ($P < 0.01$). When MELD-Na scores were added as predictors with the effect of Child-Pugh class C, only MELD-Na scores were a significant predictor of adverse events ($P < 0.01$). Our data demonstrates a correlation between cirrhosis severity and adverse events and suggests that MELD-Na score may be useful in assessing procedural risk.

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INTRODUCTION

Liver cirrhosis is a major public health issue around the world, including in the United States where it affects over half a million people[1]. These individuals are just as likely, if not more so, as the general population to develop biliary or pancreatic tract diseases, many of which require interventional endoscopic retrograde cholangiopancreatography (ERCP) and/or endoscopic ultrasound (EUS) procedures[2,3]. The impaired hepatic function of cirrhotic patients cause systemic derangements which have been shown to increase the risk of morbidity and mortality in surgical or invasive procedures[4]. The presence of cirrhosis has been thought to increase the risk of post-procedural complications, including pancreatitis, bleeding,

infection, and perforation[5-8]. Data examining the risks associated with cirrhotic patients undergoing ERCP/EUS procedures remains limited, though the available data suggests cirrhotic patients have a higher adverse event rate than the general population and that increasing severity of cirrhosis correlates with higher adverse event rates[5-8]. Given the relative dearth of information on the topic, we performed a retrospective review of cirrhotic patients who underwent interventional ERCP and/or EUS procedures at our safety net hospital to determine whether increasing severity of cirrhosis was associated with greater incidence of adverse outcomes with these procedures.

MATERIALS AND METHODS

We performed a retrospective review of all patients diagnosed with hepatic cirrhosis who underwent inpatient or outpatient ERCP and/or interventional EUS [defined as EUS-guided liver biopsies or fine needle aspirations (FNA)/fine needle biopsies (FNB) of pancreatic and/or biliary masses/cysts] procedures from January 1, 2016 to March 14, 2019, at our tertiary referral safety net hospital in Southern California. EUS procedures that did not have an interventional component as detailed above were excluded. We recorded the age, sex, and ethnicity of the patients, etiology for cirrhosis, Child-Pugh and Model for End-stage Liver Disease (MELD-Na) scores at the time of procedure, indications for procedure, any interventions completed during the procedure, presence of advanced techniques (defined as single-operator cholangioscopy, laser or electrohydraulic/ electrohydraulic lithotripsy, or needle-knife techniques), and 30-day post-procedural adverse events (defined as evidence of infection, significant gastrointestinal (GI) bleeding, perforation, post-ERCP pancreatitis, and death). Statistical analysis was done to determine whether higher Child-Pugh scores and MELD-Na scores were associated with increased risk of adverse events (after controlling for repeat cases) and whether the presence of advanced techniques was associated with increased risk of adverse events.

Statistics

All statistical analyses were performed using the RStudio software (Version 1.0.153). Chi-squared tests for independence were used to examine associations between categorical test variables (*e.g.*, Child-Pugh scores, advanced procedures) and adverse events. Point-biserial correlation was used to examine the association between MELD-Na scores and adverse events. Multiple variable logistic regression was used in our prediction analyses to assess the associations between Child-Pugh class, advanced techniques, MELD-Na and adverse events, while controlling for age, gender, and repeat patients. Adverse events and advanced techniques were dummy coded in this analysis. Child-Pugh classes were effects coded using difference regression coding since they are ordinal categorical variables. A P value of less than 0.05 was considered statistically significant.

RESULTS

77 procedures (63 ERCP, 14 EUS-guided FNA/FNB/liver biopsies) performed on 36 patients were included. Of note, each procedure was treated as a unique case for the purposes of our study given that each procedure was an isolated event with differences in lab values and clinical status even among the same patient. The mean age of the study population was 58.7 years old (ranging from 21-83 years old) with males forming the majority of the group (58.4%). Individuals of Hispanic descent made up 56% of the cases. All 3 Child-Pugh classes were represented (31 Procedure with Child's A, 34 procedures with Child's B, 11 procedures with Child's C, and 1 procedure with unreported Child-Pugh class). The mean MELD-Na score was 14 (range of 6-26). Cirrhosis was documented as being secondary to alcoholism (36.4%), viral hepatitis (24.7%), nonalcoholic steatohepatitis (18.2%), pyogenic cholangitis (16.9%), cryptogenic/unknown (14.3%), malignancy (9.1%), autoimmune hepatitis (3.9%), and primary biliary cirrhosis/primary sclerosing cholangitis (2%). A summary of patient demographics can be seen in Table 1.

Documented indications for ERCP procedures included choledocholithiasis (n = 38, 49.4%), biliary stricture (n = 12, 15.6%), biliary leak (n = 11, 14.3%), cholelithiasis (n = 8, 10.4%), biliary obstruction secondary to mass (n = 8, 10.4%), cholangitis (n = 4, 5.2%), gallstone pancreatitis (n = 3, 3.9%), biliary obstruction due to stent-related issues (n = 1, 1.3%), and evaluation of common bile duct dilatation without choledocholithiasis or mass (n = 1, 1.3%). Indications for interventional EUS

Table 1 Summary of patient demographics

	***n* = 77**
Average age (yr)	58.7
Sex, *n* (%)	
Male	45 (58.4)
Female	32 (41.6)
Race, *n* (%)	
Hispanic	56 (72.7)
Asian	8 (10.4)
Caucasian	4 (5.2)
African-American	5 (6.5)
Not stated	4 (5.2)
Average MELD-Na	14
Childs-Pugh Class, *n* (%)	
A	31 (40.3)
B	34 (44.2)
C	11 (14.3)
Unreported	1 (1.3)
Etiology for cirrhosis, *n* (%)	
Pyogenic cholangitis	13 (16.9)
NASH	14 (18.2)
Malignancy	7 (9.1)
Alcoholism	28 (36.4)
Hepatitis B virus	10 (13)
Hepatitis C virus	9 (11.7)
PBC/PSC	2 (2.6)
Autoimmune hepatitis	3 (3.9)
Cryptogenic/unknown	11 (14.3)

Of note, each procedure was treated as a unique individual; as such, n = 77. NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis.

procedures included pancreatic or biliary mass biopsy (n = 12, 15.6%) and liver biopsy (n = 3, 3.9%). Interventions included stent placement/removal (n = 53, 68.8%), stone removal (n = 38, 49.3%), sphincterotomy (n = 22, 28.5%), FNA/FNB (n = 10, 13%), and liver biopsy (n = 3, 3.9%). Advanced techniques employed included single-operator cholangioscopy (n = 24, 31.2%), electrohydraulic lithotripsy (n = 13, 16.9%), needle-knife techniques (n = 6, 7.8%), and laser lithotripsy (n = 5, 6.5%). Of note, most cases were associated with multiple indications and interventions.

Thirty-day procedure-related adverse events included GI bleeding (n = 6, 7.8%), infection (n = 5, 6.5%), and bile leak (n = 1, 1.3%). No cases of post-ERCP pancreatitis were noted. 5 cases were associated with death within 30 d of the procedure date; however, none of the deaths were determined to be secondary to the procedure itself, with 4 of the deaths attributable to progression of previously known cancer and 1 case being associated with septic shock secondary to intraabdominal infection in the setting of cholangiocarcinoma. A summary of the procedures can be seen in Table 2.

Chi-square test of independence analyses indicated that Child-Pugh class was significantly associated with adverse events [χ^2 (3, n = 76) 14.45, $P < 0.01$]. Adverse events were more likely to occur for Child C class patients than for Child A or B class patients. Presence of advanced techniques were not associated with adverse events [χ^2 (2, n = 77) 0.02, $P > 0.05$]. MELD-Na scores were moderately positively correlated with adverse events occurring [r (74) = 0.49, $P < 0.01$].

Multiple logistic regression analyses were used to examine if Child-Pugh class and MELD-Na scores significantly predicted adverse events. When analyzed in separate regression models, the effect of Child-Pugh class C *vs* class A and B significantly predicted the occurrence of adverse events (β = 0.55, $P < 0.01$) after controlling for age, gender and repeat cases (Figure 1). MELD-Na scores also significantly predicted adverse events (β = 0.037, $P < 0.01$) after controlling variables (Figure 2). The effect of Child-Pugh class B *vs* class A was not a significant predictor of adverse events ($P >$

Table 2 Summary of included procedures and procedure-related complications

	n = 77
Procedure type, *n* (%)	
EUS-guided FNA/FNB/liver biopsy	14 (16.9)
ERCP	63 (74)
Indication for procedure, *n* (%)	
Biliary stricture	12 (15.6)
Biliary leak	11 (14.3)
Choledocholithiasis	38 (49.4)
Cholelithiasis	8 (10.4)
Cholangitis	4 (5.2)
Gallstone pancreatitis	3 (3.9)
Obstruction secondary to mass	8 (10.4)
Obstruction secondary to stent issue	1 (1.3)
CBD dilatation w/o known mass	1 (1.3)
Biopsy of mass	12 (15.6)
Liver biopsy	3 (3.9)
Interventions employed, *n* (%)	
Stone removal	38 (49.3)
Stent placement/removal	53 (68.8)
Sphincterotomy	22 (28.5)
FNA/FNB	10 (13)
Liver biopsy	3 (3.9)
Spyglass cholangioscopy	24 (31.2)
EHL	13 (16.9)
Laser lithotripsy	5 (6.5)
Needle-knife papillotomy	6 (7.8)
Complications, *n* (%)	
Infection	5 (6.5)
Gastrointestinal bleeding	6 (7.8)
Bile leak	1 (1.3)
Pancreatitis	0 (0)

EUS: Endoscopic ultrasound; FNA/FNB: Fine needle aspiration/biopsy; ERCP: Endoscopic retrograde cholangiopancreatography; CBD: Common bile duct; EHL: Electrohydraulic lithotripsy.

0.05). Age, gender and repeat cases were also insignificant predictors in all regression models ($P > 0.05$).

When MELD-Na scores were added as predictors with the effect of Child-Pugh class C, logistic regression results indicated that only MELD-Na scores were a significant predictor of adverse events ($\beta = 0.027$, $P < 0.01$) after controlling for age, gender and repeat cases. The effect of Child-Pugh class C *vs* class A and B was insignificant ($P > 0.05$). MELD-Na scores and the effect of Child-Pugh class C were moderately positively correlated $r(74) = 0.58$, $P < 0.01$.

DISCUSSION

Our study examined all cirrhotic patients who underwent ERCP/interventional EUS procedures at our safety net hospital to evaluate the relationship between the severity of cirrhosis and rate of adverse events following these procedures. Analysis of our data noted a significantly increased risk of bleeding, infection, and bile leaks with both increasing MELD-Na score and higher Child-Pugh class even after controlling for age, gender and repeat cases. Interestingly, when Child-Pugh class and MELD-Na scores were combined in a logistical regression analysis, Child-Pugh class no longer became a significant predictor of adverse events while MELD-Na remained so. However, when performing the combined regression analysis separately with Child-Pugh class, the effect of Child-Pugh class C approached significance ($P = 0.056$). As

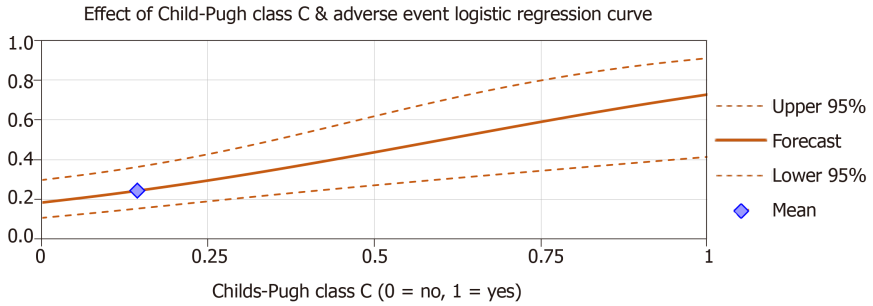

Figure 1 Child-Pugh class C was associated with higher probability of adverse events ($P < 0.01$).

such, the analyses suggest that MELD-Na score may be a more precise predictor of adverse outcomes with these procedures as it explains a unique portion of variance not attributable to Child-Pugh class. This finding adds to a growing body of research suggesting that only Child-Pugh class C is truly predictive of adverse events[5,8,9]. The implication that MELD-Na may be a more useful predictive tool is particularly notable as our review of the literature found that only a few studies evaluated MELD-Na score when examining outcomes of interventional GI procedures in patients with cirrhosis[6].

Our study also demonstrated a relatively high rate of post-procedural bleeding and infection, which occurred in 7.8% and 6.5% of cases respectively (all within ERCP procedures); these rates are notably higher than those seen among the general population (2% and 1.4%, respectively)[10]. Interestingly, our population did not experience any post-ERCP pancreatitis. These findings support those seen in previously published literature comparing ERCP outcomes between cirrhotics and non-cirrhotics and adds to the admittedly small data pool reporting safe outcomes with EUS-guided biopsies in cirrhotic individuals[5-8,11,12]. However, it is important to note that our study did not find an association between the use of advanced techniques and adverse events, suggesting that refinement of endoscopic techniques has improved safety of these procedures even in cirrhotic individuals.

The findings we present do have some limitations. Our study utilized a moderate sample size (n = 77 procedures), which restricts the interpretation of the Chi-square and logistic regression analyses. Additionally, many of our included patients underwent multiple procedures; 41 of our included procedures were repeat cases, with each unique patient undergoing an average of 2.14 procedures. The repeated cases further limited our interpretation of the statistical analyses. Finally, our study was performed at a single center and consisted primarily of middle aged Hispanic men from a lower socioeconomic class, affecting the generalizability of our results. However, our findings still held significance after correcting for age, gender, and repeat cases.

In conclusion, the findings presented above highlight the correlation between greater severity of cirrhosis and increasing risk of adverse events when performing interventional ERCP/EUS procedures. Our results support established literature yet offer intriguing implications regarding the use of MELD-Na score for assessing procedure risk and provides more data regarding safety of EUS-guided biopsies in cirrhotic patients. Further research is warranted in both these areas as the field continues to evolve.

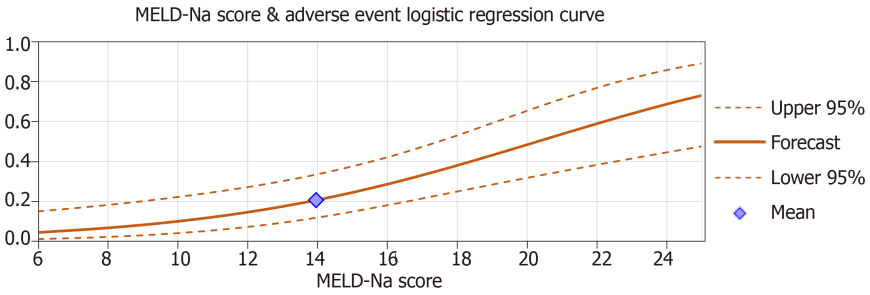

Figure 2 Rising Model for End-stage Liver Disease score was associated with higher probability of adverse events ($P < 0.01$).

ARTICLE HIGHLIGHTS

Research background

Liver cirrhosis is a major health issue around the world and is associated with physiologic changes that have been shown to increase the risk of adverse events in surgical and other interventional procedures. Prior studies examining endoscopic retrograde cholangiopancreatography (ERCP) specifically have demonstrated increased risk of adverse outcomes with worsening cirrhosis severity within these individuals. We sought to evaluate the risk of adverse outcomes against cirrhosis severity with ERCP and interventional endoscopic ultrasound (EUS) procedures within our safety net hospital population as data on this population is lacking.

Research motivation

The study is designed to evaluate the risk of adverse events when performing ERCP and/or interventional EUS procedures on patients with liver cirrhosis. Knowing the adverse event risk against cirrhosis severity will help clinicians assess the risks/benefits of gastrointestinal (GI) procedures in cirrhotic individuals through the use of Child-Pugh Class or Model for End-stage Liver Disease (MELD-Na) score.

Research objectives

Our objective was to examine whether increasing severity of cirrhosis is associated with greater incidence of adverse events after interventional ERCP/EUS procedures in cirrhotic individuals within our safety net population.

Research methods

We performed a retrospective study of patients diagnosed with hepatic cirrhosis who underwent ERCP and/or EUS-guided fine needle aspirations/fine needle biopsies over a 3 years span at our safety net hospital. Statistical analyses were done to assess whether Child-Pugh class and MELD-Na score were associated with greater adverse event rates and whether advanced techniques (single-operator cholangioscopy, electrohydraulic/laser lithotripsy, or needle-knife techniques) were associated with higher complication rates.

Research results

Our study included 77 procedures with the study population consisting primarily of middle-aged Hispanic men. 30-d procedure-related adverse events included GI bleeding (7.8%), infection (6.5%), and bile leak (2%). The effect of Child-Pugh class C *vs* class A and B significantly predicted adverse events ($P < 0.01$). MELD-Na scores also significantly predicted adverse events ($P < 0.01$). The presence of advanced techniques was not associated with higher adverse events ($P > 0.05$). When MELD-Na scores were added as predictors with the effect of Child-Pugh class C, logistic regression showed MELD-Na scores were a significant predictor of adverse events ($P < 0.01$). The findings held after controlling for age, gender, ethnicity and repeat cases. Our findings demonstrated that Child-Pugh class C and increasing MELD-Na scores were significant predictors of adverse events.

Research conclusions

Increasing cirrhosis severity (as defined by MELD-Na score and Child-Pugh Class C) predicted adverse events while the presence of advanced techniques did not. The findings were largely in line with our initial hypothesis and the conclusions drawn by prior studies. Our research suggests that advanced techniques should not be withheld in cirrhotic individuals as they did not significantly contribute to increased adverse event rates. Additionally, our data implies that MELD-Na score may be more useful in predicting adverse events than Child-Pugh class.

Research perspectives

The study confirms the results of prior studies and replicates those findings within a safety-net population, a population that has not been studied comprehensively in regards to this subject. Future research can consider comparing the usefulness of MELD-Na score *vs* Child-Pugh Class in assessing risk with ERCP/EUS procedures in patients with cirrhosis or consider replicating

this study with a larger-scale safety net population.

REFERENCES

1 **Scaglione S**, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, Volk ML. The Epidemiology of Cirrhosis in the United States: A Population-based Study. *J Clin Gastroenterol* 2015; **49**: 690-696 [PMID: 25291348 DOI: 10.1097/MCG.0000000000000208]

2 **ASGE Standards of Practice Committee**. Chathadi KV, Chandrasekhara V, Acosta RD, Decker GA, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fanelli RD, Fisher DA, Foley K, Fonkalsrud L, Hwang JH, Jue TL, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Shaukat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The role of ERCP in benign diseases of the biliary tract. *Gastrointest Endosc* 2015; **81**: 795-803 [PMID: 25665931 DOI: 10.1016/j.gie.2014.11.019]

3 **ASGE Standards of Practice Committee**. Early DS, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Hwang JH, Jue TL, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf RN, Shergill AK, Cash BD. Adverse events associated with EUS and EUS with FNA. *Gastrointest Endosc* 2013; **77**: 839-843 [PMID: 23684089 DOI: 10.1016/j.gie.2013.02.018]

4 **Mosko JD**, Nguyen GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011; **9**: 897-901 [PMID: 21782772 DOI: 10.1016/j.cgh.2011.07.007]

5 **Adler DG**, Haseeb A, Francis G, Kistler CA, Kaplan J, Ghumman SS, Laique SN, Munigala S, Taylor LJ, Cox K, Root B, Hayat U, Siddiqui A. Efficacy and safety of therapeutic ERCP in patients with cirrhosis: a large multicenter study. *Gastrointest Endosc* 2016; **83**: 353-359 [PMID: 26297868 DOI: 10.1016/j.gie.2015.08.022]

6 **Leal C**, Prado V, Colan J, Chavez-Rivera K, Sendino O, Blasi A, Roura P, Juanola A, Rodriguez de Miguel C, Pavesi M, Gomez C, Guarner C, Guarner-Argente C, Fernández J, Cardenas A. Adverse Events and Acute Chronic Liver Failure in Patients With Cirrhosis Undergoing Endoscopic Retrograde Cholangiopancreatography: A Multicenter Matched-Cohort Study. *Am J Gastroenterol* 2019; **114**: 89-97 [PMID: 30177786 DOI: 10.1038/s41395-018-0218-1]

7 **Navaneethan U**, Njei B, Zhu X, Kommaraju K, Parsi MA, Varadarajulu S. Safety of ERCP in patients with liver cirrhosis: a national database study. *Endosc Int Open* 2017; **5**: E303-E314 [PMID: 28393104 DOI: 10.1055/s-0043-102492]

8 **Li DM**, Zhao J, Zhao Q, Qin H, Wang B, Li RX, Zhang M, Hu JF, Yang M. Safety and efficacy of endoscopic retrograde cholangiopancreatography for common bile duct stones in liver cirrhotic patients. *J Huazhong Univ Sci Technolog Med Sci* 2014; **34**: 612-615 [PMID: 25135737 DOI: 10.1007/s11596-014-1325-x]

9 **Kim JY**, Lee HS, Chung MJ, Park JY, Park SW, Song SY, Bang S. Bleeding Complications and Clinical Safety of Endoscopic Retrograde Cholangiopancreatography in Patients with Liver Cirrhosis. *Yonsei Med J* 2019; **60**: 440-445 [PMID: 31016905 DOI: 10.3349/ymj.2019.60.5.440]

10 **Talukdar R**. Complications of ERCP. *Best Pract Res Clin Gastroenterol* 2016; **30**: 793-805 [PMID: 27931637 DOI: 10.1016/j.bpg.2016.10.007]

11 **Inamdar S**, Berzin TM, Berkowitz J, Sejpal DV, Sawhney MS, Chutanni R, Pleskow DK, Trindade AJ. Decompensated cirrhosis may be a risk factor for adverse events in endoscopic retrograde cholangiopancreatography. *Liver Int* 2016; **36**: 1457-1463 [PMID: 26913829 DOI: 10.1111/liv.13100]

12 **Choudhary N**, Bansal RK, Puri R, Singh RR, Nasa M, Shah V, Sarin H, Guleria M, Saigal S, Saraf N, Sud R, Soin AS. Impact and safety of endoscopic ultrasound guided fine needle aspiration on patients with cirrhosis and pyrexia of unknown origin in India. *Endosc Int Open* 2016; **4**: E953-E956 [PMID: 27652300 DOI: 10.1055/s-0042-112585]

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ORIGINAL ARTICLE

Observational Study

Endoscopic ultrasound-through-the-needle biopsy in pancreatic cystic lesions: A large single center experience

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Conflict-of-interest statement: No financial support was received from the company of microforceps to conduct this study. Dr Samarasena is a consultant to US Endoscopy. None of the other authors have any relevant conflicts of interest.

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Abstract

BACKGROUND

Establishing a diagnosis of pancreatic cystic lesions (PCLs) preoperatively still remains challenging. Recently, endoscopic ultrasound (EUS)-through-the-needle biopsy (EUS-TTNB) using microforceps in PCLs has been made available.

AIM

To assess the efficacy and safety of EUS-TTNB in the diagnosis of PCLs.

METHODS

We retrospectively collected data of patients with PCLs who underwent both EUS-fine-needle aspiration (FNA) for cytology and EUS-TTNB at our institution since 2016. EUS-FNA for cytology was followed by EUS-TTNB in the same session. Evaluation of the cyst location, primary diagnosis, adverse events, and comparison between the cytologic fluid analyses and histopathology was performed. Technical success of EUS-TTNB was defined as visible tissue present after biopsy. Clinical success was defined as the presence of a specimen adequate to make a histologic or cytologic diagnosis.

RESULTS

A total of 56 patients (mean age 66.9 ± 11.7, 53.6% females) with PCLs were enrolled over the study period. The mean cyst size was 28.8 mm (12-85 mm). The EUS-TTNB procedure was technically successful in all patients (100%). The clinical success rate using EUS-TTNB was much higher than standard EUS-FNA, respectively 80.4% (45/56) *vs* 25% (14/56). Adverse events occurred in 2 patients (3.6%) who developed mild pancreatitis that resolved with medical therapy. Using TTNB specimens, 23 of 32 cases (71.9%) with intraductal papillary

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mucinous neoplasm were further differentiated into gastric type (19 patients) and pancreaticobiliary type (4 patients) based on immunochemical staining.

CONCLUSION
EUS-TTNB for PCLs was technically feasible and had a favorable safety profile. Furthermore, the diagnostic yield for PCLs was much higher with EUS-TTNB than standard EUS-FNA cytology and fluid carcinoembryonic antigen. EUS-TTNB should be considered as an adjunct to EUS-FNA and cytologic analysis in the diagnosis and management of PCLs.

Key words: Pancreatic cyst lesion; Endoscopic ultrasound; Endoscopic ultrasound-guided fine needle aspiration; Cyst fluid; Biopsy

Core tip: Establishing a diagnosis of pancreatic cystic lesions (PCLs) preoperatively still remains a challenge. Endoscopic ultrasound (EUS)-through-the-needle biopsy (EUS-TTNB) using microforceps was recently used to make a definitive diagnosis of PCLs. The aim of this study was to assess the safety and efficacy of EUS-TTNB compared with EUS-fine-needle aspiration (FNA), and feasibility of intrapapillary mucinous neoplasm (IPMN) subtyping using EUS-TTNB specimen. Fifty-six patients underwent EUS-TTNB. The rates of technical success, clinical success, and adverse events were 100%, 80.4% and 3.6%, respectively. The clinical success rate was higher in EUS-TTNB (80.4%) than in EUS-FNA (15%). IPMN subtyping was successful in 71.9% (23/32) in patients with IPMN.

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INTRODUCTION

Establishing a diagnosis of pancreatic cystic lesions (PCLs) preoperatively still remains challenging. PCLs are discovered more often than before as a result of the widespread use of highresolution imaging techniques[1]. The prevalence of the PCLs is reported from 2.4% to 13.5% with increasing incidence with age[2]. The incidence of PCLs has been reported in 12.9% in a population-based study over a period of 5-year follow-up[3]. Some PCLs have the potential for malignant transformation to adenocarcinoma of the pancreas. On the other hand, the rate of malignant transformation is low in general[4] and is estimated approximately 0.24% per year[5]. The assessment of the risk of malignant transformation relies on information such as clinical history, results of radiological examinations, endoscopic ultrasound (EUS), cystic fluid analysis, and cytohistological testing. However, no single diagnostic tool has been found to be reliable for the differential diagnosis of PCLs.

EUS-fine needle aspiration (FNA) improves diagnostic accuracy in PCLs for differentiating mucinous versus non-mucinous PCLs, and malignant versus benign PCLs, in cases where computed tomography or magnetic resonance imaging are unclear. Evaluation of cyst fluid carcinoembryonic antigen (CEA), combined with cytology is often used for differentiating an IPMN or mucinous cystic neoplasm (MCN) from other PCLs. A recent meta-analysis showed EUS-FNA-based cytology had 42% sensitivity and 99% specificity to differentiate mucinous from non-mucinous pancreatic cystic neoplasm[6]. A cyst fluid CEA level of ≥ 192ng/mL can distinguish mucinous, from non-mucinous cysts, with a sensitivity of 52%-78%and specificity of 63-91%[7-13]. In two meta-analysis, EUS-FNA-based cytology showed a sensitivity of 51% and specificity of 94% for the diagnosis of malignant PCLs[14] and CEA seems not accurate to predict malignancy with sensitivity and specificity of 63%[15]. Targeted cyst wall sampling using FNA can provide adequate specimen for cytologic or histologic evaluation in 65%-81% and offer additional diagnostic yield for mucinous cyst over fluid analysis/cytology alone[16-18]. However, the diagnostic yield remains not enough

high due to the relatively small tissue sample that can be obtained using conventional FNA.

Recently, EUS-through-the-needle biopsy (EUS-TTNB) using microforceps (Figure 1; MorayTM microforceps, US Endoscopy, OH, United States) in PCLs has been made available[19-27]. This method can provide a fragment of the cyst wall improving the diagnostic yield. However, there still remains limited data regarding the efficacy and its safety profile. The aim of this study is to evaluate EUS-TTNB in terms of diagnostic yield and safety in the diagnosis of PCLs. A secondary aim is to evaluate the additive value in diagnostic yield over standard EUS-FNA.

MATERIALS AND METHODS

Patient selection

We retrospectively reviewed all of the patients with PCLs who had EUS-FNA and EUS-TTNB at our institution between Jan 2016 and November 2018 using electronic endoscopy database. The indication of EUS-TTNB was judged by the endoscopists based on clinical background, size, radiologic imaging findings, existence of worrisome features like solid mass or nodule, and patient anxiety. This study protocol was approved by the University of California Irvine Medical Center Institutional Review Board.

Data collection

Patients demographics, radiologic imaging, endoscopy imaging, cyst fluid analysis, cytology and pathology results were reviewed. Follow-up data were obtained from clinical encounters or telephone interview after the procedure to discuss pathology results. Continuous variables were reported as median and range. Categorical variables were summarized as frequency and percentage.

Aims

The aim of this study was to assess the feasibility and safety of EUS-TTNB for PCLs, and evaluate the diagnostic yield compared with EUS-FNA.

Definitions

Technical success of EUS-TTNB was defined as visible tissue present after biopsy. Clinical success was defined as the presence of a specimen adequate to make a histologic or cytologic diagnosis. Safety was assessed by recording adverse events following American Society for Gastrointestinal Endoscopy Criteria. PCLs were classified as mucinous cysts (intraductal papillary mucinous neoplasms and mucinous cystic neoplasms), serous cystadenomas, or benign and/or inflammatory cysts (pseudocysts) based on cytology, pathology, and cyst fluid analysis. The histology evaluation of the TTNB specimen followed standard histology definitions for epithelial type. For diagnosis of mucinous cyst, mucinous epithelium with cytoplasmic mucin should be visible on routine hematoxylin and eosin stain. The presence of subepithelial ovarian type stroma defined an MCN, and the absence of such stroma defined an IPMN. If the diagnosis of IPMN was established, the expression of MUC1, MUC2, MUC5AC, MUC6 mucins were evaluated immunohistochemically for subtyping, if it was feasible.

Procedure

Three endosonographers performed or supervised all the EUS-TTNB procedures. Prophylactic antibiotics (Cefazolin 1g) were administered to all patients before needle puncture of PCLs. All the procedures were performed by using a linear echoendoscope (Olympus America, Center Valley, PA, United States). Careful evaluation was done for cyst location, size and presence of a mural nodule, solid mass or wall thickness. EUS-FNA was performed using the 19-gauge EUS-FNA needle (EchoTip Ultra needle; Cook Medical, Bloomington, IN, United States) with a stylet. Before puncturing PCLs, the stylet was removed and the microforceps was preloaded in the FNA needle. The needle was inserted into the PCL under EUS guidance and with the use of Doppler to avoid interposed vessels. After puncturing PCLs, the microforceps was inserted through the bore of the FNA needle. Once the forceps was seen within the cyst, the forceps was opened and the open jaws of the forceps were retracted and hubbed to the end of the needle (Figure 2). The needle with forceps open were then advanced using the FNA needle handle and gently pushed against the opposite walls, then closed and pulled back until the 'tent sign' was seen (Figure 3). Finally, the microforceps was pulled back inside the needle, and the specimen obtained was placed directly in formalin. In this manner, three to four passes were made with microforceps. After completion of biopsies, cyst fluid was aspirated and

Figure 1 Image of Moray™ microforceps (US Endoscopy, OH, United States).

sent for CEA and cytology. A minimum of 1 mL of intracystic fluid was aspirated and sent for CEA and amylase level. An experienced pathologist evaluated all the specimen and cytology. If IPMN was suspected, immunostaining was performed to determine the subtype. After the procedure, patients were followed up for any possible adverse events including abdominal pain, pancreatitis, or perforation.

Statistical analysis

In order to describe the patient cohort, descriptive statistical analyses were used, such as means, standard deviations, percentages, and frequency distribution, based on the nature of the statistical variables reported in the study. The value of $P < 0.05$ was considered statistically significant. Statistical analyses were done with R software (version 3.3.3; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient demographics, and clinical features of the PCLs are shown in Table 1. A total of 56 patients (mean age 66.9 ± 11.7, 53.6% females) with PCLs were enrolled over the study period. The mean cyst size was 28.8 mm (12-85 mm). Cysts were in the uncinate (4 patients), head (13), neck (16), body (7) and tail (16). The average number of biopsies taken during EUS-TTNB was 3.14 per patient.

Technical and clinical success

The EUS-TTNB procedure was technically successful in all patients (100%). The clinical success rate using EUS-TTNB was much higher than standard EUS-FNA, respectively 80.4% (45/56) *vs* 25% (14/56). The results of histology confirmed by TTNB is shown in Table 2. There was one case of neuroendocrine tumor that was diagnosed by TTNB, which was not demonstrated by cytologic analysis. TTNB changed the diagnosis in one patient from mucinous cystadenoma to serous cystadenoma. TTNB made a diagnosis of adenocarcinoma in two cases. The one seemed to arise from IPMN and the other seemed to be cystic adenocarcinoma. Both cases were un-resectable.

Cyst fluid analysis

Fluid CEA analysis was available in 38/56 PCLs (67.9%). For the 25 PCLs with CEA < 192 ng/mL indicating a non-mucinous cyst, TTNB provided a diagnosis of mucinous cyst in 13/25 (52%) cases while EUS FNA provided a mucinous cyst diagnosis in 3/25 (12%) cases ($P < 0.01$). For 13 PCLs with CEA > 192 ng/mL, 10 PCLs (76.9%) were diagnosed as mucinous cyst based on TTNB histology while EUS-FNA gave a mucinous cyst diagnosis in 2/13 (15.4%) ($P < 0.01$) (Table 3).

Subtype of IPMN

Using TTNB specimens and immunostaining, 23 cases (71.9%) among 32 cases of intraductal papillary mucinous neoplasm were further differentiated into gastric type (19 patients) and pancreatico-biliary type (4 patients) based on histological assessment and immunohistochemical staining.

Correlation between EUS-TTNB and surgical specimen

Four patients had surgery after EUS-TTNB in our case series. In three of four cases,

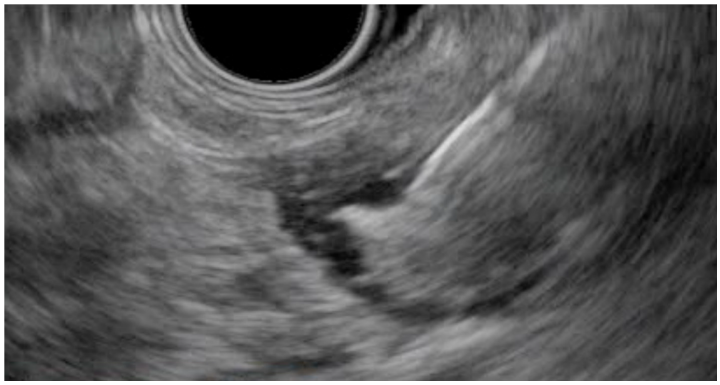

Figure 2 Endosonographic image of the microforceps opened within a pancreatic cystic lesion.

the diagnosis based on EUS-TTNB was the same as the one on surgical specimen. In one case, EUS-TTNB diagnosis was pancreato-biliary type IPMN, although it changed to gastric type IPMN on the surgical specimen.

Adverse events

Two patients (3.6%) developed acute pancreatitis after EUS-TTNB. Both patients were treated with supportive care and were discharged within 2 d without any invasive intervention.

DISCUSSION

EUS is useful in the diagnostic evaluation and estimating malignant potential of PCLs. EUS-FNA of PCLs is a well-established procedure and gives rise to information such as cytology and intracystic fluid marker analysis, to assist in differentiating mucinous from non-mucinous lesions. Differentiating PCLs is very important because SCAs do not require surgery, while on the other hand, MCNs need to be resected. However, the diagnostic accuracy of cytology and fluid markers such as CEA are still not enough high. Cyst fluid molecular analysis seemed promising but has issues with cost and availability[6,12,28,29]). Some studies have shown that EUS-guided confocal laser endomicroscopy could be helpful but inter-observer agreement is very variable[30,31]. EUS-TTNB is a straightforward procedure and some case series have already shown promising outcomes[20-27].

Our study results showed 100% technical success and 80.4% of clinical success, which are very similar to previous case series study[20-23,25-27]. In our study, 13 of 25 cysts with CEA < 192 ng/mL ended up having the diagnosis of mucinous cyst based on EUS-TTNB specimen. This result confirmed that fluid analysis for CEA is not reliable for differentiation of a mucinous cyst and non-mucinous cyst at our institution. EUS-TTNB demonstrated higher accuracy in providing the diagnosis of a mucinous cyst than EUS-FNA based cytology regardless of the value of CEA. This suggests EUS-TTNB is likely superior to the current standard of EUS-FNA cytology combined with fluid CEA analysis for detection of mucinous cysts.

With regards to complications, 2/56 patients (3.6%) developed acute pancreatitis after EUS-TTNB. Based on previous studies, the complications after this procedure are usually acute pancreatitis and local bleeding from the biopsy site. In the largest multicenter study of EUS-TTNB study with 114 patients[26], pancreatitis occurred in 6 patients (5.3%). pancreatitis occurred in 6 patients (5.3%). This study contained one patient with severe acute pancreatitis who required cystogastrostomy for pseudocyst. In our study, pancreatitis in both patients were self-limited and mild.

In contrast to previous studies on TTNB, our institution attempted to subtype IPMN using the EUS-TTNB specimen. Several studies have suggested the histologic subtype of IPMN may be an important factor in its natural history. Studies have indicated in particular that the pancreaticobiliary subtype of IPMN may be associated with a poor prognosis[32,33] although this is controversial[34]. Using a combination of histologic analysis and immunohistochemical staining, we were successfully able to subtypes the majority of IPMNs in our series. Subtyping using EUS-TTNB may be helpful to decide how to follow the IPMN without resection. Our study is the first study indicating that subtype of IPMN with EUS-TTNB can be reproducible. In one surgical case, IPMN subtype based on EUS-TTNB was not consistent with that based on the surgical specimen. In this particular case, the surgical specimen was a mixed

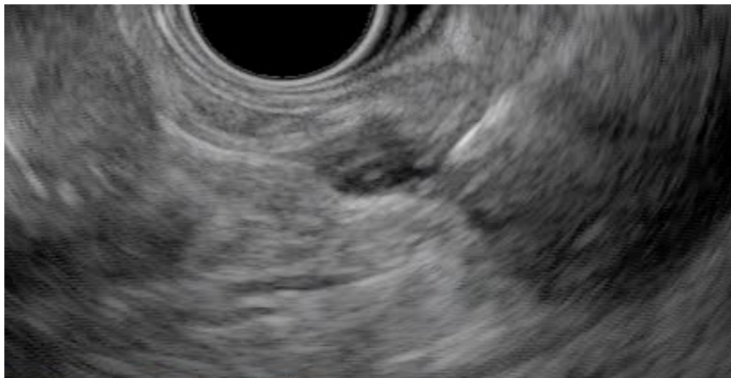

Figure 3 Endosonographic image of the microforceps bite of the wall tenting tissue within a pancreatic cystic lesion.

subtype and we do need to keep in mind that IPMN subtype based on EUS-TTNB may not represent the predominant subtype of the entire PCL in some cases.

Our study has several limitations. First, this is a single center, retrospective study. Secondly, the number of enrolled patients is relatively low, although this is the largest study at a single center study to our knowledge using a standardized technique. Lastly, we cannot conclude the correlation between TTNB specimen and surgical specimen because only 4 patients had surgery after EUS-TTNB in this cohort.

In conclusion, EUS-TTNB for PCLs was technically feasible and had a favorable safety profile in this study. Furthermore, the diagnostic yield for PCLs was much higher with EUS-TTNB than standard EUS-FNA cytology and fluid CEA. EUS-TTNB should be considered as an adjunct to EUS-FNA and cytologic analysis in the diagnosis and management of PCLs.

Table 1 Patient characteristics

Patient characteristics	
Age, mean ± SD, yr	66.9 ± 11.7
Sex, male/female	26/30
Cyst size, mm	28.8 (12-85)
Location	
Uncinate	4
Head	13
Neck	16
Body	7
Tail	16
Biopsy times	3.14 (1-6)
Pre-biopsy clinical diagnosis	
Intraductal papillary mucinous neoplasm	31
Unknown	18
Pseudocyst	5
Mucinous cystadenoma	1
Neuroendocrine tumor	1

Table 2 Results of endoscopic guided through the needle biopsy

Technical success	100% (56/56)
Clinical success	80.4% (45/56)
Adverse events	3.6% (2/56)
Histopathological diagnosis by EUS-TTNB	
IPMN	32
Pseudocyst	4
Serous cyst neoplasm	4
Neuroendocrine tumor	2
Adenocarcinoma	2
Paraganglioma	1
Inconclusive	11
Subtyping of IPMN (n = 32)	
Gastric type	19
Pancreatobiliary type	4
Inconclusive	9

IPMN: Intraductal papillary mucinous neoplasm; EUS-TTNB: Endoscopic ultrasound-through-the-needle biopsy.

Table 3 Comparison between endoscopic ultrasound-fine-needle aspiration and endoscopic ultrasound-through-the-needle biopsy

	EUS-FNA	EUS-TTNB	*P* value
Clinical success	25% (14/56)	80.4% (45/56)	< 0.001
Mucinous cyst diagnosis in cysts > CEA 192 ng/mL	12% (3/25)	52% (13/25)	0.005
Mucinous cyst diagnosis in cysts < CEA 192 ng/mL	15.4% (2/13)	76.9% (10/13)	0.005

EUS-FNA: Endoscopic ultrasound-fine-needle aspiration; EUS-TTNB: Endoscopic ultrasound-through-the-needle biopsy; CEA: Carcinoembryonic antigen.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cysts are increasingly being identified in asymptomatic patients. Establishing a diagnosis of pancreatic cystic lesions (PCLs) preoperatively still remains a challenge. Endoscopic

ultrasound (EUS)-fine-needle aspiration (FNA) showed high specificity in diagnosing mucinous cysts and high grade atypia. However, the sensitivity is not enough high because of relatively acellular samples. Recently, EUS-through-the-needle biopsy (EUS-TTNB) using microforceps was recently used to make a definitive diagnosis of PCLs. There have been some studies showing the efficacy and safety of EUS-TTNB for PCLs.

Research motivation

The number of studies describing the safety and efficacy of EUS-TTNB is still small. There have been no study evaluating the feasibility of intraductal papillary mucinous neoplasm (IPMN) subtyping using EUS-TTNB specimen.

Research objectives

The aim of this study was to evaluate the safety and efficacy of EUS-TTNB, compare the tissue acquisition and diagnostic tissue yield of EUS-TTNB with EUS-FNA, and assess the feasibility of IPMN subtyping using EUS-TTNB specimen.

Research methods

A retrospective analysis of endoscopy reporting system and medical records of patients who underwent EUS-TTNB for PCLs was conducted. The review and analysis were conducted through our endoscopy reporting system (endoPRO iQ®) and medical records.

Research results

A total of 56 patients with PCLs were included. The clinical success rate using EUS-TTNB (80.4%) was much higher than EUS-FNA (25%). Adverse events occurred only in 2 patients (3.6%) who developed mild pancreatitis that resolved with medical therapy. Subtyping of IPMN was successful in 23 of 32 cases (71.9%) using TTNB specimens.

Research conclusions

EUS-TTNB is a safe and feasible procedure for evaluation of PCLs. The clinical success rate was higher in EUS-TTNB than in EUS-FNA. IPMN subtype was also possible in many cases.

Research perspectives

Given recent development of genetic mutation analysis of PCLs, risk stratification using EUS-TTNB specimen might be possible in the future.

REFERENCES

1 **Ketwaroo GA**, Mortele KJ, Sawhney MS. Pancreatic Cystic Neoplasms: An Update. *Gastroenterol Clin North Am* 2016; **45**: 67-81 [PMID: 26895681 DOI: 10.1016/j.gtc.2015.10.006]

2 **Lee KS**, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J Gastroenterol* 2010; **105**: 2079-2084 [PMID: 20354507 DOI: 10.1038/ajg.2010.122]

3 **Kromrey ML**, Bülow R, Hübner J, Paperlein C, Lerch MM, Ittermann T, Völzke H, Mayerle J, Kühn JP. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut* 2018; **67**: 138-145 [PMID: 28877981 DOI: 10.1136/gutjnl-2016-313127]

4 **Gardner TB**, Glass LM, Smith KD, Ripple GH, Barth RJ, Klibansky DA, Colacchio TA, Tsapakos MJ, Suriawinata AA, Tsongalis GJ, Pipas JM, Gordon SR. Pancreatic cyst prevalence and the risk of mucin-producing adenocarcinoma in US adults. *Am J Gastroenterol* 2013; **108**: 1546-1550 [PMID: 24091499 DOI: 10.1038/ajg.2013.103]

5 **Scheiman JM**, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 2015; **148**: 824-48.e22 [PMID: 25805376 DOI: 10.1053/j.gastro.2015.01.014]

6 **Gillis A**, Cipollone I, Cousins G, Conlon K. Does EUS-FNA molecular analysis carry additional value when compared to cytology in the diagnosis of pancreatic cystic neoplasm? A systematic review. *HPB (Oxford)* 2015; **17**: 377-386 [PMID: 25428782 DOI: 10.1111/hpb.12364]

7 **Al-Haddad M**, DeWitt J, Sherman S, Schmidt CM, LeBlanc JK, McHenry L, Coté G, El Chafic AH, Luz L, Stuart JS, Johnson CS, Klochan C, Imperiale TF. Performance characteristics of molecular (DNA) analysis for the diagnosis of mucinous pancreatic cysts. *Gastrointest Endosc* 2014; **79**: 79-87 [PMID: 23845445 DOI: 10.1016/j.gie.2013.05.026]

8 **Brugge WR**, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004; **126**: 1330-1336 [PMID: 15131794]

9 **Cizginer S**, Turner BG, Bilge AR, Karaca C, Pitman MB, Brugge WR. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. *Pancreas* 2011; **40**: 1024-1028 [PMID: 21775920 DOI: 10.1097/MPA.0b013e31821bd62f]

10 **Gaddam S**, Ge PS, Keach JW, Mullady D, Fukami N, Edmundowicz SA, Azar RR, Shah RJ, Murad FM, Kushnir VM, Watson RR, Ghassemi KF, Sedarat A, Komanduri S, Jaiyeola DM, Brauer BC, Yen RD, Amateau SK, Hosford L, Hollander T, Donahue TR, Schulick RD, Edil BH, McCarter M, Gajdos C, Attwell A, Muthusamy VR, Early DS, Wani S. Suboptimal accuracy of carcinoembryonic antigen in differentiation of mucinous and nonmucinous pancreatic cysts: results of a large multicenter study. *Gastrointest Endosc* 2015; **82**: 1060-1069 [PMID: 26077458 DOI: 10.1016/j.gie.2015.04.040]

11 **Kadayifci A**, Al-Haddad M, Atar M, Dewitt JM, Forcione DG, Sherman S, Casey BW, Fernandez-Del Castillo C, Schmidt CM, Pitman MB, Brugge WR. The value of KRAS mutation testing with CEA for the diagnosis of pancreatic mucinous cysts. *Endosc Int Open* 2016; **4**: E391-E396 [PMID: 27092317 DOI: 10.1055/s-0042-101755]

12 **Khalid A**, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA,

Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc* 2009; **69**: 1095-1102 [PMID: 19152896 DOI: 10.1016/j.gie.2008.07.033]

13 **Winner M**, Sethi A, Poneros JM, Stavropoulos SN, Francisco P, Lightdale CJ, Allendorf JD, Stevens PD, Gonda TA. The role of molecular analysis in the diagnosis and surveillance of pancreatic cystic neoplasms. *JOP* 2015; **16**: 143-149 [PMID: 25791547 DOI: 10.6092/1590-8577/2941]

14 **Wang QX**, Xiao J, Orange M, Zhang H, Zhu YQ. EUS-Guided FNA for Diagnosis of Pancreatic Cystic Lesions: a Meta-Analysis. *Cell Physiol Biochem* 2015; **36**: 1197-1209 [PMID: 26138881 DOI: 10.1159/000430290]

15 **Ngamruengphong S**, Bartel MJ, Raimondo M. Cyst carcinoembryonic antigen in differentiating pancreatic cysts: a meta-analysis. *Dig Liver Dis* 2013; **45**: 920-926 [PMID: 23790480 DOI: 10.1016/j.dld.2013.05.002]

16 **Barresi L**, Tarantino I, Traina M, Granata A, Curcio G, Azzopardi N, Baccarini P, Liotta R, Fornelli A, Maimone A, Jovine E, Cennamo V, Fabbri C. Endoscopic ultrasound-guided fine needle aspiration and biopsy using a 22-gauge needle with side fenestration in pancreatic cystic lesions. *Dig Liver Dis* 2014; **46**: 45-50 [PMID: 23916241 DOI: 10.1016/j.dld.2013.06.008]

17 **Hong SK**, Loren DE, Rogart JN, Siddiqui AA, Sendecki JA, Bibbo M, Coben RM, Meckes DP, Kowalski TE. Targeted cyst wall puncture and aspiration during EUS-FNA increases the diagnostic yield of premalignant and malignant pancreatic cysts. *Gastrointest Endosc* 2012; **75**: 775-782 [PMID: 22317883 DOI: 10.1016/j.gie.2011.12.015]

18 **Rogart JN**, Loren DE, Singu BS, Kowalski TE. Cyst wall puncture and aspiration during EUS-guided fine needle aspiration may increase the diagnostic yield of mucinous cysts of the pancreas. *J Clin Gastroenterol* 2011; **45**: 164-169 [PMID: 20818233 DOI: 10.1097/MCG.0b013e3181eed6d2]

19 **Attili F**, Pagliari D, Rimbaş M, Inzani F, Brizi MG, Costamagna G, Larghi A. Endoscopic ultrasound-guided histological diagnosis of a mucinous non-neoplastic pancreatic cyst using a specially designed through-the-needle microforceps. *Endoscopy* 2016; **48** Suppl 1: E188-E189 [PMID: 27213974 DOI: 10.1055/s-0042-108194]

20 **Barresi L**, Crinò SF, Fabbri C, Attili F, Poley JW, Carrara S, Tarantino I, Bernardoni L, Giovanelli S, Di Leo M, Manfrin E, Tacelli M, Bruno MJ, Traina M, Larghi A. Endoscopic ultrasound-through-the-needle biopsy in pancreatic cystic lesions: A multicenter study. *Dig Endosc* 2018; **30**: 760-770 [PMID: 29808529 DOI: 10.1111/den.13197]

21 **Basar O**, Yuksel O, Yang DJ, Samarasena J, Forcione D, DiMaio CJ, Wagh MS, Chang K, Casey B, Fernandez-Del Castillo C, Pitman MB, Brugge WR. Feasibility and safety of microforceps biopsy in the diagnosis of pancreatic cysts. *Gastrointest Endosc* 2018; **88**: 79-86 [PMID: 29510146 DOI: 10.1016/j.gie.2018.02.039]

22 **Kovacevic B**, Karstensen JG, Havre RF, Pham KD, Giovannini M, Dabizzi E, Arcidiacono P, Santo E, Sequeiros EV, Klausen P, Rift CV, Hasselby JP, Toxværd A, Kalaitzakis E, Hansen CP, Vilmann P. Initial experience with EUS-guided microbiopsy forceps in diagnosing pancreatic cystic lesions: A multicenter feasibility study (with video). *Endosc Ultrasound* 2018; **7**: 383-388 [PMID: 30168479 DOI: 10.4103/eus.eus_16_18]

23 **Kovacevic B**, Klausen P, Hasselby JP, Karstensen JG, Rift CV, Kalaitzakis E, Toxværd A, Hansen CP, Storkholm J, Hassan H, Vilmann P. A novel endoscopic ultrasound-guided through-the-needle microbiopsy procedure improves diagnosis of pancreatic cystic lesions. *Endoscopy* 2018; **50**: 1105-1111 [PMID: 29980151 DOI: 10.1055/a-0625-6440]

24 **Mittal C**, Obuch JC, Hammad H, Edmundowicz SA, Wani S, Shah RJ, Brauer BC, Attwell AR, Kaplan JB, Wagh MS. Technical feasibility, diagnostic yield, and safety of microforceps biopsies during EUS evaluation of pancreatic cystic lesions (with video). *Gastrointest Endosc* 2018; **87**: 1263-1269 [PMID: 29309781 DOI: 10.1016/j.gie.2017.12.025]

25 **Yang D**, Samarasena JB, Jamil LH, Chang KJ, Lee D, Ona MA, Lo SK, Gaddam S, Liu Q, Draganov PV. Endoscopic ultrasound-guided through-the-needle microforceps biopsy in the evaluation of pancreatic cystic lesions: a multicenter study. *Endosc Int Open* 2018; **6**: E1423-E1430 [PMID: 30574535 DOI: 10.1055/a-0770-2700]

26 **Yang D**, Trindade AJ, Yachimski P, Benias P, Nieto J, Manvar A, Ho S, Esnakula A, Gamboa A, Sethi A, Gupte A, Khara HS, Diehl DL, El Chafic A, Shah J, Forsmark CE, Draganov PV. Histologic Analysis of Endoscopic Ultrasound-Guided Through the Needle Microforceps Biopsies Accurately Identifies Mucinous Pancreas Cysts. *Clin Gastroenterol Hepatol* 2019; **17**: 1587-1596 [PMID: 30471456 DOI: 10.1016/j.cgh.2018.11.027]

27 **Zhang ML**, Arpin RN, Brugge WR, Forcione DG, Basar O, Pitman MB. Moray micro forceps biopsy improves the diagnosis of specific pancreatic cysts. *Cancer Cytopathol* 2018; **126**: 414-420 [PMID: 29660844 DOI: 10.1002/cncy.21988]

28 **Kadayifci A**, Atar M, Wang JL, Forcione DG, Casey BW, Pitman MB, Brugge WR. Value of adding GNAS testing to pancreatic cyst fluid KRAS and carcinoembryonic antigen analysis for the diagnosis of intraductal papillary mucinous neoplasms. *Dig Endosc* 2017; **29**: 111-117 [PMID: 27514845 DOI: 10.1111/den.12710]

29 **Singhi AD**, McGrath K, Brand RE, Khalid A, Zeh HJ, Chennat JS, Fasanella KE, Papachristou GI, Slivka A, Bartlett DL, Dasyam AK, Hogg M, Lee KK, Marsh JW, Monaco SE, Ohori NP, Pingpank JF, Tsung A, Zureikat AH, Wald AI, Nikiforova MN. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. *Gut* 2018; **67**: 2131-2141 [PMID: 28970292 DOI: 10.1136/gutjnl-2016-313586]

30 **Nakai Y**, Iwashita T, Park DH, Samarasena JB, Lee JG, Chang KJ. Diagnosis of pancreatic cysts: EUS-guided, through-the-needle confocal laser-induced endomicroscopy and cystoscopy trial: DETECT study. *Gastrointest Endosc* 2015; **81**: 1204-1214 [PMID: 25634486 DOI: 10.1016/j.gie.2014.10.025]

31 **Napoléon B**, Lemaistre AI, Pujol B, Caillol F, Lucidarme D, Bourdariat R, Morellon-Mialhe B, Fumex F, Lefort C, Lepilliez V, Palazzo L, Monges G, Filoche B, Giovannini M. A novel approach to the diagnosis of pancreatic serous cystadenoma: needle-based confocal laser endomicroscopy. *Endoscopy* 2015; **47**: 26-32 [PMID: 25325684 DOI: 10.1055/s-0034-1390693]

32 **Furukawa T**, Hatori T, Fujita I, Yamamoto M, Kobayashi M, Ohike N, Morohoshi T, Egawa S, Unno M, Takao S, Osako M, Yonezawa S, Mino-Kenudson M, Lauwers GY, Yamaguchi H, Ban S, Shimizu M. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. *Gut* 2011; **60**: 509-516 [PMID: 21193453 DOI: 10.1136/gut.2010.210567]

33 **Distler M**, Kersting S, Niedergethmann M, Aust DE, Franz M, Rückert F, Ehehalt F, Pilarsky C, Post S,

Saeger HD, Grützmann R. Pathohistological subtype predicts survival in patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas. *Ann Surg* 2013; **258**: 324-330 [PMID: 23532107 DOI: 10.1097/SLA.0b013e318287ab73]

34 **Kang MJ**, Lee KB, Jang JY, Han IW, Kim SW. Evaluation of clinical meaning of histological subtypes of intraductal papillary mucinous neoplasm of the pancreas. *Pancreas* 2013; **42**: 959-966 [PMID: 23462330 DOI: 10.1097/MPA.0b013e31827cddbc]

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CASE REPORT

Oesophageal carcinoma mimicking a submucosal lesion: A case report

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Abstract

BACKGROUND

Oesophageal cancer is the fourth most common cause of cancer-related deaths in India. Esophageal squamous cell carcinomas (ESCCs) arise from the epithelial layer, and commonly present as polypoidal, ulcerative or ulceroproliferative growth in the oesophageal lumen. In contrast, oesophageal submucosal tumours are a distinct group of tumours arising from the mesenchyme (examples include leiomyoma, fibrovasculoma, lipoma, granular cell tumour or carcinoid), and mostly do not breach the mucosa. Oesophageal submucosal tumours are a distinct group of tumours arising from the mesenchyme, and mostly do not breach the mucosa. Complete intramural growth of an advanced primary ESCC is an exceedingly rare presentation, with only six cases reported in the literature thus far. We herein report a case of primary ESCC with complete intramural invasion that endoscopically mimics a submucosal lesion.

CASE SUMMARY

A 50 year old male presented with a progressive mechanical type of dysphagia for one month. His history was significant, including squamous cell carcinoma of the tongue that was treated with surgery and chemoradiation 1 year prior. Upper gastrointestinal endoscopy revealed a large, hemispherical lesion with normal-appearing overlying mucosa about 4 cm × 5 cm in size extending from 30-34 cm from incisors. The patient underwent endoscopic ultrasound (EUS), and a fineneedle biopsy was performed, which was suggestive for squamous cell carcinoma. We herein report a case of primary ESCC with complete intramural invasion, endoscopically mimicking a submucosal lesion. The diagnosis could be established only by a EUS-guided biopsy.

CONCLUSION

This case report highlights that intramural ESCC may look like a submucosal

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lesion in endoscopy, and EUS biopsy is needed for final diagnosis.

Key words: Intramural esophageal squamous cell carcinoma; Submucosal lesion of esophagus; Endoscopic ultrasound; Case report

Core tip: A 50 year old male presented with a progressive mechanical type of dysphagia. Upper gastrointestinal endoscopy revealed a large, hemispherical lesion with normal-appearing overlying mucosa. An endoscopic ultrasound (EUS) fine needle biopsy was done. Histopathology was consistent with well-differentiated squamous cell carcinoma. This is to highlight that intramural esophageal squamous cell carcinoma may look like a benign submucosal lesion upon endoscopy, and that a EUS biopsy is needed for final diagnosis.

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INTRODUCTION

Oesophageal cancer is the fourth most common cause of cancer-related deaths in India. It is prevalent among both men and women. Squamous cell carcinoma accounts for up to 80% of these cancers[1]. The etiologic factors for esophageal squamous cell carcinomas (ESCCs) show a regional variation in different parts of India, but tobacco consumption in various forms, as well as alcohol, hot beverages and poor nutrition remain the predominant predisposing factors. The majority of patients with advanced disease are symptomatic, most often presenting with dysphagia and weight loss.

ESCCs arise from the epithelial layer, and commonly present as polypoidal, ulcerative or proliferative ulcer growth in the oesophageal lumen. In contrast, oesophageal submucosal tumours are a distinct group of tumours arising from the mesenchyme (examples include leiomyoma, fibrovasculoma, lipoma, granular cell tumour or carcinoid), and mostly do not breach the mucosa. Complete intramural growth of an advanced primary ESCC is an exceedingly rare presentation, with only six cases reported in the literature thus far[2-7]. We herein report a case of primary ESCC with complete intramural invasion that endoscopically mimics a submucosal lesion. The diagnosis could only be established by an endoscopic ultrasound (EUS)-guided biopsy. This article was published after obtaining informed consent from the patient.

CASE PRESENTATION

Chief complaints

A 50 year old male presented with a progressive mechanical type of dysphagia for a month, which was associated with a significant loss of weight.

History of illness

There was an occasional history of regurgitation present. He denies loss of appetite, retrosternal chest pain or discomfort. He also denies any history of heartburn, caustic ingestion, fever, cough, haemoptysis, change in voice, difficulty in breathing, hematemesis, melena or any drug intake.

Past history was significant for squamous cell carcinoma of the tongue, which was treated with surgery and chemoradiation 1 year prior. He lost follow up for the above. He quit smoking and alcohol after being diagnosed with tongue carcinoma.

Physical examination upon admission

Upon examination, his vitals were stable and there was no significant lymphadenopathy. Oral examination was significant for a scar on the left lateral border of

the tongue. His respiratory and gastrointestinal system examination was unremarkable.

Diagnostic assessment and interventions

He was further investigated. The basic metabolic panel was normal.

Upper gastrointestinal endoscopy was performed, which revealed a large, hemispherical lesion with a normal-appearing overlying mucosa about 4 cm × 5 cm in size and extending from 30-34 cm from the incisors, as shown in Figure 1. That impression was that is was possibly a submucosal lesion of the distal oesophagus. Endoscopic biopsy was not done, and further evaluation of the lesion was planned using EUS.

EUS was done using the linear echoendoscope model MAJ1597 (EUS scope, Olympus, Tokyo, Japan). EUS showed a large hyperechoic lesion arising from the third layer at 30 cm, as shown in Figure 2, with a provisional diagnosis of lipoma.

However, in view of the patient's past history of malignancy, a fine needle biopsy was done using a 19-gauge Boston scientific acquired EUS fine needle biopsy device, and sent for histopathologic examination.

Histopathology revealed fragments of malignant neoplasm composed of cells arranged in sheets, as in Figure 3. The neoplastic cells were round to polygonal, with moderate amounts of eosinophilic cytoplasm with moderate nuclear atypia. Keratin pearl formation was abundant. Histopathology was reported as well-differentiated squamous cell carcinoma. Immunohistochemistry confirmed the same.

Computed tomography (CT) on the thorax was then performed. CT of the thorax with IV and oral contrast showed heterogeneously enhancing soft tissue thickening noted in the retro cardiac oesophagus, with a thickness measuring 38 mm and a length of 68 mm, with proximal oesophageal dilatation noted. The OG junction was normal. The lesion has contact with the descending thoracic aorta at about 90°. The loss of flat plane was noted between the lesion and left atrium. Cavitatory metastatic nodules measuring 26 mm × 18 mm × 33 mm were noted in the posterior basal segment of the left lower lobe. Bilateral hilar nodes were noted, as shown in Figure 4. The CT of the thorax was finally reported as a Retro cardiac oesophageal growth with lung metastasis.

FINAL DIAGNOSIS

Oesophageal squamous cell carcinoma stage 4.

TREATMEN

The patient is currently receiving palliative care.

OUTCOME AND FOLLOW-UP

Not available.

DISCUSSION

The history of intramural ESCC dates back to a case report from McGregor *et al*[4], wherein a case of squamous cell carcinoma was found to arise from an oesophageal intramural squamous epithelial cyst. There were reports of oesophageal benign cysts as well as carcinoma arising from oesophageal diverticulum. However, for the first time, they reported a case of ESCC arising from an oesophageal cyst. In their case, esophagoscopy revealed a stricture upper oesophagus, and repeat biopsies only revealed mucosal hyperplasia. However, the patient was started on chemoradiation, but he later succumbed to bronchopneumonia. Autopsy demonstrated a 1.5-cm long intramural oesophageal squamous epithelial cyst, from which arose a locally invasive squamous cell carcinoma, without mucosal involvement or metastases. There are several other rare case reports of advanced primary ESCC masquerading as a completely intramural growth.

For this case report, we reviewed the literature, which elucidated the role of EUS in the evaluation of oesophageal submucosal lesions. We could find only two such cases where EUS diagnosis of a submucosal lesion was made, which upon further investigation turned out to be intramural ESCC. One such study was by Choudhary *et*

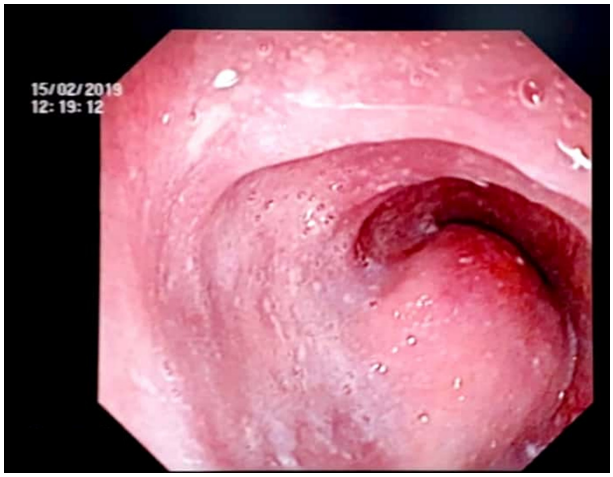

Figure 1 Upper gastrointestinal endoscopy. A large, hemispherical lesion measuring about 4 cm × 5 cm in size, with a normal-appearing overlying mucosa extending from 30-34 cm from the incisors.

al[2], where ESCC presented as a submucosal lesion with repeatedly negative endoscopic biopsies. The patient underwent EUS, and fineneedle aspiration was done. The cytopathological report was suggestive of squamous cell carcinoma. There were no distant metastases in this case. The second case report was from Sonthalia *et al*[3]. In their report, EUS revealed a heteroechoic solid mass originating from the muscularis propria of the distal oesophagus. Cytological study of EUS-guided fine needle aspiration from the mass was suggestive of squamous cell carcinoma, which was confirmed upon immunohistochemistry. However, this case had bone metastasis. Also, there are certain limitations in EUS-guided fine needle aspiration cytology (FNAC) for the diagnosis of submucosal tumours, as the average diagnostic accuracy rate of EUS-FNA is 60–80%[3].

Compared to the above case reports, our case differs in that our patient had a past history of malignancy. In addition, an EUS fine needle biopsy was done for the evaluation of a submucosal lesion in the oesophagus, which has not been done in the past.

Gibiino *et al*[8] have also advocated that EUS fine-needle biopsy has high diagnostic accuracy, and is expected to move the practice of EUS from cytology to histology. This should thereby expand the utilization of EUS throughout the world, and facilitate targeted therapies as well as the monitoring of treatment response in a more biologically-driven manner.

CONCLUSION

This case report highlights that intramural ESCC may look like a submucosal lesion in endoscopy, and that EUS biopsy is therefore needed for final diagnosis.

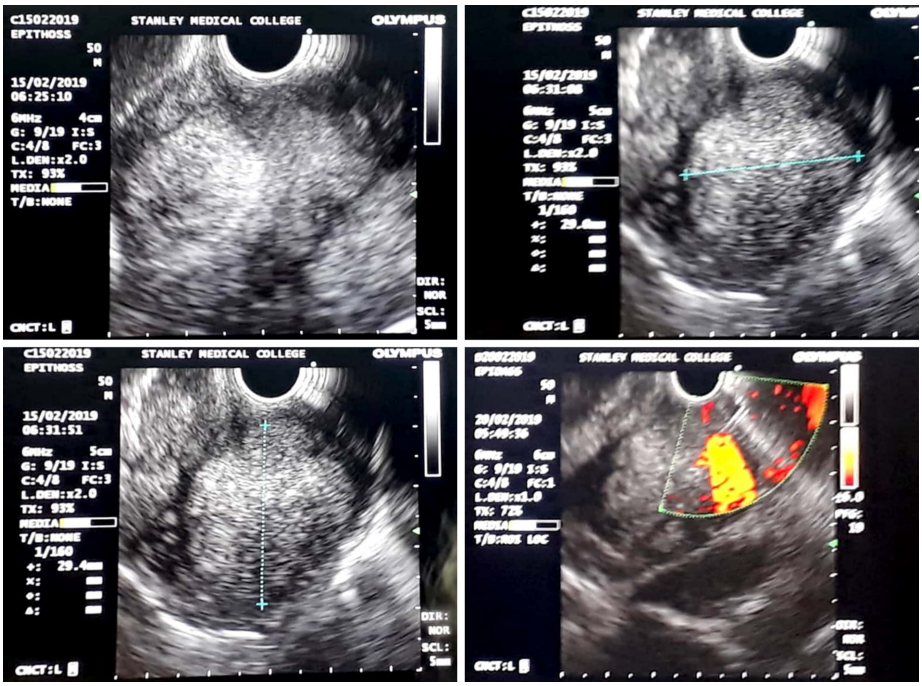

Figure 2 Endoscopic ultrasound images. Endoscopic ultrasound showing a hyperechoic mass lesion measuring 4 cm × 5 cm arising from the third layer of the oesophagus.

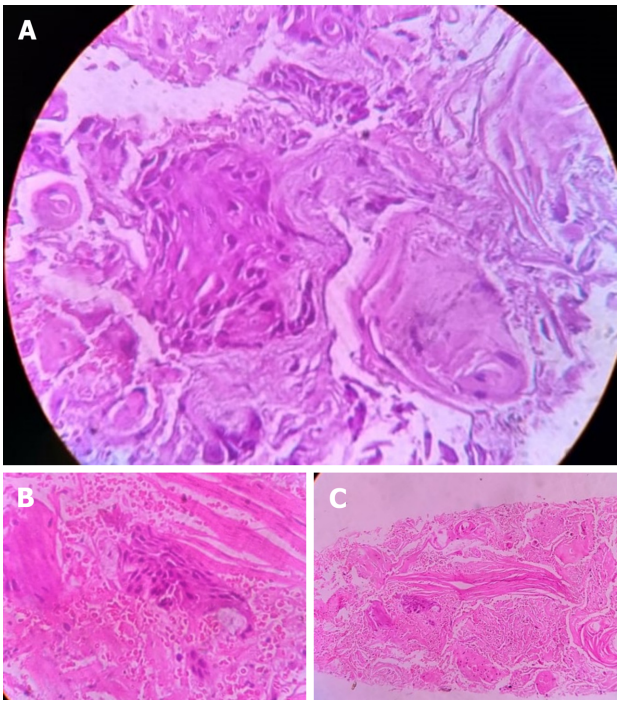

Figure 3 Photomicrography of oesophageal mucosal. A-C: Photomicrography of oesophageal mucosa showing round-to-polygonal neoplastic cells with moderate amounts of eosinophilic cytoplasm, with moderate nuclear atypia and abundant keratin pearl formation. This is consistent with well-differentiated esophageal squamous cell carcinoma (Hematoxylin-eosin staining).

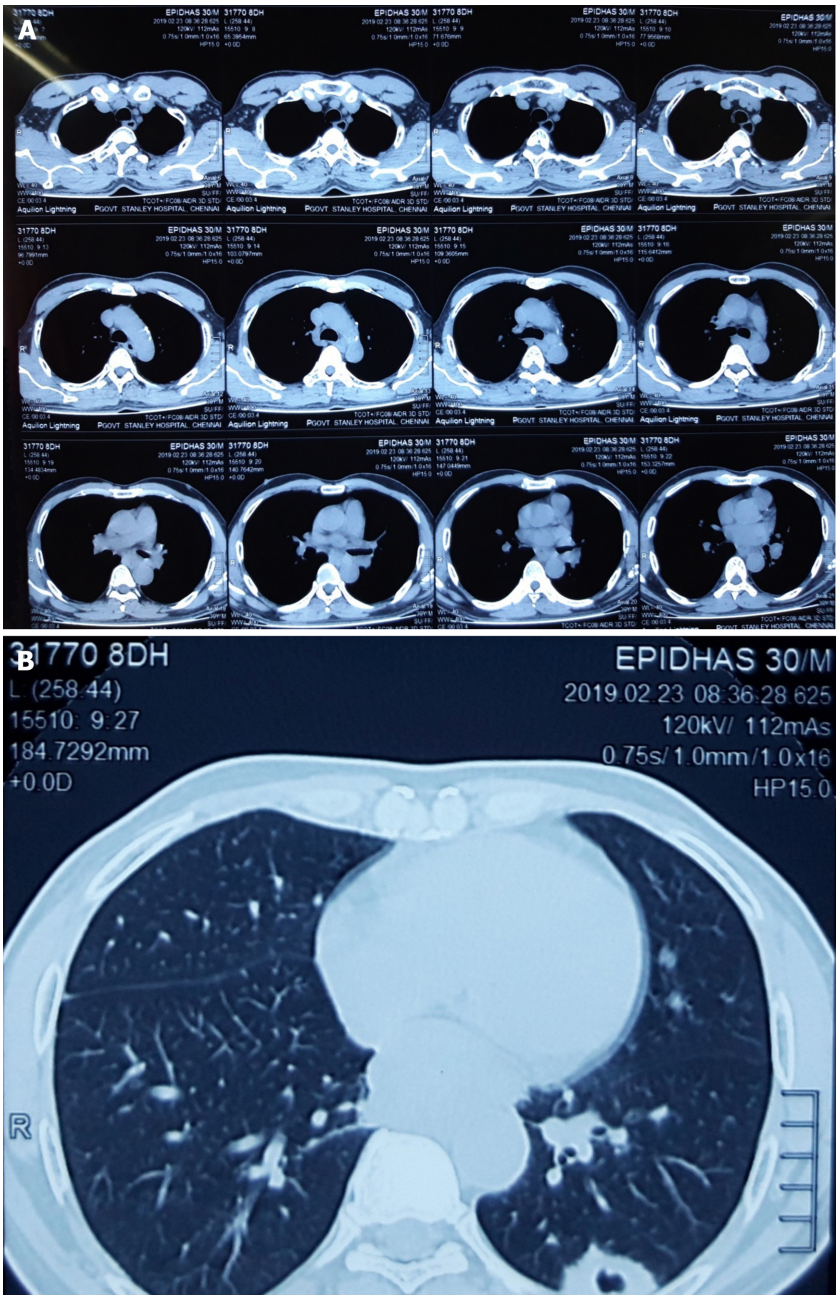

Figure 4 Computed tomography images. A and B: Computed tomography chest with oral and IV contrast, showing a cavitatory metastatic nodule measuring 26 mm × 18 mm × 33 mm in the posterior basal segment of the left lower lobe.

REFERENCES

1 **Samarasam I**. Esophageal cancer in India: Current status and future perspectives. *Int J Adv Med Health Res* 2017; **4**: 510 [DOI: 10.4103/IJAMR.IJAMR_19_17]
2 **Choudhary NS**, Bansal RK, Puri R, Guleria M, Sud R. Esophageal squamous cell carcinoma presenting as submucosal lesion with repeatedly negative endoscopic biopsies. *J Dig Endosc* 2016; **7**: 153-154 [DOI: 10.4103/0976-5042.195767]
3 **Sonthalia N**, Jain SS, Surude RG, Pawar VB, Udgirkar S, Rathi PM. Primary Esophageal Intramural Squamous Cell Carcinoma Masquerading as a Submucosal Tumor: A Rare Presentation of a Common Disease. *Clin Med Insights Gastroenterol* 2016; **9**: 63-66 [PMID: 27721663 DOI: 10.4137/Cgast.s40605]
4 **McGregor DH**, Mills G, Boudet RA. Intramural squamous cell carcinoma of the esophagus. *Cancer* 1976; **37**: 1556-1561 [PMID: 1260674 DOI: 10.1002/1097-0142(197603)37:3<1556::aid-cncr2820370345>3.0.co;2-e]
5 **von Rahden BH**, Brücher BL, Sarbia M. Esophageal squamous cell carcinoma with entirely intramural growth pattern. *Virchows Arch* 2006; **448**: 862-866 [PMID: 16572347 DOI: 10.1007/s00428-006-0185-6]
6 **Kishino T**, Yamaguchi Y, Yamagishi T, Hashimoto T, Kyomasu Y, Mori H, Sugiyama M, Atomi Y, Saito S, Ishida H, Takahashi S. Submucosal tumor (SMT)-like esophageal squamous cell carcinoma with gastric metastasis. *Hepatogastroenterology* 2000; **47**: 1581-1584 [PMID: 11149006]
7 **Schmitz KJ**, König C, Riesener KP. Intramural carcinoma of the oesophagogastric junction. *BMJ Case*

Rep 2012; **2012**: bcr0320126080 [PMID: 22787183 DOI: 10.1136/bcr.03.2012.6080]
8 **Gibiino G**, Larghi A. EUS-guided fine-needle biopsy for histological examination: Is it time to change our sampling technique? *Endosc Ultrasound* 2018; **7**: 71-72 [PMID: 29451175 DOI: 10.4103/eus.eus_56_17]

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