Does General Anesthesia Increase the Diagnostic Yield of Endoscopic Ultrasound-guided Fine Needle Aspiration of Pancreatic Masses?

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ABSTRACT

Background: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of the pancreas has become the preferred method for tissue diagnosis for pancreatic solid masses. The yield of EUS-FNA in this setting is influenced by multiple factors. We hypothesized that general anesthesia (GA) may improve EUS-FNA yield by improving patient cooperation and stillness during the procedure. Our objective was to assess the association between the sedation method employed and the diagnostic yield of EUS-FNA.

Methods: A retrospective cohort study was conducted involving consecutive patients who received EUS-FNA for diagnosis of a solid pancreatic mass at the Cleveland Clinic (Cleveland, OH) gastrointestinal endoscopy units from 2007 to 2009. We compared the diagnostic yield of EUS-FNA between patients receiving GA provided by an anesthesiologist (GA group) and patients receiving conscious sedation (CS) provided by a qualified registered nurse (CS group).

Results: Of 371 patients, a cytological diagnosis was obtained in 73/88 patients (83%) in the GA group and 206/283 patients (73%) in the CS group. Anesthesiologist-delivered GA was associated with an increased odds of having a successful diagnosis as compared with CS (adjusted odds ratio [95% CI]: 2.56 [1.27–5.17], $P = 0.01$). However, the incidence of complication during or after the procedure was not different between the groups ($P > 0.99$).

Conclusions: Anesthesiologist-delivered GA was associated with a significantly higher diagnostic yield of EUS-FNA. GA should be considered a preferred sedation method for EUS-FNA of a solid pancreatic mass.

What We Already Know about This Topic

- Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has become the preferred diagnostic method for pancreatic solid masses
- Whether this technique should be performed under general anesthesia or not remains unknown

What This Article Tells Us That Is New

- In a retrospective single center cohort (n = 371) study with propensity score analysis, general anesthesia was associated with a significantly higher diagnostic yield of EUS-FNA (adjusted odds ratio 2.56 [95% CI 1.27-5.17], P = 0.01)

EARLY diagnosis may improve the outcome and survival in patients with pancreatic cancer. Tissue acquisition is a central aspect of diagnosis because it helps guide appropriate oncologic and surgical therapy. Options include computed tomography or ultrasound-guided percutaneous biopsy, brush cytology at endoscopic retrograde cholangiopancreatography, open biopsy at surgery, and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Of these, EUS-FNA has emerged as a preferred method, combining attributes of safety, minimal invasiveness, and good yield.[1] In published studies, the diagnostic yield for EUS-FNA ranges from 71 to 100%.[2–8] Diagnostic yield may be affected by several factors, including endoscopist experience, type of needle, and use of an in-room cytopathologist.[9–11] We are unaware of any data comparing the impact of sedation technique on the diagnostic yield of EUS-FNA in the diagnosis of solid pancreatic lesions.

We therefore compared the diagnostic yield (defined as the proportion of patients for whom a diagnosis was deemed possible by the cytologist) of EUS-FNA between patients undergoing the procedure with general anesthesia (GA) and

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with conscious sedation (CS). Due to a temporal change in sedation practice at our institution, we are able to make this comparison. We investigated the relationship between sedation method and diagnostic yield, adjusting for potential confounding variables. Specifically, we tested the *primary hypothesis* that GA improves diagnostic yield for EUS-FNA by improving patient cooperation and stillness during the procedure. Secondary hypothesis included GA decreases bleeding, infection, or perforation by same reason.

Materials and Methods

This study was approved by the institutional review board at the Cleveland Clinic, Cleveland, Ohio. This is a retrospective, single-center, controlled cohort study of patients who received EUS-FNA for diagnosis of a solid pancreatic mass at the gastrointestinal endoscopy unit in the Cleveland Clinic from January 2007 to December 2009. Patients who presented with solid pancreatic lesions based on previous imaging studies and patients found to have a pancreatic mass undetected on previous imaging studies were included. An in-room cytopathologist or cytopathology technician was not present for any of the procedures. Only initial EUS-FNA procedures were analyzed.

Sedation Methods

Two methods of sedation were employed for EUS-FNA during the study period. In one approach, CS was administered by a registered nurse under the direction of an endoscopist by the intermittent administration of midazolam 0.5–2 mg, and an opioid consisting of either meperidine 25–50 mg or fentanyl 25–50 μg injection every 5–15 min as necessary. In the other approach, anesthesiologist-delivered GA was administered. Our institute has two GA protocols for endoscopic procedure sedation, one is GA without intubation, and the other is GA with intubation. Anesthesiologist can select either GA protocol, and in most cases these cases were done without intubation. The GA protocol without intubation case is propofol (1 mg/kg), and alfentanil (5.0 μg/kg) loading was administered followed by a 100–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol infusion mixed with alfentanil 0.5–0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. During the procedure, a MAC-SAFE CO_2 monitoring nasal cannula (Unomedial, Inc., McAllen, TX) was used to administer oxygen and monitor end-tidal carbon dioxide. In cases where endotracheal intubation was employed, propofol 1.5–2 mg/kg and fentanyl 100 μg intravenous induction doses were given for intubation and then maintained with sevoflurane inhalation. All intubation cases were determined to be elective by the anesthesiologist depending on patient conditions. Pulse oximetry, blood pressure, and electrocardiographic monitoring were used in addition to careful visual inspection in both sedation groups according to established the American Society of Anesthesiologists guidelines. The sedation method is based on many parameters, including the patient and/or physician preference, with the latter taking into account significant comorbidities or other factors such as the use of sedatives and analgesics. Due to Ohio State nursing policy changes regarding the unplanned administration of deep sedation, our endoscopy suite began using GA for the most complex endoscopy procedures in 2008; therefore, most of the CS cases were done before 2008, and most GA cases were completed during 2008 and after.

Data Collection

Relevant clinical variables were extracted from hospital records, endoscopy reports, and anesthesiology records. The complete procedural records were reviewed for each patient and separated into two groups according to the sedation regimen employed (GA or CS). Variables recorded included number of needle passes, size of needle, experience level of the endosonographer (gastroenterologist *vs.* gastrointestinal fellow), location and size of the pancreatic mass, cytological results, and procedural complications. Gastrointestinal physician measured tumor sizes and location by ultrasound in EUS-FNA procedure for all the patients. In those in whom the initial EUS-FNA failed to yield the diagnosis, we reviewed the subsequent biopsy procedures (*e.g.*, surgical biopsy, computer tomography/ultrasound guided biopsy or repeat EUS-FNA). We also reported the clinical follow-up in those without pathology diagnosis.

Cytology and Histology Materials

A cytopathologist or cytopathology technician was not present in the endoscopy room. Material obtained at each FNA pass was prepared onsite as air-dried smears and fixed in alcohol. Any remaining material was collected in normal saline for subsequent preparation of a cell block. A specimen was considered subjectively adequate if there was sufficient number of representative cells from the lesion. The cytology diagnosis was classified as one of five diagnostic categories according to Logroño and Waxman[12]: (1) unsatisfactory specimen, (2) negative for malignancy, (3) atypical/indeterminate, (4) suspicious for malignancy, and (5) positive for malignancy. A diagnosis of atypical most likely represented reactive/reparative and inflammatory changes, and indicated that no severe/high-grade changes of malignancy were present.

Study Definitions

The EUS-FNA was defined as "successful" if it was completed, if a specimen was collected, and if a cytological diagnosis was obtained. Similarly, cases categorized in Logroño and Waxman category 1, unsatisfactory specimen, were defined as "failure." The diagnostic yield was defined as the proportion of patients who had successful EUS-FNA. The final diagnosis of pancreatic malignancy was based on a composite gold standard[4]; either of the following was sufficient for a diagnosis of malignancy: (1) histologic or cytologic evidence (from surgery or biopsy) of malignancy reviewed by a pathologist; or (2) clinical progression compatible with the diagnosis or death from malignancy.

Statistical Analysis

Summary statistics was presented as mean ± SD for normally distributed continuous measures, median [Q1, Q3] for non-normal continuous measures, and percentage of patients for factors. We compared the GA and CS groups on baseline variables using the standardized difference (*i.e.*, difference in means or proportions divided by the pooled standard deviation) and by appropriate statistical tests (*i.e.,* Pearson chi-square test, Student *t* test, and Wilcoxon rank-sum test). Standardized difference enables direct comparison independent of the sample size in contrast to a *P* value resulting from an appropriate statistical test. We prespecified a conservative criterion of greater than 0.1 absolute standardized differences as indication of imbalance. Such variables were considered for inclusion in the analyses when GA and CS groups were compared on the outcomes.

We assessed the association between sedation method and the diagnostic yield using a multivariable logistic regression model, adjusting for the imbalanced baseline variables. The fit of model was assessed by the Hosmer and Lemeshow goodness-of-fit test[13], and collinearity was diagnosed by the variance inflation factor. Also, the *C* statistic ranges from 0.50 (association by chance) to 1.0 (perfect discrimination), as a measure of the model discrimination, was estimated along with its confidence interval. We also assessed the interaction effect each of age, type of tumor, location of tumor, performance of the EUS-FNA by a fellow, or reason for biopsy, on diagnostic yield separately.

In addition, we performed a sensitivity analysis where each patient who received GA was matched to a patient who received CS, using propensity-score matching. Specifically, we first estimated the probability of receiving GA (*i.e.*, the propensity score) for each patient using logistic regression with GA (*vs.* CS) as the outcome and all the potential confounding variables listed in table 1 as predictors. We then 1:1 matched GA and CS patients using a greedy distance matching algorithm (SAS macro: gmatch), restricting successful matches to those with estimated propensity scores within 0.01 units of one another. Matched GA and CS patients were compared on the diagnostic yield of EUS-FNA using logistic regression, adjusting for all the covariables used for matching.[14] The *C* statistic,, the Hosmer and Lemeshow goodness-of-fit test, and the variance inflation factor were reported.

Table 1. Patient and Tumor Characteristics (N = 371)

	Before Propensity-score Matching				After Propensity-score Matching			
Variable	GA Group (n = 88)	CS Group (n = 283)	*P* Value*	STD†	GA Group (n = 57)	CS Group (N = 57)	*P* Value*	STD†
Age, yr	63 ± 14‡	66 ± 12	0.045§	−0.24‖	64 ± 12	64 ± 12	0.94§	−0.01
Sex, female, %	50	47	0.62#	0.06	51	58	0.45#	−0.14
Body mass index, kg/m^2	27 [23, 29]‡	26 [22, 30]**	0.62	0.06	26 [23, 28]	27 [23, 29]	0.63	−0.09
Tumor location, %			0.02#	0.45‖			0.99#	0.10
Head of pancreas	70‡	59‡			74	77		
Neck of pancreas	3	2			4	4		
Uncinate of pancreas	3	6			4	4		
Body of pancreas	10	26			7	5		
Tail of pancreas	13	7			12	11		
Tumor type, %			0.42#	−0.21‖			0.95#	−0.11
Adenocarcinoma	70	74			70	70		
Normal pancreas	25	18			23	21		
Neuroendocrine	3	6			5	5		
Metastatic/lymphoma	1	2			2	4		
Size of tumor, cm^2	12 [5, 28]‡	12 [5, 28]**	0.74	−0.04	11 [5, 20]	10 [5, 28]	0.98	0.01
Reason for biopsy, image (*vs*. not), %	80	88‡	0.05#	−0.25‖	82	79	0.64#	0.09
Biopsy conducted by a fellow, yes, %	28	12	<0.001#	0.41‖	21	19	0.82#	0.04
No. of needles passed	3 [2, 3]‡	3 [2, 4]**	0.67	−0.06	3 [2, 3]	3 [2, 4]	0.17	−0.31‖

Statistics were presented as mean ± SD, median [Q1, Q3], or %, as appropriate.

*Wilcoxon rank-sum test, unless specified. †Standardized differences (GA–CS) in means or proportions divided by the pooled standard deviation. ‡1–6 patients had a missing value. §Student *t* test. ‖Greater than 0.1 in absolute value suggests small imbalance. #Pearson chi-square test. **32–48 patients had a missing value.

CS = conscious sedation; GA = general anesthesia; STD = standardized difference.

Secondary Analyses

We compared GA and CS groups on complications during or after the EUS-FNA procedure by the Fisher exact test due to the very low incidences.

With a total of 371 patients (approximate ratio of 1 GA to 3 CS patients) and a diagnostic yield of 73% in the CS group, we had 80% power to detect an odds ratio of 2.5 or more between GA and CS on the diagnostic yield at the 0.05 significance level.

Two-sided *P* values of less than 0.05 were considered to indicate statistical significance. SAS software version 9.2.2 for Windows (SAS Institute, Cary, NC) and R software version 2.12.0 for Windows (the R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

Results

A total of 371 patients were included in the study. In total, 283 patients received CS; 88 patients received GA (5 with planned intubations and 83 without intubation).

Table 1 (left panel) provides a summary of demographics and baseline tumor characteristics for all patients. The GA patients were, on average, younger, less likely to have the biopsy due to image evidence, less likely to have a malignant lesion, more likely to have the biopsy conducted by a fellow, and to have different tumor locations as compared with the CS patients (standardized difference >0.10 in absolute value).

Out of the 371 patients, a successful diagnosis was yielded in 73 patients (83%, 73/88) in the GA group and in 206 patients (73%, 206/283) in the CS group. All failure cases were due to inadequate specimen. Successful diagnosis was about twice as likely with GA compared with CS (OR: 2.56 [95% CI: 1.27–5.17], $P = 0.01$; table 2), after adjusting for the above-mentioned imbalanced variables. Our multivariable model had a moderate discriminative ability with *C* statistic (95% CI) of 0.69 (0.63–0.76) (chance discrimination = *C* statistic of 0.50). The Hosmer and Lemeshow goodness-of-fit chi-square statistic (*df*) of 9.7 ($df = 8$, $P = 0.29$) and the maximum variance inflation factor of 1.1 suggest the model fits the data adequately well. Furthermore, no interaction between the sedation method and age, type of tumor, location of tumor, performance of the EUS-FNA by a fellow, or reason for biopsy on diagnostic yield was found (all *P* values greater than 0.30). Seven patients with missing covariable(s) were excluded from the analysis.

Table 2. Primary Results: Association between the Sedation Method and the Diagnostic Yield of the Endoscopic Ultrasound-guided Fine Needle Aspiration of Pancreatic Masses

Association	OR (95% CI)	*P* Value
Crude analysis—univariable model (N = 371)		
Sedation method (GA *vs.* CS)	*1.82 (0.98–3.36)*	*0.056*
Primary analysis—multivariable model (N = 364)*		
Sedation method (GA *vs.* CS)	*2.56 (1.27–5.17)*	*0.01*
Age	1.01 (0.91–1.12)†	0.85
Tumor location		0.15
Head *vs.* tail	1.30 (0.53–3.15)	
Neck *vs.* tail	0.53 (0.11–2.61)	
Uncinate *vs.* tail	1.49 (0.38–5.80)	
Body *vs.* tail	2.64 (0.95–7.35)	
Tumor type		0.01
Adenocarcinoma *vs.* normal	2.85 (1.54–5.28)	
Neuroendocrine *vs.* normal	3.32 (0.93–11.9)	
Metastatic/Lyn *vs.* normal	1.55 (0.24–10.0)	
Reason for biopsy (image *vs.* not)	1.08 (0.53–2.18)	0.84
Biopsy conducted by a fellow (yes *vs.* no)	0.57 (0.25–1.30)	0.18
Sensitivity analysis—propensity-score matching (n = 114)‡		
Sedation method (GA *vs.* CS)	*2.97 (1.16–7.58)*	*0.02*

Values are in italics to easily compare the primary results of the two sedation methods.

*This multivariable model had moderate predictive ability, with C-index (95% CI) of 0.69 (0.63–0.76) (chance association = C-index of 0.50). Hosmer–Lemeshow goodness-of-fit chi-square statistics (*df*) and *P* values were 9.7 ($df = 8$) and $P = 0.29$, which suggests the model fits the data adequately well. The maximum variance inflation factor (VIF) of 1.1 suggests no evidence of collinearity problem. Seven patients with missing covariable(s) were excluded from the analysis. †For a 5-yr increase in age. ‡We successfully propensity-score matched 57 GA patients (65% of the total) with 57 CS patients for a total of 114 patients. Then, the matched patients were compared on the diagnostic yield of the endoscopic ultrasound-guided fine needle aspiration, adjusting for all the covariables used for the matching. This model had moderate predictive ability, with C-index (95% CI) of 0.73 (0.63–0.83). Hosmer–Lemeshow goodness-of-fit chi-square statistics (*df*) and *P* values were 5.82 ($df = 8$) and $P = 0.67$, which suggests the model fits the data adequately well. The maximum VIF of 1.3 suggests no evidence of collinearity problem.

CS = conscious sedation; GA = general anesthesia.

Our sensitivity analysis provided very similar results. We successfully propensity-matched 57 GA patients (65% of the total) with 57 CS patients (table 1). In the propensity-matched subset, a successful diagnosis was yielded in 46 patients (81%, 46/57) in the GA group and in 36 patients (63%, 36/57) in the CS group. GA was independently associated with increased odds of having a successful diagnosis (OR [95% CI]: 2.97 [1.16–7.58] GA *vs.* CS, $P = 0.02$; table 2). The logistic models for estimating the propensity score and comparing the matched patients on the outcome both fit the data adequately well indicated by the *C* statistics of 0.74 and 0.73, Hosmer and Lemeshow chi-squares of 9.8 ($df = 8$, $P = 0.28$) and 5.8 ($df = 8$, $P = 0.67$), respectively, and the maximum variance inflation factor of 1.3 for both.

Secondary Analyses

Self-limited bleeding during or after the EUS-FNA procedure occurred in two patients in the CS group; no bleeding was observed in the GA group (*P* value greater than 0.99). There was no infection or perforation present in either group. No major anesthesia-related complication (aspiration, apnea requiring intubation, and cardiac event) occurred in either group. All intubation cases in the GA group were scheduled intubation.

Discussion

We found that the sedation method used for EUS-FNA was associated with diagnostic yield: 83% in the GA group and 73% in the CS group had a successful diagnosis achieved ($P = 0.01$). The EUS-FNA complication rate was very small in both sedation groups. Sedation affected cytopathological diagnostic yields, but complication rate was unaffected. It is well known that the EUS-FNA yield is in part controlled by the environment. However, this is the first study to demonstrate that sedation technique affects the diagnostic yield of EUS-FNA in the diagnosis of solid pancreatic lesions. The presence of an in-room cytopathologist or cytopathology technician has been shown to improve yield.[3,7,8,11] When a cytopathologist is present for EUS-FNA, it appears that the diagnostic yield increases by 10%.[3] Several studies have reported the yield of adequate cytological specimen without an onsite cytopathologist and reported 71–95% of cases.[2,3,5,7,8] Some of those reports do not include benign cases. The study by Voss *et al.*[2] included benign pancreatitis and neuroendocrine tumors. Their population is similar to that of our study as they too were without an onsite cytopathologist. They reported technical failure and uncompleted procedures in 9 of 99 cases. For 17 (19%) of the 90 successful cases, the specimens could not be used in analysis as no pancreatic tissue was obtained. Therefore, the diagnostic yield of EUS-FNA was 73.7% (73/99); they did not describe their sedation methods. In our study, CS group's yield rate (73%) is very similar to Dr. Voss's report, whereas GA group's yield rate (83%) is higher than the reported rate. One study estimated the required number of needle passes without an onsite cytopathologist. The authors of this study prospectively recorded the number of needle aspirations on 121 consecutive EUS-FNA patients until a cytopathologist in the room reported that material adequate for a cytologic diagnosis had been obtained. The average number of needle passes into the mass was 3.4 ± 2.2 (SD), with a range of 1–10 passes.[4] In this study, there was no significant difference in the average number of needle passes between GA and CS groups, and average needle passes was three in both groups. Although both groups obtained enough needle passes, diagnostic yield of GA group was higher than that of the CS group. We suspected that GA might improve patient cooperation, each needle pass targeted the mass more accurately, and that tissue was acquired more effectively.

In the United States, patients undergoing gastrointestinal endoscopic procedures are routinely sedated. The sedatives generally consist of a benzodiazepine in combination with an opiate.[15] An alternative sedative drug is propofol. There are several studies from the gastrointestinal literature comparing propofol and CS for use in endoscopic procedures.[16–19] Propofol typically provides deeper levels of sedation, giving improved patient comfort during the procedure with a consistent level of sedation during longer endoscopic procedures. For these reasons propofol continues to grow in popularity for sedation for endoscopic examination, especially long and complicated procedure. However, the actual clinical benefit is unclear, and propofol sedation for endoscopy has become controversial because of cost and safety concerns. In our study, most of GA was completed with propofol and alfentanil infusion without intubation. Propofol and alfentanil are both rapid and short-acting drugs, and that combination infusion is used for sedation and analgesia for outpatient surgery.[20–24] There are studies that demonstrate that the administration of an intravenous propofol, in combination with alfentanil infusion, provides sedation analgesia and amnesia with a low incidence of side effects, such as nausea, vomiting, and respiratory depression in outpatients.[20,23]

The combination of even small doses of an opioid analgesic and a sedative hypnotic can produce significant respiratory depression.[20] If this opioid analgesic is carefully titrated, excessive sedation is avoided, though patients must be adequately monitored. The American Society of Anesthesiologists Task Force guideline states that patients who receive deep sedation may enter a state of GA; privileges to administer deep sedation should be granted only to practitioners who are qualified to administer GA or to appropriately supervised anesthesia professionals.[25] However, the routine assistance of an anesthesiologist for average-risk patients undergoing standard endoscopic procedures is cost prohibitive. In this study, among the 77 patients who had a failed initial EUS-FNA diagnosis under CS, 21 patients needed surgical laparotomy and 39 patients could not obtain histological diagnosis (fig. 1). The cost saving from EUS-FNA based upon avoided surgeries was approximately $3,300 per patient.[26] Early histological diagnosis by initial EUS-FNA is likely to improve the

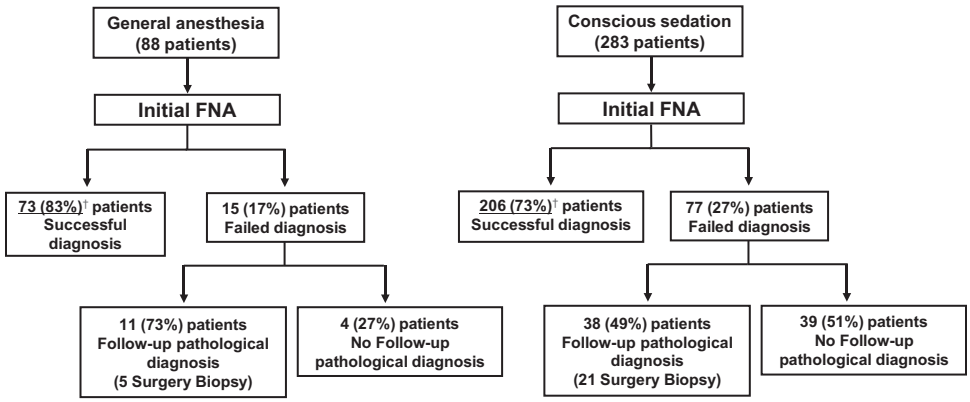

Fig. 1. Types of follow-up diagnosis and clinical course. In the general anesthesia (GA) group, 15 patients failed initial EUS-FNA (endoscopic ultrasound-guided fine needle aspiration) diagnosis and 11 patients obtained second pathological diagnosis: 5 patients had surgical laparotomy and 6 patients received repeat FNA. Among the 77 patients who had a failed initial EUS-FNA diagnosis under conscious sedation (CS), 21 patients needed surgical laparotomy biopsy. Thirty-nine patients of the CS group could not obtain histological diagnosis. †The percent of successful initial diagnosis was higher in the GA group (83%) than in the CS group (73%), $P = 0.01$.

outcome and quality of life in patients who have pancreatic mass. It is also important to plan chemotherapy or radiotherapy for patients who have other types of malignancy involving another type of pancreatic tumor. More research is needed about the cost performance and follow-up to determine any difference of prognosis between GA and CS.

There are several limitations in our study. This is a retrospective study conducted utilizing perioperative data from a single institution. Sedation methods were not chosen randomly, thus the result of the study does not suggest causative relationship of sedation method and diagnostic yield of EUS-FNA, but rather suggest only association. Our adjustment for confounding factors was limited to the variables that were measured and recorded in the hospital medical records. For example, the selective sedation way by gastrointestinal doctors was not available. Although our study had adequate power for our primary endpoint, it was underpowered for detecting important clinical differences (were they to exist) in the rare incidence complications (*i.e.*, self-limited bleeding, infection, and perforation).

Advances in endoscopic technology and techniques are paving the way for the increased application of not only simple diagnostic tools, but also minimally invasive treatment and tissue diagnostic tools. With technical innovation, there is growing interest in sedation to facilitate endoscope procedures. This is the first study to compare the impact of sedation technique of the diagnostic yield of EUS-FNA in the diagnosis of solid pancreatic lesions. We analyzed 371 consecutive patients who received EUS-FNA for diagnosis of solid a pancreatic mass and demonstrated that the sedation method was associated with a higher diagnostic yield of EUS-FNA of pancreatic masses. If a sedation method makes EUS-FNA easier and increases the accuracy of the tissue diagnosis, a "best practice" could be defined. However, our study has several limitations. As in any retrospective study, our adjustment for confounding factors was limited to the variables that were measured and recorded in the hospital medical records. A multicenter, randomized trial is needed in order to make a recommendation for clinical practice.

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