Study title:

EUS-guided Core Needle Biopsy (EUS-CNB) Versus EUS-guided Single-incision With Needle Knife (SINK) for the Diagnosis of Upper Gastrointestinal Subepithelial Lesions - a Multicenter Randomized Controlled Trial

NCT No: **NCT02282111**

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Upper gastrointestinal (GI) subepithelial tumors (SETs) are tumors arising from subepithelial layers of esophageal, gastric or duodenal wall, mostly from the submucosa and muscular layer. The incidence of SETs on routine endoscopy is 0.36% [1]. The differential diagnosis of SETs include, though are not limited to: lipoma, leiomyoma, aberrant pancreas, varices, carcinoid, gastrointestinal stromal tumors (GISTs), and lymphomas [2]. Therefore, a correct diagnosis of these tumors is important to guide subsequent management. These lesions are often not accurately diagnosed on cross-sectional imaging [2]. Endoscopic ultrasound (EUS) aids in narrowing the differential diagnosis of the lesion as it is often able to establish the layer of origin [2]. However, an accurate diagnosis and targeted therapy is not made solely on the morphological features but on histologic type and at times mitotic index. Thus the need for techniques to obtain histology is beneficial in guiding management.

Since standard endoscopy with pinch biopsies of the overlying mucosa often fails to provide an adequate sample for analysis, multiple other modalities to sample the lesion have been utilized: EUS-guided fine needle aspiration (EUS-FNA), EUS-guided core needle biopsy (EUS-CNB), bite-on-bite forceps biopsies, EUS-guided single-incision with needle knife (SINK) and endoscopic resection.

EUS-FNA is now considered to be the usual method of sampling; however, the diagnostic yield is low: 38% to 82% [3-6]. Moreover, EUS-FNA often provides insufficient specimens which may not allow for immunohistochemistry that is often essential for diagnosis [7]. Thus EUS-CNB has been assessed for the purpose of obtaining a core sample which allows for histological assessment. Published data reveals a diagnostic (though not histologic) yield using EUS-CNB of 75% [7].

In 2011, the SINK technique for sampling was presented with a reported diagnostic accuracy of 92.8% [8]. The technique utilizes a conventional needle-knife connected to an electrosurgical unit. A 6 to 12-mm mucosal incision is made over the lesion. Then

conventional biopsy forceps are introduced to obtain 3-5 samples. Subsequently, the incision is closed with 2 to 3 endoclips.

The purpose of this study is to prospectively compare the efficacy and safety of EUS-CNB with SINK in patients with upper GI SETs. Our hypothesis is that the SINK technique will be superior to the EUS-CNB in obtaining a histological specimen. The results of the study would provide data which may improve the diagnostic ability for SETs. This in turn will guide appropriate surveillance or management (surgical or endoscopic) for patients with these lesions.

2. Objectives (include all primary and secondary objectives)

Primary Outcome Measures

To compare the diagnostic accuracy of the single-incision with needle knife (SINK) with the EUS-guided core needle biopsy (CNB)

Secondary Outcome Measures

1. To compare rates of diagnostic histological tissue acquisition
2. To compare the rates of technical failure between the 2 techniques
3. To compare the rate of adverse events between the 2 techniques
4. To compare the procedure time of EUS-CNB and SINK
5. To compare the diagnostic contribution of immunohistochemistry (when needed) between the 2 techniques

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Subepithelial lesions of the upper gastrointestinal tract are frequently detected incidentally during upper endoscopy, with a prevalence of 0.36% [1]. The imaging modalities currently utilized are unable to accurately distinguish between the different types: lipoma, pancreatic rest, spindle cell tumor, fibroma, neuroendocrine tumor, hamartoma, hemangioma, and others. Karaca et al. reported a series of 22 patients with gastric subepithelial lesions that underwent a diagnostic EUS [9]. The accuracy based on songographic imaging alone was 45.5% (10/22). There are multiple modalities to sample these lesions, including EUS-guided FNA, EUS-guided CNB, bite-on-bite forceps biopsies, mucosal incision with a fixed flexible snare, EUS-Trucut core biopsy (TCB), EUS-guided SINK and endoscopic resection.

EUS-FNA has been reported in the literature to be the current standard of care; however, it lacks sensitivity as the diagnostic yield was as low as 38% [8]. Another study by Sepe et al. revealed the sensitivity of EUS-FNA cytology for the diagnosis of GIST was 78.4% and was influenced by size, location, shape, and layer of origin [10]. Therefore, the

patient was often required to undergo further procedures to confirm the diagnosis. Thus a simple, safe, and more reliable technique is warranted for definitive diagnosis

DeWitt et al. demonstrated that a19-gauge EUS-TCB provided diagnostic histology of 79% in 38 patients [11]. When including these 38 patients, these same authors summarized previous studies and found that the same needle yielded diagnostic histology in 74% of patients with mesenchymal GI tumors. Gwang et al. compared the 22G EUS-FNA technique with the 22G Procore needle (ECHO-HD-22-C, Cook Endoscopy, USA) on 28 patients revealing that the 22G biopsy group had a significantly lower median number of needle passes to obtain macroscopically optimal core samples (4 vs. 2, p = 0.025); higher yield rates of histologically optimal core samples with three needle passes (20% vs. 75%, p = 0.010, respectively); and a higher diagnostic sufficiency rate (20% vs. 75%, p = 0.010) [7].

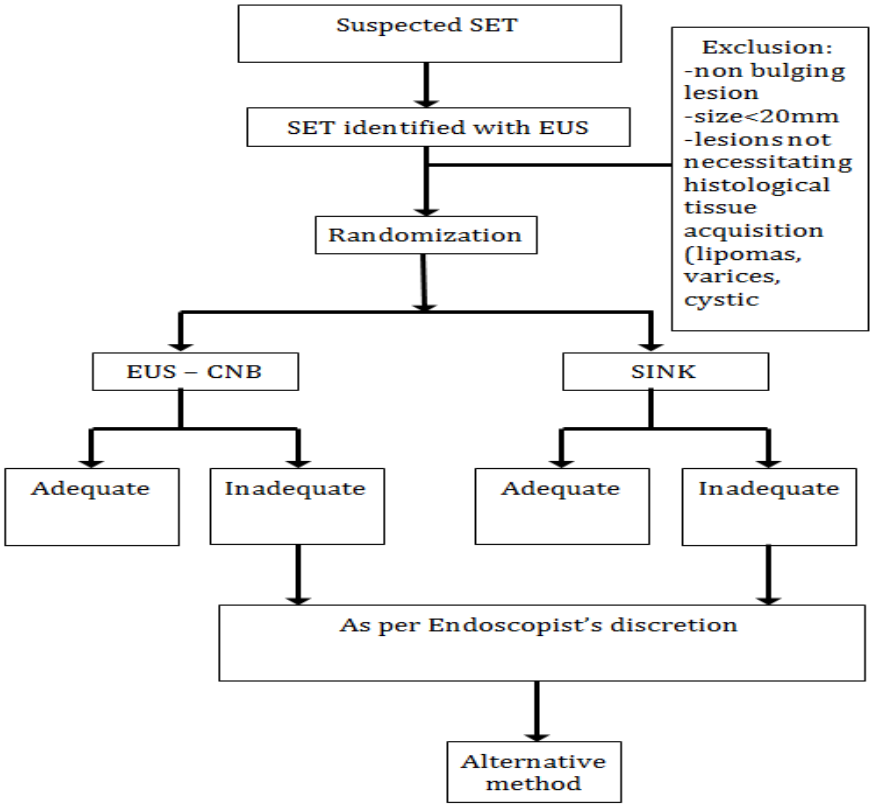
The SINK technique has been described in a study involving 14 patients revealing a diagnostic yield of 92.8%, with no adverse events. Eight patients underwent both EUS-FNA and SINK, with final histologic diagnosis determined in 6 of 8 cases (75%) by SINK versus 1 of 8 cases (12.5%) by EUS-FNA (Fisher exact test, P =0.023) [8].

Thus, this study will provide essential data on two techniques to help decipher which is the optimal method of tissue acquisition.

We hypothesize that the SINK technique will have a higher diagnostic accuracy than EUS-CNB for the diagnosis of UGI SETs.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).



This is a prospective, randomized study. All procedures are part of routine care and not experimental. All patients will begin their endoscopy with a standard gastroscope followed by electronic radial/linear scanning video echoendoscope prior to randomization to ascertain the wall layer of origin for the tumor. This EUS exam will be performed under the same anesthetic as the study intervention. Patients will be consented prior to endoscopy.
Patients who are candidates for this study (see inclusion criteria) will be randomized as to receive either EUS-CNB or SINK technique (computer generated randomization sequence, sealed envelopes). The endoscopist will not be blinded to the type of technique used however the study pathologist will be blinded.

Patients receiving the EUS-CNB technique:

Linear EUS will be used with color and pulsed Doppler to scan the area for vessels. The accessory channel is used to pass through devices for tissue sampling The lesion will be sampled with a 22-gauge Procore needle (ProCore, Cook Medical Inc., Winston-Salem, NC) using the slow capillary suction technique with 5 to 15 to-and-fro movements with each pass. The slow capillary suction technique and fanning techniques will be used with each pass. The slow capillary suction technique involves the assistant simultaneously pulling out the stylet slowly and continuously over approximately 20s while the stylet is simultaneously removed up to 2/3 of its entire length. The fanning technique will be used. This technique involves positioning the needle at 3 different areas within the mass and then moving it back and forth 5 times in each area to procure tissue (3×5). The needle will be positioned at different areas within the mass by using the "up-down" dial of the echoendoscope and with minimal use of the elevator to avoid needle dysfunction. A total of 4 passes will be performed and then the procedure terminated. No cytopathologist will be present to review the specimens. All specimens will be placed in formalin bottles and sent for histopathology
If the samples are of insufficient quality such that a histological diagnosis would not likely be obtained after a total of 4 passes as per the impression of the endoscopist, he/she will be permitted to perform an alternative method; such as, SINK, EUS-FNA, EUS-CNB etc…

Definitions:

Technical Failure: Inability to complete the 4 assigned passes as determined by randomization. Malfunction of the needle before 4 needle passes is an example.

Adverse events: Refer to Tables 1 and 2. [12]

Operation Time: Time from the beginning of the incision or needle insertion, to completion of tissue acquisition per protocol.

Patients receiving the EUS-SINK technique:

A conventional needle-knife sphincterotome (Microknife XL; Boston Scientific Inc, Natick, Mass) connected to an electrosurgical unit (ICC 200; ERBE Electromedizin, Tübingen, Germany) will be utilized. The setting used would be ENDOCUT I, Effect 3, Duration 2 and Interval 1. Under direct endoscopic vision, a 6 to 12–mm linear incision is made from the periphery of the lesion to the highest convexity zone of the lesion. This direction of cut is important as it will help avoid unnecessary extension of the incision outside the lesion from

slipping of the knife off the lesion. The incision should be deep enough such that it penetrates the mucosa and submucosa. A conventional biopsy forceps (Radial Jaw4, Boston Scientific, Natick, Mass) is then deeply introduced through the hole, and 2 bites are obtained per pass. A total of 4 passes will be performed, by passing the biopsy forceps through the incision on each occasion. The mucosal incision will then be closed with endoclips whenever possible. If the endoscopist at the time is concerned about inadequate tissue acquisition and plans to perform a subsequent intervention (i.e. EUS-CNB, EUS-FNA) then the endoclips will be placed after the EUS. Biopsies will be placed in formalin bottles and sent for histopathology. In case of technical failure, the endoscopist is permitted to choose another method to obtain biopsies (e.g. EUS-CNB, EUS-FNA…)

Pathologic evaluation

Specimens will be placed in buffered formalin and processed as normal forceps biopsy specimens; however, special care will be taken not to lose tiny specimen fragments. The pathologists will be blinded to the type of technique used, but all other information about the clinical history and site biopsied will be given. A positive diagnosis of a specific malignancy or of a specific benign disease by either technique will be accepted as a true positive. A histological diagnosis of atypical cells or abnormal cells will be considered a negative result. For malignancy, an "accurate diagnosis" will be considered one in which a tissue diagnosis obtained is compatible with that seen by subsequent surgery, alternative biopsy by another needle or sites, or clinical follow up.

Final diagnosis and definition

In the absence of surgical resection, diagnostic histology obtained by either technique will be considered the gold standard. When diagnostic histology is not available, a definitive diagnosis is established on the basis of long-term follow-up, surgery, or further procedures with biopsy. The diagnostic accuracy will be defined as the ratio between the sum of true positive and true negative values divided by the total number of procedures done in either technique. As per the discretion of the pathologist, the specimens may be subjected to immunostaining and if performed, the contribution to the diagnostic yield will be noted.

Different immunostains can be used by pathology laboratories for diagnosing the SETs: CD117(c-kit), CD34, smooth muscle actin, DOG1 etc. As different laboratories may use selective immunostains, the particular stains used will be at the discretion of the pathology laboratory. Our preference would be that GIST be defined based on CD 117 and DOG1 positivity.

Study parameters and calendar

	Day 0*	Day 1	Day 7
Sedation administered	X		
Procedure	X		
Recovery	X		
Follow-up		X	X

* Day 0 is the day of the procedure.

The patients will be observed for immediate complications in the recovery area for 2 hours. For all outpatients, telephone contact will be made the day after the procedure to monitor for any complications and another phone call 1 week later. Patients will be discharged on the same day as their procedure. Long-term clinical follow up will be based on clinical indications.

Table 3 [13]

Drug	**Recommended interval between last dose and procedure**	**Reinstitution**
Aspirin	Continue	N/A
Aggrenox	7-10 days	Reinitiate within 24 hours
Cilostazol	2 days	Reinitiate within 24 hours
Clopidorgrel and Ticagrelor	5 days	Reinitiate at 24 hours after the procedure
Prasugrel	7days	Reinitiate at 24 hours after the procedure
Ticlopidine	10-14 days	Reinitiate within 24 hours after the procedure
Warfarin	5 days	Reinstitute after the procedure
Unfractionated heparin	2-6hrs (IV) 12-24 hrs (SubQ)	Reinstitute after 24 hours
LMWH	24 hrs	Reinitiate at 24 hours after the procedure
Fondaparinux	36-48hrs	Reinitiate at 24 hours after the procedure
Dabigatran	1-2days CrCl>50, 3-5days CrCl <50	Delay initiation for at least 48 hours
Rivaroxaban	≥1day for normal CrCl, 2 days CrCl 60-90, 3 days CrCl 30-59, 4 days CrCl 15-29	Delay initiation for at least 48 hours
Apixaban	1-2 days with CrCl>60, 3 days with CrCl 50-59, 5 days for CrCl <30-49	Delay initiation for at least 48 hours
Desirudin	2hrs	Reinitiate within 24 hours

In general, prophylactic anticoagulation therapy is resumed once hemostasis is secured. In patients receiving bridging therapy, heparin at a therapeutic dose should be withheld

for 48 hours after the procedure. If the risk of postprocedural bleeding is deemed acceptably low, full-dose anticoagulation therapy may be initiated after a shorter interval. **We leave the decision for the reinstitution of the antithrombotic agent at the discretion of the physician to be taking into account the different variables implicated in hemostasis for each patient.**

The study will be continued until the sample size of 90 patients is reached (estimated 2 years). The patients will only need to attend for the procedure as scheduled. No further visits are required.

b. Blinding, including justification for blinding or not blinding the trial, if applicable.

Blinding of the endoscopist is not practical as the endoscopist will be performing the technique. However, the pathologist will be blinded to the technique used.

c. Justification of why participants will not receive routine care or will have current therapy stopped.

Not applicable. This study compares two techniques which are considered standard of care for the diagnosis of these tumors. These procedures are not experimental.

d. Justification for inclusion of a placebo or non-treatment group.

This is not applicable to this study. All patients are presenting for a procedure they require for diagnosis as determined by their referring physician.

e. Definition of treatment failure or participant removal criteria.

In case of failure of the initial method to obtain adequate sample, another method may be performed at the discretion of the endoscopists. An inadequate sample is defined as samples of insufficient quality such that a histological diagnosis would not likely be obtained**.** This will be determined at the time of tissue acquisition if the samples obtained are only tiny fragments, no visible core tissue (i.e no worms) or it appears that only blood clot is present. Post procedure, an inadequate sample will be determined based on an inconclusive formal pathology report. In these cases, the patients may cross over to EUS-CNB or SINK (depending on their initial randomization) or undergo an EUS-FNA either at the time of the procedure (if it is appears that no tissue has been obtained) or the patient will return at a later date for an EUS-CNB, SINK, EUS-FNA/be referred to surgery/undergo surveillance at 6-12 months etc, depending on the differential diagnosis.

f. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

This is not applicable in this study. The patient only attends for their diagnostic procedure; there is no further follow-up or treatment necessary as part of the study protocol.

5. Inclusion/Exclusion Criteria

Inclusion criteria:

1. Patients referred for EUS evaluation of upper GI SETs measuring an estimated 15mm or greater in maximal diameter.
2. Location of SET: esophagus, stomach, duodenum
3. Age >18 years and older
4. Patient consent obtained

Exclusion Criteria:

1. Endoscopically non bulging lesion
2. Upper GI SETs <15mm in size as measured during study EUS
3. Lesions not necessitating tissue acquisition: i.e. lipomas, varices
4. Cystic lesion
5. Patients < 18 years of age
6. Uncorrectable Coagulopathy (INR >1,5, platelets <100,000)
7. Patients with stigmata of portal hypertension
8. Patients with post-surgical UGI anatomy (Roux-en-Y gastric bypass, esophagectomy etc)
9. Uncooperative patients
10. Pregnant women (women of childbearing age will undergo urine pregnancy testing, which is routine for all endoscopic procedures)
11. Refusal to consent form

Drop-outs (anyone will be considered a drop-out after randomization had been made):

1. Mass<15mm
2. Cystic
3. Lipoma
4. Varices

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The 25 G needle is too small to be used for histological sampling, and the 19 G needle is too rigid impeding the sampling from the duodenum or the fundus of the stomach. The 22G Procore needle is readily available and clinically used for tissue sampling.
The needle knife sphincterotome and pinch biopsy forceps are readily available and used clinically for controlled mucosal incision and tissue sampling allowing, respectively.

Although used clinically, neither of these techniques has been compared at our institution.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Not applicable

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Not applicable

7. Study Statistics

a. Primary outcome variable.

We hypothesize that the diagnostic accuracy of single incision using needle knife (SINK) technique will "be superior" in obtaining histological samples than EUS-CNB.

Based on the previously published references that demonstrated the diagnostic accuracy of SINK is 92.8%[8] and that of EUS-CNB is 70% [12], we assume that the diagnostic accuracy of SINK and EUS-CNB to be 95% and 70% respectively

b. Secondary outcome variables.

Not applicable

c. Statistical plan including sample size justification and interim analysis

With the assumption that diagnostic yield of "EUS-CNB" is 70% and that of "SINK" is 95%, and considering $\alpha = 5\%$ and $1-\beta = 80\%$, the required sample size is 36 patients in each group (total of 72 patients).
We will account for 20% drop out rate, giving a total of 90 patients, 45 in each arm.

Statistical analyses

Categorical parameters including gender, location of lesion, technical success and diagnostic accuracy will be compared by χ^2-test or Fisher's exact test. To compare diagnostic accuracy between the two techniques, we will use McNemar's test. Continuous variables including age, size of lesion, follow-up period, needle passes and adequacy of specimens will be compared by the Student's *t*-test or Wilcoxon rank sum test. All statistical analyses will be performed using SPSS software (version 15.0; SPSS, Chicago, IL), with results considered significant at *P* values < 0.05.

d. Early stopping rules.
A data safety and monitoring board (DSMB) will be appointed comprised of interventional endoscopists, mainly of Dr. Vikesh K. Singh, Dr. Anne-Marie Lennon, and Dr. Martin A. Makary. The DSMB will be responsible for reviewing all major complications (perforation, hospitalization for > 48 hours, bleeding requiring transfusion, deaths etc). If any serious adverse event is noted during the study then the DSMB will be required to meet. Additionally. The DSMB will perform a blinded analysis after enrolment and initial outpatient follow-up of 50% of the study cohort.

Interim analysis will be performed at 50% recruitment. If a > 20% difference in sensitivity is found between both methods then the study will be terminated early.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

This study is classified as greater than minimal risk and potential complications related to EUS-CNB or SINK procedure are following:

1) The needle puncture may cause inflammation or scarring of the lining of the digestive tract which may cause abdominal pain and ulceration.
2) Perforation: Only physicians specially trained in EUS will be performing these procedures. Patients will be kept a minimum of 2 hours after the procedure is completed, during which time any perforation would be clinically recognized.
3) Infection: It is not standard practice to give antibiotics to all patients prophylactically. Therefore, no subjects will receive antibiotics prophylactically for EUS-CNB or SINK except those patients at risk for infective endocarditis according to American Heart Association guidelines.
4) Bleeding is unlikely, but probably is at slightly increased risk SINK over EUS-CNB. The risk of bleeding with either technique is probably higher than that of EUS-FNA. The exact risk is minimal (approximately 1 in 1,000 chance). Doppler examination will be performed under EUS guidance prior to biopsy to ensure that the needle does not traverse a blood vessel. Specifically for the SINK technique, the mucosal incision will be closed with endoclips to prevent bleeding from the incision. Additionallu, as a precautionary measure, furthermore, all patients will have had PTT, PT/INR, hemoglobin, and platelet count reviewed prior to the procedure. Those below acceptable standards will not be offered inclusion into the study. Frequent vital signs will be measured and recorded for at least 2 hours after the procedure. If these vital signs are abnormal and prolonged, a repeat CBC and possibly CT scan will be performed to ensure the absence of internal or external hemorrhage. These measures should ensure any clinically significant hemorrhage is detected and treated in a timely manner.
5) Sepsis

b. Steps taken to minimize the risks.

Adherence to the standard of practice of the Johns Hopkins Hospital Division of Gastroenterology will be kept. Procedure will be performed by members of the Division of Gastroenterology at Johns Hopkins Hospital who are board certified Gastroenterologists trained in advanced endoscopy.

c. Plan for reporting unanticipated problems or study deviations.

If a serious or unexpected adverse event (AE) occurs, it will be reported to IRB within 24 hours by email or telephone. Serious adverse events include: perforation, hospital stay> 24 hours, bleeding requiring transfusion, death or any event resulting in prolonged significant disability or incapacity

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There are no legal risks associated with participation in this study. All measures to protect confidentiality will be taken.

e. Financial risks to the participants.
None

9. Benefits

a. Description of the probable benefits for the participant and for society.

Potential improvement in diagnostic techniques and ultimately patient outcome.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There will be no payment or remuneration

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

All procedures are part of routine clinical care and will be billed to the patient's insurance company.

Table1: [12]

Category	Event	Definition	Qualifiers
Cardiovascular	Hypotension	<90/50 or down 20%	
	Hypertension	>190/30 or up 20%	
	Dysrhythmia		Specify
	Arrest		
	Myocardial infarction		
	Cerebrovascular event		Specify
Pulmonary	Hypoxia	O_2 < 85%	
	Hypopnea		
	Laryngospasm		
	Bronchospasm		
	Pneumonia		
	Pneumonitis		
Thromboembolic	Deep venous thrombosis		
	Pulmonary embolus		
Instrumental	Perforation	Evidence of air or luminal contents outside the GI tract	Organ, site instrument
	Penetration	Visual or radiographic evidence of unintended penetration beyond the mucosa or duct, without perforation	Organ, site, instrument
	Impaction	Unable to remove instrument or device	Site, instrument
	Malfunction		Specify site, instrument
Bleeding		Hematemesis and/or melena or hemoglobin drop >2 g	Units
Infection	Cholangitis	>38C >24 hours with cholestasis	
	Pancreatic infection	>38C >24 h with collection	
	Fever?cause	>38C >24 h without obvious source	
	Transmission		Organism
Drug reaction	Allergy		Agent, reaction
Pain	Abdominal	Not caused by pancreatitis or perforation	
	Nonabdominal		Site
Pancreatitis		Typical pain with amylase/lipase >3 times normal	
Integument		Damage to skin, eyes, bones, muscles	Specify
Other			Specify

Continuation of Table 1:

Category	Event	Definition	Qualifiers
Qualifiers for all events			
Timing	Preprocedure, intra, post (<14 days), late; day of onset for postprocedure events		
Attribution	Definite, probable, possible, unlikely		
Severity	See Table 2		

*An adverse event is one that prevents completion of the planned procedure (does not include failure of completion because of technical failure or interference by poor preparation or disturbed anatomy or disease or surgery) and/or results in hospital admission, prolongation of existing hospital stay, another procedure (needing sedation/anesthesia), or subsequent medical consultation.

Table 2: [12]

	Severity grade			
Consequence	**Mild**	**Moderate**	**Severe**	**Fatal**
Procedure aborted (or not started) because of an adverse event	x			
Postprocedure medical consultation	x			
Unplanned anesthesia/ventilation support, ie endotracheal intubation during conscious sedation		x		
Temporary ventilation support by bagging or nasal airway during conscious sedation, and endotracheal intubation during a modified anesthesia care procedure are not adverse events				
Unplanned hospital admission or prolongation of hospital stay for ≤3 nights	x			
Unplanned admission or prolongation for 4-10 nights		x		
Unplanned admission or prolongation for >10 nights			x	
ICU admission for 1 night		x		
ICU admission >1 night			x	
Transfusion		x		
Repeat endoscopy for an adverse event		x		
Interventional radiology for an adverse event		x		
Interventional treatment for integument injuries		x		
Surgery for an adverse event			x	
Permanent disability (specify)			x	
Death				x

ICU, Intensive care unit.

12. References:

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