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Clinical Study Protocol

A Prospective Randomized Controlled Study Comparing EUS Sonopsy CY(R) and 22-gauge Biopsy Needles for Endoscopic Ultrasound-guided Fine-Needle Aspiration of Solid Pancreatic Mass Lesions

Sho Mizukawa[a], Hironari Kato[a]*, Shinichiro Muro[a], Yutaka Akimoto[a], Daisuke Uchida[a], Takeshi Tomoda[a], Kazuyuki Matsumoto[a], Naoki Yamamoto[a], Shigeru Horiguchi[a], Koichiro Tsutsumi[a], Hiroyuki Okada[a], Hirofumi Inoue[b], and Noriyuki Tanaka[b]

Departments of [a]Gastroenterology and Hepatology and [b]Diagnostic Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a standard procedure for precise histological diagnosis of pancreas tumors, but it is sometimes difficult to obtain adequate specimens. EUS Sonopsy CY® is a newly designed needle with original features. This randomized study will compare the tissue collection rate of EUS Sonopsy CY® to that of a conventional needle in EUS-FNA. The major eligibility criteria are as follows: Patients with a pancreatic mass referred for EUS-FNA; age ≥ 20 years, and performance status < 4. The primary outcome is the tissue collection rate. This study will elucidate the efficacy of EUS Sonopsy CY®.

Key words: endoscopic ultrasound-guided fine needle aspiration, pancreatic cancer, Menghini type needle tip

Solid pancreatic masses occur for many reasons [1]. Therefore, accurate histological diagnosis is essential for precise diagnosis and treatment.

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has become the standard procedure for sampling solid pancreatic masses [2]. EUS-FNA is performed with 19- to 25-gauge needles [3-5]. EUS-FNA with 25-gauge needles achieves a higher technical success rate than other needles. However, an adequate specimen for histological diagnosis sometimes cannot be obtained, especially from neuroendocrine tumors (NET), solid pseudo papillary neoplasms (SPN), malignant lymphoma, and benign inflammatory lesions such as tumor-forming pancreatitis and autoimmune pancreatitis [2]. This is sometimes the case even with the 19-gauge needles [5,6]; some lesions, such as the head of pancreas, are difficult to puncture with 19-gauge needles. On the other hand, 22-gauge needles can puncture a wider variety of lesions [7] and are commonly used in clinical practice.

Recently, various needles have been developed to obtain a greater amount of tissue and achieve a more accurate diagnostic rate [8]. EUS Sonopsy CY® is a newly designed ultrasonographic biopsy aspiration needle. This needle features the Menghini Type Needle Tip biopsy system, an outer needle shape suitable for a biopsy, and good supersonic wave depiction characteristics. In this biopsy system, the inner needle remains inside the outer needle during aspiration

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*Corresponding author. Phone:+81-86-235-7219; Fax:+81-86-223-5991
E-mail:katou-h@cc.okayama-u.ac.jp (H. Kato)

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so it can obtain sufficient good-quality tissue without crushing the tissue. Furthermore, owing to the tapered bevel edge, tissue can be taken in the outer needle, and we postulate that EUS Sonopsy CY® can achieve a greater amount of appropriate tissue collection for diagnosis. We have initiated a prospective, randomized, controlled study to determine the diagnostic accuracy of this modality.

Endpoints

The primary outcome is the tissue collection rate. The secondary outcome is the tissue collection rate of the 2 punctures in terms of tumor size, location, puncture route, tissue diagnosis rate, and adverse events.

Eligibility Criteria

All patients who meet the inclusion and exclusion criteria listed in Table 1, Table 2 will be invited. An investigator will obtain written informed consent from each patient before any screening or inclusion procedure.

This study was conducted in compliance with the principles of the Declaration of Helsinki, and the protocol was approved by the ethics committee of Okayama University Hospital (No1601-003). This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000020668).

Treatment Methods

Study design. This is a prospective, single-blind, randomized, controlled trial to investigate which needle can obtain the greatest amount of suitable tissue for histological diagnosis in EUS-FNA, the EUS Sonopsy CY® (HAKKO, Ngano, Japan) or a conventional needle (Sonotip® 22G; Medicos Hirata,

Table 1 The inclusion and exclusion criteria

The inclusion criteria
Patients with pancreatic mass who are refered to EUS-FNA
The exclusion criteria
Patients with Performance status 4, 5 (ECOG) (Table 2)
Patients who have risk of bleeding, or patients with platelet count less than 50,000/mm^2
Patients with antithrombotic agent 2 agent or more
Patients with pancreatic mass which we cannot detect by EUS
Pregnant woman
Patients less than 20 years old
Patients who do not agree to participate in this study
Patients who determined to be inappropriate

EUS-FNA, endoscopic ultrasonography-guided fine needle aspiration; EUS, endoscopic ultrasonography; ECOG, Eastern Cooperative Oncology Group.

Table 2 ECOG Performance Status

GRADE	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

ECOG, Eastern Cooperative Oncology Group.

Tokyo, Japan).

Intervention. Patients with solid pancreatic masses detected by ultrasonography, computed tomography, or magnetic resonance imaging will be enrolled in this study.

For each lesion, 2 needle punctures will be performed with EUS Sonopsy CY® (needle S) and a conventional needle (Sonotip® 22-gauge [needle N]). The procedures are randomly set in one of 2 patterns: (1) needle S followed by needle N (Group S) and (2) needle N followed by needle S (Group N).

All procedures will be performed by an experienced endo-sonographer who has performed more than 50 procedures over the past year or 100 procedures in total. Patients will be placed in the left lateral decubitus position and will be administered conscious sedation with intravenous midazolam and pethidine. EUS and EUS-FNA will be performed with a curved linear array echo-endoscope (GF-UCT-260-AL5; OLYMPUS Medical System, Tokyo, Japan). The puncture with needle S will be performed as follows: After puncturing the mass, we will draw back the aspiration piston to the locking position. After waiting for more than 3 sec until negative pressure becomes active at the needle tip, we will push forward the puncture needle several times to pass the target lesion. After removing the outer puncture needle from the protective tube, we will attach a syringe to the proximal end of the outer barrel and then push tissue pieces from the outer puncture needle with saline. The puncture with needle N will be performed as follows: After we puncture the mass, the stylet will be withdrawn. An accessory syringe will be attached to the proximal end of the needle. The needle will then be moved back and forth 10 times while performing suction [3,4]. Tissue material will be expressed onto the slides by loading the stylet into the needle assembly. Obtained samples will be categorized according to needle type and fixed with formalin for histological examination. Rapid on-site evaluation will be performed at all institutions. If adequate samples are not obtained during the two punctures, additional punctures will be permitted (Fig. 1).

Randomization. After confirming fulfillment

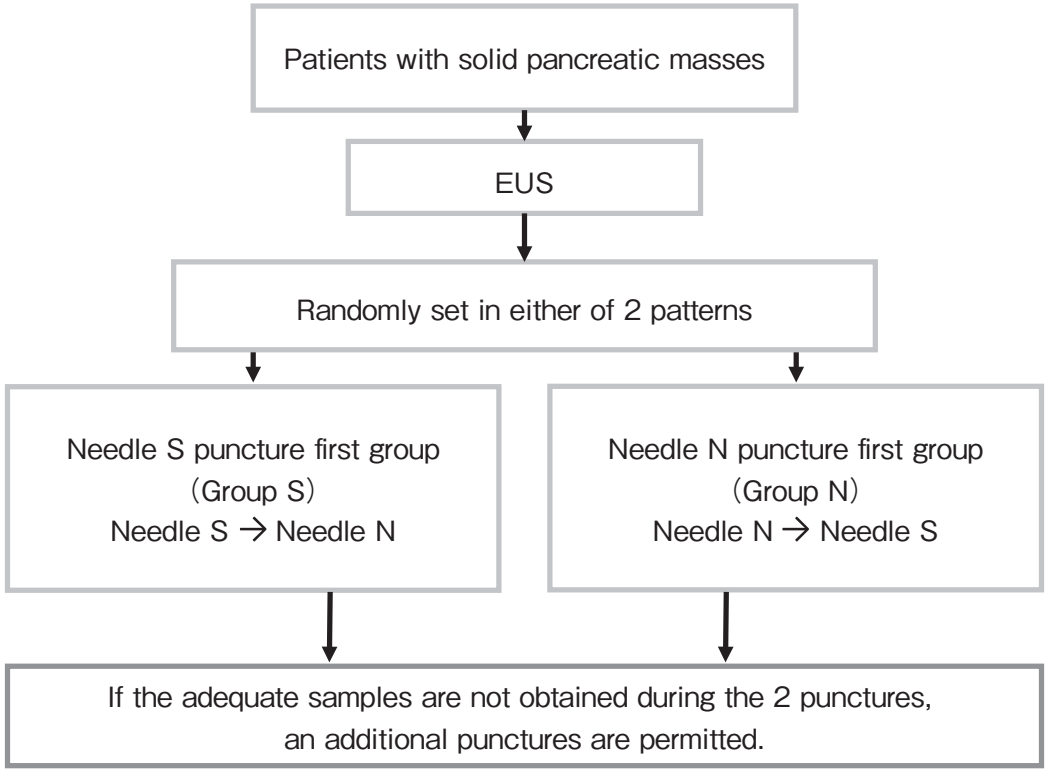

Fig. 1 Study flow

of the eligibility criteria, registration will be made via a web-based system to the data center. Patients will be randomized to either Group S or Group N by a blocked randomization method, balancing the arms with age, sex (male vs. female), and lesion (the head of the pancreas vs. the body and tail of the pancreas).

Statistical Consideration

The primary endpoint is obtaining adequate specimens for histological diagnosis on the first puncture in each group. The adequacy of samples will be evaluated by an experienced pathologist using the Cellularity scoring system [9] as follows: Score 0: Insufficient material for interpretation, Score 1: Sufficient material for limited cytological interpretation, probably not representative, Score 2: Sufficient material for adequate cytological interpretation, Score 3: Sufficient material for limited histological interpretation, Score 4: Sufficient material for adequate histological interpretation, low quality (total material $< 1 \times 10$ power field in length), Score 5: Sufficient material for adequate histological interpretation, high quality ($> 1 \times 10$ power field in length). In this study, a sample with a score of 3–5 is defined as an adequate specimen for histological diagnosis. The tissue collection rate is defined as the proportion of the number of adequate specimens to the number of randomized patients in each arm. All statistical analyses will be conducted using JMP software (ver. 11; SAS Institute, Cary, NC, USA).

It has been reported that the tissue collection rate for histological diagnosis by using a conventional 22-gauge needle in pancreatic masses is 62.5% [10]. We estimate a 20% increase of the tissue collection rate by using EUS Sonopsy CY® in the retrospective study in our hospital. Based on this, a sample size of 200 patients is calculated with a power of 0.8 and a 2-sided alpha of 0.05.

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