Acta Med. Okayama, 2016
Vol. 70, No. 4, pp. 313-316
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Acta Medica Okayama
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Clinical Study Protocol

Efficacy and Safety of Endoscopic Ultrasound-guided Ethanol Ablation Therapy for Pancreatic Neuroendocrine Tumors

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Recently, endoscopic ultrasonography (EUS)-guided ethanol ablation for small pancreatic neuroendocrine tumors (p-NETs) has been reported. However, the efficacy and safety of the technique remain unclear. We have launched a prospective pilot study of EUS-guided ethanol ablation for p-NETs. The major eligibility criteria are the presence of a pathologically diagnosed grade (G) 1 or G2 p-NET, a tumor size of ≤2 cm, and being a poor candidate for surgery. A total of 5 patients will be treated. The primary endpoint will be the complete ablation rate at 1 month after treatment.

Key words: pancreatic neuroendocrine tumor, ethanol ablation, EUS-guided

Pancreatic neuroendocrine tumors (p-NETs) are fairly rare, and they account for 1-2% of primary pancreatic malignancies [1]. However, the incidence of p-NETs has increased substantially because of the widespread use of advanced endoscopic and radiological imaging techniques [2]. The 5-year overall survival rates range from 30% for nonfunctional neuroendocrine tumors to 97% for benign insulinomas [3].

For patients with resectable p-NETs that are >2 cm, surgical resection is the standard of care [4]. On the other hand, there is no survival benefit associated with surgery for those with nonfunctional small p-NETs that are <2 cm [5], and the benefit of surgery must be balanced against operative morbidity and mortality. Pancreatic resection, especially pancreaticoduodenectomy (PD), has been associated with high rates of major complications, including death [6, 7]. The PD mortality and major complications rates are about 4% and 15%, respectively [6].

Recently, endoscopic ultrasonography (EUS)-guided ethanol ablation has been proposed for the treatment of patients with small p-NETs who refuse surgery or are poor surgical candidates [8, 9]. Levy *et al.* [8] reported that EUS-guided ethanol ablation for insulinomas was technically feasible and safe, and symptomatic improvement was achieved in all 8 of their patients. Park *et al.* [9] reported that after a single session of ethanol ablation therapy, 54% (8/13) of their patients showed complete responses at the 3-month radiologic imaging assessments and that adverse events had occurred in 27% (3/11) of the patients who had small p-NETs that were <2 cm in diameter.

Received June 6, 2016; accepted July 13, 2016.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

However, these studies were not prospective studies, and the efficacy and safety of this procedure remain unclear. Indeed, the complete ablation rate is inadequate. Therefore, we were prompted to launch the current trial to determine whether planned repeat ethanol ablation sessions might improve the complete ablation rate and, hence, to determine whether EUS-guided ethanol ablation therapy could be a very useful and less invasive therapy for patients with small p-NETs who refuse surgery or are poor candidates for surgery.

Endpoints

Primary and secondary endpoints and other evaluations. The primary endpoint will be the complete ablation rate at 1 month after the first treatment session. The complete ablation rate will be defined as the ratio of patients in whom any enhanced areas within the tumors disappear on contrast-enhanced-computed tomography (CE-CT) images after 1 month of the first discharge following treatment. The CE-CT images will be reviewed by an expert radiologist and an independent expert gastroenterologist. The secondary endpoints will be the adverse events associated with the procedure, the procedure time, the number of ethanol injections administered, the volume of ethanol injected, the total number of sessions, the number of days spent in hospital, the incidence of diabetes after treatment, the recurrence rate, and the retreatment results. For patients with functional p-NETs, the rate of symptom improvement and changes in the serum hormone levels after treatment will be evaluated. The secondary endpoints will be prospectively evaluated from the patients' records. We will also establish a safe evaluation committee, which will comprise 3 additional doctors who are not associated with the study, to determine whether the study should continue when severe adverse events occur, which will include death, life-threatening complications, severe pancreatitis requiring intensive care unit management and surgical intervention and, thus, a significant extension of the hospitalization period, and persistent or a significant disability of a patient's general functions.

Eligibility Criteria

All of the patients who meet the main inclusion and exclusion criteria, which are listed in Table 1, will be invited for screening. The major eligibility criteria are the presence of a pathologically diagnosed grade (G) 1 or G2 p-NET, a tumor size of ≤ 2 cm, and being a poor candidate for surgery.

Study setting. We have launched a single-arm, prospective, nonrandomized, noncomparative, open-label, single-center, pilot study.

Ethical considerations. The investigators must obtain written informed consent from the patients before any screening takes place or inclusion procedures are considered. This study will be conducted in a manner that complies with the principles of the Declaration of Helsinki. The study's protocol has been approved by the institutional review board of our hospital (approval number: 1510–003, UMIN Trial registration number: 000018834).

Treatment Methods

Endoscopic ultrasonography-guided intervention and study flow. Fig. 1 presents the study's flow chart. For the first treatment we will slowly advance the 22 G or 25 G fine needle aspiration (FNA) needle into the center of the tumor under real-time EUS, then pure ethanol (Mylan Seiyaku Ltd, Tokyo, Japan) will be injected until a hyperechoic blush extends to the tumors' margins. Blood testing at 2 h postoperatively, and on postoperative day (POD) 1 and POD 3 will evaluate the secondary endpoints. CE-CT performed on PODs 3–5 will evaluate tumor viability and the adverse events. When the CE-CT images show enhancement, 1 session of EUS-guided ethanol reablation therapy will be scheduled between POD 3 and POD 5 of the same hospitalization period.

For EUS-guided ethanol reablation therapy, contrast-enhanced harmonic-EUS (CEH-EUS) imaging will confirm the tumor's viable regions using perflubutane (Daiichi-Sankyo Company, Limited, Tokyo, Japan) as the contrast agent. The methods used will be the same as those used previously.

Follow-up CE-CT imaging at 1 month after discharge will evaluate the tumor's viability and the adverse events. Complete ablation will be defined as the absence of enhanced areas within the tumor on the

Table 1 Patient eligibility criteria

Inclusion criteria
A diagnosis of a p-NET (G1 or G2) that was confirmed by the pathology of a needle specimen obtained by EUS-FNA (WHO 2010 classification)
Poor surgical candidate (ASA grade $\geq$ III) or refusal of surgery
Tumor diameter $\leq$ 2 cm according to CE-CT
A p-NET diagnosed as a nonfunctional tumor or an insulinoma
Exclusion criteria
Severe drug allergy history
Allergy to contrast media
Allergy to ethanol
Tumor not visualized or could not be punctured using EUS
Diagnosed with an NEC based on a needle specimen obtained by EUS-FNA (WHO 2010 classification)
Tumor located near the main pancreatic duct
PT $\leq$ 50% or INR $\geq$ 1.5
PLT $\leq 50 \times 10^9$/L
eGFR $\leq$ 30 mL/min
Administered $\geq$ 2 antithrombotic agents
Performance status $\geq$ 2
Estimated poor prognosis of $<$ 3 years
Age $<$ 20 years
Patient did not provide informed consent
Patients who were judged as being inappropriate by the chief medical examiner

p-NET, pancreatic neuroendocrine tumor; G, grade; EUS, endoscopic ultrasonography; EUS-FNA, endoscopic ultrasonography-fine needle aspiration; NEC, neuroendocrine carcinoma; ASA, American Society of Anesthesiologists; WHO, World Health Organization; CE-CT, contrast-enhanced-computed tomography; PT, prothrombin time; INR, international normalized ratio; PLT, platelet; eGFR, estimated glomerular filtration rate.

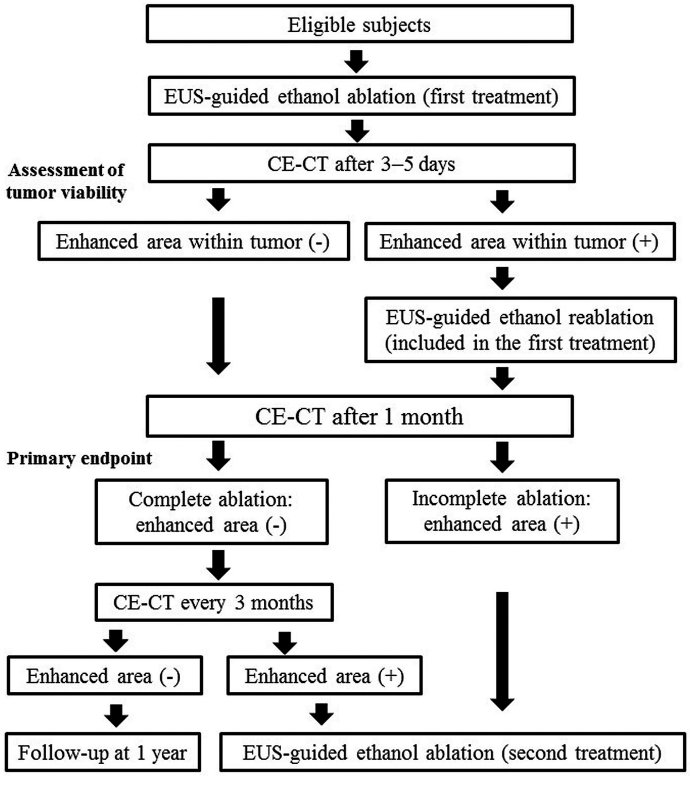

Fig. 1 The study's flow chart. EUS, endoscopic ultrasonography; CE-CT, contrast-enhanced-computed tomography.

arterial or the portal venous phase images. Incomplete ablation will be defined as the presence of enhanced areas within the tumor. When incomplete ablation has occurred, the protocol for a second treatment will be followed. Three-monthly follow-up CE-CT imaging will be performed on patients who have achieved complete ablations at the first follow-up assessment. Enhanced areas found following complete ablation will be defined as recurrences, and the protocol for a second treatment will be followed. Blood testing at 1 month after discharge and every 3 months thereafter will evaluate the secondary endpoints. The blood from the patients who have functional p-NETs will undergo serum hormone assays. Patients will be followed up for 1 year after the first treatment. The first and second treatment protocols will be the same. If incomplete ablation occurs after the second treatment, we will consider other treatments.

Statistical Consideration

We have determined that the sample size should be 5, because p-NETs are fairly rare, accounting for 1–2% of the primary pancreatic malignancies [1]. During the past 4 years, 26 patients have presented at the participating hospitals with small p-NETs that measure <2 cm. Given the incidence of these tumors at the participating hospitals and the eligibility criteria, we anticipate that 5 patients will present with p-NETs every 2 years.

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