

Endoscopic Color Doppler Ultrasonography in Predicting the Safety of Endoscopic Submucosal Dissection for Antral Heterotopic Pancreas

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ABSTRACT

Background/Aims: Complications are important determining factors for safety of endoscopic submucosal dissection (ESD) for gastric heterotopic pancreas (HP). This study investigated whether endoscopic color Doppler ultrasonography (ECDUS) could be used to predict the feasibility, efficacy, and safety of ESD. **Patients and Methods:** The study included 52 patients with heterotopic pancreas of the gastric antrum who underwent ECDUS before ESD. ECDUS was used to evaluate the submucosal vascular structure and the location of HP in gastric wall. The patients who had a vessel at least 500 μm in diameter or at least 10 vascular structures per field of view were classified into the rich group (Group R), and others were classified into the non-rich group (Group N). Procedure time, decrease in hemoglobin, frequency of clip use, complications, recurrence rate, and others were retrospectively evaluated. **Results:** There were 18 patients in Group R and 34 patients in Group N. Mean procedure time was significantly longer in group R (55.4 min) than in group N (35.5 min) ($P = 0.014$). The incidence of muscle injury and clip use were significantly higher in group R (77.8/83.3%) than in group N (20.6/23.5%) ($P < 0.05$). Mean decrease in hemoglobin was 2.5 g/dL in group R and 2.4 g/dL in group N, with no significant difference. There were no recurrences in any cases during the follow-up period. **Conclusion:** Preoperative identification of submucosal vascular structure by ECDUS can predict procedure time and the incidence of muscle injury and clip use, which is particularly suitable for predicting ESD safety in heterotopic pancreas of stomach.

Key Words: ECDUS, endoscopic submucosal dissection, gastric antrum, heterotopic pancreas

Received: 28.02.2016, Accepted: 11.05.2016

How to cite this article: Xin L, Jun LQ, Hua XL, Hong Z, Bao CT, Hai TJ. Endoscopic color doppler ultrasonography in predicting the safety of endoscopic submucosal dissection for antral heterotopic pancreas. Saudi J Gastroenterol 2016;22:380-4.

Heterotopic pancreas (HP) is a benign congenital anomaly defined as pancreatic tissue that lacks anatomic or vascular continuity with the pancreas itself.^[1] This condition is also referred to as pancreatic heterotopia, pancreatic rests, ectopic pancreas, aberrant pancreas, and accessory pancreas. Endoscopic submucosal dissection (ESD) has been gaining widespread acceptance as a treatment for gastric neoplasms, including early gastric cancer, GIST (gastrointestinal stromal tumor), and HP because

of its high rate of *en bloc* resection.^[2,3] However, there are several unsolved problems associated with ESD use, such as prolonged procedure time and high incidence of perforation, bleeding, and other complications.^[4,5] Endoscopic Color Doppler Ultrasonography (ECDUS) is a useful procedure for evaluating the depth of invasion of gastric neoplasms, vessels, the presence or absence of ulcer scars, and thus, widely performed before endoscopic treatment.^[6,7]

The stomach is the most common site of occurrence of the HP cases, representing 25–38% of the total cases, with the antrum being the site in 95% of gastric HPs.^[8,9] It is known that ESD for lesions in the antrum has been associated with a lower volume

Access this article online	
Quick Response Code: 	Website: www.saudijgastro.com
	DOI: 10.4103/1319-3767.191144

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of intraoperative bleeding than lesions in other regions of stomach.^[2] In the present study, we retrospectively investigated the association between submucosal vascular findings by ECDUS performed before ESD for antral heterotopic pancreas and procedure time, decrease in hemoglobin, muscle injury, and clip use during ESD procedures.

MATERIALS AND METHODS

Inclusion criteria

This study was commenced after obtaining approval from the Ethics Committee at The First People's Hospital of Wujing District, Suzhou and Huai'an First People's Hospital, Nanjing Medical University in January 2011. Inclusion criteria^[2] were (1) age between 20–80 years, (2) heterotopic pancreas located in the gastric antrum, and the lesion fit to be treated by ESD, (3) having received ECDUS prior to ESD, and (4) having provided written informed consent. The exclusion criteria^[10] for patients were: (1) Resection of multiple lesions during a single procedure, (2) any surgical procedure involving the stomach or esophagus, (3) a lesion that extended to the gastric body or pyloric ring, (4) serious liver/kidney dysfunction or hematological disorder, (5) receiving antiplatelet or anticoagulation therapy the past week, or (6) inappropriate for participation in the study.

Patients

From January 2011 to May 2015, 68 patients underwent ECDUS before ESD for antral heterotopic pancreas, of which, 52 patients were enrolled in the study. The ages of the 52 patients ranged from 21 to 78 years old, and the mean age was 47.5 years. The history of presenting problems was upper abdominal pain in 15 patients (28.8%), abdominal distension in 7 (13.5%), and black stools in 7 (13.5%), while the rest of the subjects were discriminated incidentally with endoscopy without specific clinical symptoms.

METHODS

ECDUS

The Pentax EG3630U curvilinear array echoendoscope (Pentax Precision Instruments, Orangeburg, USA) /Hitachi EUB525 echoendoscope (Hitachi-Aloka Medical, Tokyo, Japan) with real-time ultrasound imaging linear scanning transducers (7.5 and 5.0 MHz) and Doppler information was used in the present study. 200–500 mL deaerated water was injected into the stomach. On the tip of the endoscope, a balloon was placed which was filled by deaerated water for improved coupling of the ultrasound waves to the gastrointestinal wall by producing a fluid interface and displacing intraluminal air. Five layers of the gastric wall were visualized. A hyperechoic line observed in the third layer was identified as the submucosa and a hypoechoic line discerned in the fourth layer was delineated as the proper muscle layer. ECDUS was used to

evaluate the depth and size of a lesion invasion and measure the diameter and density of vessels delineated in the third layer or nearby the proper muscle layer. In the study, lesions were retrospectively classified into the following two groups according to the vascular structure discriminated by ECDUS: The rich group (Group R), who had a vessel at least 500 μm in diameter or at least 10 vascular structures per field of view, and others were classified into the non-rich group (Group N).

Endoscopic submucosal dissection

ESD was operated by skilled endoscopists who had performed more than 100 gastric ESDs. GIFQ260J or 2TQ 260M endoscope (Olympus Optical, Tokyo, Japan) was used during the procedures, along with a hook knife (Olympus Optical, Tokyo, Japan), insulated-tip knife (KD-611L, IT2; Olympus, Japan), an ICC200 or VIO300D high-frequency apparatus (ERBE, Tübingen, Germany), and CR4500 CO₂ Regulation Unit (AGS MedTech, Hangzhou, China). A short, transparent cap (ND-201-11802, Olympus, Japan) was attached to the tip of the gastroscope to furnish a constant endoscopic view and to apply tension to the connective tissue for dissection. All the endoscopic procedures were executed under general anesthesia. The solution for the submucosal injection was prepared by adding small amounts of epinephrine and indigo carmine to 0.9% physiological saline (5 ml indigo carmine, 1 ml epinephrine, and 100 ml physiological saline). After marker dots were placed around the lesion, a solution (mentioned above) was injected around the lesion to lift it off the muscularis propria layer, and the incision was started outside the marker dots using the hook knife/insulated-tip knife. Followed by the submucosa identified under direct vision, *en-bloc* resection of the lesion was separated from the submucosa. If the lesion was involving the muscularis propria layer, it was peeled with the hook knife/insulated-tip knife to the muscularis propria layer along the edge of the lesion. Intraoperative bleeding was controlled by coagulation hemostasis with the tip of the knife (swift coagulation, effect 4, 40 W) for mild bleeding or with hemostatic forceps (Olympus Optical, Japan; soft coagulation, effect 4, 50 W) for moderate bleeding. When hemostasis was difficult using these procedures, clips (Olympus Optical, Japan) were used to hold the vessel for hemostasis. A damaged muscle layer was clipped for plication at the discretion of the operator.

On the first day of ESD, the patient was fasted and received fluid replacement. On the second day of ESD, abdominal, blood, and X-ray examinations were executed, and the operator decided when to resume eating based on the results of the examinations. The patients who developed symptoms such as hematemesis or melena underwent urgent endoscopic examination, or the patients who required a hemostatic operation for a post-ESD ulcer were considered to have developed postoperative bleeding.

Evaluation items

The aim of this study was to evaluate the effect of ECDUS on the risk of ESD in the treatment of heterotopic pancreas which was performed as a retrospective study. The following items were used: (1) The decrease in hemoglobin after ESD, (2) incidence of injury or perforation of the muscle layer during ESD, (3) the frequency of clip use during ESD, (4) the procedure time (defined as the time from endoscope insertion to removal), (5) incidence of postoperative fever of $\geq 38^{\circ}\text{C}$, (6) incidence of postoperative bleeding, (7) percentage of participants who resumed eating on the day after ESD, (8) incidence of perforation which was defined as the detection of free air or mediastinal emphysema on postoperative x-ray.

Pathologic evaluation

Pathological examination of the resected specimen was performed using parallel 2-mm thick sections stained with hematoxylin and eosin. An *en-bloc* resection was considered when both the lateral and basal margins were free of HP cells.

Follow up

Endoscopy and ECDUS were followed up for the patients at 2, 6, and 12 months after the last endoscopic resection, and yearly thereon.

Statistical analysis

Data were analyzed using the unpaired *t*-test, χ^2 -test. *P* values of less than 0.05 were considered statistically significant.

RESULTS

En-bloc resection was executed by ESD in all cases. ECDUS displayed involvement of the muscular layer of the mucosa in 4 cases (7.7%), the submucosal layer in 34 cases (65.4%), and of the muscularis propria in 14 cases (26.9%). The lesions in 33 patients (63.5%) detected hypoechoic changes on ECDUS. A medium echo was revealed in 3 cases (5.8%), 2 cases (3.8%) were hyperechoic, and 14 cases (26.9%) had heterogeneous echo. Of them, 34 were classified into group N and 18 into group R on the basis of ECDUS findings. Their demographic characteristics are presented in Table 1. The depth of invasions were significantly different between the two groups ($P < 0.05$). However, no significant intergroup difference was observed in mean age, gender, gross type, location of the lesion, mean maximum diameter of tumor, or mean maximum diameter of specimen.

All lesions were affirmed histopathologically. The results of outcome measures are shown in Table 2. The median procedure time was 55.4 min in Group R and 35.5 min in Group N ($P < 0.05$). The incidence of clip use was also significantly higher in group R (83.3%) than in group P (23.5%) ($P < 0.05$). Incidence of muscle layer

Table 1: Comparison of clinicopathological factors between the two groups

Group	Group N	Group R	<i>P</i> value
Patients	34	18	
Gender (male:female)	14:20	7:11	0.35
Mean age (years \pm SD ^a)	48.0 \pm 9.8	46.2 \pm 10.5	0.24
Gross type (umbilication: No umbilication)	24:10	11:7	0.93
Location of the lesion (A:P:L:S)	4:9:19:2	1:4:12:1	0.91
Median maximum diameter of tumor (mm \pm SD ^a)	14.4 \pm 5.6	15.7 \pm 7.7	0.31
Median maximum diameter of specimen (mm \pm SD ^a)	19.3 \pm 6.5	21.6 \pm 9.1	0.22
Depth of invasion (mucosal/submucosal/muscularis propria)	3/26/5	1/8/9	0.024

Group N: Non-rich group, Group R: Rich group, SD^a: Standard deviation.
A (region): The anterior wall of the gastric antrum, P (region): The posterior wall of the antrum, L (region): The greater curvature side of the antrum, S (region): The small curved side of the antrum

Table 2: Comparison of outcome measures between the two groups

Group (n)	Group N (34)	Group R (18)	<i>P</i> value
Mean decrease in Hb ^o (g/dL \pm SD ^a)	2.4 \pm 0.7	2.5 \pm 0.8	0.075
Mean procedure time (min \pm SD ^a)	35.5 \pm 19.6	55.4 \pm 20.2	0.014
Incidence of clip use (%)	8 (23.5)	15 (83.3)	0.046
Incidence of muscle injury (%)	7 (20.6)	14 (77.8)	0.044
Incidence of postoperative bleeding (%)	2 (5.9)	3 (16.7)	0.820
Incidence of postoperative fever (%)	2 (5.9)	2 (11.1)	0.055
Restart food on POD 1 (%)	27 (79.4)	7 (38.9)	0.370
The median hospital stay	3.0 \pm 2.0	5.0 \pm 3.5	0.600

^oHb: Hemoglobin, SD^a: Standard deviation, Group N: Non-rich group, Group R: Rich group, POD: Postoperative day

injury was found intraoperatively in 77.8% of patients in Group R, compared with 20.6% in Group N ($P < 0.05$), all of which were significantly different between the two groups. The proportion of patients who resumed eating on the day after ESD was 38.9% in Group R and 79.4% in Group N, with no significant difference. The median reduction in hemoglobin was 2.5 g/L in Group R and 2.4 g/L in Group N, with no significant difference between groups ($P = 0.075$). The incidence of postoperative bleeding and postoperative fever was not significantly different between groups. There was no occurrence of perforation or delayed bleeding in the study. There was no significant difference between the two groups of the median hospital stay ($P = 0.60$) or restarting food consumption on postoperative day (POD) ($P = 0.37$).

In all successful cases, 23 (44%) wounds had healed at 1-month follow-up and the remaining 29 (56%) had

completely recovered at 2-month follow-up. During the median 18-month (range: 10–40 months) follow-up period, there were no recurrences in any of the cases. The patients reported good quality of life, and no reflux, weight loss, poor appetite, intestinal adhesions, or other complications that usually occur after conventional open surgery.

DISCUSSION

HP exists in 2% of the general population, and the etiological factors of it remain unknown.^[11] Customarily, the diagnosis of HP has often been made based on the histological examination of surgical specimens. The preoperative imaging studies (ultrasonography, EUS, and computed tomography) lack evident specificity. Biopsy of the gastric mucosa of suspected HP rarely discloses the heterotopic pancreatic tissue because HP is usually located under mucosal tissue, however, the specimens by biopsy contain only mucosa.^[12]

When HP causes symptoms, it should be resected, however, the management of asymptomatic HP is ambiguous.^[13,14] Zhong^[8] believes that treatment of asymptomatic HP is also necessary: (1) It is difficult to acquire a definitive diagnosis of HP preoperatively; (2) although HPs are usually characterized as entirely benign lesions, malignant transformation has been identified in several reports; (3) even asymptomatic benign tumors can cause complications such as obstruction or bleeding due to tumor growth; (4) ESD is a minimally invasive technique that offers the possibility of localized treatment of HP with relatively few complications and low mortality; ESD is becoming a very important therapeutic technique. However, ESD is related with problems of technical difficulty, higher incidence of complications (such as bleeding and perforation), and a longer procedure time.

In general, the use of titanium clips, muscle damage, and longer operating time are associated with tumor size and depth. In this study, Group R had a significantly higher frequency of clip use, muscle injury, and longer time in ESD than Group N. This is probably because of vessel-rich lesions, a longer time is required for hemostatic procedures, and because the incidence of complications is increased due to the reduced visibility of the operative field by bleeding. This finding indicates that ESD for lesions with many blood vessels in the submucosa by ECDUS is more likely to cause muscle layer injury and clip use, as well as requiring a longer procedure time. These parameters suggested that the safety of ESD can be predicted by using ECDUS to some extent.

There were several limitations of the present study. First, only two centers evaluated ECDUS findings; multiple centers may improve diagnostic objectivity and reliability. Second, the variability in the skill levels of operators and

small sample size may also significantly affect the result of ESD.^[10] Third, frequency of muscularis propria heterotopic pancreas was significantly different. There is a possibility that ESD of muscularis propria heterotopic pancreas may be more difficult and dangerous than that of mucosal and submucosal heterotopic pancreas.

In conclusion, identifying blood vessels of HP by ECDUS could help predict the risk of intraoperative bleeding, the safety of ESD, procedure time, risk of muscle layer injury, and use of clips. It can suggest proper selection of ESD treatment strategy and the skilled operator. However, large, prospective, multi-centered studies are required for more definitive conclusions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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