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BRIEF ARTICLE

Endoscopic submucosal dissection training with pig models in a Western country

Adolfo Parra-Blanco, María Rosa Arnau, David Nicolás-Pérez, Antonio Z Gimeno-García, Nicolás González, Juan A Díaz-Acosta, Alejandro Jiménez, Enrique Quintero

Adolfo Parra-Blanco, David Nicolás-Pérez, Antonio Z Gimeno-García, Juan A Díaz-Acosta, Enrique Quintero, Department of Gastroenterology, University Hospital of the Canary Islands, Ofra s/n, La Laguna, 38320 Tenerife, Spain
Adolfo Parra-Blanco, Endoscopy Unit, Department of Gastroenterology, Asturias Central University Hospital, Celestino Villamil s/n, 33006 Oviedo, Spain
María Rosa Arnau, Research Animal Laboratory, Ofra s/n, La Laguna University, 38320 Tenerife, Spain
Nicolás González, Department of Gastroenterology, Montevideo Clinic Hospital, Avda Italia s/n, 11600 Montevideo, Uruguay
Alejandro Jiménez, Research Unit, University Hospital of the Canary Islands, Ofra s/n, La Laguna, 38320 Tenerife, Spain
Author contributions: Parra-Blanco A designed the research; Parra-Blanco A, Arnau MR, González N, Díaz-Acosta JA, Nicolás-Pérez D and Gimeno-García AZ performed the research; Parra-Blanco A, Jiménez A and Quintero E analyzed the data; Parra-Blanco A, Arnau MR and Quintero E drafted the manuscript; all authors read and approved the final manuscript.
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Correspondence to: Adolfo Parra-Blanco, MD, PhD, Head of the Endoscopy Unit, Department of Gastroenterology, Asturias Central University Hospital, Celestino Villamil s/n, 33006 Oviedo, Principado de Asturias, Spain. parrablanco@hotmail.com
Telephone: +34-985-108000 Fax: +34-985-108115
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Abstract

AIM: To test a strategy for endoscopic submucosal dissection (ESD) training in animal models designed to overcome the initial learning curve.

METHODS: ESD was attempted in *ex vivo* and *in vivo* pig models. Thirty ESD procedures were attempted in the esophagus (n = 9) or the stomach (n = 21). The *ex vivo* model was used until initial competence was achieved. In the *in vivo* model, several ESD procedures were performed in up to 3 sessions. The following variables were analyzed: specimen size, complete and *en bloc* resection rate, time for circumferential incision, time for submucosal dissection, total ESD duration, and complications.

RESULTS: Complete resection was achieved in 28 cases (*en bloc* 27); 2 could not be completed (one perforation, one technical difficulty). The mean ± SD time for circumferential incision was 36.2 ± 16.8 min (range: 8-87 min), and the mean ± SD time for submucosal dissection was 45.1 ± 35.7 min (range: 9-196 min). The mean ± SD size of the resected specimens was 45.2 ± 17.8 mm. The mean ± SD total resection time was significantly increased for the gastric cases performed in the first half of the study (n = 13) than in the second half (n = 8) (98.9 ± 62.4 min *vs* 61.7 ± 17.6 min, P = 0.04), although the specimen size did not differ.

CONCLUSION: Training in animal models could help endoscopists overcome the learning curve before starting ESD in humans.

Key words: Endoscopic submucosal dissection; Training; Animal model

Peer reviewers: Grigoriy E Gurvits, MD, Department of Gastroenterology, St. Vincent's Hospital and Medical Center, New York Medical College, 153 West 11th Street, Smith 2, New York, NY 10011, United States; Yuk-Tong Lee, MD, Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is an emerging technique for the treatment of early digestive neoplasms *en bloc*, which was developed in Japan and has been proven efficacious and safe in expert hands[1,2]. However, the applicability of ESD in Western countries is still unclear for several reasons. First, the most frequent indication for ESD is early gastric cancer, which is a common finding in Japan but rare in the Western world[3]. Second, ESD is a very operator-dependent technique, and a learning curve exists; it has been estimated that 30 gastric cases need to performed under the supervision of an expert to overcome this learning curve[4,5]. For endoscopists at the beginning of the learning curve, the perforation rate can reach 20%, especially in the colon. Third, colorectal ESD could probably become a frequent indication for ESD in Western countries, but that is the most difficult location in which to perform ESD[6]. Although experts have suggested that ESD should be carried out in pigs before starting to apply it in humans - especially when it is performed without the supervision of an expert - there is no full published study reporting the results of ESD in pigs as a part of the training for this difficult therapeutic procedure[5]. Our hypothesis is that the strategy of learning ESD from experts, followed by training in harvested pig stomachs and then in live pigs, may be useful for overcoming the learning curve. The aim of our study was to prospectively determine the results, efficacy, and safety of ESD performed in pigs by an endoscopist at the beginning of the learning curve prior to its application in humans.

MATERIALS AND METHODS

Prior learning

One author (Parra-Blanco A) spent 1 mo (November 2006) at the National Cancer Center Hospital (NCCH), Tokyo, where he observed approximately 25 cases of ESD (esophageal, gastric, and colonic). He also performed 7 gastric ESD procedures in harvested stomachs under the supervision of an expert. The results of these procedures were not recorded, but all of them were gastric resections with an approximate greater diameter of the resected specimen of 3 cm.

Animal models

***Ex vivo* model:** A model for training in isolated esophaguses and stomachs, similar to the one previously used at the NCCH, was prepared at the first author's institution. A plastic box (40 cm × 25 cm × 15 cm) was used that had a 15 mm in diameter hole in one of the short sides. Stomachs with the whole esophagus attached were obtained from female, 70 kg, domestic pigs. They were washed vigorously with lukewarm water and a mucolytic (10% N-acetyl-cysteine). The stomach was laid on a metal plate inside the plastic box. An overtube was introduced into the hole and then inserted into the esophagus. Plastic clamps were employed to tighten the esophagus to the overtube and prevent it from sliding with the movements of the endoscope.

A dedicated endoscope was used (Fujinon EG-200HR) for all procedures in this study.

***In vivo* model:** Live, *Sus scrofa,* female, 30 kg, domestic pigs were used. The pigs fasted for 48 h prior to the procedure, and clear liquids were allowed *ad libitum*. Intramuscular (im) ketamine (11 mg/kg) was administered as a premedication. Induction was accomplished with intravenous (iv) propofol (16 mg/kg) and inhalation anesthesia with isoflurane.

When the procedure was finished, im buprenorphine (0.01-0.04 mg/kg) and iv omeprazole (40 mg) were administered. After ESD, the pigs only had clear liquids for 24 h, hypercaloric enteral nutrition solution for the next 24 h, and then fodder. Esomeprazole (40 mg) *per os* was given daily until the sacrifice of the pigs.

Each pig could be subjected to general anesthesia a maximum of 3 times, with an interval of 2 wk between sessions. One to 3 ESD procedures were performed during each session at the endoscopist's will, depending on the duration of the procedures. The pigs were monitored by the veterinary staff for signs of sepsis, distress, pain, and changes in feeding habits or behavior. The animals were sacrificed either at the end of the third session or at any time before that in the event of complications that could not be easily managed endoscopically.

The study was approved by the Animal Study Committee of our university.

Endoscopic procedures

All endoscopic procedures were carried out by a single experienced endoscopist (Parra-Blanco A). During each session, both with the harvested stomach and the live pig, he performed as many ESD procedures as desired, although a maximum limit of 5 h for the whole session was set. The ESD technique applied was basically similar to the one generally performed at the NCCH. ESD was attempted in the gastric body or the antrum of the stomach, excluding the fundus and the subcardial area. In the esophagus, generally the middle portion was selected, avoiding the esophago-gastric junction.

A needle knife (Olympus, KD 10Q-1) was usually used for the marking of the periphery of the selected area and the initial cut. After submucosal injection of fluid (10% glycerin) to raise the submucosal layer, at least 2 cuts were made usually at the 12 and 6 o'clock positions on the endoscopic image 5-10 mm away from the marking line. The insulated-tip (IT) knife (Olympus KD-610L, Tokyo, Japan) was generally used for the circumferential cutting of the mucosa surrounding the lesion and the dissection of the submucosal layer under the lesion. However the endoscopist could switch to any of the other devices: needle knife, Flex knife (Olympus KD-630L, Tokyo, Japan), and Hook knife (Olympus

KD-620 LR, Tokyo, Japan). For the dissection phase, a transparent hood was used (Olympus D-201-12704, Tokyo, Japan). Snaring of the partially dissected mucosa was considered only as the last choice in cases in which it was not possible to resect the lesion *en bloc* with the other devices. The Erbotom ICC 200 ERBE system was used (ERBE, Elektromedizin GmbH, Tübingen, Germany) as a high-frequency generator.

In both models, the resected specimens were pinned on a cork and then measured.

The following variables were prospectively recorded: (1) location of the targeted area (esophagus *vs* stomach); (2) endoscopic accessories employed; (3) time required from the marking until the end of the circumferential incision (circumferential cutting); (4) time from the end of the circumferential cutting until the end of the dissection (submucosal dissection); (5) size of the resected specimen; (6) completeness of the resection (complete *en bloc*, complete piecemeal, incomplete); and (7) complications (immediate bleeding, delayed bleeding that occurred after completion of the ESD, open perforation, and nontransmural damage to the proper muscle layer when electrocoagulation produced a distinct depression in that layer but without any open perforation).

Statistical analysis

A global χ^2 test was used to compare qualitative data. Continuous variables were compared with the nonparametric Mann-Whitney *U* test, and mean ± SD are reported. Calculated P values < 0.05 were considered to indicate statistical significance.

RESULTS

Thirty ESD procedures were carried out, 8 in the *ex vivo* model (esophagus 2, stomach 6) in 6 harvested organs and 22 in the *in vivo* model (esophagus 7, stomach 15) in 6 live pigs, during a 51 wk period (0.57 ESD/wk). Specific technical aspects corresponding to the 30 cases, including the types of knives employed, are presented in Table 1.

The mean ± SD time to perform the circumferential incision was 36.2 ± 16.8 min (range: 8-87 min), and the mean ± SD time to perform the submucosal dissection was 45.1 ± 35.7 min (range: 9-196 min). One procedure had to be stopped before completion because of a technical difficulty (case 20). This and another case in which a large perforation occurred were the only 2 cases of incomplete resection. Therefore, the resection was complete in 28/30 (93.3%). In 2 cases, the dissection had to be completed with a snare; this resulted in a piecemeal resection in one of these cases (case 12). Therefore *en bloc* resection was achieved in 90% (27/30) cases. Prophylactic hemostasis was conducted on the post-resection ulcer in 16/22 (72.7%) cases in the live pig model (with the IT knife or Flex knife). The mean ± SD size of the resected specimens was 45.2 ± 17.8 mm (22-116 mm). Table 2 presents results of the ESD procedures performed in the *ex vivo* and *in vivo* models.

When the first half of the cases was compared with the second half, no significant difference in the duration of the procedures was observed (93.1 ± 59.9 min *vs* 70.1 ± 24.6 min, P = 0.34). However, when only the gastric cases were considered, the mean ± SD time required from the end of the circumferential cutting until the end of the dissection was significantly longer in the gastric cases performed in the first half of the study (n = 13) than in the second half (n = 8) (58.6 ± 47.8 min *vs* 25.2 ± 11.4 min, P = 0.025). The mean ± SD total time for the resection was also significantly increased in the initial 13 gastric cases compared to the last 8 cases (98.9 ± 62.4 min *vs* 61.7 ± 17.6 min, P = 0.045). However, the size of the resected gastric specimens did not differ between cases performed during the first *vs* the second half of the study (49.3 ± 23.1 mm *vs* 50.1 ± 10.7 mm, respectively, P = 0.34).

Comparison of the gastric cases revealed that the mean total procedure times for the 6 *ex vivo* cases, the first 8 *in vivo* cases, and the last 7 *in vivo* cases were not significantly different. The mean sizes of the resected specimens also did not differ among the groups (Table 2).

In the *ex vivo* model, the locations of the resected areas were the lesser curvature (n = 4) and the greater curvature (n = 2). In the first 8 *in vivo* cases, the locations of the resected areas were the lesser curvature (n = 1), greater curvature (n = 6), and anterior wall (n = 1), and in the last 7 *in vivo* cases, the locations were the lesser curvature (n = 2), greater curvature (n = 3), and anterior wall (n = 2).

Comparison of the esophageal cases revealed that the mean total procedure times for the 2 *ex vivo* cases, the initial 3 *in vivo* cases, and the last 4 *in vivo* cases were 55.0 ± 7.1 min, 98.7 ± 23.2 min, and 65.5 ± 26.5 min, respectively, without significant differences among the groups (Table 2).

Complications

In 5/22 (22.7%) cases there was bleeding requiring coagulation with hot biopsy forceps, and all were easily managed without hemodynamic instability. There was nontransmural damage to the muscular layer in 4/9 (44.4%) esophageal cases and in 3/21 (14.3%) gastric cases, which was generally closed with clips. In the fourteenth case, a large upper gastric perforation occurred when the Hook knife was being used, requiring animal sacrifice. The only complication observed during follow-up was one case of esophageal stricture, which was easily dilated endoscopically.

One pig died 1 wk after undergoing gastric and esophageal ESD procedures; a necropsy showed signs consistent with cardiac tamponade, apparently unrelated to the endoscopic resections.

DISCUSSION

ESD is an emerging technique that allows for safe and effective *en bloc* resection of gastrointestinal neoplasms in expert hands[7]. However, it is technically demanding and, therefore, very operator-dependent. In Japan and some other Asian countries, training in this technique relies on supervision by experts, who take over the examination

Table 1 Technical details of the 30 ESD procedures

	Model type	Organ	Type of knife	Specimen size (mm)	Procedure duration (min)		Immediate complications
					CC	D	
1	EV	Stomach	NN + IT	31	28	46	-
2	EV	Stomach	NN + IT	35	23	28	-
3	EV	Esophagus	NN	28	15	35	-
4	EV	Stomach	NN + IT	35	56	33	-
5	EV	Esophagus	NN + IT	31	44	16	NDML
6	EV	Stomach	FN	38	35	23	-
7	EV	Stomach	FN + IT	48	25	60	NDML
8	EV	Stomach	FN + HN	49	35	45	NDML
9	IV	Stomach	FN + IT	48	25	80	-
10	IV	Stomach	NN + IT	67	15	30	NDML
11	IV	Stomach	NN + IT	41	57	23	-
12	IV	Stomach	NN + IT + S	37	38	24	Bleed
13	IV	Stomach	NN + IT	116	60	83	Bleed
14	IV	Stomach	NN + FN + HN + IT	-[1]	87	196	Perforation
15	IV	Stomach	NN + IT	45	40	91	Bleed
16	IV	Esophagus	NN + FN + HN + IT	45	39	42	-
17	IV	Esophagus	FN + IT	50	55	70	NDML
18	IV	Stomach	NN + IT	45	28	9	-
19	IV	Esophagus	FN + IT	53	42	48	Bleed
20	IV	Stomach	NN + IT	-[1]	47	26	-
21	IV	Stomach	NN + IT	54	43	27	-
22	IV	Stomach	NN + IT	62	49	27	-
23	IV	Esophagus	NN + FN + HN + IT	32	28	27	-
24	IV	Stomach	NN + IT	62	45	16	-
25	IV	Stomach	NN + IT	45	20	17	-
26	IV	Esophagus	NN + FN + IT	22	8	25	-
27	IV	Esophagus	NN + IT + S	35	17	73	NDML
28	IV	Stomach	FN + IT	51	35	45	Bleed
29	IV	Esophagus	FN + IT	30	32	52	NDML
30	IV	Stomach	NN + IT	32	15	35	-

[1]Resection was not completed, and therefore, no specimen was pinned or measured. ESD: Endoscopic submucosal dissection; EV: *Ex vivo*; IV: *In vivo*; NN: Needle knife; IT: Insulated-tip knife; HN: Hook knife; FN: Flex knife; S: Snare; CC: Time from marking until circumferential cutting; D: Time from circumferential cutting until end of dissection; Bleed: Bleeding requiring hot forceps coagulation; NDML: Non-transmural damage of the proper muscular layer.

Table 2 Results of the 30 ESD procedures performed in the *ex vivo* model, *in vivo* model 1 (first 11 resections in the live pigs), *in vivo* model 2 (last 11 resections in the live pigs) (mean ± SD)

	n	Size (mm)	Time from marking until circumferential cutting (min)	Time from circumferential cutting until end of dissection (min)	Total time (min)	Proper muscle layer injury (*n*)	Open perforation (*n*)	Major bleeding (*n*)
Esophagus								
Ex vivo	2	29.5 ± 2.1	29.5 ± 20.5	25.5 ± 13.4	55.0 ± 7.1	1	0	0
In vivo 1	3	49.3 ± 4.0	45.3 ± 8.1	53.3 ± 14.7	98.7 ± 23.2	1	0	0
In vivo 2	4	29.7 ± 7.6	21.2 ± 10.9	44.2 ± 22.8	65.5 ± 26.5	2	0	0
Stomach								
Ex vivo	6	45.3 ± 8.5	33.7 ± 12.0	39.2 ± 13.7	72.8 ± 15.2	2	0	0
In vivo 1	8	57.0 ± 27.7	43.7 ± 23.3	67.0 ± 61.1	110.7 ± 79.5	1	1	0
In vivo 2	7	51.0 ±11.3	36.3 ± 13.6	27.6 ± 10.0	65.3 ± 15.7	0	0	0

when the trainees face technical difficulties or when serious complications (e.g. perforation) occur[5,8]. Because the technique is seldom practiced in Western countries, the best training strategy and the applicability of ESD remain unclear. Dinis-Ribeiro *et al*[9] have published results from an initial series of gastric ESD procedures performed in humans in a Western country. The ESD procedures in that study were performed by a single endoscopist who was trained in Japan, and animal training preceded application to human cases. However, the authors did not specifically describe the nature of the animal cases performed. Probst *et al*[10] reported 71 epithelial or submucosal lesions treated by ESD in a single German institution. They showed good results, with open gastric perforations in only 2 cases. The authors found a significant reduction in the procedural time in the second half of the cases; however this improvement might be also related to the training by a Japanese expert at that time. No previous animal training was described in this study.

In this study, we proposed a strategy for training in ESD in the absence of experts to supervise the procedures and ensure the patients' safety. In some previous studies, pig models have been used to investigate new methods for ESD[11-13]. A European study evaluated the usefulness of a new endoscope with a double channel[14]. Six expert endoscopists participated in this study, in which 17 ESD procedures were performed in live pigs and 10 in humans during the clinical part of the study. The mean number of resections per endoscopist in this study was less than 5 - less than the estimated 30 cases of ESD needed to overcome the learning curve - and the effect of learning was not assessed. Therefore, to our knowledge, ours is the first study to evaluate the usefulness of pig models for ESD training, including a significant number of cases. Vázquez-Sequeiros *et al*[15] recently described the use of porcine models similar to those employed in this study, prior to attempting a human gastric ESD which was successful.

Choi *et al*[4] showed that when prior knowledge of advanced resection techniques is limited and no supervision by an expert in ESD is available, there is a learning curve in which not only the *en bloc* resection rate and procedure duration improve with increasing experience but, more importantly, the perforation rate decreases too. However, the technique employed in that study was not really what is currently understood as ESD, because a snare was used to encircle the lesion after margin cutting. Therefore, it is likely that if the real ESD technique is applied without any previous experience or supervision by experts, the complication rate would be greater than what was reported by Choi *et al*[4]. Therefore, self-taught learning is not desirable[6]. On the contrary, there do not seem to be any differences in the perforation rates between trainees and experts when the former are supervised by the latter[8]. Hence, training in animal models may not be needed in Japanese institutions where supervision by experts is available.

The incidence of gastric cancer is higher in Japan compared to that in most Western countries, where the number of early gastric lesions detected is low[16]. In those countries, it could be expected that colorectal and esophageal lesions (mainly Barrett's dysplasia) could be a frequent therapeutic indication for ESD. Performing ESD in such locations is especially complex and technically demanding, with an increased perforation risk[7]. Training in animal models appears to be a compulsory step before attempting to perform ESD in the absence of experts, which is the current situation in Western countries. Otherwise, it can be expected that the development of ESD outside of Japan and neighbouring countries will be very limited. Besides, prior training in animal models may carry medico-legal implications, and such previous experience could support the idea that the endoscopist is fit to perform ESD.

Our results suggest that there exists a learning curve for ESD in animal models. In the gastric cases, the time required for dissection was significantly reduced in the second half of the study, although the sizes of the resected specimens were similar. A large perforation occurred in one of the live pigs in our study, for which suture by clipping was considered impossible. Had such a large perforation occurred in a real patient, emergent surgery would certainly have been required.

In our strategy, we included previous learning from world experts in ESD, although the effect of that variable was not been tested in our study. Training in pigs could be started without such previous learning. However, there are certain technical tricks and tips that are difficult to learn by oneself, and ESD involves manoeuvres that traditionally have not been used during flexible endoscopy, such as the lateral cutting. Thus, to achieve the ability to perform ESD safely in humans, we believe that learning from experts is a must. Other possible strategies would be to organize training courses (with animal and/or human training) under the supervision of experts, or to attempt ESD procedures supervised by means of a videoconference. We have carried out both actions in our department, but its impact on ESD performance has yet to be reported.

The main limitation of our study may be the fact that the effect of training was assessed only in animal models; thus, there is no description of results from when the technique is applied in humans by the same endoscopist. The endoscopist who performed the cases in the present study has performed thereafter 6 cases in humans (5 gastric, 1 rectum) without any serious complication. A greater number of cases in humans has to be performed and the results monitored in order to determine the usefulness of ESD training with the strategy described in this study.

Although the endoscopic manoeuvres are certainly similar, regardless of whether a human or a pig is being endoscoped, there are several differences between the pig and human stomach that may contribute to technical differences. Firstly, it is accepted that bleeding in the pig is more infrequent and subtle. Secondly, the pig's mucosal layer appears to be thicker, as suggested by the fact that the submucosal injection frequently becomes very difficult to accomplish. Thirdly, as normal mucosa is resected in the pig model, no significant fibrosis is expected to be encountered during pig ESD. In contrast, fibrosis is a relatively frequent finding during ESD in humans, which makes the procedure more challenging. Fourthly, *ex vivo* and *in vivo* models were analyzed together in our study, and there might be certain peculiarities related to the 2 different models that could have influenced our results. However, our *ex vivo* model was prepared just a few hours after the animal was sacrificed. This is in contrast to some *ex vivo* models that are prepared after having kept the stomach frozen, which makes the tissue harder and probably more difficult to resect. Moreover, the sizes of the organs in the *ex vivo* models were quite larger than those in the *in vivo* models, as the former organs were obtained from 70 kg pigs and the latter, from 30 kg pigs. It was our impression that in the cases involving large *ex vivo* stomachs (which more closely resembled real human stomach), it was much easier to approach the lesser curvature. However, in the cases involving small *in vivo* stomachs, the lesser curvature was short and difficult to approach adequately with the gastroscope. For that reason, more areas in the greater curvature were targeted in the *in vivo* cases.

In order to fully understand the usefulness of *ex vivo* and *in vivo* models, future studies should compare the results of ESD performed in similarly sized stomachs in *ex vivo* and *in vivo* models.

Lastly, 7 gastric ESD procedures performed in the *ex vivo* model by the author supervised by the Japanese experts were not included in this study, as they were not videotaped or the procedure times registered. As they were done at the beginning of the learning curve, they were especially time consuming. Had those cases been included, the evidence of a learning curve might have been stronger.

In conclusion, ESD is a technically challenging procedure and there seems to be a learning curve, as suggested by this study. As potentially serious complications can occur in the absence of local expertise, it should probably not be applied to humans by endoscopists without any previous animal training. The learning strategy described provided good results in terms of efficacy and safety, as a prior step to its application in humans.

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COMMENTS

Background

Endoscopic submucosal dissection (ESD) allows for *en bloc* resection of early neoplasms in the gastrointestinal tract. However, it is associated with a high rate of perforations, and it should be learnt from experts. In the absence of experts in western countries, practising in animal models may be helpful to overcome the learning curve.

Research frontiers

The results of large series of ESD in humans after previous training with animal models have to be clarified.

Innovations and breakthroughs

In this study, a strategy was proposed for ESD training, which included visiting an expert center, and then practicing gastric and esophageal ESD on *ex vivo* and finally on *in vivo* porcine model. The results of these ESDs were analyzed. The number of cases included was 30, as this is considered to represent the workload required to overcome the initial learning curve.

Applications

Complete resection was achieved in 93% cases. The dissection phase was the most time consuming, and as suggested by other studies this seems to be the most challenging for beginners. There seems to be a learning curve for gastric ESD when this training model is applied; therefore it would be justified to start training on animal models instead of on real patients, if experts are not available to supervise the procedures.

Terminology

Endoscopic submucosal dissection: this is an endoscopic method for complete *en bloc* resection of early gastrointestinal neoplasms, whose major drawback is that it is technically challenging and associated with a significant risk of complications mainly during the learning curve.

Peer review

It is a useful, structured experiment to demonstrate the effectiveness of using a pig model for ESD training. It showed technical skill of ESD could be improved by practice in the pig. It provides an alternative way to learn ESD in the future.

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