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A deep learning-based system for mediastinum station localization in linear EUS (with video)

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ABSTRACT

Background and Objectives: EUS is a crucial diagnostic and therapeutic method for many anatomical regions, especially in the evaluation of mediastinal diseases and related pathologies. Rapidly finding the standard stations is the key to achieving efficient and complete mediastinal EUS imaging. However, it requires substantial technical skills and extensive knowledge of mediastinal anatomy. We constructed a system, named EUS-MPS (EUS-mediastinal position system), for real-time mediastinal EUS station recognition.

Methods: The standard scanning of mediastinum EUS was divided into 7 stations. There were 33 010 images in mediastinum EUS examination collected to construct a station classification model. Then, we used 151 videos clips for video validation and used 1212 EUS images from 2 other hospitals for external validation. An independent data set containing 230 EUS images was applied for the man-machine contest. We conducted a crossover study to evaluate the effectiveness of this system in reducing the difficulty of mediastinal ultrasound image interpretation.

Results: For station classification, the model achieved an accuracy of 90.49% in image validation and 83.80% in video validation. At external validation, the models achieved 89.85% accuracy. In the man-machine contest, the model achieved an accuracy of 84.78%, which was comparable to that of expert (83.91%). The accuracy of the trainees' station recognition was significantly improved in the crossover study, with an increase of 13.26% (95% confidence interval, 11.04%-15.48%; P < 0.05).

Conclusions: This deep learning–based system shows great performance in mediastinum station localization, having the potential to play an important role in shortening the learning curve and establishing standard mediastinal scanning in the future.

Key words: EUS; Mediastinum; Training; Deep learning

INTRODUCTION

EUS is one of the significant breakthroughs in the field of advanced endoscopy.^[1] The extent of endosonographic assessment allows for the evaluation of the mediastinal anatomy (the mediastinum is an anatomic region located between the lungs and contains various vascular structures, organs, and lymph nodes, LNs).^[2,3] The mediastinal scanning under EUS has provided a valuable chance for minimally invasive vascular intervention, pathological sampling of lymph nodes that endobronchial ultrasound cannot reach, and

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staging of central malignant lung lesions (accuracy 89%).^[4,5] With the evolution of EUS-guided diagnostic and interventional procedures, it is vital to master the mediastinal anatomy during the EUS examination.

Multistation approach has been proposed to ensure the critical areas and landmarks can be comprehensively evaluated during EUS mediastinal examination.^[6,7] Endosonographic scanning of the mediastinum can be divided into 7 stations: station 1: inferior vena cava, station 2: celiac trunk, station 3: cardiac atrium, station 4: thoracic aorta, station 5: right pulmonary artery, station 6: aortopulmonary, and station 7: aortic arch/common carotid artery. The key principle in achieving efficient and complete linear EUS imaging in the mediastinum is rapidly finding the standard stations and then using these locations as a grand landmark for determining the structure within the current station and the subsequent operation.

However, as an advanced endoscopic procedure, EUS examination requires substantial technical skill and extensive knowledge of mediastinal anatomy.^[8] The examination technique consists of fundamental manual skills, including echoendoscope manipulations and effective rotation and knowledge of the anatomical landmarks to achieve the optimal position.^[9] Although the linear EUS offers the capability of puncture, the narrow field of view makes the evaluation more challenging. Therefore, the use of EUS has been limited because of a shortage of adequately trained physicians. Most experienced sonographers believe that the key to acquiring competence in EUS procedure is pattern recognition obtained through repetitive examinations. However, the resources for clinical practice are limited, and thus, an automatic system for station recognition and operation is needed when performing EUS mediastinal examination and training.

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In recent years, artificial intelligence (AI) has achieved tremendous progress in EUS.^[10,11] Previous work from our group showed that the endoscopists' capability of ultrasonographic interpretation can be significantly improved with deep learning–based system for both pancreatic and biliary EUS scanning.^[12,13] However, the role of deep learning in EUS mediastinal examination remains unknown. Although the EUS assumes importance in the routine diagnosis, treatment, and follow-up of diseases of the mediastinum, it is vital to explore the role of deep learning in mediastinal ultrasonographic interpretation.

In our current study, we constructed a deep learning–based system, named EUS-MPS (EUS–mediastinal position system), for real-time mediastinal EUS station recognition. Such a system was followed by internal validation both in images and videos and external validation in images and subsequently compared with the performance of EUS endoscopists. The effect of the EUS-MPS system on eliminating the difficulty of ultrasonographic interpretation was evaluated among trainees using consecutively prospectively collected EUS videos. The purpose of this study is to explore the role of deep learning in linear EUS mediastinal scanning.

MATERIALS AND METHODS

Development of the EUS-MPS system

The EUS-MPS system for linear EUS mediastinal station localization was designed to achieve 3 functions, which are respectively implemented by 3 DCNN models. First, DCNN1 was applied to filter out white light images and input the ultrasound images to DCNN2. Upon receiving these ultrasound images, DCNN2 classified them into standard and nonstandard categories and activated DCNN3 with standard images. Then DCNN3 divided these images into 7 standard mediastinal stations (station 1: inferior vena cava, station 2: celiac trunk, station 3: cardiac atrium, station 4: thoracic aorta, station 5: right pulmonary artery, station 6: aortopulmonary, and station 7: aortic arch). The EUS-MPS workflow chart is shown in Figure 1.

Data preparation and preprocessing

For EUS-MPS system training and internal validation, ultrasound images of patients 18 years and older who received mediastinal EUS examinations were collected from Wuhan Fourth Hospital. Patients with pancreatic and biliary diseases such as pancreatic cancer were excluded from this study. Independent image data set used for the man-machine contest and video data set used for video validation and crossover study were also retrospectively collected from Wuhan Fourth Hospital. In addition, ultrasound images from Renmin Hospital of Wuhan University and Wuhan Union Hospital were collected as an external validation set. The format and criteria were the same as those of the previous data set. Specifically, the following data sets were used for the construction of the EUS-MPS system.

For DCNN1 training and validation, we used 2000 white light images of gastroscopy and 2000 EUS images to classify the white light images and EUS images at a 9:1 ratio; 100 white light images and 100 EUS images were used as external validation set; 32 905 standard station and 21,724 nonstandard EUS images were used to construct DCNN2 for nonstandard image filtering, among which 30 182 standard station and 19 888 nonstandard EUS images were used as the train set; 2723 standard station and 1836 nonstandard EUS images were used to test DCNN2; 1287 standard station and 1451 nonstandard EUS images were used as an external validation set. The criteria for unqualified images were jointly negotiated by 2 EUS experts, including obscure, large lesions, pancreas, kidney, spleen, abdominal aorta, enhanced ultrasound, radial EUS, and elastography. Representative images of the nonstandard images are shown in Figure S1, http://links.lww. com/ENUS/A331.

Five data sets were used for training, internal validation, and external validation:

- (1) 30 182 images from 156 EUS procedures were used to train the model for mediastinal stations (DCNN3). All the images were from Wuhan Fourth Hospital during July 2011 to October 2021;
- (2) 2828 images from 105 EUS procedures from Wuhan Fourth Hospital during July 2011 to October 2021 were used for internal validation; 151 video clips from the same procedures were applied for station recognition video validation;
- (3) 230 images from 35 EUS procedures from Wuhan Fourth Hospital during February 2021 to October 2021 were used



Figure 1. Workflow chart of the EUS-MPS. DCNN1 was applied to filter out white light images. DCNN2 classified ultrasound images from DCNN1 into standard and nonstandard categories and activated DCNN3 with standard images. DCNN3 divided these images into 7 standard mediastinal stations. EUS-MPS, EUS-mediastinal position system.

to compare the performance of DCNN3 with that of EUS endoscopists (man-machine contest); and

(4) for the external validation, an external testing data set contained 1212 images from 19 examinations (Wuhan Union Hospital), and 26 examinations (Wuhan Renmin hospital) were collected.

The mediastinal stations and their representative images predicted by the DCNN models are shown in Figure 2. All images for a single patient were assigned to exactly one of these data sets.

Image and video clip annotation

The images and video clips in the training, internal, and external validation sets were annotated by 2 EUS expert endoscopists, A and B, using a negotiation process. When the 2 experts disagreed,



Figure 2. The representative images of mediastinal stations. Station 1: inferior vena cava; station 2: celiac trunk; station 3: cardiac atrium; station 4: thoracic aorta; station 5: right pulmonary artery; station 6: aortopulmonary; station 7: aortic arch.

a third expert, C, carried out the arbitration. Their labels were used as the criterion standard for all the training and validation. For the man-machine contest, expert D, senior endoscopists E and F, and junior endoscopists H and G were required to classify each image in the comparison data set. Both endoscopists' and models' results were compared with ground truth annotated by experts A, B, and C. For annotators' level of expertise, expert endoscopists were defined as those who had at least 10 years, senior endoscopists were defined as those who had more than 1 year of experience in performing EUS scanning.

Training algorithm of DCNN models

In this study, an architecture called ResNet-50 (IEEE; Seattle, WA), which is a classic framework and most widely used in the ResNet family to solve complex image classification tasks, was used for image classification.^[14] We trained all our models on a NIVIDIA GeForce GTX 3080 (NVIDIA, Santa Clara, California, USA), and the detailed network architectures are illustrated in the Supplementary Data, http://links.lww.com/ENUS/A336. ResNet-50, a state-of-the-art DCNN architecture pretrained by data from ImageNet (1.28 million images from 1000 object classes), was used to train DCNN1, DCNN2, and DCNN3. We replaced the final classification layer with another fully connected layer using transfer learning^[15] and then used our data sets to retrain them and fine-tune the parameters to fit our needs. The data set was randomly divided into 5 subsets, and the size of the image was adjusted to 224×224 pixels. Then one subset was validated individually with the remaining for training in Google's TensorFlow (Google, Santa Clara, California, USA). Moreover, to minimize the overfitting risk, we used dropout, data augmentation, and early stopping.[16,17]

Construction of the deep learning system

To smooth noises, the rule of "output results only when 7 of the 10 consecutive images show the same result" was used for station recognition prediction. We ran the system in videos on a graphics processing unit (GPU) at 4.78 FPS (frames per second). The DCNN output a prediction per frame in the clinical setting every 200 to 300 milliseconds, including the time consumed in the client (image capture, image resizing, and rendering images based on predicted results), network communication, and the server (reading and loading images, running the 3 networks, and saving images). All the models were trained and ran on a server with a GPU NVIDIA RTX2080Ti (with 8 GB GPU memory).

Mediastinal ultrasonographic crossover study

Thirty video clips from 21 mediastinal EUS procedures from Wuhan Fourth Hospital during October 2021 to November 2021 were prospectively consecutively collected to evaluate the effectiveness of the EUS-MPS in reducing the difficulty of mediastinal ultrasound image interpretation. Each participant in our tests was under informed consent. The study was approved by the ethics committee of Wuhan Fourth Hospital (KY 2020-001-01). Patients with lower gastrointestinal EUS, radial EUS, contrast-enhanced EUS, or no standard station scanned were excluded from this study.

We conducted a crossover study using the above prospectively collected videos, and then 12 trainees and 2 junior endoscopists (all with more than 1-year gastroenterology fellowship experience, but none with any experience or training in EUS) were included to evaluate the effectiveness of the EUS-MPS in improving the trainees' ability to recognize mediastinal station positions. Before conducting the reader study, all participants were required to study references about mediastinal multistation scanning and 20 typical images of each station 1 week in advance.

We divided the trainees into 2 groups randomly (generated by a random grouping software) and equally using a crossover design. Specifically, the videos without EUS-MPS augmentation were first to read in group A, those with EUS-MPS augmentation were first to read in group B, and the reading order of the 2 groups was reversed after a 2-week washout period. The details are shown in Figure 3. All readers were asked to record the point in time when they first recognized each standard station while watching each video. They can choose to consider or disregard it based on their own judgment with the model augmentation. Meanwhile, the time point and accuracy at which the EUS-MPS first recognized each station were also recorded.

Statistical analysis

We used accuracy, which was defined as the number of correctly classified images divided by the total number of images to evaluate the performance of our model. The SD was calculated as follows:

$$\mathrm{SD} = \sqrt{\frac{1}{\mathrm{N}} \sum_{t=1}^{\mathrm{N}} (x_i - u)^2}.$$

Cohen κ coefficient was used to evaluate interobserver and intraobserver agreement of the endoscopists and intraobserver agreement of the DCNN in the man-machine contest. For the crossover study, we compared the time point accuracy for each trainee with or without augmentation. The accuracy of the trainees' station recognition in the crossover study is the primary endpoint. Sample size calculation was based on comparing the accuracy station prediction in a paired design. We assumed that the accuracy of a physician without AI was approximately 75%, and a physician with AI was approximately 80% based on the results of the preliminary evaluation. For proportion comparison, with a power of 80% and type I error rate of 0.05, a volume of at least 12 physicians will be included in this study. Moreover, McNemar test with a significance level of .05 was performed to assess whether the 14 trainees achieved significant increases in performance with model augmentation. All calculations were performed using SPSS 25 (IBM Corp, Chicago, Illinois).

RESULTS

Performance of DCNN models in image and video validation

The accuracy of DCNN1 in white light image and EUS image classification achieved 100%, and it showed an accuracy of 100% in external validation. Figure S2, http://links.lww.com/ENUS/A332, shows the confusion matrices of DCNN1 in the test set and external validation set. The accuracy of DCNN2 in standard and nonstandard image classification achieved 98.7%, and it showed an accuracy of 97.63% in external validation. Figure S3, http://links.lww.com/ENUS/A333, shows the confusion matrices of DCNN2 in the test set and external validation set. For the classification of mediastinal standard station images, the overall accuracy rates of DCNN3 on the internal and external image validation sets were 90.49% and 89.85%, respectively [Table 1]. The specific accuracy of each station is shown in Table 2, and the confusion matrices of DCNN3 on internal and external validation are shown in Figure S4, http://links.lww.com/ENUS/A335, respectively.

In the video validation set, the model had a per-frame accuracy of 83.80%, which is shown in Table 2. In addition, the accuracy rates for stations 1 to 7 in the video validation set were 86.46%, 96.99%, 80.81%, 88.27%, 71.76%, 83.88%, and 88.07%, respectively. Video demonstration of the EUS-MPS system is shown in Video 1.

Comparison between the performance of the EUS-MPS and endoscopists

Table 3 shows the predictions of the DCNN3 and endoscopists for identifying 7 standard stations in the testing data set for the man-machine contest. As shown in Table 3, it correctly classified the mediastinal stations with an accuracy of 84.78%. The accuracy rates for expert D and endoscopists E, F, H, and G were 83.91%, 73.04%, 79.57%, 66.09%, and 67.83%, respectively. The inter-observer agreement between DCNN3 and the experts is shown in Table S1, http://links.lww.com/ENUS/A337.

Performance of individual trainees in the crossover study

Trainees achieved a time point accuracy of 70.76% without augmentation, whereas the accuracy achieved 84.02% with augmentation in



Figure 3. Flowchart of the crossover study. The videos without EUS-MPS augmentation were first to be read in group A; those with EUS-MPS augmentation were first to be read in group B, and the reading order of the 2 groups was reversed after a 2-week washout period. EUS-MPS, EUS-mediastinal position system.

Table 1 Baseline information and sample distribution.

			Те			
	Training set (frames)	Internal validation set (frames)	Video validation set (video clips)	Man-machine contest set (frames)	External validation set (frames)	Crossover study set (video clips)
Patients, n	156	105	38	35	45	21
Station 1	3446	355	21	28	117	23
Station 2	1803	260	27	16	246	24
Station 3	8907	750	33	32	304	25
Station 4	2403	281	13	30	138	20
Station 5	6001	348	15	53	160	22
Station 6	2966	278	22	21	130	24
Station 7	4656	451	20	50	117	22
Total	30 182	2828	151	230	1212	160

the reader study. With the augmentation of the EUS-MPS, the overall accuracy of the trainees increased from 70.76% to 84.02%, with an increase of 13.26% (95% confidence interval, 11.04%–15.48%; P < 0.05). The specific data can be found in Table 4.

DISCUSSION

In this study, we constructed a deep learning–based system for mediastinum station localization under linear EUS in real time. The EUS-MPS has been fully validated with both internal and external validation. In the man-machine contest, the EUS-MPS has achieved an expert comparable performance. With the augmentation of the EUS-MPS, the endoscopists have significantly improved their capability on mediastinal station recognition. The EUS-MPS has potential to remove the obstacle in mediastinal endosonography interpretation.

In recent years, interventional EUS and training competency for advanced endoscopy have been identified as 2 of the top 10 advances in gastrointestinal endoscopy.^[18,19] EUS has been widely used in mediastinum examination. Treatment of non–small cell lung cancer is stage dependent, and EUS helps sample lymph nodes at stations 4 L, 5, 7, 8, 9, as well as the celiac and the left adrenal nodes.^[20] A biopsy can also be safely performed on the primary lung tumors in a periesophageal location and those invading the mediastinum.^[21] EUS provides for biopsy of these enlarged nodes easily, safely, and with a high diagnostic yield. EUS is the most accurate locoregional staging modality for esophageal cancer with T stage and N stage accuracy rates of 75% to 85% and 65% to 75%, respectively.^[22] Despite increasing worldwide enthusiasm for EUS and its expanding applications, the path to attaining proficiency is long and arduous. It is considered one of the most technically challenging procedures for the endoscopist to learn, as it requires the development and mastery of ultrasonographic interpretative skills, which means operators must become familiar with normal and diseased anatomical patterns based on ultrasonographic images.^[23,24] The American Society of Gastrointestinal Endoscopy guidelines states that a minimum of 225 procedures are needed to achieve competence, whereas the European Society of Gastrointestinal Endoscopy states that 300 procedures were needed instead.^[25] However, such experience can be acquired only at a training center performing a large volume of cases, and few centers are able to provide this experience. Thus, training of novice doctors is a huge challenge in areas with limited resources. Although various simulators are available to alleviate this problem, there are also deficiencies with using simulator training because of lack of fidelity.^[26] Nevertheless, high skills in obtaining clear lesion images are necessary for endoscopists to maintain a high diagnostic accuracy in clinical practice. The ability to proficiently and safely perform EUS and accurately interpret endoscopic image results is an important indicator to evaluate the level of endoscopists.^[25] As we all know, knowledge of anatomy and radiology is essential to better perform EUS operations and understand images under EUS, especially in an anatomically complex area such as the mediastinum.^[2]

At present, deep learning has been widely applied in the medical field, and previous work by our team has shown that DCNNs can improve the detection of lesions and avoid blind spots in gastrointestinal endoscopy.^[27,28] In the field of EUS, our deep learning–based pancreas segmentation and station recognition system BP Master (Wuhan ENDOANGEL Medical Technology Co., LTD Company, Wuhan, Hubei, China) could help the endoscopists better understand

Table 2

	DCNN3 station recognition accura	cv ((95% confidence interva	l) in interna	I. video	 and external validation
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	Internal validation	Video validation	External validation
Station 1	92.39 (89.16–94.72)	86.46 (81.54–91.38)	80.34 (76.22-86.53)
Station 2	89.62 (85.32-92.77)	96.99 (92.65-101.33)	99.59 (97.73-99.93)
Station 3	98.80 (97.74–99.37)	80.81 (75.67–85.95)	95.72 (92.82–97.48)
Station 4	87.90 (83.57–91.21)	88.27 (83.53–93.01)	86.23 (79.49–91.00)
Station 5	91.95 (88.61–94.37)	71.76 (66.32–77.20)	83.75 (77.25–88.66)
Station 6	93.17 (89.58–95.58)	83.88 (78.91–88.85)	86.15 (79.17–91.06)
Station 7	95.57 (93.26-97.11)	88.07 (83.19-92.95)	80.34 (72.22-86.53)
Average	90.49 (89.35–91.52)	83.80 (78.72–88.88)	89.85 (88.02–91.43)

DCNN3, standard mediastinal stations classification.

Table 3

Different performance of the DCNN3 versus endoscopists (accuracy, %).								
	Station 1	Station 2	Station 3	Station 4	Station 5	Station 6	Station 7	Total
EUS-MPS	100	61.54	81.59	86.21	97.78	72.73	85.11	84.78
Expert D	82.61	73.08	92.11	89.66	86.67	72.73	82.98	83.91
Endoscopist E	91.30	65.38	81.59	86.21	35.56	90.91	80.85	73.04
Endoscopist F	91.30	92.31	86.84	86.21	60.00	81.82	74.47	79.57
Endoscopist H	86.96	84.62	47.37	82.76	60.00	63.64	57.45	66.09
Endoscopist G	86.96	96.15	34.21	72.41	62.22	81.82	65.96	67.83

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DCNN3, standard mediastinal stations classification; EUS-MPS, EUS-mediastinal position system.

the anatomy under EUS and prompt them in real time to reduce the blind spots during operation. With the new system, we make it possible to perform a complete and effective pancreatic scanning.^[12] However, as far as we know, no studies have explored the effectiveness of AI for operator assistance during real-time mediastinal EUS scanning. Our study was based on 7 standard stations of mediastinum scanning, mainly including the inferior vena cava, celiac trunk, cardiac atrium, thoracic aorta, right pulmonary artery, aortopulmonary, and aortic arch. This deep learning-based system was developed for localization in linear endoscopic mediastinum station ultrasound, with an accuracy of 90.49%. This new system can provide real-time information about the station scanned currently and the unscanned ones, which is helpful for novice endoscopists to quickly find landmarks, achieving continuous scanning of the mediastinum and effective interpretation of mediastinal images. In addition, we further verified the practicality and validity of the model using a mediastinal EUS video. For video validation, the accuracy was 83.80%, which was comparable to the result of the EUS expert (83.91%) in the man-machine contest. However, compared with the image validation in the man-machine contest, making prediction in a series of successive videos seems more difficult; thus, our system still performs well in actual clinical settings. To our knowledge, this is the first time that a system such as EUS-MPS has been developed for mediastinum station localization in linear EUS.

In this study, compared with endoscopists, the performance of the EUS-MPS for mediastinal 7-standard-station classification was comparable to that of experts, suggesting that this system is sufficient to provide accurate and effective hints to novice physicians in actual EUS operation and then assist them to perform efficient and complete mediastinal scanning. The accuracy of EUS-MPS classification reached 89.85% in external validation, which was also clinically applicable. Therefore, the system has the ability to be applied in different hospitals. Moreover, with the augmentation of the EUS-MPS, trainees from different hospitals who participated in the reader study have significantly improved their accuracy of mediastinum station recognition, with an increase of 13.26% (95% confidence interval, 11.04%–15.48%; P < 0.05), which has further illustrated the effectiveness of the EUS-MPS.

Unfortunately, there are still several limitations to our study. Primarily, this study is observational. Although we conducted a reader study to verify the effectiveness of the system, randomized controlled trials in a clinical practical environment are needed to verify the effectiveness of the system. Second, our data are mainly from 3 hospitals in China. The effectiveness of this system in Western populations needs to be further verified by international multicenter studies.

CONCLUSIONS

The deep learning-based system for mediastinum station localization in linear EUS constructed by the authors can effectively prompt the station endoscopist currently scanned in real time, having the potential to play an important role in shortening the learning curve and establishing standard mediastinal scanning in the future. In the

Table 4

		Without augmentation	With augmentation	Increase (95% confidence interval)	Р
Group A	Trainee 1	70.00	88.75	18.75 (10.78 to 26.72)	< 0.05
	Trainee 2	75.63	85.00	9.38 (1.86 to 16.89)	< 0.05
	Trainee 3	70.63	87.50	16.88 (9.48 to 24.27)	< 0.05
	Trainee 4	61.88	84.38	22.50 (13.02 to 31.98)	< 0.05
	Trainee 5	70.63	78.13	7.50 (0.04 to 14.96)	0.074
	Trainee 6	61.25	72.50	11.25 (0.71 to 21.79)	0.051
	Trainee 7	64.38	86.88	22.50 (14.76 to 30.24)	< 0.05
Group B	Trainee 8	86.25	91.25	5.00 (-1.44 to 11.44)	0.186
[Trainee 9	83.13	86.88	3.75 (-3.37 to 10.87)	0.391
	Trainee 10	74.38	85.00	10.63 (3.15 to 18.10)	< 0.05
	Trainee 11	73.13	88.75	15.63 (7.58 to 23.67)	< 0.05
	Trainee 12	46.25	76.25	30.00 (19.78 to 40.22)	< 0.05
	Trainee 13	81.88	85.63	3.75 (-3.37 to 10.87)	0.391
	Trainee 14	71.25	79.38	8.13 (-1.20 to 17.45)	0.118

future, prospective multicenter clinical trials are needed to further validate the system.

Video Legend

Videos are only available at the official website of the journal (http://www.eusjournal.com).

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Conflicts of Interest

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

XWD and HGY conceived and designed the study; LWY and CXZ trained and tested the models; BX and SSY collected and reviewed images; LWY and CXZ collected, collated and analyzed the data; LWY and CXZ contributed to analysis, interpretation of data, drafting of the manuscript and statistical analysis; XWD and HGY performed extensive editing of the manuscript. These authors contribute equally to this work. All authors read and approved the final version of the manuscript and critical revision of the manuscript.

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