

## Basic Study

## Ultrasound virtual endoscopy: Polyp detection and reliability of measurement in an *in vitro* study with pig intestine specimens

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### Abstract

**AIM:** To present our initial experience regarding the feasibility of ultrasound virtual endoscopy (USVE) and its measurement reliability for polyp detection in an *in vitro* study using pig intestine specimens.

**METHODS:** Six porcine intestine specimens containing 30 synthetic polyps underwent USVE, computed tomography colonography (CTC) and optical colonoscopy (OC) for polyp detection. The polyp measurement defined as the maximum polyp diameter on two-dimensional (2D) multiplanar reformatted (MPR) planes was obtained by USVE, and the absolute measurement error was analyzed using the direct measurement as the reference standard.

**RESULTS:** USVE detected 29 (96.7%) of 30 polyps, remaining a 7-mm one missed. There was one false-positive finding. Twenty-six (89.7%) of 29 reconstructed

images were clearly depicted, while 29 (96.7%) of 30 polyps were displayed on CTC with one false-negative finding. In OC, all the polyps were detected. The intraclass correlation coefficient was 0.876 (95%CI: 0.745-0.940) for measurements obtained with USVE. The pooled absolute measurement errors  $\pm$  the standard deviations of the depicted polyps with actual sizes  $\leq$  5 mm, 6-9 mm, and  $\geq$  10 mm were  $1.9 \pm 0.8$  mm,  $0.9 \pm 1.2$  mm, and  $1.0 \pm 1.4$  mm, respectively.

**CONCLUSION:** USVE is reliable for polyp detection and measurement in *in vitro* study.

**Key words:** Three-dimensional ultrasound; *In vitro*; Virtual endoscopy; Intestinal polyps; Technical feasibility

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**Core tip:** We present our initial experience regarding the feasibility of ultrasound virtual endoscopy (USVE) and its measurement reliability for polyp detection in an *in vitro* study using pig intestine specimens. USVE is a new technique that simulates views of computed tomography colonography (CTC). We found that USVE is an accurate screening method for simulated polyp detection and compares favorably to CTC and optical colonoscopy. As a dynamic, non-invasive, radiation-free, cost-effective method, USVE shows great promise for the screening and surveillance of colorectal cancers.

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## INTRODUCTION

Colorectal cancer (CRC), which generally develops from benign adenomatous polyps, is a major cause of morbidity and mortality worldwide<sup>[1,2]</sup>. Evidence-based guidelines recommend CRC screening<sup>[3,4]</sup> because the early detection and removal of polyps has been shown to reduce both the incidence and the mortality of CRC<sup>[5,6]</sup>. Optical colonoscopy (OC) is the primary method employed for CRC screening and the removal of polyps. As a primary imaging test, computed tomography colonography (CTC) is performed in average-risk individuals, particularly when endoscopy is contraindicated or incomplete<sup>[4,7]</sup>. It is highly sensitive for CRC screening with a sensitivity of 96.1% according to a meta-analysis<sup>[8]</sup>. Unfortunately, these tests have some drawbacks, such as OC related invasiveness, procedure-related discomfort, the risk of bowel perforation, and CTC related ionizing

radiation<sup>[9]</sup>. Ultrasound virtual endoscopy (USVE) is a new technique that simulates views of CTC. It allows for the reconstruction of inner bowel-surface structures from the dynamic three-dimensional (3D) ultrasound data sets. Based on a surface reconstruction algorithm by interactive settings of threshold values and surface displays, endoscopic views can be obtained within seconds. Similar ultrasound virtual endoscopy imaging has been used for detection of carotid atherosclerosis and portal vein thrombus<sup>[10-12]</sup>. But, USVE has never been used for polyp detection. It has several potential advantages for CRC screening over other modalities. USVE is dynamic, non-invasive, radiation-free, and cost-effective. Therefore, this new method shows great promise for the screening and surveillance of CRC.

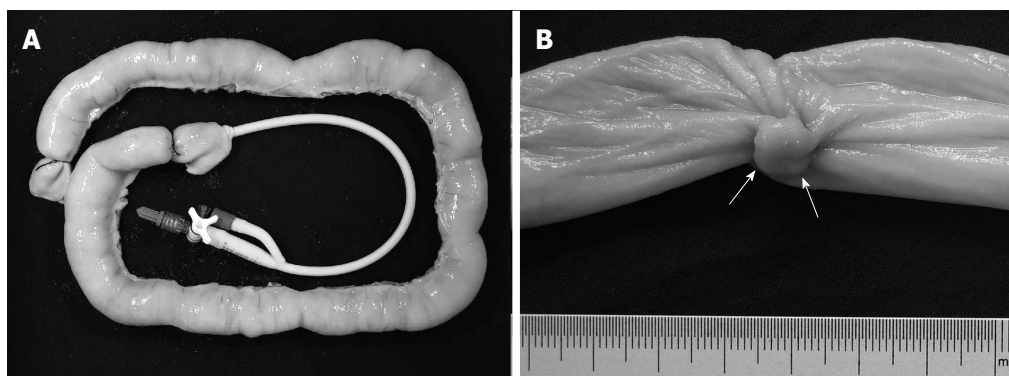
The likelihood that a given polyp develops into malignancy or demonstrates high-grade dysplasia is directly related to its size<sup>[13-15]</sup>. This risk is estimated to be less than 1% for lesions 5-mm or smaller, whereas the risk increases to approximately 10%-25% for lesions 10 mm or larger. Polyps of 6-9 mm are also almost always benign. Advanced adenomas, defined as lesions 10 mm or larger, are the target of CRC screening and should be referred for polypectomy<sup>[16]</sup>. However, radiologists suggested 6-mm as the minimum size for reporting polyp lesions<sup>[17]</sup>. Hence, understanding of the polyp size measurement error by USVE is very important for accurate polyp matching in the diagnostic performance.

Currently, there is no published report regarding the role of USVE in polyp detection, and its sensitivity and specificity for the detection of polyps are unknown. In this ideal *in vitro* study, we investigated the detection rate of simulated polyps using USVE compared with CTC and OC. We estimated the conspicuity of the reconstructed endoscopic images. Additionally, we evaluated the reliability of the two-dimensional (2D) optimized polyp measurements of USVE using the direct measurement as the reference standard. The goal of this study was to report our initial experience regarding the feasibility of USVE and its measurement reliability in an *in vitro* study using porcine intestine specimens.

## MATERIALS AND METHODS

### Specimen preparation

Six porcine small intestine specimens, each approximately 50 cm long, were acquired from fresh pig intestines that were commercially available at an abattoir. Each specimen was cleansed to remove fecal matter, and no polypoid structures were found on the mucosal surface. Thirty simulated sessile polyps with maximum diameters of 4-13 mm were created from pork wrapped by other intestinal mucosa with sutures. The maximum diameter of the polyp was confirmed by means of physical measurement with a caliper and a millimeter marked ruler. Then, the polyps were sutured to the mucosa of the inverted specimens and randomly



**Figure 1** A pig intestine specimen and simulated polyps. A: A porcine intestine specimen with a flexure configuration was placed on a black sponge. One end was double-tied with sutures. A catheter used for intestinal distention during the USVE and CTC was placed through the other end. Optical colonoscopy was also performed through the latter end after removal of the catheter; B: A simulated polyp with a maximum diameter of 8 mm (arrows) was sutured to the inverted intestine specimen. USVE: Ultrasound virtual endoscopy; CTC: Computed tomography colonography.

placed with different distances between adjacent polyps. Either the number or the size of the polyps was randomized in each specimen. A detailed polyp map of the specimen was recorded. Next, each specimen was re-inverted, and the distal end was double-tied with sutures. An 18-F urinary catheter was inserted into the open proximal end, which was then closed with a double-tied suture (Figure 1). A 50-mL syringe with a 3-way stopcock was attached to the urinary catheter.

#### **US virtual endoscopy**

A 0.9% saline solution was introduced through the syringe, and the specimen was maximally distended to a diameter of approximately 3.5 cm. Then, it was placed in a plastic container containing water. The wall and the bottom of the container were covered with 2-mm-thick black sponges that helped absorb the ultrasound and reduce echo reflection.

The USVE was performed with an ultrasound scanner (Aplio 500, Toshiba, Ottawa, Japan) equipped with a volume transducer (7-14 MHz) (PLT-1204MV, Toshiba Medical Systems). Imaging was performed by one radiologist (Wang W) who was unaware of the locations, numbers and sizes of the polyps in each specimen. After optimal 2D images were obtained, 3D scan mode was initiated, and volume data were acquired, including the following parameters: longitudinal scanning orientation (running along the longitudinal axis of the specimen); 3D frequency, 8 MHz under the difference mode; 3D gain, 70%-80%; dynamic range, 40-50 dB; depth (distance between the probe and the proximal colon wall), approximately 30 mm; focus, placed in the middle of the lumen; 3D Aplipure, on; and 3D scanning angle, 60°. Each specimen was scanned from the distal to the proximal end, and 3D volume data were obtained once approximately every 5 cm because of the sweeping length of the PLT-1204MV volume transducer. Therefore, one specimen was artificially separated into several approximately 5-cm-long segmentations. Then, the data from the scanning were loaded to the Fly Thru

workstation (Fly Thru 3.0, Toshiba Medical Systems), which was capable of producing 2D multiplanar reformatted (MPR) images and 3D endoluminal surface renderings (Figure 2, Video 1). Virtual endoscopic images were shown by setting optimal threshold values based on a surface reconstruction algorithm. To prevent holes in the intestinal wall and intraluminal artifact, a threshold value (0-150) was selected for all reconstructions with other defined settings as follows: transparency, 20; and filter, 3. All machine parameters remained unchanged between the examinations and were verified before the imaging.

#### **Interpretation of the findings and measurements with USVE**

Two independent readers (Chen LD and Xu M), who did not know the size ranges and numbers of polyps, reviewed all the ultrasound examinations and recorded the numbers, positions (distance between adjacent polyps) and sizes of the simulated polyps. To achieve a valid match between virtual endoscopy and specimen, a polyp had to appear with the same segment, same position and similar diameters.

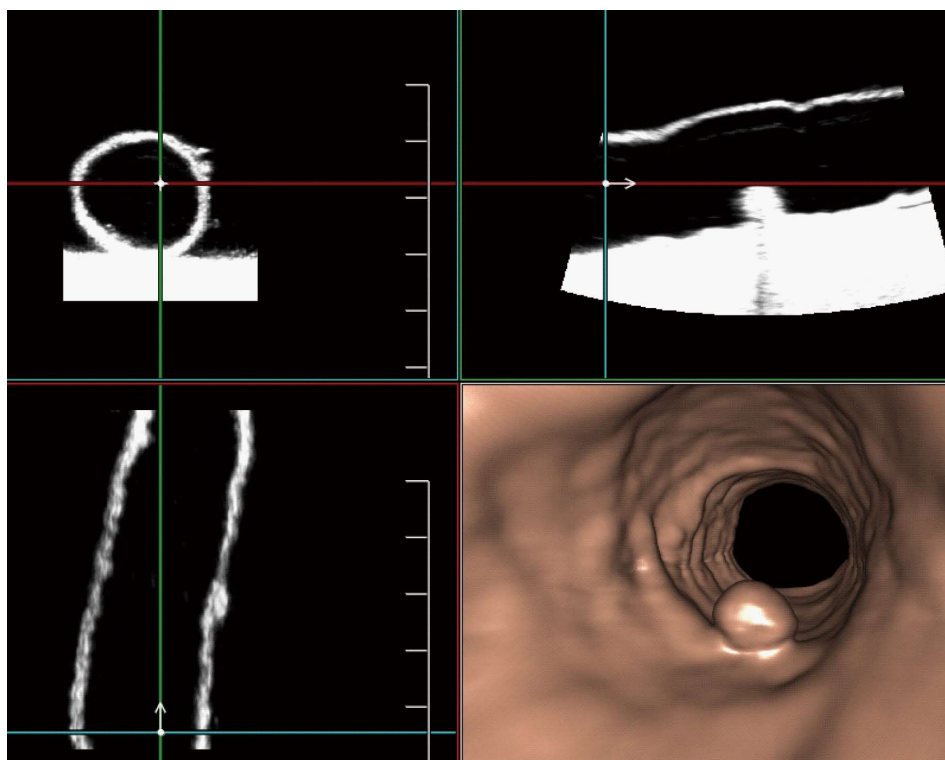
Lesion size is best defined as the single largest diameter of the polyp head, excluding the stalk<sup>[17]</sup>. With electronic calipers, the two readers independently measured the polyp size on an optimized 2D MPR plane, on which the maximum polyp diameter was viewed. The measurements were determined to the nearest millimeter. For the same polyp, the mean measured size was the average of measurements from the two readers. For the analysis of measurement accuracy, the absolute measurement error referred to the difference between the actual size and the mean measured size. The standardized polyp size was defined as the mean measured optimized 2D diameter divided by the reference diameter, multiplied by 100%.

An overall ranking of image quality of the USVE protocol was performed. Both radiologists graded conspicuity and evaluated the images together to resolve any disagreements. The image conspicuity of

**Table 1** Detection rate for the simulated polyps by ultrasound virtual endoscopy, computed tomography colonography and optical colonoscopy

Actual polyp size, mm	Referenced No. of polyps	OC		CTC		USVE	
		No. of detected polyps	Sensitivity	No. of detected polyps	Sensitivity	No. of detected polyps	Sensitivity
≤ 5	9	9	100%	8	88.9%	9	100%
6-9	15	15	100%	15	100%	14	93.3%
≥ 10	6	6	100%	6	100%	6	100%
All	30	30	100%	29	96.7%	29	96.7%

USVE: Ultrasound virtual endoscopy; CTC: Computed tomography colonography; OC: Optical colonoscopy.



**Figure 2** The 3D endoluminal reformatted image of ultrasound virtual endoscopy clearly depicting an 8-mm polyp. We could observe the polyp on the 2D transversal, sagittal and coronal ultrasonography simultaneously.

each polyp was graded on a three-point scale<sup>[18,19]</sup>: grade 1 = not visible or very poorly depicted; grade 2 = poorly depicted, with some artifacts that but do not affect diagnosis; and grade 3 = clearly depicted, without artifacts.

### CTC

After US examination, the six specimens were transferred to the CT suite. They were placed in a plastic container and then manually distended with room air using a syringe. Five liters of 93.7% soybean oil was poured into the container until the specimen was completely submerged<sup>[20]</sup>. To avoid flotation, the specimen was fastened to the bottom of the container by adhesion of plastic tape, before the oil was poured into the container.

Blinded to the locations, sizes and numbers of polyps, two independent radiologists (Feng ST and

Cai HS), performed the CT examinations with a 64-detector row CT scanner (Aquillion 64, Toshiba, Japan). The images were obtained with these parameters: 120 kV; 200-250 mA; section thickness, 0.5 mm; beam collimation, 64 mm × 0.5 mm; reconstruction interval, 0.5 mm; reconstructed section thickness, 0.5 mm; beam pitch, 0.828; gantry rotation time, 0.4 second; and field of view, 5 cm. The scanning matrix was 512 × 512. Then, the data were loaded to a workstation (HP workstation XW8200, Vitrea 2, Version 3.7). The reconstructed virtual endoscopic images were read by the above radiologists, who synchronously recorded the locations, numbers and sizes of the simulated polyps.

### OC

The OC of the six specimens was performed with a colonoscope (CF-H260AI, CV-260, Olympus, Tokyo,

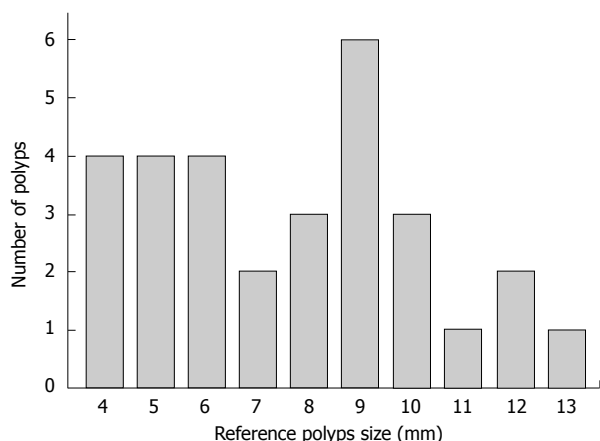


Figure 3 Polyp size and number.

Table 2 Relationship between conspicuity grade and polyp size *n* (%)

Actual polyp size, mm	Conspicuity grade 2	Conspicuity grade 3	<i>P</i> value
≤ 5 ( <i>n</i> = 9)	1 (11.1)	8 (88.9)	0.627
6-9 ( <i>n</i> = 14)	2 (14.3)	12 (85.7)	
≥ 10 ( <i>n</i> = 6)	0 (0)	6 (100)	
All ( <i>n</i> = 29)	3 (10.3)	26 (89.7)	

Japan) by two independent endoscopists (Liang JY and Xie XY) immediately after CT scanning. The oil mixture was removed. The gastroenterologists were unaware of the locations, numbers and sizes of the polyps in each specimen, but were aware of the presence of polyps. The colonoscope was introduced through the open proximal end after the urinary catheter was removed. The examination was started, and endoscopy views of the entire specimen were acquired. The same endoscopists recorded the locations, numbers and sizes of the simulated polyps.

### Statistical analysis

The relationship between conspicuity grades and polyp sizes was examined using Pearson's Chi-square test (SPSS 18, IBM Corporation, New York, NY, United States). A *P* value of less than 0.05 was considered to indicate a statistically significant difference. The intraclass correlation coefficient (MedCalc version 10.2.0.0, Medcalc Software, Mariakerke, Belgium) was applied to analyze the inter-observer agreement for polyp measurement.

## RESULTS

### Simulated polyps detection

The reference polyp size and the number of the 30 simulated polyps for evaluating the detectability are shown in Figure 3. The polyps were classified into three groups according to size (≤ 5 mm, 6-9 mm, and ≥ 10 mm)<sup>[21,22]</sup>. The detection rates for each group of the three modalities are shown in Table 1. With USVE, 29

Table 3 Mean error of the optimized two-dimensional multi-planar reformatted measurement and the pooled standardized polyp size with ultrasound virtual endoscopy

Actual polyp size, mm	Mean measurement error ± SD, mm	Pooled standardized polyp size ± SD, %
≤ 5 ( <i>n</i> = 9)	1.9 ± 0.8	142.5 ± 18.7
6-9 ( <i>n</i> = 14)	0.9 ± 1.2	111.2 ± 16.7
≥ 10 ( <i>n</i> = 6)	1.0 ± 1.4	109.2 ± 12.2
≥ 6 ( <i>n</i> = 20)	0.9 ± 1.3	110.5 ± 14.6

(96.7%) of the 30 polyps were detected; only a 7-mm polyp was missed. There was one false-positive finding (identified as a 10-mm polyp). An initial analysis of the polyp conspicuity data revealed that no observation was assigned a grade of 1. Twenty-six (89.7%) of 29 polyps were clearly depicted (grade 3) (Figure 4), whereas the remaining 3 (10.3%) polyps were poorly depicted (grade 2). There was no significant interaction between polyp conspicuity grade and polyp size (*P* = 0.627) (Table 2).

Twenty-nine (96.7%) of the 30 polyps were depicted on the CTC. All of the polyps 6 mm or larger were detected. One 5-mm polyp, which was located behind a fold, was not prospectively detected by the observer on any of the images but was depicted in a retrospective review. There was one false-positive finding (identified as a 6-mm lesion) as well. All of the polyps were clearly detected by OC.

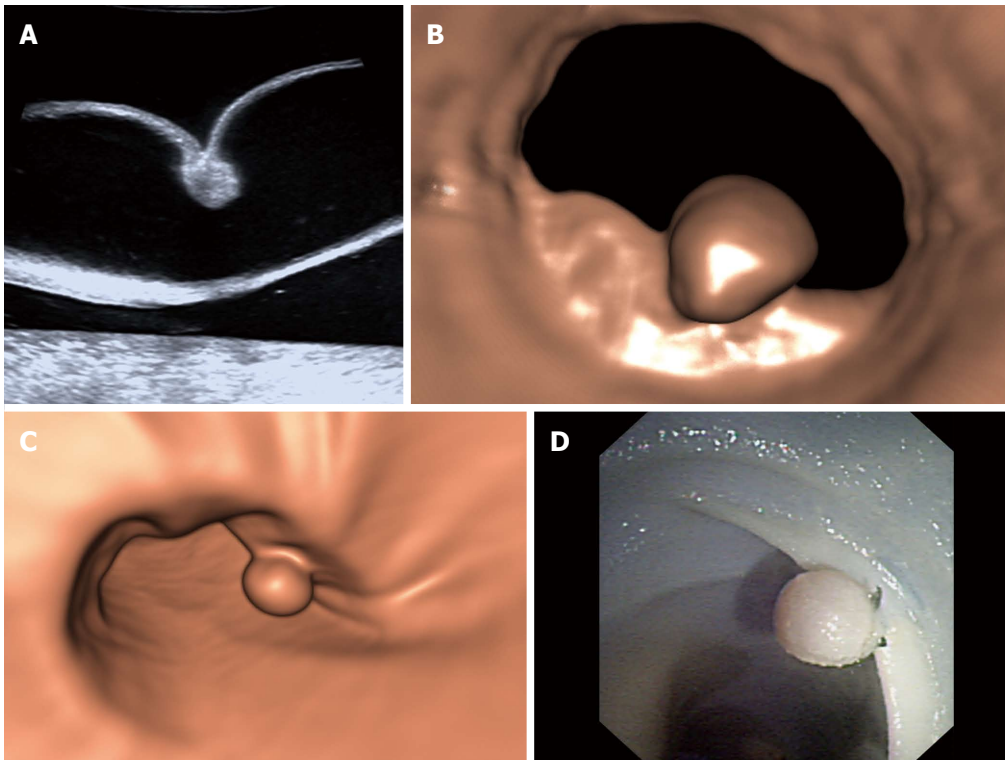
### Polyp measurement

The intraclass correlation coefficient was 0.876 (95% confidence interval: 0.745, 0.940) for measurements obtained with USVE. The pooled absolute measurement errors ± standard deviations of the depicted polyps with actual sizes of 5-mm or smaller, 6-9-mm, and 10-mm or larger were 1.9 ± 0.8 mm, 0.9 ± 1.2 mm, and 1.0 ± 1.4 mm, respectively. The pooled standardized polyp size of the depicted polyps with actual sizes of 5-mm or smaller, 6-9-mm, and 10-mm or larger were 142.5% ± 18.7%, 111.2% ± 16.7%, and 109.2% ± 12.2%, respectively (Table 3).

## DISCUSSION

This study demonstrates, for the first time, that USVE is technically feasible in an *in vitro* intestinal specimen. We found that 96.7% (29/30) of the simulated polyps with different sizes ranging from 4 to 13 mm in diameter were depicted using USVE. Thus, USVE is an accurate screening method and compares favorably with CTC and OC for polyp detection. With USVE, the pooled error ± standard deviation and the pooled standardized polyp size of the optimized 2D MPR measurements were 0.9 ± 1.3 mm and 110.5% ± 14.6% for polyps ≥ 6 mm, respectively. These results indicate that USVE is reliable for polyp measurement.

Gastrointestinal tract ultrasonography is challenging.



**Figure 4** A 6-mm created polyp is clearly depicted on two-dimensional ultrasonography (A), ultrasound virtual endoscopy (B), computed tomography colonography (C) and optical colonoscopy (D).

Gas and fecal residue within the colonic lumen make visibility difficult. The value of abdominal ultrasound in the diagnosis of CRC has previously studied<sup>[23-26]</sup>. Following the standard bowel preparation, including colonic cleansing and oral administration of a solution for adequate luminal distention<sup>[19]</sup>, transabdominal ultrasound is capable of acquiring 3D data of the colon which then generates virtual endoscopic imaging. Additionally, transabdominal ultrasound can observe the presence of lymphadenopathy, the extracolonic extension of a mass, and the presence of distant metastases.

In 2001, a study reported on ultrasound virtual endoscopic imaging<sup>[27]</sup>, using a curved array probe or a linear array probe with a position-sensing sweeper device. A series of 2D images were manually scanned and then stored in a graphics workstation. In our study, however, we used a new 3D image processing system, called the Fly Thru workstation, and a 3D volume probe. The new method is simpler, more convenient, and has higher spatial resolution. In this ideal pig intestine specimen, USVE was capable of efficiently depicting polyps as small as 4-mm in diameter. In total, 89.7% of the reconstructed images were clearly depicted (Grade 3), which was approximately equal to the polyp conspicuity of CTC<sup>[18]</sup>. Furthermore, the detection rate of polyps  $\geq$  6-mm on USVE approached 100% with only sporadic failures, which was similar to the detection rate of *in vitro* CTC<sup>[28]</sup>. With the high resolution and high sensitivity of detecting polyps  $\geq$  6-mm, USVE is expected to be a new colon neoplasm

screening and surveillance modality.

Neither of the observers found one of the four 7-mm polyps during the retrospective reviews of USVE. In contrast, a 10-mm polyp, which was located at the division of two adjacent scan areas, was depicted twice and was regarded as a false-positive finding by both observers. These missing depiction and false-positive findings resulted from the limited sweeping range of the 3D volume transducer. When performing USVE, this transducer scanned approximately 5-cm of the intestine specimen for each acquisition. Thus, as one specimen was artificially separated into several segmentations, the polyps located at the division of adjacent scan areas could be repeatedly depicted or even missed. Based on our preliminary experience, we conclude that the limited scanning range is a major limitation of USVE.

The achievement of precise polyp matching is critical for the sensitivity of USVE. According to previous *in vitro* studies of CTC, the optimized 2D MPR measurement was as accurate as the 3D endoluminal measurement<sup>[20,29]</sup>. In our study, we adapted the optimized 2D MPR measurement as the standard method of measurement. The mean absolute optimized 2D measurement errors and the mean standardized polyp sizes in the  $\geq$  6-mm group were generally consistent with values of CTC<sup>[20,29]</sup>. This important finding demonstrates that the optimized 2D MPR measurement of USVE is reliable for clinical practice.

This study has some limitations. First, we assessed

the technical accuracy of USVE performed under ideal conditions, which includes the absence of patient motion or peristaltic bowel activity, the clean, debris-free mucosal surface without folds, and maximal lumen distention. The study was not able to reflect an *in vivo* examination on human. The polyps, either their morphologic features or locations, may show more variability in patients. Also, polyp detection and measurement can be affected by colonic curvature, haustral folds, and even different degrees of colonic distention. Additionally, we did not attempt to create flat adenomas in our specimens. Second, polyp size was not measured on the 3D view because the system is currently not able to obtain 3D measurements. Typically, 3D polyp measurements are closer to the "truth" than 2D measurements as the maximum diameter of a polyp is straightforward with the former measurement. Although 2D measurements would optimize polyp diameter by comparing measurements on MPR planes, even using nonstandard oblique planes, this complex procedure would prolong the measurement<sup>[29]</sup>.

In summary, USVE enables the reliable detection and measurement of small simulated mucosal polyps in our *in vitro* model. It is a good potential alternative for colorectal polyp detection. Further *in vivo* studies are required to determine its sensitivity and specificity for polyp detection in patients.

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## COMMENTS

### Background

Most colorectal cancers (CRC) arise from adenomatous polyps, and the early detection and removal of polyps resulted in reducing both the incidence and mortality of CRC. Optical colonoscopy (OC) is widely accepted as the best available method for CRC screening. Computed tomography colonography (CTC) has yielded promising results. However, these tests have some drawbacks such as invasiveness or ionizing radiation. Ultrasound virtual endoscopy (USVE), a novel non-invasive, radiation-free modality, shows great promise for the screening of CRC. Currently, the role of USVE in polyp detection has never been investigated, and its sensitivity and specificity are unknown.

### Research frontiers

Virtual colonoscopy is an attractive alternative for CRC screening. According to some guidelines, CTC has been regarded as the leading imaging technique for CRC screening and the preferred test following incomplete OC.

### Innovations and breakthroughs

This *in vitro* study has revealed, for the first time, the feasibility of USVE and its measurement reliability in pig intestine specimens.

### Applications

USVE enables reliable detection and measurement of small simulated mucosal

polyps in the *in vitro* specimens. It is a good alternative for colorectal polyp screening.

### Terminology

USVE is a novel trans-abdominal ultrasonic technique that simulates views of CTC. It allows for the reconstruction of inner bowel-surface structures from dynamic three-dimensional ultrasound data sets.

### Peer-review

This is an *in vitro* study that reports the feasibility of a new, non-invasive, radiation-free technique (USVE) in detecting and measuring polyps. The authors compared USVE with CTC and colonoscopy, as the reference standard, with interesting results. The authors performed a well-designed study. It is detailed, easy to read and the subject (with all of the important limitations of a preliminary approach) may be relevant in medicine in future. *In vivo* studies were encouraged.

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