Linear-array EUS improves the accuracy of predicting deep submucosal invasion in non-pedunculated rectal polyps compared with radial EUS: a prospective observational study

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Abstract

Background Radial endoscopic ultrasound (EUS) is typically used to estimate the depth of rectal polyp invasion, however, there are no data on linear EUS in this setting and its relative accuracy compared to radial EUS.

Methods In this prospective cohort study, 89 patients with non-pedunculated rectal polyp who underwent linear EUS or radial EUS were prospectively enrolled. The invasion depth was measured for each polyp and categorized as mucosal to shallow submucosal(SM_s) or deep submucosal(SM_d) invasion. Invasion measurements were compared with the final diagnosis on histopathology.

Results A total of 58 patients underwent radial EUS and 31 patients underwent linear EUS examination. There were 38 lesions correctly diagnosed in the radial EUS group and 29 correctly diagnosed lesions in the linear EUS group. The diagnostic accuracy of SM_d invasion for linear EUS was significantly higher than radial EUS (0.936 vs. 0.655, $p = 0.003$). A significant difference was also noted for specificity between the two groups (0.963 vs. 0.659, $p = 0.003$). Univariate analysis showed radial EUS type (OR 0.131, 95% CI 0.028–0.606, $p = 0.009$) to be an independent predictor for incorrect diagnosis. The area under the receiver operating curve (ROC) was 0.856 and 0.651 for linear EUS and radial EUS, respectively. It was noted that four patients underwent unnecessary surgery for radial EUS while there were no such patients in the linear EUS group.

Conclusions Linear EUS was more accurate for determining SM_d invasion and contributed to the selection of appropriate treatment modalities in patients with non-pedunculated rectal polyp.

Keywords Diagnostic accuracy · Linear EUS · Non-pedunculated rectal polyp · Radial EUS

Zhixian Lan and Kangyue Sun have contributed equally to this paper.

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Recent progress in endoscopic techniques and gastrointestinal cancer screening in China have contributed to an increase in identification of early-stage colorectal cancer (CRC) [1–3]. Non-pedunculated colorectal polyps (NPCP) are classified as sessile and flat colonic lesions, and can be further subclassified as laterally spreading type polyp (LST) [4]. NPCP is closely associated with increased risk of malignancy and more often presents as submucosal (SM) invasive cancer when compared to pedunculated colorectal polyp and requires endoscopic or surgical resection [4]. The most important aspect for choosing the appropriate therapeutic strategy is to determine invasion depth accurately before treatment [5]. Accurate determination of NPCP without deep SM (SM_d) invasion is essential in guiding the decision to proceed with endoscopic resection. Endoscopic ultrasonography (EUS), Narrow-Band Imaging (NBI), and magnifying

chromoendoscopy (MCE) are often utilized as diagnostic tools to predict the invasion depth of early CRC [6–9]. However, none of these procedures have sufficient accuracy to meet the clinical requirement. Currently, most results pertinent to EUS have been obtained using radial EUS or mini probe, and there are limited data on linear EUS for identifying invasion depth in the non-pedunculated rectal polyp. It has been widely recognized that linear array EUS performs better than radial EUS in the pancreas and biliary system in most clinical situations [10–12]. It is yet to be determined if the linear array EUS is superior for predicting tumor depth in non-pedunculated rectal polyp. Therefore, this prospective cohort study was conducted to compare linear EUS and radial EUS for preoperative diagnosis of SM_d invasion in patients with non-pedunculated rectal polyp.

Materials and methods

Patients

Patients who met all of the following inclusion criteria were prospectively enrolled from November 2018 to May 2019 at Nanfang Hospital, Southern Medical University in this study: (1) Age 18–85 years; (2) Diagnosis of non-pedunculated rectal polyps larger than 10 mm or rectal LST determined by colonoscopy; (3) The patient who planned to undergo pre-treatment T staging using radial EUS or linear EUS; (4) The patient who planned to undergo endoscopic resection or surgical resection with detailed histopathological results to be available. Patients were excluded if any of the following conditions existed: (1) They had synchronous cancer in another organ; (2) Accompanied severe comorbidities, such as heart failure. (3) Pregnant patients; (4) The patient who had a contraindication to EUS examination; (5) The patient who could not provide informed consent.

Study design

The present study is a prospective observational study and the enrolled patients received linear EUS or radial EUS as determined by the endoscopist and technical expertise, equipment availability. Standard demographic and clinicopathologic data were collected among the EUS groups, and EUS-related procedural details were also recorded. The primary study endpoint was diagnostic accuracy for invasion depth. The secondary endpoints were sensitivity, specificity, and observation time. The study protocol was approved by the Institutional Review Board of Nanfang Hospital, Southern Medical University (IRB no. NFEC-2019-030) and was carried out according to the ethical guidelines of Declaration of Helsinki (6th revision, 2008). All patients provided their written informed consent prior to study enrollment. All the authors had access to the study data and had approved the final manuscript.

EUS equipment and examination procedure

We used a radial array echoendoscope (EG-580UR, Fujifilm, Tokyo, Japan or EU-ME2, GF-UE260-AL5, Olympus, Tokyo, Japan) for radial EUS examination and a linear array echoendoscope (EG-580UT, Fujifilm, Tokyo, Japan or EU-ME2, GF-UCT2600, Olympus, Tokyo, Japan) for linear EUS examination. Bowel preparation was composed of two liters of hypertonic polyethylene glycol solution taken in all patients 6–12 h prior to the procedure. Carbon dioxide was used for insufflation during the procedure. Normal saline was routinely used to cover the lesion and acquire better EUS image when necessary. All the EUS procedures were performed by experienced endoscopists who have performed over 1000 cases of EUS. The ultrasound frequency was set from 10 to 12 MHz.

EUS diagnosis of tumor invasion depth

The intestinal wall was assessed based on the standard five-layer sonographic structure and the T staging was determined according to AJCC 7th edition TNM staging system. In EUS, T1a was defined as a tumor confined to the first and second mucosal layer, T1b was a tumor that invaded into the third submucosal layer, T2 was a tumor that invaded the muscularis propria (fourth layer), T3 was a tumor that invaded the sub-serosa without interruption of serosa, T4a was a tumor that invaded the serosa (fifth layer), and T4b tumors invaded adjacent organs. In the present study, we mainly focused on the diagnostic accuracy of SM_d invasion and EUS imaging was categorized into mucosal to shallow submucosal (M-SM_s) invasion and $\geq SM_d$. A hypoechoic mass limited to within the first and second layers and slight irregularity on the upper side of the third layer was defined as M-SM_s cancer. A hypoechoic mass that clearly invades and penetrates into the third layer was defined as SM_d cancer (Fig. 1). All the EUS-based diagnoses were blinded and the EUS images were reviewed by a second senior EUS endoscopist. If disagreement occurred between the two diagnoses, a third endoscopist was consulted and the final impression was based on majorities. For M-SM_s cancer, endoscopic resection such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) was performed, while the tumor was SM_d cancer or deeper, surgical resection was needed according to current recommendations for colorectal ESD.
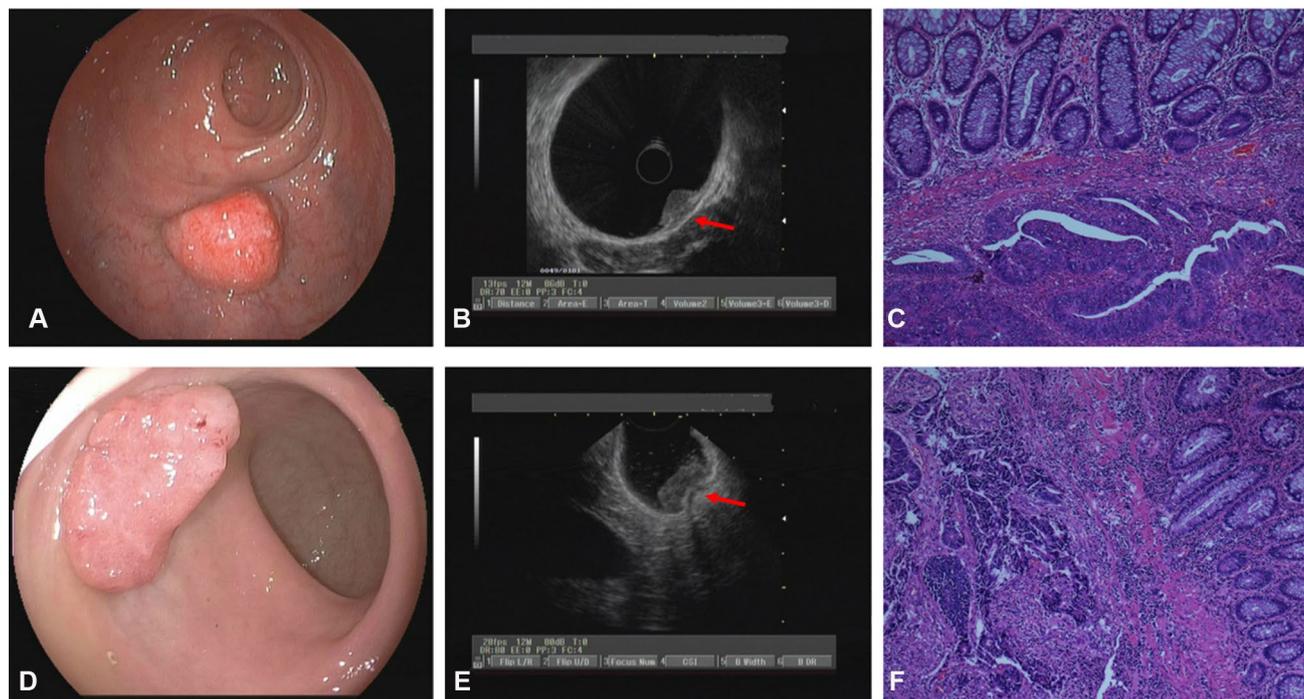
Fig. 1 Non-pedunculated rectal polyps diagnosed as SM_d cancers in radial EUS and linear EUS. Figure legend: A 68-year-old man with a sessile polyp (Is) about 15 mm in diameter located in rectum (**A**). Preoperative radial EUS examination showed that the lesion (red arrow) invaded and penetrated into with SM layer (**B**). Surgery was then performed and the pathological result revealed SM_d carcinoma (**C**). A 60-year-old female patient with superficial protrude type (IIa) rectal lesion measuring about 20 mm in diameter (**D**). Preoperative linear EUS examination showed that the lesion penetrated into with SM with abruption of SM layer (red arrow) (**E**). The pathological result showed SM_d carcinoma (**F**)

Histopathological diagnosis

Resected specimens were fixed in formalin and sectioned into 2-mm(mm)-thick slices and then embedded in paraffin. The resection margin status including vertical margin and horizontal margin were evaluated histopathologically. The depth of submucosal invasion was subclassified histologically into one of two grades: depth of invasion submucosal invasion depth < 1000 μm was defined as < pSM_d and submucosal invasion depth ≥ 1000 μm was defined as ≥ pSM_d. All the final histopathological diagnoses of tumor invasion were considered the true diagnoses and classified into < pSM_d and ≥ pSM_d. Complete resection was defined as negative horizontal and vertical margins in the pathological specimen and was determined on the basis of a review of postoperative pathology reports. All histological diagnoses were performed by an experienced pathologist who was blinded to the EUS diagnosis.

Statistical analysis

Data are presented as frequencies and percentages, means (standard deviation, SD), or median (range) as appropriate. Categorical data are presented as the number of cases. Data were analyzed by using the chi-square test, Fisher's exact probability test, and Student t test as appropriate. Risk factors were evaluated using univariate and multivariate logistic regression. Results were presented as odds ratio (OR) and associated 95% CI. All tests for significance were two-tailed, and p values less than 0.05 were considered significant. All calculations were done in SPSS v19 (IBM, Armonk, NY, USA).

Results

A total of 104 patients were screened with 89 patients fulfilling the inclusion criteria and were included in the analysis. Of these, 58 patients underwent radial EUS and 31 patients underwent linear EUS examination (Fig. 2). The mean age was 60.53 ± 11.76 years (range 18–85 years), and there were 49 male patients (49/89, 55.06%). Most of the non-pedunculated polyps were sessile and flat polyp (54/89, 60.67%), and the rest were LST (35/89, 39.33%) according to the Paris classification. The mean polyp size was 32.28 ± 16.97 mm (range 12–85 mm). Pathological results showed that majority of the lesions (63/89, 70.79%) were adenomatous polyp with the remaining 26 (29.21%)
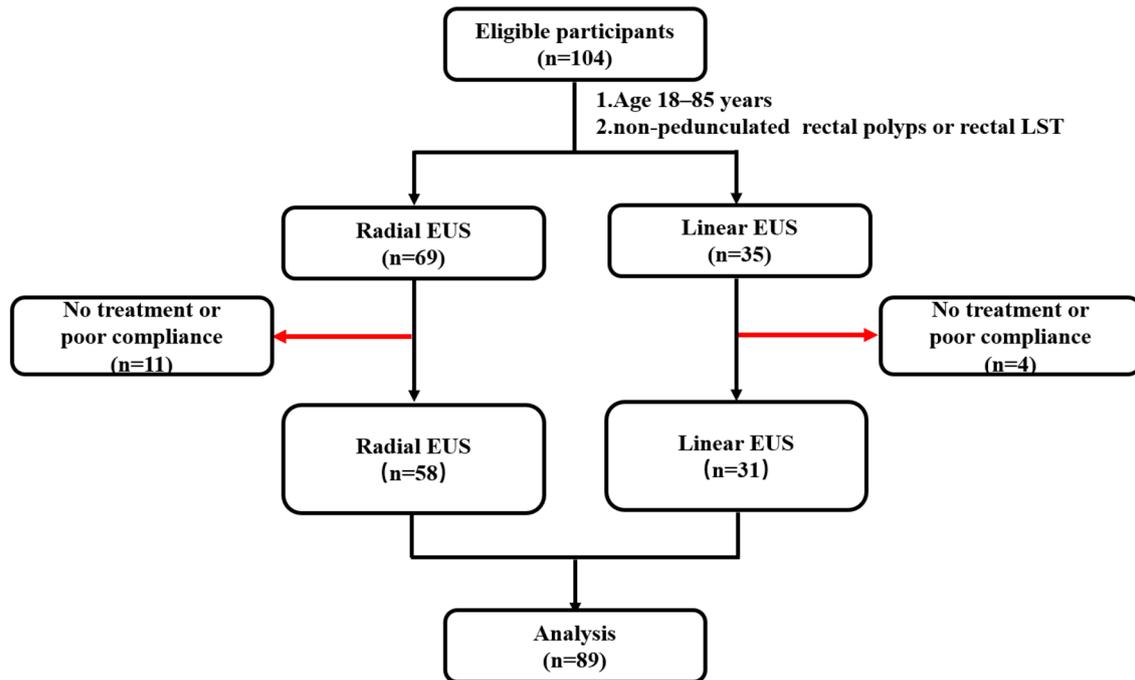
Fig. 2 Study flow diagram

Table 1 Clinical characteristics of study patients between linear EUS and radial EUS group

Patients	Total ($N=89$)	Radial EUS ($N=58$)	Linear EUS ($N=31$)	p value
Gender, Male	49 (55.06%)	35 (60.34%)	14 (45.16%)	0.170
Age, (mean ± SD) (years)	60.53 ± 11.76	60.88 ± 10.80	59.87 ± 13.53	0.702
Endoscopic morphology	89 (100%)	58 (100%)	31 (100%)	0.713
Sessile and flat	54 (60.67%)	36 (62.07%)	18 (58.06%)	
LST	35 (39.33%)	22 (37.93%)	13 (41.94%)	
Distance from anus (mean ± SD) (cm)	7.88 ± 3.81	8.31 ± 4.13	7.06 ± 3.01	0.143
Maximum Diameter (mean ± SD) (cm)	32.28 ± 16.97	33.45 ± 18.52	30.00 ± 13.62	0.364
Pathological type	89 (100%)	58 (100%)	31 (100%)	0.135
Adenomatous polyp	63 (70.79%)	38 (65.52%)	25 (80.65%)	
Adenocarcinoma	26 (29.21%)	20 (34.48%)	6 (19.35%)	
Observation time, (mean ± SD) (mins)	15.44 ± 9.06	15.50 ± 7.79	15.32 ± 11.21	0.930
EUS diagnosis (No. %)	89 (100%)	58 (100%)	31 (100%)	0.006
M-SMs	61 (68.54%)	34 (58.62%)	27 (87.10%)	
SM_d or deeper	28 (31.46%)	24 (41.38%)	4 (12.90%)	
Operation methods	89 (100%)	58 (100%)	31 (100%)	0.298
EMR	9 (10.11%)	4 (6.90%)	5 (16.13%)	
ESD	54 (60.68%)	35 (60.34%)	19 (61.29%)	
Surgery	26 (29.21%)	19 (32.76%)	7 (22.58%)	
Histological diagnosis	89 (100%)	58 (100%)	31 (100%)	0.209
M-SMs	71 (79.77%)	44 (75.86%)	27 (87.10%)	
SM_d or deeper	18 (20.23%)	14 (24.14%)	4 (12.90%)	

identified as differentiated adenocarcinoma. The baseline characteristics of patients in the two groups were well balanced (Table 1). The mean observation time of all EUS procedures was 15.44 ± 9.06 min (radial EUS 15.50 ± 7.79 vs. linear EUS 15.32 ± 11.21, $p = 0.930$). Based on the EUS evaluation, 61 patients (34 in radial EUS group and 27 in linear EUS group) were diagnosed as M-SMs and 28 patients (24 in radial EUS group and 4 in linear EUS group) were diagnosed as $\geq SM_d$. Eventually, 63 patients underwent endoscopic resection (including 54 ESD procedures and 9 EMR procedures) and 26 patients received surgery. For final histopathological diagnosis, 71 patients (44 in radial EUS group and 27 in linear EUS group) were diagnosed as M-SMs and 18 patients (14 in radial EUS group and 4 in linear EUS group) were diagnosed as $\geq SM_d$.

Comparison of diagnostic efficiency between linear EUS and radial EUS

There were 22 misdiagnosed lesions (22/89, 24.72%), with 20 lesions in the radial EUS group (20/58, 34.48%) and the remaining 2 lesions in linear EUS group (2/31, 6.45%) when we compared EUS-based diagnosis with the final histopathological diagnosis. Conversely, 67 lesions (67/89, 75.28%) were correctly diagnosed for all EUS procedures, with 38 lesions in radial EUS group (38/58, 65.52%) and 29 lesions in linear EUS group (29/31, 93.55%). As shown in Table 2, we found that the overall accuracy of linear EUS was significantly better than radial EUS (0.936 vs. 0.655, $p = 0.003$). The diagnostic sensitivity and the specificity were 0.750 (95% CI 0.301–0.954) and 0.963 (95% CI 0.817–0.993) for linear EUS, and 0.643 (95% CI 0.388–0.837) and 0.659 (95% CI 0.511–0.781) for radial EUS, respectively. A significant difference was also noted for specificity between the two groups (0.963 vs. 0.659, $p = 0.003$). The false-positive rate was 0.037 (95% CI 0.007–0.183) for linear EUS and 0.341 (95% CI 0.219–0.489) for radial EUS. The false-negative rate was 0.250 (95% CI 0.046–0.699) for linear EUS and 0.357 (95% CI 0.163–0.612) for radial EUS. We also evaluated the diagnostic performance of linear EUS and radial EUS for SM_d staging using receiver operating curve (ROC), and the area under the ROC was 0.856 and 0.651 for linear and radial EUS, respectively (Fig. 3).
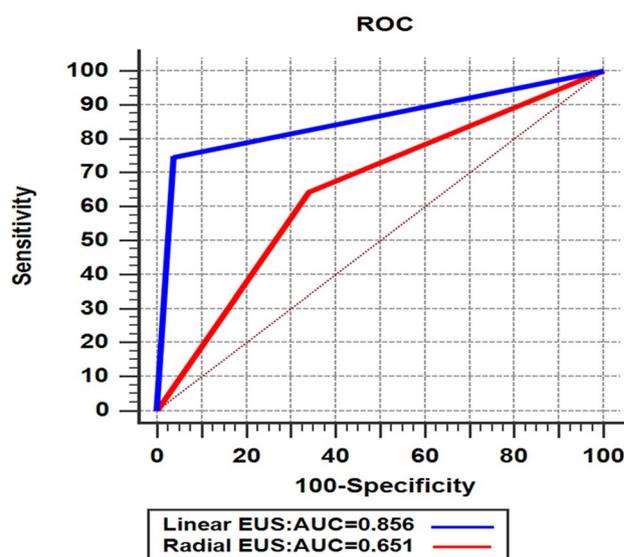

Fig. 3 ROC curve between radial EUS and linear EUS method in predicting deep submucosal invasion in non-pedunculated rectal polyp

Risk factors associated with incorrect diagnosis of SM_d invasion in patients with non-pedunculated rectal polyp

We reviewed the incorrect diagnosis of all enrolled patients to identify risk factors related to the misdiagnosis. Possible factors for incorrect EUS diagnosis that were analyzed included tumor size, tumor location, endoscopic morphology, pathologic type, and EUS examination type. Univariate analysis showed that EUS type (OR 0.131, 95% CI 0.028–0.606, $p = 0.009$) was a risk factor of incorrect SM_d invasion (Table 3). Furthermore, multivariate analysis confirmed that EUS type (OR 0.153, 95% CI 0.032–0.743, $p = 0.020$) was a risk factor of incorrect T1b staging in NPCP patients (Supplementary Table 1). Radial EUS examination was associated with more incorrect diagnosis compared with linear EUS. No complications such as perforation or bleeding were observed during the EUS examination procedures. The most common reason of the misdiagnosis was over-staging, which occurred in 16 lesions (16/22, 72.73%). It was noted that four misdiagnosed patients (4/20, 20%) underwent unnecessary surgery in the radial EUS group while there were no patients who underwent unnecessary surgery in the

Table 2 Comparison of diagnostic efficiency between linear EUS and radial EUS group in patients with non-pedunculated rectal polyp

Statistics	Radial EUS	Linear EUS	*p* value
Accuracy, [95%CI]	0.655 [0.527,0.764]	0.936 [0.793,0.982]	0.003
Sensitivity, [95%CI]	0.643 [0.388,0.837]	0.750 [0.301,0.954]	0.999
Specificity, [95%CI]	0.659 [0.511,0.781]	0.963 [0.817,0.993]	0.003
False-positive rate, [95%CI]	0.341 [0.219,0.489]	0.037 [0.007,0.183]	0.003
False-negative rate, [95%CI]	0.357 [0.163,0.612]	0.250 [0.046,0.699]	0.999

Table 3 Associated factors for incorrect T1b staging in patients with non-pedunculated rectal polyp

Variables	Univariate OR	95% CI		p value
		Lower	Upper	
Distance from anus	1.041	0.918	1.180	0.530
Maximum diameter	1.019	0.992	1.047	0.163
Endoscopic morphology				
Sessile and flat	1 (reference)			
LST	1.400	0.528	3.709	0.499
Pathological type				
Adenomatous polyp	1 (reference)			
Adenocarcinoma	2.656	0.968	7.291	0.058
EUS type				
Radial EUS	1 (reference)			
Linear EUS	0.131	0.028	0.606	0.009

linear EUS group, suggesting that linear EUS contributed to accurate decision-making.

Discussion

Accurate prediction of invasion depth less than SM_d is essential for proceeding with endoscopic resection. To date, this is the first prospective study comparing linear EUS and radial EUS for prediction of SM_d invasion in non-pedunculated rectal polyp. Significant higher accuracy (0.936 vs. 0.655) and specificity (0.963 vs. 0.659) were observed in linear EUS.

Although estimation of the invasion depth based on the gross morphology, NBI or MCE has been reported to be useful in previous studies, its diagnostic accuracy was not established [7–9]. A recent study showed that the NBI classification system identified colorectal lesions with deep invasion with 58.4% sensitivity (95% CI 47.5–68.8) and 96.4% specificity (95% CI 95.5–97.2) [7]. Another study demonstrated that the sensitivity and specificity for optical diagnosis of endoscopically unresectable lesions (i.e., $\geq$ T1 CRC with deep invasion) in large NPCP were 63.3% (95% CI 43.9 to 80.1) and 99.0% (95% CI 97.1 to 100.0), respectively [13]. These studies suggest that NBI classification system is inadequate for clinical decision-making. A systematic review compared NBI and MCE in the differential diagnosis of SM_d colorectal cancers from SM_s colorectal cancers and found that these two methods had comparable specificities in diagnosing SM_d, though the sensitivity of NBI was slightly lower than that of MCE [8]. There were also several studies comparing MCE with EUS for the prediction of invasion depth of early CRC [14–18]. Two such prospective studies demonstrated superiority of EUS (91.8–93%) to MC (59–63.3%) with regard

to accuracy [16, 17]. Another study showed that MCE and EUS are equally accurate in estimating the invasion depth of early-stage CRC lesions, and the study also pointed out that neither procedure had sufficient diagnostic accuracy to be used as the standard [18]. All these data pertaining to EUS were obtained by using high-frequency 20 MHz miniprobe or radial EUS and the diagnostic accuracy of linear EUS for estimating the depth of invasion remains unclear. In our prospective study, linear EUS yielded a high accuracy of 0.936, a sensitivity of 0.750, and specificity of 0.963, demonstrating to be a promising modality with good diagnostic efficiency. The reason for better performance of the linear EUS may be attributed to better image resolution. The main problem of all the EUS diagnosis was over-staging, especially with radial EUS, with a false-positive rate of 34.1%. The over-staging of radial EUS directly lead to four cases of unnecessary surgery in this study, while there was no patient undergoing unnecessary surgery in linear EUS group. We also analyzed various factors affecting the diagnostic accuracy of EUS in non-pedunculated rectal polyp. As demonstrated by our data, EUS type was an independent risk factor of incorrect diagnosis and linear EUS was associated with less incorrect cases compared with radial EUS. It should be noted that linear array EUS can only be easily manipulated in the rectum, and it is not suitable for other parts of colon due to the high risk of perforation.

To our knowledge, this study is the first study to report the pre-resection accuracy of linear EUS for diagnosis of SM_d invasion in non-pedunculated rectal polyp. There are a few limitations to this study. First, this prospective study was conducted without randomization and therefore selection bias should be considered. Second, this is not a tandem study with the two methods each performed in different patients, which may limit the generalizability of the study results.

In conclusion, linear EUS yielded higher accuracy and specificity than radial EUS for the diagnosis of SM_d invasion in non-pedunculated rectal polyp, and it contributed to better clinical decision-making. The method could be widely applied in clinical practice for preoperative assessment in experienced centers. However, large-scale randomized controlled study is further needed to confirm the diagnostic efficiency of linear EUS in differentiating M-SM_s from SM_d invasion in non-pedunculated rectal polyp.

Compliance with ethical standards

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