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Value of endorectal ultrasonography in the assessment of invasion staging of low rectal cancer with local progression after neoadjuvant radiochemotherapy.

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Key words: endorectal ultrasonography; low rectal cancer; local progression; neoadjuvant radiochemotherapy; invasion; staging.

Abstract. Although stages T3 and T4 rectal cancer can be reduced to T1 or T2 after neoadjuvant radiochemotherapy, the accuracy of the endorectal ultrasonography (ERUS) for the post-radiochemotherapy evaluation of low rectal cancer has seldom been reported. We aimed to investigate the value of ERUS in the assessment of invasion staging in low rectal cancer with local progression, and the factors affecting its accuracy, after neoadjuvant radiochemotherapy. A total of 114 patients administered with neoadjuvant radiochemotherapy for stages II and III low rectal cancer (local stage T3/T4) from February 2018 to December 2020 were enrolled in the study. The changes in local lesions were evaluated using ERUS before and after radiochemotherapy, and compared with the pathological T staging. The accuracy of post-neoadjuvant radiochemotherapy re-staging examined with ERUS was evaluated, and univariate analysis was used to identify the factors affecting the accuracy. After neoadjuvant radiochemotherapy, the blood flow distribution within the lesion significantly declined ($P<0.05$), the max length and max thickness of the longitudinal axis of the lesion were reduced ($P<0.05$), and the uT staging was decreased ($P<0.05$), when compared with lesions before the treatment. Compared with postoperative pathological T staging, the accuracies of ERUS in T1, T2, T3 and T4 stages were 11.11%, 28.57%, 27.27% and 100%, respectively. Univariate analysis

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indicated that review time of ERUS, post-operative T staging and Wheeler rectal regression stage were factors affecting the accuracy of ERUS re-staging. ERUS is more accurate for T4 re-staging, follow-up reviewed six weeks after neoadjuvant radiochemotherapy and low regression tumors, with a high application value for the assessment of the efficacy of neoadjuvant radiochemotherapy for low rectal cancer.

Valor de la ultrasonografía endorectal en la evaluación de la estadificación de la invasión del cáncer rectal bajo con progresión local, después de administrar radioquimioterapia neoadyuvante.

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Palabras clave: pancreatitis; cloruros; soluciones isotónicas; tiempo de internación.

Resumen. Aunque el cáncer de recto en estadios T3 y T4 se puede reducir a T1 o T2 después de la radioquimioterapia neoadyuvante, rara vez se ha informado la precisión de la ecografía endorrectal (ERUS) para la evaluación posterior a la radioquimioterapia del cáncer de recto inferior. Nuestro objetivo fue investigar el valor de ERUS en la evaluación de la estadificación de la invasión en el cáncer de recto inferior con progresión local, después de la radioquimioterapia neoadyuvante y los factores que afectan su precisión. Se incluyeron en el estudio un total de 114 pacientes a los que se les administró radioquimioterapia neoadyuvante para el cáncer de recto inferior en estadios II y III (estadio local T3/T4), desde febrero de 2018 hasta diciembre de 2020. Los cambios en las lesiones locales se evaluaron mediante ERUS antes y después de la radioquimioterapia y se compararon con la estadificación patológica T. Se evaluó la precisión de la re-estadificación examinada con ERUS, después de la radioquimioterapia neoadyuvante y se utilizó un análisis univariado para identificar los factores que afectan su precisión. Después de la radioquimioterapia neoadyuvante, la distribución del flujo sanguíneo dentro de la lesión disminuyó significativamente (P<0,05), la longitud máxima y el espesor máximo del eje longitudinal de la lesión se redujeron (P<0,05) y la estadificación uT disminuyó (P<0,05), en comparación con las lesiones antes del tratamiento. En comparación con la estadificación T patológica posoperatoria, las precisiones de ERUS en las etapas T1, T2, T3 y T4 fueron del 11,11%, 28,57%, 27,27% y 100%, respectivamente. El análisis univariable indicó que el tiempo de revisión de ERUS, la estadificación T postoperatoria y la etapa de regresión rectal de Wheeler fueron factores que afectaron la precisión de la re-estadificación con ERUS. ERUS es más preciso para la re-estadificación de T4, el seguimiento seis semanas después de la radioquimioterapia neoadyuvante y en tumores de baja regresión, con un alto valor de aplicación para la evaluación de la eficacia de la radioquimioterapia neoadyuvante para el cáncer rectal bajo.

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INTRODUCTION

Rectal cancer is a common malignancy of the digestive system, and the incidence rate exhibits an increasing trend annually[1]. Different stages of rectal cancer should be administered with different therapeutic strategies. Local resection is feasible for early-stage rectal cancer, and standard treatment mode, neoadjuvant radiochemotherapy combined with radical surgery, is recommended for locally advanced rectal cancer[2]. Neoadjuvant radiochemotherapy helps to reduce tumor size, degrade the staging, increase the sphincter preservation rate, reduce local recurrence rate and prolong the survival time of patients [3,4]. The "watch-and-wait" strategy can be adopted for rectal cancer patients with clinical complete response after neoadjuvant radiochemotherapy. Hence, tumors should be accurately re-staged after neoadjuvant therapy.

The endorectal ultrasonography (ERUS) offers an important means for preoperative staging of the primary lesion of rectal cancer, characterized by low cost, high efficiency, and accurate rectal wall stratification, and it is far superior to magnetic resonance imaging (MRI) in the differential diagnosis of T1 and T2 stages [5,6]. Although stages T3 and T4 rectal cancer will be reduced to T1 or T2 after neoadjuvant radiochemotherapy, there are currently only few reports on the accuracy of ERUS in the post-radiochemotherapy evaluation of low rectal cancer [7]. In this study, ERUS was utilized to evaluate the primary lesion of stage T3 and T4 low rectal cancer before and after neoadjuvant radiochemotherapy, aiming to evaluate the accuracy of ERUS after radiochemotherapy and before surgery, and to investigate the correlations between clinical indices and accuracy.

MATERIALS AND METHODS

A total of 114 patients diagnosed as low rectal cancer in our hospital from February 2018 to December 2020 were enrolled, including 69 males and 45 females, aged (57.3±6.2) years old. Digital anal examination showed that the distance between the tumor lower edge and the anal verge was 4-7 cm. The inclusion criteria were as follows: a) patients who were diagnosed with stage II or III low rectal cancer (regional stage T3/T4) by ERUS and MRI for the first time, and ultrasound probe could scan the tumor completely through the intestinal cavity. b) those who had no surgical contraindications, and were administered with surgery at eight weeks after neoadjuvant radiochemotherapy (2 Gy/time, 22 times, for a total radiotherapy dose of 44 Gy, while oral capecitabine 2500 mg/(m^2·d), bid for two weeks followed by one week rest as one cycle, for two cycles. And c) those who underwent neoadjuvant radiochemotherapy and total mesorectal excision, with ERUS examination at 4-8 weeks after neoadjuvant therapy and before surgery, and postoperative pathological staging and Wheeler rectal cancer regression grade (RCRG). The exclusion criteria involved: a) patients whose dosage of neoadjuvant radiochemotherapy did not reach the standard, or b) those whose radical excision did not reach the requirement. In the present study, the staging standard met the National Comprehensive Cancer Network (NCCN) guidelines of 2014.

METHODS

Philips iU 22 color Doppler ultrasound system (Netherlands) with C8-4V intracavitary ultrasonic probe was selected. The frequency of ERUS was 5-10 MHz. The probe was inserted into the rectal cavity to complete a "360-degree view" of the tumor. The location, length, diameter, shape, echo, and depth of invasion, followed by the number, size, and echo of the peri-intestinal lymph nodes were observed, and the blood flow distribution in the lesion, the max length of the longitudinal axis of the lesion, the max thickness of the tumor, and T staging (T1: hypoechoic shadow is confined to the first three layers; T2: hypoechoic shadow is present in the fourth

layer, but the fifth layer is smooth; T3: hypoechoic shadow is present in the fifth layer; T4: hypoechoic shadow is present in the intestinal lining and partly surrounding tissues or organs) were determined. Color Doppler blood flow imaging grading was performed according to the intensity of blood flow signals: grade 0: no blood flow signal, grade I: blood flow signals of focal region, grade II: multi-point and strip blood flow signals, and grade III: large amounts of dot and strip blood flow signals. ERUS was compared with pathological T staging to evaluate under-stage, over-stage and accuracy, and the correlations of patient's age, gender, distance between the lower edge of the tumor and the anus, review time of ERUS, nerve invasion, vascular invasion, lymph node metastasis, postoperative T staging and Wheeler rectal cancer regression grade with ERUS re-staging accuracy after neoadjuvant radiochemotherapy were subjected to univariate analysis to identify the factors affecting the accuracy.

STATISTICAL ANALYSIS

SPSS 20.0 software was employed for statistical analysis. Numerical data were expressed as percentage [n (%)] and analyzed using chi-square test. Measurement data were expressed as mean ± standard deviation ($\bar{\chi} \pm s$), and *t*-test was used for comparison between two groups. The factors affecting the accuracy of post-neoadjuvant radiochemotherapy re-staging examined with ERUS was evaluated by logistic regression analysis. $P<0.05$ indicated that the difference was statistically significant.

RESULTS

Changes in indices after neoadjuvant radiochemotherapy with ERUS

ERUS showed that the blood flow distribution within the lesion significantly declined ($\chi^2=159.723$, $p<0.001$) after neoadjuvant radiochemotherapy, when compared with the pre-treatment lesion. The max length of the longitudinal axis of the lesion and the max thickness of the tumor were reduced [(5.38±0.34) cm *vs.* (2.15± 0.14) cm, (3.03±0.24) cm *vs.* (0.96±0.12) cm] ($t=93.792$, $p<0.001$; $t=82.368$, $p<0.001$). Compared with before pre-neoadjuvant radiochemotherapy, uT staging had a significant difference after neoadjuvant radiochemotherapy ($\chi^2=58.455$, $p<0.001$) (Table 1).

Table 1
Changes in indices after neoadjuvant radiochemotherapy with ERUS (n=114).

Group	Pre-neoadjuvant radiochemotherapy	Post-neoadjuvant radiochemotherapy	χ^2/t	p
Blood flow (n)			$\chi^2=159.723$	<0.001
0	0	42		
□	0	51		
□	51	15		
□	63	6		
Max length (cm)	5.38±0.34	2.15±0.14	t=93.792	<0.001
Max thickness (cm)	3.03±0.24	0.96±0.12	t=82.368	<0.001
uT stage(n)			$\chi^2=58.455$	<0.001
T1	0	12		
T2	0	36		
T3	63	52		
T4	51	24		

ERUS and pathological T staging after neoadjuvant radiochemotherapy

Compared with postoperative pathological T staging, ERUS showed 88.89% of over-stage in T1 stage, 21.43% of under-stage and 50% of over-stage in T2 stage, 45.45% of under-stage and 27.27% of over-stage in T3 stage, 0 of under-stage and over-stage in T4 stage, and 21.05% of under-stage and 47.37% of over-stage in T stage (overall), and the accuracies of ERUS in T1, T2, T3, T4 and T stages (overall) were 11.11%, 28.57%, 27.27%, 100% and 31.58%, respectively (Table 2).

Clinicopathological factors affecting ERUS re-staging accuracy after neoadjuvant radiochemotherapy

Univariate and multivariate logistic analyses indicated that review time of ERUS, post-operative T staging and Wheeler rectal regression stage were factors affecting ERUS re-staging accuracy. ERUS was more accurate in patients with review time of ERUS ≥6 weeks after neoadjuvant radiochemotherapy, ypT4 and RCRG3 (Tables 3 and 4).

DISCUSSION

The incidence rate of low rectal cancer is higher among colorectal tumors. The anatomical structure of the low rectum is different from that of the high rectum, and the effect of radical surgery is poor for low locally advanced rectal cancer in the past, with a poor prognosis. With the extensive development, the role of neoadjuvant radiochemotherapy with the advantages of increasing the radical cure rate of low locally advanced rectal cancer, reducing the recurrence rate, increasing the sphincter preservation rate and prolong the survival time, has been confirmed [7,8]. In the NCCN guidelines, it has been definitely proposed to perform neoadjuvant radiochemotherapy for stages II and III low rectal cancer (regional stage T3 and T4). For low rectal cancer within 5 cm from the anus, ERUS has unique advantages [9]. In a previous study, it showed that the accuracy of ultrasound is 63-96% in the preoperative staging of low rectal cancer, which is 87-98% in MRI [10]. However, there are still few reports on the evaluation value of ERUS after neoadjuvant radiochemotherapy and before surgery.

The accuracy of ultrasound in different locations of rectal cancer differs greatly during the determination of the degree of invasion of the primary rectal cancer. Especially, ultrasound endoscopic scanning is required for middle and upper rectal cancer, which greatly affects the accuracy, but for low rectal cancer, intracavitary ultrasound probes can easily and completely scan the primary lesion to evaluate the length, thickness, depth of invasion, blood flow, and circumferential margins [11,12]. Under ERUS, the normal rectal wall is a 5-layer structure with a thickness of 2-3 mm with alternating high and low echoes, containing mucosa, mucosal muscle, submucosa, propria muscle, serous membrane and subserosal layer, surrounding with adipose tissues, mesangial fascia

Table 2
EURS and pathological T staging after neoadjuvant radiochemotherapy.

	EURS stage(n)				Total	EURS stage		
	uT1	uT2	uT3	uT4		Over staging	Underestimate staging	Accuracy
ypT1	3	9	15	0	27	0	88.89% (24/27)	11.11% (3/27)
ypT2	9	12	18	3	42	21.43% (9/42)	50.00% (21/42)	28.57% (12/42)
ypT3	0	15	9	9	33	45.45% (15/33)	27.27% (9/33)	27.27% (9/33)
ypT4	0	0	0	12	12	0	0	100.00%(12/12)
Total	12	36	52	24	114	21.05% (24/114)	47.37%(54/114)	31.58% (36/114)

outside the adipose tissues, and the primary lesion is characterized by irregularly shaped masses, with uneven low echoes, some multiple micro-calcifications, different depths of invasion into intestinal wall, disappearance of normal intestinal wall structure, abundant arteriovenous blood flow in the tumor, and high resistance of arterial blood flow [13,14].

Table 3
Univariate analysis results of factors affecting ERUS re-staging accuracy after neoadjuvant radiochemotherapy

Item	n	ERUS stage		χ^2	p
		Accurate (n=36)	Inaccurate (n=78)		
Age (years)				1.661	0.197
≤60	48	12	36		
>60	66	24	42		
Gender				3.013	0.083
Male	69	26	43		
Female	45	10	35		
Distance from low margin of tumor to anus (cm)				2.537	0.111
<3	60	15	45		
≥3	54	21	33		
Follow up check of ERUS (weeks)				9.204	0.002
<6	42	6	36		
≥6	72	30	42		
Nerve invasion				0.506	0.477
Negative	93	28	65		
Positive	21	8	13		
Vessel invasion				0.050	0.822
Negative	27	9	18		
Positive	87	27	60		
Lymph node metastasis				0.201	0.654
Negative	51	15	36		
Positive	63	21	42		
Post-operation stage				37.948	<0.001
ypT1	27	3	24		
ypT2	42	12	30		
ypT3	33	9	24		
ypT4	12	12	0		
PCRG				21.732	<0.001
PCRG1	33	3	30		
PCRG2	39	9	30		
PCRG3	42	24	18		

Table 4
Multivariate logistic analysis results of factors affecting ERUS re-staging accuracy after neoadjuvant radiochemotherapy.

Item	Regression coefficient	Standard error	Wald χ^2	OR	95% CI	p
Review time of ERUS ≥6 weeks	2.203	0.297	5.389	1.727	1.063~2.804	0.004
ypT4	2.687	0.172	6.835	2.010	1.928~4.400	0.000
PCRG3	2.236	0.238	4.623	2.581	1.689~3.479	0.022
Constant term	1.784	0.348	76.436	6.053		0.006

After neoadjuvant radiochemotherapy, the primary tumor is prone to pathological features such as necrosis, fibrosis, reduced density, and decreased blood supply, and the original 5-layer structure of the intestinal wall is destroyed, so that MRI or ERUS re-staging accuracy is poor [15]. Compared with before pre-neoadjuvant radiochemotherapy, ERUS showed that the blood flow distribution within the lesion significantly declined, the max length of the longitudinal axis of the lesion and the max thickness of tumor were significantly reduced, most stage T3 or T4 rectal cancer was reduced to T1 or T2, and the uT staging was decreased after neoadjuvant radiochemotherapy.

These results demonstrated that ERUS is of clinical guiding significance in the evaluation of tumor length, thickness and blood flow after radiochemotherapy, and can effectively evaluate the efficacy of adjuvant therapy. Compared with postoperative pathological T re-staging, the results displayed that ERUS showed 88.89% of over-stage in T1 stage, 21.43% of under-stage and 50% of over-stage in T2 stage, 45.45% of under-stage and 27.27% of over-stage in T3 stage, 0 of under-stage and over-stage in T4 stage, and 21.05% of under-stage and 47.37% of over-stage in T stage (overall), and the accuracy of ERUS in T1, T2, T3, T4 and T stage (overall) was 11.11%, 28.57%, 27.27%, 100% and 31.58%, respectively. The above results suggested that ERUS has extensive under-stage in T1 and T2 stages, and the accuracy is extremely poor. The reason may be that neoadjuvant therapy is absolutely effective for the primary lesion of T1 and T2 re-staging, and the 5-layer structure of the intestinal wall is difficult to distinguish. Because of tumor regression, fibrous interstitial tissue proliferation, reduced distribution of tumor cells in the interstitium, and decreased blood flow of the tumor, the accuracy of the stratification of the mucosal layer, mucosal muscle, submucosal layer and muscularis propria is poor, and the fibrous interstitial tissue with incomplete shrinkage may be mistaken for residual tumors, resulting in excessive staging [16]. A previous study indicated that the total accuracy of ERUS T staging after neoadjuvant radiochemotherapy is 48%, with 38% of over-staging and 14% of under-staging, tumor regresses notably in the primary tumor that is sensitive to radiochemotherapy, and the accuracy of re-staging is poor [17], similar to the results of this study. The results of this study showed that ERUS was more accurate for T4 re-staging, because T4 re-staging indicates ineffective or extremely poor effect of neoadjuvant radiochemotherapy. Studies have displayed that the accuracy of ERUS and MRI is close to 100% in T4 stage with larger tumor, so the depth of invasion is more accurate, and the evaluation accuracy is higher. Further univariate analysis showed that review time of ERUS, postoperative T staging and Wheeler rectal cancer regression grade are factors

affecting ERUS re-staging accuracy in low rectal cancer. The accuracy is higher in patients with review time of ERUS ≥6 weeks. The reason may be that the edema begins to subside 4 weeks after radiotherapy, and the boundary of tumor regression is more obvious, achieving the maximum effect at 6-8 weeks. Hence, ERUS can more accurately distinguish the intestinal wall level after six weeks. Patients with ypT4 and PCRG3 have poor response of tumor to radiochemotherapy, consistent with RCR3 of regression, and higher accuracy of T4 staging mentioned above. ERUS is poorly accurate for regional re-staging of obvious regression after radiochemotherapy, and more accurate for T4 re-staging of unobvious regression after radiochemotherapy. Besides, different operators with experience, different types of probes and fuselages are also factors that affect the results of ERUS.

In conclusion, ERUS can effectively allow the evaluation of the efficacy of low rectal cancer after neoadjuvant radiochemotherapy, including length, volume and blood flow. However, it is poorly accurate for those with prominent effect of neoadjuvant radiochemotherapy and T staging with effective regression, and more accurate for those primary lesions with non-prominent effect of neoadjuvant radiochemotherapy and poor tumor regression. Besides, ERUS has a higher accuracy for the review time at 6 weeks after neoadjuvant radiochemotherapy. Regardless, this study still has limitations. First, the sample size is small, and further verification is needed with a large population. Second, the scan range of ERUS is limited, which cannot display tumors in the upper rectal segment. Third, ERUS does not work well for rectal cancer in the immediate vicinity of the anus or mesorectal lymph nodes. Particularly, patients after receiving neoadjuvant radiotherapy probably cannot tolerate the pain during examination because the mucosa is damaged.

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Authors contribution

SG and CS designed this study and prepared this manuscript; LY, HY, JH, ZY and XW performed this study and analyzed the clinical data. All authors have approved the submission and publication of this manuscript.

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