Selective lateral lymph node dissection after neoadjuvant chemoradiotherapy in rectal cancer

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BACKGROUND
Lateral lymph node metastasis is one of the leading causes of local recurrence in patients with advanced mid or low rectal cancer. Neoadjuvant chemoradiotherapy (NCRT) can effectively reduce the postoperative recurrence rate; thus, NCRT with total mesorectal excision (TME) is the most widely accepted standard of care for rectal cancer. The addition of lateral lymph node dissection (LLND) after NCRT remains a controversial topic.

AIM
To investigate the surgical outcomes of TME plus LLND, and the possible risk factors for lateral lymph node metastasis after NCRT.

METHODS
This retrospective study reviewed 89 consecutive patients with clinical stage II-III mid or low rectal cancer who underwent TME and LLND from June 2016 to October 2018. In the NCRT group, TME plus LLND was performed in patients with short axis (SA) of the lateral lymph node greater than 5 mm. In the non-NCRT group, TME plus LLND was performed in patients with SA of the lateral lymph node greater than 10 mm. Data regarding patient demographics, clinical workup, surgical procedure, complications, and outcomes were collected. Multivariate logistic regression analysis was performed to evaluate the possible risk factors for lateral lymph node metastasis in NCRT patients.

RESULTS
LLN metastasis was pathologically confirmed in 35 patients (39.3%): 26 (41.3%) in the NCRT group and 9 (18.8%) in the non-NCRT group. The incidence and extent of LLN metastasis did not differ significantly between the two groups. The most common complications were gastrointestinal perforation and wound infection. The overall complication rate was not significantly different between the two groups.

CONCLUSION
Selective lateral lymph node dissection after neoadjuvant chemoradiotherapy in rectal cancer can effectively reduce the risk of local recurrence. Further study is needed to determine the optimal approach for lateral lymph node dissection.
INTRODUCTION

Lateral lymph node metastasis in mid and low rectal cancer was first described in 1895 by Gerota using dye injection. Since then, many anatomical and pathological studies have divided the rectal lymphatic drainage into three main directions: Upward, lateral, and downward. Among them, lateral lymphatic drainage nodes comprise an important rectal approach below the peritoneal reflection. According to the Japanese Classification of Colo-rectal, Appendiceal, and Anal Carcinoma: The 3rd English Edition, lateral lymph nodes are two groups of lymph nodes: One group along the internal iliac arteries and the obturator vessels and nerves, and the other along the common iliac, external iliac, and median sacral arteries. The incidence of lateral lymph node metastasis from lower rectal cancer is about 15% \[1\], whereas the incidence of lateral lymph node metastasis in T3 and T4 patients is reported in more than 20% of cases \[2\]. Local recurrence of rectal cancer, specifically lateral local recurrence, remains a significant clinical problem associated with severe morbidity, low salvage likelihood, and eventual death in the majority of patients \[3\]. There is a lack of consensus leading to an East (mainly Japan)-West divide concerning the management of lateral lymph nodes associated with lower rectal cancer. Preoperative chemoradiotherapy followed by total mesorectal excision is a standard procedure in the west. Our study shows that lateral lymph node metastasis cannot be eradicated by neoadjuvant chemoradiotherapy. Selective total mesorectal excision plus lateral lymph node dissection should be performed in advanced mid or low rectal cancer patients.

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inevitably results in a longer operative time and increased blood loss compared to TME alone. The adoption of NCRT followed by TME has demonstrated increased local control resulting in local recurrence in less than 10% of cases\cite{11}. On the other hand, the Japanese Society for Cancer of the Colon and Rectum cites different guidelines for the treatment of rectal cancer and recommends LLND for advanced rectal cancer that extends below the peritoneal reflection to address the possibility of LLN metastasis\cite{12}. Several studies from Japan argue that LLN metastasis should be considered a local disease rather than systemic disease, and that LLND can significantly reduce local recurrence rates\cite{6,13}. In recent years, a growing body of evidence has supported conflicting standard strategies in both Japan and Western countries, culminating in similar local recurrence rates\cite{14}. Recent studies have suggested that perhaps a middle-ground selective LLND should be considered after preoperative chemoradiotherapy based on magnetic resonance imaging/computed tomography (MRI/CT) findings\cite{15,16}.

In China, preoperative chemoradiotherapy followed by TME is still the standard of care, as most surgeons do not perform an LLND most commonly citing extended operative time and potential nerve damage as the reason. We collected data from 89 consecutive patients with mid or low rectal cancer who underwent TME plus LLND in this study to investigate the therapeutic effect of preoperative CRT on LLN metastasis and identify the associated risk factors.

**MATERIALS AND METHODS**

**Patients**

The study was approved by the ethics committee of the National Cancer Center and conformed to the ethical standards of the World Medical Association Declaration of Helsinki. All patients signed an informed consent form. A total of 89 mid or low rectal cancer patients who underwent TME plus LLND at the National Cancer Center/National Sciences Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College from June 2016 to October 2018 were consecutively collected in this study. The inclusion criteria of this study were as follows: (1) Histologically confirmed adenocarcinoma of the middle or low rectum (the distal verge of the tumor located below the peritoneal reflection); (2) All patients were confirmed to have clinical tumor-node-metastasis stage II-III by MRI/CT at the time of diagnosis; and (3) All patients underwent TME plus LLND. Patients with distant metastasis were excluded.

**Treatment strategy**

Treatment strategies for each patient were determined by a multidisciplinary meeting and the patient’s wishes. In the NCRT group, patients received short-course radiotherapy for a total dose of 25 Gy or received 5-fluorouracil-based NCRT, with a total dose of 45 Gy or 50.4 Gy before surgery. Both the obturator and internal iliac compartments were included in the standard radiation field. MRI after 4 wk of NCRT were done to evaluate swollen lymph nodes. Patients with swollen lymph nodes with an SA ≥ 5 mm underwent LLND plus TME. The operation was carried out within 1 wk after short-course radiotherapy or 8 wk after the end of a long-course NCRT. For patients without NCRT, if the lateral swollen lymph nodes with an SA ≥ 10 mm, TME plus LLND were performed. All patients were placed in the modified lithotomy position after anesthesia. They all underwent TME with LLND. The pelvic peritoneum was opened, and the hypogastric nerves were identified and preserved. LLND included six regions: Common iliac, internal iliac, external iliac node, obturator, aortic bifurcation, and median sacral regions\cite{17}. Typically, the external iliac node and median sacral region are not dissected because of a low metastatic incidence. The probability of bilateral lymph node metastasis is extremely low and results in a significantly higher postoperative complication rate, longer operation time, and more bleeding. Thus, bilateral lymph node dissection is not routinely performed unless the MRI/CT strongly suggests bilateral lymph node involvement\cite{19,20}.

**Pathological diagnosis**

After resection of the surgical specimens, LLNs are separated according to the anatomical position, fixed in formalin, and sent for pathological examination. The tumor stage was decided by professional pathologists according to the 7th and 8th edition of the American Joint Committee on Cancer.

**Statistical analysis**

The Statistical Package for the Social Sciences version 21.0 for Windows (IBM Corp,
Armonk, NY, United States) was used for data analyses. Quantitative data are shown as the mean ± standard deviation and were analyzed by a t-test. Categorical data are shown as frequencies and percentages and were analyzed by the χ² or Fisher’s exact test as appropriate. Univariate logistic regression analysis was used to evaluate the association between lateral lymph node metastasis and various parameters. Multivariate logistic regression analysis was performed to examine the predictors of lateral lymph node metastasis to calculate the 95% confidence intervals (CIs) for each risk factor, and differences were considered statistically significant when \( P < 0.05 \). The data were statistically reviewed by a biomedical statistician from the National Cancer Center.

**RESULTS**

The demographics of 89 rectal cancer patients treated with TME plus LLND at the National Cancer Center/Chinese Academy of Medical Sciences are summarized in **Table 1**. Clinical T3 and T4 rectal cancer accounted for 60.7% and 39.3% of the cases, respectively, and clinical N1 and N2 stage accounted for 56.2% and 43.8%, respectively. Among the 89 patients, 63 received neoadjuvant therapy. Of these, three received short-course radiotherapy (25 Gy administered doses of 5 Gy over 5 d) and underwent TME plus LLND within 1 wk. Sixty patients received 5-fluorouracil-based long-course NCRT (45-50.4 Gy administered in 25-28 fractions), and then surgery after an 8-wk interval. Twenty-six patients were treated with TME plus LLND directly without receiving any NCRT. **Table 2** shows the surgery-related data. Two patients initially received laparoscopic surgery that was subsequently converted to open surgery, while the others underwent a laparoscopic TME plus LLND. Low anterior resection was done in 44 (49.4%) patients. Unilateral and bilateral LLNDs were performed in 76 (85.4%) and 13 (14.6%) patients, respectively. Nine (10.1%) patients received a temporary ileum stoma during the surgery.

Fifteen patients (16.8%) had postoperative complications reported after LLND (**Table 3**). According to the Clavien-Dindo classification[21], most of the patients developed to Grade II or Grade III complications, there were no grade IV or grade V postoperative complications. Four (4.5%) patients suffered an anastomotic leakage, three of which received an ileostomy while the fourth recovered after conservative treatment. Two (15.4%) of thirteen bilateral LLND patients were discharged from the hospital with an indwelling catheter due to urinary retention. In both cases, after 4 wk of bladder training, the catheter was successfully removed. Tissue liquefaction occurred in three (3.4%) patients, after a careful dressing change, and the wound finally healed well. Four (4.5%) patients had small bowel obstruction, and they all recovered with conservative medical treatment.

The median follow-up duration was 24.5 mo (range 6-38 mo). During follow-up, mortality occurred in 8 (9.0%) patients due to distant metastasis and the 2-year disease-free survival was 80.9%. Two (2.2%) patients suffered lateral local recurrence during follow-up and both underwent unilateral LLND.

**Table 4** describes the pathological outcomes. Thirty-five (39.3%) patients were pathologically confirmed with lateral lymph node metastasis. Of these, 26 (41.3%, 26/63) patients received NCRT before surgery, while 9 (34.6%, 9/26) did not receive NCRT. Moreover, the pathological results revealed that the obturator region was the location with the highest lymph node metastasis involvement, accounting for 60.0% in the 35 patients. Twelve (34.3%) cases of LLNs metastasis were in the internal iliac region and two (5.7%) were located at the bifurcation of the abdominal aorta. An R0 margin status was observed in 87 (97.8%) cases, while the other 2 patients had a positive circumferential resection margin.

**Table 5** depicts an LLN metastatic rate for different cutoff values along the short axis (SA) in patients who received preoperative (chemo)radiotherapy. Patients with a SA of LLN ≥ 10 mm after NCRT had the highest positive LLN metastasis rate (51.9%). The pathological positive rates of the SA of 5-7 mm and 7-10 mm were 23.1% and 39.1%, respectively.

**Table 6** summarizes the univariate analysis, which revealed that the clinical T stage \( (P = 0.003) \), histological type \( (P = 0.183) \), and the SA diameter of LLN after NCRT \( (P = 0.135) \) were candidate variables that may be associated with LLN metastasis. After multivariate analysis, clinical T4 stage (95%CI: 1.419-18.508; \( P = 0.013 \)), poor histological type (95%CI: 1.038-15.520; \( P = 0.044 \)), and SA diameter of LLN after NCRT (95%CI: 1.487-38.214; \( P = 0.015 \)) were independent risk factors associated with LLN metastasis.
### Table 1 Patient demographics, *n* = 89

| Variables                        | Value                     |
|----------------------------------|---------------------------|
| Gender, *n* (%)                  |                           |
| Male                             | 51 (57.3)                 |
| Female                           | 38 (42.7)                 |
| Age in yr, mean ± SD             | 54.4 ± 10.1               |
| BMI in kg/m², mean ± SD          | 24.9 ± 4.6                |
| ASA score, *n* (%)               |                           |
| ASA I                            | 13 (14.6)                 |
| ASA II                           | 56 (62.9)                 |
| ASA III                          | 20 (22.5)                 |
| cT stage                         |                           |
| cT3                              | 54 (60.7)                 |
| cT4                              | 35 (39.3)                 |
| cN stage                         |                           |
| N1                               | 50 (56.2)                 |
| N2                               | 39 (43.8)                 |
| Neoadjuvant chemoradiotherapy    |                           |
| No                               | 26 (29.2)                 |
| Short-course radiotherapy        | 3 (3.4)                   |
| Long-course radiotherapy + chemo | 60 (67.4)                 |

ASA: American Society of Anesthesiologists; BMI: Body mass index; SD: Standard deviation.

### DISCUSSION

This study supports the importance of selective LLND after preoperative chemoradiotherapy. Clinical T4 stage, poor histological type, and an SA diameter of LLNs ≥ 7 mm after NCRT were independent and significant risk factors associated with LLNs metastasis in patients with advanced mid or low rectal cancer treated with NCRT. Since the LLN metastatic rate in NCRT patients can be as high as 41.3%, we suggest that selective LLND be performed.

It has been reported that LLN metastasis occurs in 10%-25% of all mid or low rectal cancer patients who did not receive preoperative chemoradiotherapy treatment. Fujita et al. suggested that the incidences of local recurrence in patients without NCRT were 7% and 13% after TME plus LLND or TME alone, respectively. The European MERCURY Study Group similarly reported that 11.7% of rectal cancer patients suffer from LLN metastasis. Still, in western surgical practice, it remains uncommon to perform an LLND in advanced rectal cancer patients as preoperative CRT and TME is the standard protocol. The addition of NCRT has decreased 5-year local recurrence rates from > 25% to approximately 5% to 10%. Yet, a study in South Korea enrolled 366 patients with advanced rectal tumor and showed that TME following preoperative CRT is not enough to control LLNs metastasis. The reported incidence of LLNs metastasis was 12.5% in patients with lymph node SA of 5-9.9 mm and 68.8% in patients with an SA ≥ 10 mm. The LLNs accounted for 82.7% of all local recurrences. Oh et al. published a multicenter retrospective cohort study that included 36 patients with lateral lymph nodes greater than 5 mm after NCRT. All patients received LLND and the pathological results showed 22 (61.1%) patients had LLNs metastasis. These findings indicate that NCRT plus TME or TME plus LLND alone is not sufficient to eradicate LLN metastasis, and LLND should be considered if LLN metastasis is suspected even after chemoradiotherapy. Our data show that the incidence of LLNs metastasis in NCRT patients with SA ≥ 5 mm is 41.3% (26 of 63) and 51.9% (14 of 27) in patients with lymph nodes SA ≥ 10 mm. If these pathological metastases had not been removed by LLND, they may subsequently lead to local recurrence. In the 2-year follow-up period, 2 (2.2%) patients developed local recurrence. Thus, our results suggest that there is an oncological benefit when performing LLND for patients with clinically suspected LLN metastasis after preoperative CRT. In addition, in the present study, after LLND 80.9% of patients did not have a systemic recurrence. Therefore, we believe that LLN metastasis can be regarded as a locoregional disease rather than a systemic one.
procedure because of the complicated anatomy of the pelvic sidewall. The JCOG0212 study showed that the operation time was significantly longer in the TME + LLND group compared with the TME alone group (360 min vs 254 min, \( P < 0.0001 \)), and also blood loss was significantly higher in the TME + LLND group (576 mL vs 337 mL, \( P < 0.0001 \)). In addition, the overall postoperative complication in the LLND + TME group was higher than that in the TME alone group, but without statistical difference (22% vs 16%, \( P = 0.007 \)) [31]. In our study, the most common postoperative complications were anastomotic leakage (4.5%) and bowel obstruction (4.5%), and the overall postoperative complication rate was 16.8%, similar to a previously reported study (18%-38%) [32].

Some studies have pointed out that longer operative time and increased blood loss may increase the postoperative complication rate and thus the criteria for selecting patients for LLND is crucial [6]. Several studies have suggested that LLN size after NCRT is a powerful indicator of pathological LLNs metastasis. The European Society of Gastrointestinal and Abdominal Radiology recommended that size (SA diameter) is a reliable criterion for lymph node staging after neoadjuvant treatment, and should remain the prime criterion for malignancy in that location [33]. Akiyoshi et al [34] analyzed the data of 77 patients with advanced low rectal cancer and suspected LLNs involvement were undergone NCRT and LLND. LLNs metastasis was confirmed in 40.3% of patients. They showed that LLN metastasis was significantly higher in patients with LLN SA > 5 mm. Oh et al [28] as previously described, demonstrated that an LLN greater than 5 mm on post-NCRT MRI was significantly associated with residual tumor metastasis as 61.1% (22 of 36) of patients were found to be pathologically positive. This was comparable to the 41.2% positive rate found in our center where the criteria for LLND if the SA of LLNs greater than 5 mm after NCRT or greater than 10 mm without NCRT. Furthermore, we performed receiver operating characteristic analysis for the sizes of dissected LLNs, and the area under the curve value was 0.686 for the prediction of pathological metastasis (data not shown), which was regarded as low accuracy. In order to identify risk factors correlated with LLN metastasis after CRT, we performed multivariate analysis that revealed that clinical T4 stage (95%CI: 1.419-18.508; \( P = 0.013 \)), poor histological type (95%CI: 1.038-15.520; \( P = 0.044 \)), and SA diameter of LLN after NCRT ≥ 7 mm (95%CI: 1.487-38.214; \( P = 0.015 \)) were independently associated with LLN metastasis.

The performance of TME plus LLND dates back to the 1970s when it was associated with favorable oncological results, but had a high urinary and sexual dysfunction rate [35,36]. To preserve the function of the autonomic nerves, nerve-preserving LLND was developed in the mid-1980s in order to obtain local control with an acceptable quality of life [37]. Georgiou et al [38] conducted a meta-analysis investigating the outcomes of an extended lymphadenectomy versus conventional surgery for rectal
Table 3  Postoperative complications, n = 89

| Variables         | Value, n (%) |
|-------------------|--------------|
| Anastomotic leakage | 4 (4.5)      |
| Urinary retention  | 2 (2.2)      |
| Wound infection    | 3 (3.4)      |
| Bowel obstruction  | 4 (4.5)      |
| Lymphatic leakage  | 1 (1.1)      |
| Pelvic hemorrhage  | 1 (1.1)      |

cancer. Their results suggested that LLND was associated with increased urinary and sexual dysfunction incidence, as one of its included studies suggested that the urinary retention happened in the LLND + TME and TME along group were 16% and 4%, respectively. However, many of the retrospective studies included did not perform nerve-preservation surgeries. The Japanese Research Committee for Colorectal Cancer has emphasized that an autonomic nerve-preserving technique results in better urinary and sexual function[17]. JCOG0212 was the largest randomized clinical trial that has compared postoperative urinary and sexual dysfunction between TME and TME plus LLND in lower rectal cancer patients. They suggested that blood loss was the only independent predictor of early urinary dysfunction and that LLND did not increase sexual dysfunction incidence after rectal cancer surgery. Sexual dysfunction was independently associated with increased age[39,40]. In our study, 2 (2.2%) patients experienced urinary retention, both received bilateral lymph node metastasis and after 4 wk of bladder practice, their catheters were successfully removed. These acceptable functional results might be explained by the relatively mature nerve-preserving techniques in the laparoscopic rectal cancer surgeries. Longer operative time and increased blood loss may associate with higher postoperative complication rates according to some study results[41,42]. Thus, we do not recommend routine bilateral lymph nodes dissection unless there is strong suspicion of bilateral LLNs metastasis[6].

This study had several limitations. First, it was a single-center retrospective analysis and the sample size was relatively small; thus, a multi-center study should be conducted to confirm our conclusions. Additionally, we did not evaluate lateral lymph nodes metastasis in non-NCRT patients due to the small sample size. Next, the rectal cancer patients received either short-course or long-course radiotherapy, which might have caused heterogeneity in the pathological outcomes of the lateral lymph nodes. Third, the follow-up duration was short, because of the low local recurrence rate after NCRT, so longer follow-up may be necessary to evaluate more recurrences. Fourth, we did not study the effect of LLND on sexual functions because of poor medical records.

In conclusion, the present study showed that LLN metastasis cannot eradicate by NCRT and that selective TME plus LLND should be considered in mid or low rectal cancer patients. Our results showed satisfying perioperative and oncological outcomes.
### Table 4 Pathological outcomes

| Variables                                           | Value          |
|-----------------------------------------------------|----------------|
| Tumor size in cm, mean ± SD                         | 4.9 ± 2.3      |
| Differentiation degree, n (%)                       |                |
| Poor                                                | 28 (31.5)      |
| Moderate/well                                       | 61 (68.5)      |
| Pathological LLN metastasis, n (%)                  |                |
| With NCRT                                           | 26 (41.3)      |
| Without NCRT                                        | 9 (34.6)       |
| Position of metastasis, n (%)                       |                |
| Internal iliac                                      | 12 (34.3)      |
| Obturator                                           | 21 (60.0)      |
| Bifurcation of abdominal aorta                      | 2 (5.7)        |
| R status, n (%)                                     | 87 (97.8)      |
| R1                                                  | 2 (2.2)        |

LLN: Lateral lymph node; NCRT: Neoadjuvant chemoradiotherapy; SD: Standard deviation.

### Table 5 Lateral lymph node metastatic rate for different cutoff values in short-axis in patients who received (chemo)radiotherapy, n = 63

| Variables               | Positive, n = 26 | Negative, n = 37 | P value |
|-------------------------|------------------|------------------|---------|
| SA 5-7 mm, n (%)        | 3 (23.1)         | 10 (76.9)        | 0.216   |
| SA 7-10 mm, n (%)       | 9 (39.1)         | 14 (60.9)        |         |
| SA ≥ 10 mm, n (%)       | 14 (51.9)        | 13 (48.1)        |         |

SA: Short-axis.
| Variables                      | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|----------------------|
|                               | P value             | 95% CI               | P value     |
| Sex                           | 0.259               | 0.184-2.697          | 0.609       |
| Male                          |                     |                      |             |
| Female                        |                     |                      |             |
| Age                           | 0.987               | 0.242-3.269          | 0.889       |
| ≥ 60                          |                     |                      |             |
| < 60                          |                     |                      |             |
| cT stage                      | 0.003               | 1.419-18.508         | 0.013       |
| cT3                           |                     |                      |             |
| cT4                           |                     |                      |             |
| Histological type             | 0.183               | 1.038-15.520         | 0.044       |
| Poor                          |                     |                      |             |
| Moderate/well                 |                     |                      |             |
| Short-axis                    | 0.135               | 1.487-38.214         | 0.015       |
| 5-7 mm                        |                     |                      |             |
| ≥ 7 mm                        |                     |                      |             |
| Mixed signal intensity of LLN| 0.739               | 0.342-4.894          | 0.705       |
| Yes                           |                     |                      |             |
| No                            |                     |                      |             |
| Border irregularity of LLN    | 0.315               | 0.119-1.675          | 0.232       |
| Yes                           |                     |                      |             |
| No                            |                     |                      |             |

LLN: Lateral lymph node.

### ARTICLE HIGHLIGHTS

**Research background**
Lateral lymph node metastasis is one of the leading causes for local recurrence in patients with advanced mid or low rectal cancer. The addition of lateral lymph node dissection (LLND) after neoadjuvant chemoradiotherapy (NCRT) remains a controversial topic.

**Research motivation**
There is a lack of consensus leading to an East (mainly Japan)-West division concerning the management of lateral lymph nodes after NCRT associated with lower rectal cancer. There are few data regarding surgical outcomes of total mesorectal excision (TME) plus LLND after NCRT.

**Research objectives**
The main aim of this study was to investigate the surgical outcomes of TME plus LLND, and the possible risk factors for lateral lymph node metastasis after NCRT.

**Research methods**
We performed an observational study and enrolled patients who underwent TME plus LLND. Information regarding the clinicopathologic features and clinical outcomes was collected and analyzed. Multivariate logistic regression analysis was performed to evaluate the possible risk factors for lateral lymph node metastasis in the NCRT patients.

**Research results**
Lateral lymph node metastasis can be found in lower rectal cancer patients with enlarged lymph node size. Advanced T stage, poor differentiation type, and short axis ≥ 7 mm were statistically significant risk factors associated with LLN metastasis.

**Research conclusions**
Preoperative chemoradiotherapy is not sufficient as a stand-alone therapy to eradicate LLN metastasis in lower rectal cancer patients and surgeons should consider performing selective LLND in patients with greater lateral lymph node short axis diameter, poorer histological differentiation or advanced T stage. Selective LLND for NCRT patients can have a favorable oncological outcome.
Larger prospective multicenter clinical studies need to be performed so that standard managements regarding lateral lymph nodes in rectal cancer can be established.

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