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Original Research Article

# Long-term Outcomes of Lower Rectal Cancer Patients Treated with Total Mesorectal Excision and Lateral Pelvic Lymph Node Dissection after Preoperative Radiotherapy or Chemoradiotherapy

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**Abstract**

**Objectives:** The standard strategy for advanced rectal cancer (RC) is preoperative short-course radiotherapy (SCRT)/chemoradiotherapy (CRT) plus total mesorectal excision (TME) in Western countries; however, the survival benefit of adding chemotherapy to radiotherapy remains unclear. There is accumulating evidence that either SCRT/CRT or lateral pelvic lymph node dissection (LPND) alone may not be sufficient for local control of advanced RC. We herein retrospectively evaluated the clinical outcomes of patients who were treated by SCRT/CRT+TME+LPND, particularly focusing on the prognostic impact of lateral pelvic lymph node metastasis (LPNM).

**Methods:** Patients diagnosed as having clinical Stage II and III lower RC who received SCRT/CRT+TME+LPND between 1999 and 2012 at our hospital were enrolled. Adverse events (AEs), surgery-related complications (SRC), and therapeutic effects were retrospectively analyzed.

**Results:** Fifty cases (SCRT:25, CRT:25) were analyzed. No significant differences were observed in overall survival (OS), relapse-free survival (RFS), local recurrence (LR), AE, and SRC between the SCRT and CRT groups, although the pathological therapeutic effect was higher in the CRT group. The patients with LPNM showed significantly inferior 5-year OS and 5-year RFS than those without LPNM.

**Conclusions:** There were no significant differences in OS, RFS, or LR between SCRT and CRT, although CRT had a significantly greater histological therapeutic effect. The prognosis of the pathological LPNM-positive cases was significantly poorer than that of pathological LPNM-negative cases.

**Keywords**

lateral pelvic lymph node dissection, lateral pelvic node metastasis, rectal cancer, chemoradiotherapy, radiotherapy

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## Introduction

Total mesorectal excision (TME), which was proposed by Heald et al.[1], is the global standard of surgical procedures for rectal cancer (RC). However, local control of advanced RC whose lower margin is located at or below the peritoneal reflection (lower RC, LRC) is still under debate worldwide. Lateral pelvic lymph node (LPN) metastasis (LPNM) is reported to account for 18.1% of patients with advanced LRC in Japan[2]. Several studies revealed that the 5-year overall survival (OS) rate was 37.9%-49% in RC patients with LPNM treated without preoperative chemoradiotherapy (CRT)[3-7], and LPNM is also a risk factor of local recurrence (LR) in RC patients[8]. In this context, Sugihara et al.

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have suggested that lateral pelvic lymph node dissection (LPND) may reduce LR and improve survival rates[2]. Currently, The Japanese Society for Cancer of the Colon and Rectum guidelines recommends TME with LPND as the standard procedure for advanced LRC[9]. On the other hand, In European countries, the European Society for Medical Oncology (ESMO) practical guideline recommends preoperative short-course radiotherapy (SCRT) or preoperative CRT as neoadjuvant treatment for intermediate or bad risk group of RC patients to reduce the risk for LR[10], and in the United States, the National Comprehensive Cancer Network (NCCN) guideline recommends SCRT or CRT as neoadjuvant treatment for T3-4, any N, and M0 of RC[11]. Therefore, in Western countries, the standard treatment for LRC is TME and SCRT/CRT, differing greatly from that of the Japanese, and surgery alone is considered an insufficient strategy for advanced LRC. However, recent studies have suggested that CRT does not completely eradicate LPNM, and adding LPND can improve local control and patient survival even after CRT[12-14]; therefore, even in Western countries, LPND is focused on as a promising strategy besides SCRT/CRT for advanced LRC[15,16].

Recently, the meta-analysis, which included data from the European Organization for Research and Treatment of Cancer 22921 and the Federation Francophone de Cancérologie Digestive 9203 trials, revealed that, compared with SCRT alone, CRT did not prolong OS and progression-free survival but it improved local control[17]. This suggests that the survival benefit in the addition of chemotherapy to RT is unclear.

Interestingly, our institute has a history in which the protocol for advanced LRC changed from SCRT followed by TME+LPND, to CRT followed by TME+LPND. Herein, we can compare the long-term results of both protocols. To our knowledge, a study retrospectively comparing SCRT followed by TME+LPND and CRT followed by TME+LPND in a single institute is extremely rare.

The aims of this study are: first, to retrospectively compare the therapeutic effect of SCRT and CRT on the pathological complete response (pCR) rate, downstaging rate, OS, relapse-free survival (RFS), and LR in patients with advanced LRC in comparison with the adverse events (AEs) of SCRT and CRT; and second, to retrospectively assess the oncological impact of pathological LPNM after SCRT or CRT in patients with advanced LRC.

## Methods

### *Patients*

This study was a retrospective, observational study of 50 consecutive patients with clinical Stage II and III (Japanese Classification of Colorectal Carcinoma, 1st and 2nd English edition [[18]P6] RC with the lower margin at or below the peritoneal reflection. All patients underwent SCRT or CRT followed by curative intent surgery, including TME with bilateral LPND between 1999 and 2012 at Fukushima Medical University. Preoperative staging was performed using digital examination, colonoscopy, barium enema, and computed tomography (CT). From 2005, magnetic resonance imaging (MRI) was also used for diagnosis. Lymph nodes larger than 5 mm in the short axis were clinically diagnosed as being metastatic lymph nodes. Written consent has been obtained from all patients enrolled in this study. This study protocol was approved by the Ethics Committee of Fukushima Medical University, Approval No. 30148.

### *Radiotherapy or chemoradiotherapy*

As our protocol, SCRT was performed from August 1999 to March 2009, whereas CRT was performed from April 2009 to February 2012. Regarding SCRT, a total dose of 25 Gy was given in two fractions per day for five days. TME+LPND was performed 2 to 3 weeks after SCRT. As for CRT, the total irradiation dose was 50.4 Gy and was given in 28 fractions over 6 weeks. S-1 (80 mg/m$^2$/day) or Tegafur-uracil (300 mg/m$^2$/day) with leucovorin (75 mg/body/day) was given concomitantly with radiotherapy. TME+LPND was performed 6 to 8 weeks after CRT. Radio Therapy-fields were planned using CT to include the primary tumor, mesorectal lymph node, and LPN.

### *Surgery*

The surgical procedures consisted of low anterior resection, intersphincteric resection, and abdominoperineal resection. Lymph nodes in the mesorectum and those around the inferior mesenteric artery were dissected by the standard TME method. LPNs included the lymph nodes from four regions: the internal iliac lymph node, the external iliac lymph node, the obturator lymph node, and the common iliac lymph node. All four regions were dissected regardless of pre-therapeutic lymph node swelling. All surgical procedures used the open method.

### *Outcome measurement*

Oncological outcomes were evaluated by assessing local response to SCRT or CRT, 5-year OS, 5-year RFS, and 5-year LR. Response to SCRT/CRT was evaluated by the degree of T-factor (Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma 2nd edition, JCCRC 2nd) downstaging, TNM (JCCRC 2nd) downstaging, and pathological regression of RC. Pathological regression of the primary lesion was evaluated in accordance with the Japanese Classification of Colorectal Carcinoma[19]. The dissected LPNs were separated into each region and pathologically examined. AEs following preoperative therapy, such as dermatitis, anorexia, hematological toxicity, and surgery-related

**Table 1.** Clinical-Pathological Features of the Enrolled Patients.

| Clinical and pathological features | | SCRT (n = 25) | CRT (n = 25) | *P* value |
|---|---|---|---|---|
| Age | | 58.6 (±9.5) | 67.4 (±12.7) | n.s. |
| Gender | (M:F) | 14:11 | 16:9 | n.s. |
| Tumor location | | | | |
| | Rb | 24 | 20 | |
| | P | 1 | 5 | n.s. |
| Histological type | | | | |
| | tub1, tub2 | 24 | 19 | |
| | por, muc | 1 | 6 | n.s. |
| cT stage* before treatment | | | | |
| | T3-T4a | 24 | 21 | |
| | T4b | 1 | 4 | n.s. |
| Pre-therapeutic LPNM status | | | | |
| | Positive | 3 | 4 | |
| | Negative | 22 | 21 | n.s. |
| cStage* | | | | |
| | II | 5 | 7 | |
| | III | 20 | 18 | n.s. |
| Adjuvant chemotherapy | | 3 | 9 | $P < 0.05$ |

SCRT: preoperative short course radiotherapy, CRT: preoperative chemoradiotherapy, Rb: rectum below peritoneal reflection, P: surgical anal canal, *: Japanese Classification of Colorectal, Appendiceal and Anal Carcinoma 2nd edition. LPNM: lateral pelvic lymph node metastasis.

complications, such as surgical site infection (SSI), anastomotic leakage (AL), rectovaginal fistula, vesicorectal fistula, neurogenic bladder, and anastomotic stenosis, were examined.

### *Statistical analysis*

Fisher's exact test was used for the comparison of categorical data, and a paired t-test was used for comparison of continuous variables. The Kaplan-Meier method and log-rank test were used for the estimation and comparison of patient survival. *P* values of <0.05 were considered statistically significant. Data analyses were performed by using SPSS Statistics version 24 (IBM, Armonk, U.S.A.).

## Results

### *Clinical and pathological features*

The clinical and pathological features of the study cohort are shown in Table 1. There was no significant difference between the SCRT (n = 25) and CRT (n = 25) groups in any of the factors except for the rate of receiving adjuvant chemotherapy (SCRT: 3 vs. CRT: 9, $P < 0.05$). The median observation period was 66.2 months.

### *Adverse events of preoperative therapy and operative complications*

The summary of the AEs is shown in Table 2. AEs following preoperative therapy did not occur in the SCRT group but presented in 16% of the CRT group (four cases, perianal dermatitis). As for operative complications, AL occurred in two (8%) and one cases (4%) in the SCRT and CRT groups, respectively. SSI (Grade 2) occurred in four cases (16%) in the SCRT group and two cases (8%) in the CRT group. Overall, there was no statistical difference in the incidence of AEs between the SCRT and CRT groups.

### *Oncological outcome*

The summary of treatment outcome is shown in Table 3. Comparing the patients treated with SCRT and those with CRT, the T-category downstaging was observed in 10 (40%) and 15 (60%) cases, respectively, and TNM-downstaging was observed in 11 (44%) and 14 (56%) cases, respectively. Pathological complete response (pCR) to SCRT and CRT was observed in 0 (0%) and six patients (24%), respectively ($P = 0.01$). The histological therapeutic effect was significantly higher in the CRT group than in the SCRT group (SCRT: CRT, Grade 0-1b; 20:9, Grade 2+3; 5:18, $P < 0.001$). Pathologically radical resection (R0 resection) was achieved in 24 patients (96%) in the SCRT group and in all patients in the CRT group. LR was observed in one patient (4%) in the SCRT group and two patients (8%) in the CRT group. Distant metastasis was observed in six patients in the SCRT group and five patients in the CRT group. As for the survival, the 5-year cumulative OS (5-y OS), RFS (5-y RFS), and LR (5-y LR) of all patients were 83.2%, 81.1%, and 7.82%, respectively (Figure 1A, 1B and 1C). The 5-y OS of the SCRT group and that of the CRT group were

**Table 2.** Adverse Events of Neoadjuvant Therapy.

| Adverse events | | SCRT (n = 25) | CRT (n = 25) | *P* value |
|---|---|---|---|---|
| Adverse events of preoperative treatment | | | | |
| | perianal dermatitis | 0 (0%) | 4 (16%) | n.s. |
| Operative complications | | | | |
| | anastomotic leakage | 2 (8%) | 1 (4%) | n.s. |
| | surgical site infection (Grade 2) | 4 (16%) | 2 (8%) | n.s. |
| | rectovaginal fistula | 1 (4%) | 1 (4%) | n.s. |
| | rectovesical fistula | 1 (4%) | 0 (4%) | n.s. |
| | anastomotic stenosis | 1 (4%) | 0 (0%) | n.s. |
| | neurogenic bladder* | 0 (0%) | 0 (0%) | n.s. |

SCRT: preoperative short course radiotherapy, CRT: preoperative chemoradiotherapy, *: requiring catheterization

**Table 3.** Summary of Treatment Outcomes.

| Treatment outcome | | SCRT (n = 25) | CRT (n = 25) | *P* value |
|---|---|---|---|---|
| down staging* | | | | |
| | T factor* | 10 (40%) | 15 (60%) | n.s. |
| | Stage* | 11 (44%) | 14 (56%) | n.s. |
| pCR rate | | 0 (0%) | 6 (24%) | $P = 0.01$ |
| pathological therapeutic effects | | | | |
| | 0-1b | 20 (80%) | 9 (36%) | |
| | 2+3 | 5 (20%) | 18 (64%) | $P < 0.01$ |
| R0 resection | | 24 (96%) | 25 (100%) | n.s. |
| lateral pelvic lymph node metastasis | | 3 (12%) | 3 (12%) | n.s. |
| recurrence | | | | |
| | local | 1 (4%) | 2 (8%) | n.s. |
| | distant | 6 (24%) | 5 (20%) | n.s. |

SCRT: preoperative short course radiotherapy, CRT: preoperative chemoradiotherapy, pCR: pathological complete response, pathological therapeutic effect (-0: noresponse, -1a necrosis and degradation of cancer are observed in less than one third of the tumor, -1b are observed in more than one third and less than two thirds of the tumor, -2 are observed in more than two thirds of the tumor, -3 no viable cancer cells are observed microscopically.) R0 resection: microscopically margin-negative resection. *: Japanese Classification of Colorectal. Appendiceal and Anal Carcinoma 2nd edition

76.0% and 89.1%, respectively (Figure 1D); the 5-y RFS of the SCRT and CRT groups were 84.9% and 75.8%, respectively (Figure 1E); and the 5-y LR of the SCRT and CRT groups were 4.2% and 15.2.%, respectively (Figure 1F). Overall, there were no significant differences in 5-y OS, 5-y RFS, or 5-y LR between the SCRT and CRT groups. As for survival related to the pathological response in the main tumor, the 5-y OS, 5-y RFS, and 5-y LR were not affected by the pathological therapeutic effect (Figure 2A, 2B and 2C).

As for LPNM, patients who were LPNM-positive had a lower 5-y OS and 5-y RFS compared with those without LPNM (5-y OS; 50% vs. 88.5%, $P < 0.01$, 5-y RFS; 16.7% vs. 81.8%, $P < 0.001$) (Figure 2D and 2E).

### *The patients with LPNM*

All patients in the SCRT and CRT groups received LPND, and pathological LPNM was found in three patients in each of the SCRT and CRT groups. A summary of the cases that were clinically LPNM-positive and pathologically LPNM-positive is shown in Figure 3. Five patients were diagnosed as having clinical LPNM before neoadjuvant therapy, and pathological LPNMs were detected in six patients. One patient was diagnosed as having clinical LPNM before preoperative therapy, but pathological LPNM was not detected. The main lesion of this patient was pCR after preoperative therapy. Five patients developed distant metastasis after surgery without LR.

## Discussion

NCCN and ESMO clinical practice guidelines for RC recommend both SCRT and CRT as preoperative therapy for advanced LRC[10,11]. Our results in this retrospective study showed that there were no differences in R0 resection rate,

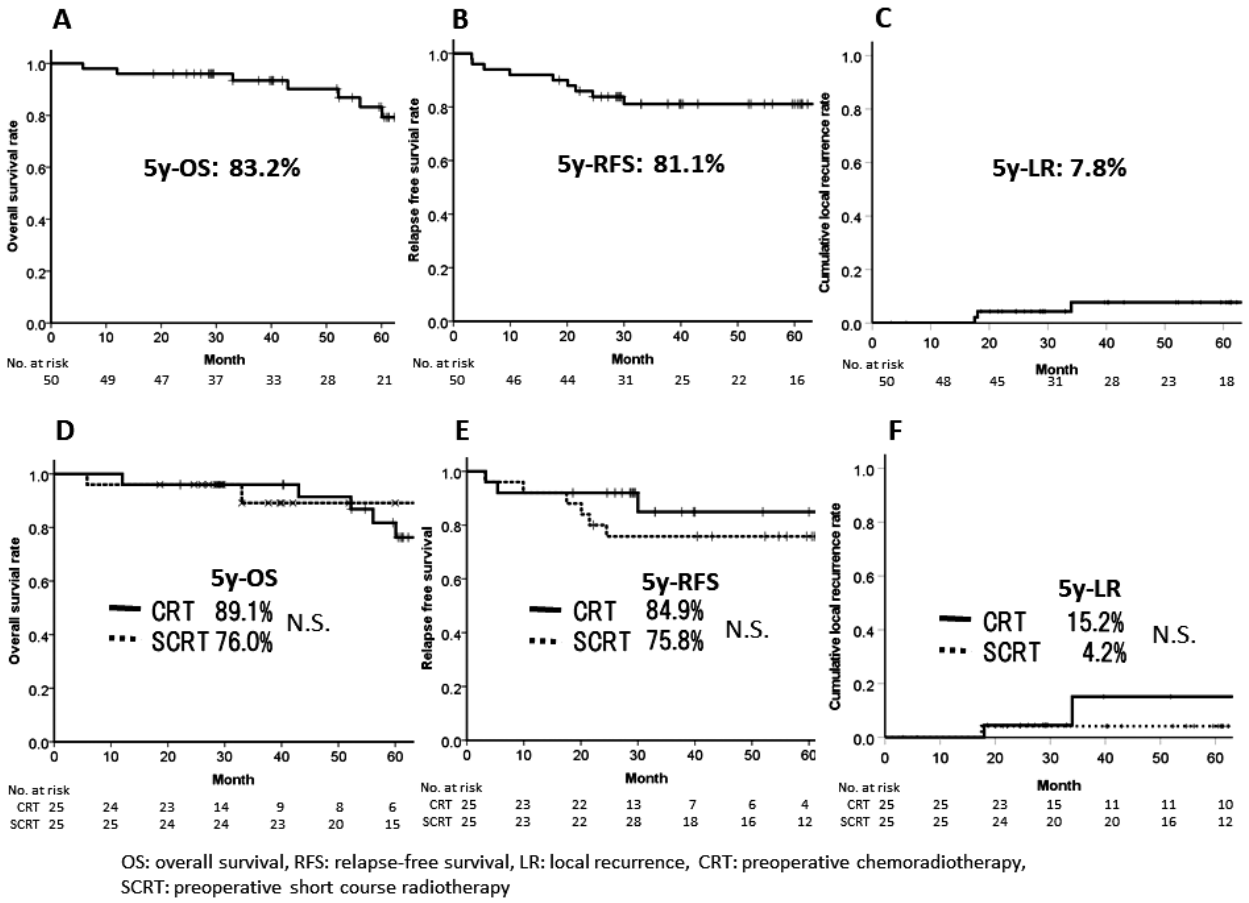
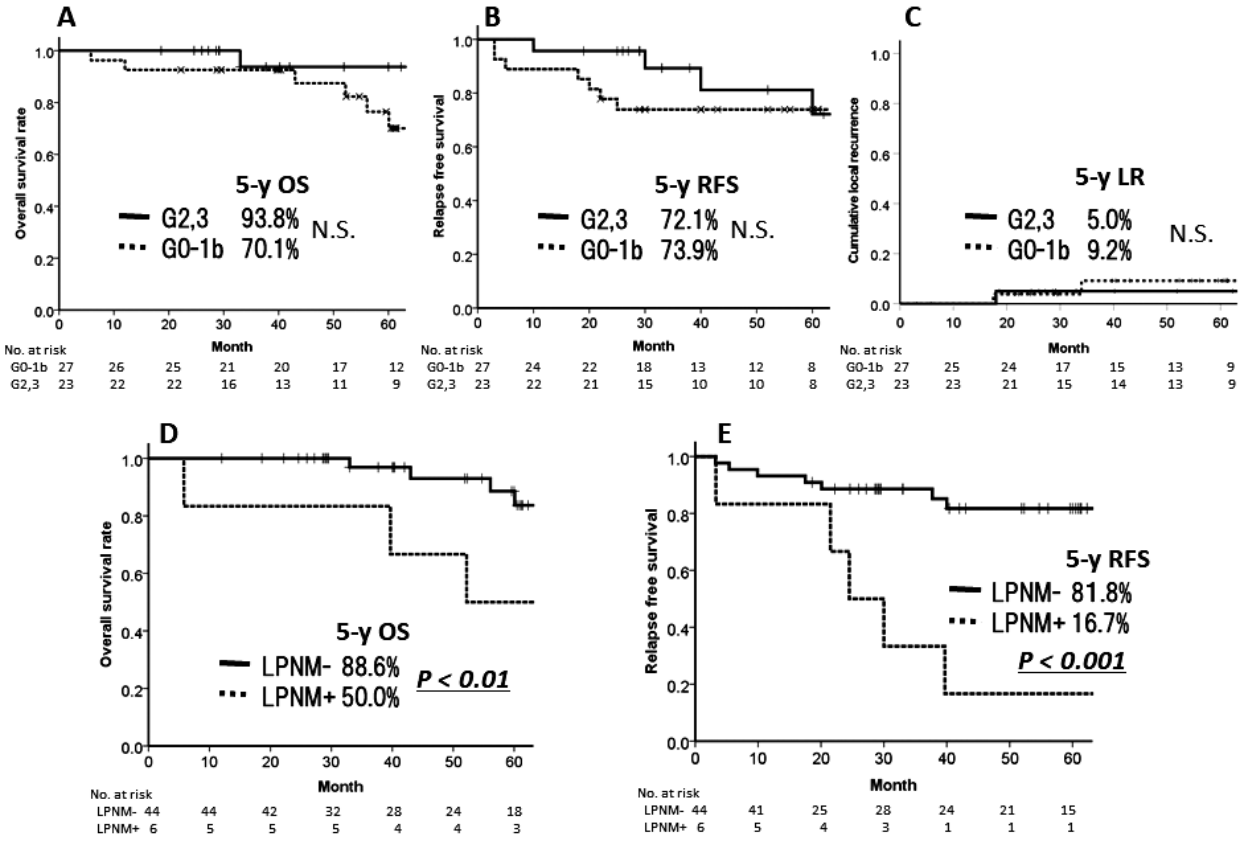



**Figure 1.** Kaplan–Meier survival curves (K–M) of (A) overall survival (OS), (B) relapse-free survival (RFS), and (C) local recurrence (LR) among all patients. Comparison of the K–M curves of (D) OS, (E) RFS, and (F) LR in the preoperative chemoradiotherapy and radiotherapy groups by the log-rank test.

5-y OS, 5-y RFS, and 5-y LR or the profiles of AEs except for Grade 2 dermatitis between SCRT and CRT, although CRT had a significantly greater histological therapeutic effect, including pCR rate, in comparison with SCRT. In general, it is recognized that SCRT takes a shorter treatment period and has cost benefits, but does not bring enough shrinkage[17]. Therefore, nowadays, CRT is widely accepted as a preoperative treatment for patients with more extensive tumor in which circumferential resection margin and/or R0 resection are predicted at risk[20,21]. In this study, there is no significant difference in the 5-y LR between the SCRT and CRT groups; a previous randomized control study already revealed that CRT has greater effect for local control[20,22]. The negative result in our study regarding 5-y LR is probably due to the small number of each cohort and events. In line with our results, Zhou ZR et al. also demonstrated that there were no significant differences in OS, DFS, LR rate, and R0 resection rate between SCRT and CRT, and CRT had an increased pCR rate and Grade 3-4 toxicity based on the results of the meta-analyses of 12 trials[23]. Taken together, it is likely that, although CRT is thought to be more powerful for tumor shrinkage than SCRT, which is a natural and reasonable outcome because of the difference of radiation dose, the local control is not linked to systemic spread and long-term survival.

In the SCRT group, we applied TME+LPND 2-3 weeks after SCRT. The Stockholm III study showed that surgery delayed 4 to 8 weeks after SCRT (SCRT with delay) gave similar oncological results compared with SCRT without delay, but SCRT with delay had better ypT categories, and a higher rate of pCRs[24]. Therefore, it should be considered that the period from irradiation to surgery may affect our result that pCR rate was higher in CRT than in SCRT.

Our results clearly demonstrated that LPNM could not be completely eradicated by SCRT or CRT since the metastases were still found in the dissected LPNs after SCRT or CRT as shown in Figure 3. Moreover, the accurate preoperative diagnosis for LPNM has not been established. Amano et al. showed that a positive predictive value of MRI for LPNM of RC was only 54.6% in a 6-mm cut-off setting[25]. Therefore, LPND could not be omitted for LRC, at least for clinically LPNM-positive cases, even after SCRT/CRT. In line with our results, Konishi et al. also concluded that in cases diagnosed as LPNM-positive before treatment, even with




OS: overall survival, RFS: relapse-free survival, LR: local recurrence, CRT: preoperative chemoradiotherapy, SCRT: preoperative short course radiotherapy,
G: grade of pathological therapeutic effect (-0: no response,-1a necrosis and degradation of cancer are observed in less than one third of the tumor, 1b- are observed in more than one third and less than two thirds of the tumor, 2-are observed in more than two thirds of the tumor, 3- no viable cancer cells are observed microscopically. )
LPNM: lateral pelvic lymph node metastasis,

**Figure 2.** Comparison of the Kaplan–Meier survival curves (K–M) of (A) overall survival (OS), (B) relapse-free survival (RFS), and (C) local recurrence (LR) between patients with Grade 2 and 3 pathological response and those with Grade 0–1b by log-rank test. Comparison of the K–M curve of (D) OS and (E) RFS between patients with pathologically positive and negative lateral pelvic lymph node metastasis by log-rank test.

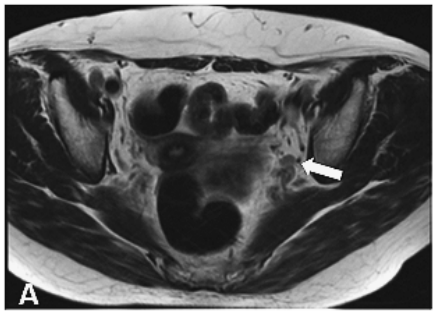
CRT, local control without LPND is difficult[26]. In our study, in one patient who was diagnosed as being clinically LPNM-positive before CRT, the LPNM was not detected pathologically (Figure 3). The main lesion of this patient was pCR by CRT; therefore, there was a possibility that pathological positive nodes were eradicated by CRT as same as the main lesion.

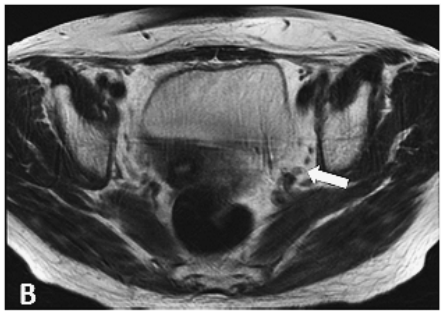
In this study, the prognosis of the LPNM-positive cases was significantly poorer, which is in line with previous reports[16,27,28]. Our results clearly showed that the 5-y OS, 5-y RFS, and 5-y LR were not different depending on the histological response to SCRT/CRT; this suggests that local control is not directly contributed to the improvement of the prognosis. Taken together, we probably need to develop combination strategies, including preoperative or postoperative systematic chemotherapy or both, in addition to SCRT/CRT followed by TME plus LPND to decrease distant metastases. Although several Phase 2 trials and retrospective studies showed the effectiveness of the addition of perioperative chemotherapy to TME plus LPND[16,29,30], a Phase 3-randomized control trial is needed to provide a treatment consensus for advanced LRC.

This study has several limitations. First, the study was retrospective, and the study population was small. We could not match the background between the groups. Second, the enrollment period was more than 10 years and started in 1999; therefore, there may be technical bias of the surgery or the radiotherapy; in addition, the concept of the strategies was outdated. In 1999, at the start of the protocol of the study, we had no clinical guidelines for RC worldwide. Japanese surgeons had a consensus for the LPND, but the mainstream treatment employed worldwide was preoperative SCRT/CRT. We combined these two strategies to achieve better local control and survival before commencing the protocol for this study. Looking around the world at 2012, we have already changed our strategy following that of the Japanese Society for Cancer of the Colon and Rectum guideline. Third, the study did not include data concerning

| Case | Age | Sex | NAT | Pretreatment LPNM | Pathological LPNM | Pathological therapeutic effect | Adjuvant chemotherapy | Local recurrence | Distant matastasis | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 50 | M | SCRT | Positive | Positive | 1a | oral 5FU | – | – | 64M alive |
| 2 | 54 | F | SCRT | Negative | Positive | 0 | oral 5FU | – | lung, | 72M death |
| 3 | 68 | F | SCRT | Positive | Positive | 1b | oral 5FU | – | lung, | 52M death |
| 4 | 68 | M | CRT | Positive | Positive | 0 | oral 5FU | – | lung,bone | 6M death |
| 5 | 81 | M | CRT | Negative | Positive | 2 | oral 5FU | – | lung | 65M death |
| 6 | 74 | M | CRT | Positive | Positive | 1a | oral 5FU | – | lung | 40M death |
| 7 | 42 | F | CRT | Positive | Negative | 3 | oral 5FU | – | – | 91M alive |

NAT: neoadjuvant therapy, LPNM: lateral pelvic lymph node metastasis, SCRT: preoperative short course radiotherapy, CRT: preoperative chemoradiotherapy
Pathological therapeutic effect :-0: no response,-1a necrosis and degradation of cancer are observed in less than one third of the tumor, -1b are observed in more than one third and less than two thirds of the tumor, -2are observed in more than two thirds of the tumor, -3 no viable cancer cells are observed microscopically.




Pre-surgical magnetic resonance imaging(MRI) of Case#7, showing left obturator area clinical lymph node metastasis.
A: pre-treatment MRI. Left obturator lymph node was swollen(10mm in short axis, white arrow).
B: post-chemoradiotherapy MRI. The lymph node was shrunk as compared to A, but still swollen(8mm in shot axis, white arrow).
After surgical dissection, no metastasis was detected in this node.

**Figure 3.** Summary of the patients with pretreatment/pathological lateral pelvic lymph node metastasis.

postoperative long-term sexual dysfunction or dysuria to evaluate quality of life. Fourth, although we applied 2 to 3 weeks of waiting period after SCRT in this study, Stockholm III trial recommended that the waiting period after SCRT should be over 4 weeks because of the highest frequency of AEs during the 2 to 3 weeks waiting period after SCRT[31]. This difference in the waiting period might affect AEs after SCRT in this study.

In conclusion, there were no significant differences in OS, RFS, or LR between SCRT and CRT, although CRT had a significantly greater histological therapeutic effect, including the pCR rate, compared with SCRT. In addition, the prognosis of the pathological LPNM-positive cases was significantly poorer than that of pathological LPNM-negative cases.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

S.T., S.O, T.M. conceived of the presented idea.

W.S. and S.O developed the theory and performed the computations.

W.S. wrote the manuscript with support from S.O., H.O., S.F., H.E. Z.S., and.K.K.

H.O. and M.S. verified the analytical methods.

K.K. supervised the findings of this work.

All authors discussed the results and contributed to the final manuscript:

Approval by Institutional Review Board (IRB)

This study protocol was approved by the Ethics Committee of Fukushima Medical University, Approval No. 30148

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