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# 수술 전 항암방사선 치료를 받은 직장암 환자에서 측방 골반림프절 전이가 종양학적 결과에 미치는 영향

# Impact of lateral pelvic lymph node metastasis on oncologic outcomes in rectal cancer treated with preoperative chemoradiotherapy

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이 논문을 의학석사학위 논문으로 제출함

2022 년 2 월

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## Abstract

**Background** Lateral pelvic lymph node is known as main local recurrence site in rectal cancer even after preoperative chemoradiotherapy (PCRT). There have been increased in interest regarding the prognostic implication of lateral pelvic lymph node (LPLN) metastasis and role of lateral pelvic lymph node dissection in rectal cancer. However, evidences regarding prognostic impact and treatment of lateral pelvic lymph node metastasis (mLPLN) in patients with rectal cancer treated with PCRT are not enough. In this study, we evaluated the impact of mLPLN identified in imaging modality on oncologic outcomes and effect of lateral pelvic lymph node sampling (LPLNs) on prognosis in rectal cancer patients received PCRT.

**Methods** We identified 1535 patients who received PCRT and radical resection between January 2008 and December 2016 at Asan Medical center, Seoul, Korea. Patients who had pre/post PCRT pelvic MRI and/or abdominopelvic CT were included. mLPLN was defined as enlarged lymph node with short axis> 5mm in pre- and post- PCRT or radiologic malignant features including round, spiculated, ill-defined margin or heterogenous signal in MRI.

Recurrence type was categorized as local recurrence (LR), distant recurrence (DR), and pelvic recurrence (PR). LR was defined as recurrence with clinical, radiologic, or endoscopic evidence of intraluminal tumor in adjacent to primary resection site, or tumor within the mesorectum or rectal wall after primary operation. PR was defined as recurrence in pelvic LN including common iliac, external iliac, internal iliac, and obturator LNs. PR was not included in both LR and DR. Distant lymph node not included in PR was categorized as DR.

Association between mLPLN and disease-free survival (DFS), overall survival (OS), local recurrence free survival (LRFS), pelvic recurrence free survival (PRFS) was analyzed and risk factors associated with OS and DFS were also analyzed. In patients who had clinical mLPLN (+), influence of LPLNs was analyzed.

**Results** Of 1535 patients, 317(20.6%) before PCRT and 264(17.1%) after PCRT were identified with mLPLN (+) on MRI. The patients with pathologic complete & near complete regression and sphincter

saving resection was more in pre-/and post- PCRT mLPLN (-) group than (+) groups (P < 0.001). LR, DR, and PR were higher in mLPLN (+) group than (-) group in both pre-PCRT (LR: 7.3% vs. 3.9%, DR: 26.5% vs. 18.7%, PR: 3.8% vs. 1.1%) and post-PCRT (LR: 12.1% vs. 4.3%, DR: 28.8% vs. 18.6%, PR: 5.3% vs. 0.9%). DFS, LRFS, PRFS and OS were higher in pre-/post-PCRT mLPLN (-) groups than (+) groups. Poor response to PCRT (moderate & minimal & no regression) was confirmed as risk factors of OS, DFS, LRFS, DRFS, and PRFS (OS; HR 1.37, P = 0.029, DFS; HR 1.36, P = 0.018, LRFS; HR 1.78, P = 0.062, DRFS; HR 1.33, P = 0.03, PRFS; HR 6.46, P = 0.013). Pre-PCRT mLPLN was associated with OS (HR 1.39, P = 0.042) and post-PCRT mLPLN was associated with DFS (HR 1.36, P = 0.048) and PRFS (HR 4.95, P = 0.002). In entire cohort, LPLNs was performed in 97 (6.3%) patients. Among patients who received LPLNs, mLPLN was pathologically confirmed in 28 (28.8%) patients and there was no significant difference between patients who were not diagnosed with mLPLN pathologically in OR and DR. However, PR was significantly higher in patients with pathologically confirmed mLPLN (16.1% vs. 3.0%). LPLNs group showed higher 5-year LRFS rate and 5-year OS rate than no LPLNs group in both pre-/and post-PCRT mLPLN (+) groups, but it was not statistically significant.

**Conclusion** According to results of this study, patients with pre-/post-PCRT mLPLN (+) had higher LR, PR, DR rate and worse OS, DFS, LRFS, PRFS rate and good primary tumor response to PCRT was associated with OS, DFS, LRFS, DRFS, and PRFS. There were no significant differences in OS and LRFS between LPLNs and no LPLNs group, and even no LPLNs group showed higher 5-year DFS and PRFS. We have to decide to perform lateral pelvic lymph node dissection carefully for this reason considering both advantages and disadvantages. LPLNs of suspicious mLPLN was not associated with oncologic benefit in this cohort. Impact of extensive LPLN dissection on oncologic outcomes need to be evaluated in further study and decision of LPLN sampling or dissection has to be based on its oncologic benefit as well as prognostic implication of mLPLN.

**Keywords: lateral pelvic lymph node metastasis, recurrence, lymph node dissection, rectal cancer**

# 목차

## List of Tables

# List of Figures

# 1. Introduction

The results of rectal cancer treatment were greatly improved by the introduction of total mesorectal excision (TME) [1-4] and preoperative chemoradiotherapy (PCRT) [5, 6]. In particular, the decrease in local recurrence (LR) is very obvious. Dutch Colorectal Cancer Study Group showed that preoperative radiotherapy followed by radical surgery reduced the 2-year LR rate from 8.2 % to 2.4 % [5]. Research of Swedish rectal cancer trial found that the 5-year LR rate was decreased from 27% to in surgery only group to 11% in the group who received preoperative radiotherapy [7]. Previous studies have been reported risk factors associated with LR such as female, clinical T stage, pathologic T and N stages, lymph node metastasis has been known as the important risk factors associated with LR as well as distant metastasis [8]. Lateral pelvic lymph node (LPLN) is one of the main areas in which developed local recurrence in rectal cancer. It is related with lymphatic drainage. In 1950s, Sauer et al. first mentioned the clinical importance of lateral spread of low rectal cancer [9]. The lymphatic vessels ascend with superior rectal vessels in upper half of the rectum, whereas lymphatic vessels in lower half of the rectum flow laterally with middle rectal vessels, reaching the internal iliac nodes [10]. The incidence of LPLN metastasis (mLPLN) in low rectal cancer varies from 10 to 25% [11], with 7% of patients harboring occult micro-metastases in lymph nodes which are negative by conventional histopathology [12]. Moreover, the presence of metastases in the LPLN in the absence of positive nodes along inferior mesenteric artery has been documented in up to 15% of patients [13]. mLPLN rate was related with tumor location and stage; the closer to the anus the low rectal cancer, the higher the risk of LPLN involvement is (above peritoneal reflection: 8.2%, below peritoneal reflection: 13.9%) and the higher the T-staging is, the greater the risk of mLPLN is (T2 :6.5%, T3 :17.9%, T4 :31.6%). LPLN has been reported as a main LR site even after PCRT [14-17].

It is thought that removal of the LPLN removes the nodes which are suspiciously enlarged or even of normal size but with possible micro-metastases and thus reducing the development of LR. The history of lateral pelvic lymph node dissection (LPLND) begins with the discovery by Gerota in 1895 of the lateral and upward lymphatic flow from the rectum by injection of dye, which was followed by

description of the three lymphatics which travels along the lateral pelvic sidewall up to the common iliac bifurcations by Poirier. Around a similar time of 1927, Senba from Japan found by injection of dye into fetal cadavers that these lateral pelvic lymphatics were around the internal iliac arteries and also inside the obturator space [18].

Japanese studies have found the therapeutic value of LPLND was greater than the that of lymphadenectomy around the superior rectal and inferior mesenteric artery, with greater 'therapeutic value index' for survival benefit [13]. On the other hand, in the Western countries (and South Korea), PCRT and TME is standard for locally advanced rectal cancers because mLPLN, apart from the internal iliac artery, has been regarded as distant metastases [19].

Therefore, with the introduction of PCRT, the need for the LPLND has not attracted much attention except in some research group. However, recent years, lateral pelvic wall has been reported as the main LR site after PCRT, and the interest in LPLND has also increased in Western countries [20-24]. What is clear from recent studies, is that PCRT and TME is not enough and LPLND might be beneficial in subgroup of patients.

But, there are variable criteria among studies regarding site of LPLN, definition of mLPLN and diagnostic methods, and LPLND implementation criteria. Size criteria of mLPLN were suggested various among studies and whether pre-/post-PCRT measurement is used [14, 25, 26]. In addition, the change in the size of the LPLN after PCRT has been also suggested as decision criteria whether LPLND was required or not. The long-term results of oncological outcomes after LPLND and extent of LPLND did not have enough evidence. In my institution, LPLNs is performed in the case of mLPLN was suspicious after PCRT. In this study, we evaluated oncologic outcomes of rectal cancer patients treated with PCRT according to mLPLN diagnosed at pre-/post-PCRT status. In patients with mLPLN in pre-/or post-PCRT, influence of LPLNs on oncologic outcomes was also evaluated.

## 2. Methods

### 2-1. Selection patients and diagnosis of lateral pelvic lymph node metastasis

The study involved 1535 patients who received PCRT and TME between January 2008 and December 2016 at Asan Medical Center, Seoul, Korea. All patients' records were retrospectively reviewed for clinicopathologic features, LPLN status in pre-/post- PCRT, recurrences and survival status.

Eligibility criteria included rectal cancer located within 15cm of the anal verge treated with PCRT; Patients who had information regarding pre-and postoperative LPLN status with abdominopelvic CT and/or pelvic MRI were included. Patients with concurrent distant metastasis at diagnosis, those with concurrent or prior malignancies within 5 years of the diagnosis of rectal cancer, or with prior history of immunotherapy or radiotherapy to the pelvis were excluded. Patients were excluded if they did not undergo surgical treatment, had no available pre/post-treatment MRI, or could not be assessed for post-treatment pathologic stage. Patients with hereditary nonpolyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP) also excluded in this study.

Of the 1665 patients who had rectal adenocarcinoma with TME following PCRT, 83 had distant metastasis found at the time of operation, 11 had no pelvic MRI either pre- or post-PCRT, 36 had no data about recurrence due to immediate follow-up loss and, therefore, they were excluded from patient selection (Figure 1).

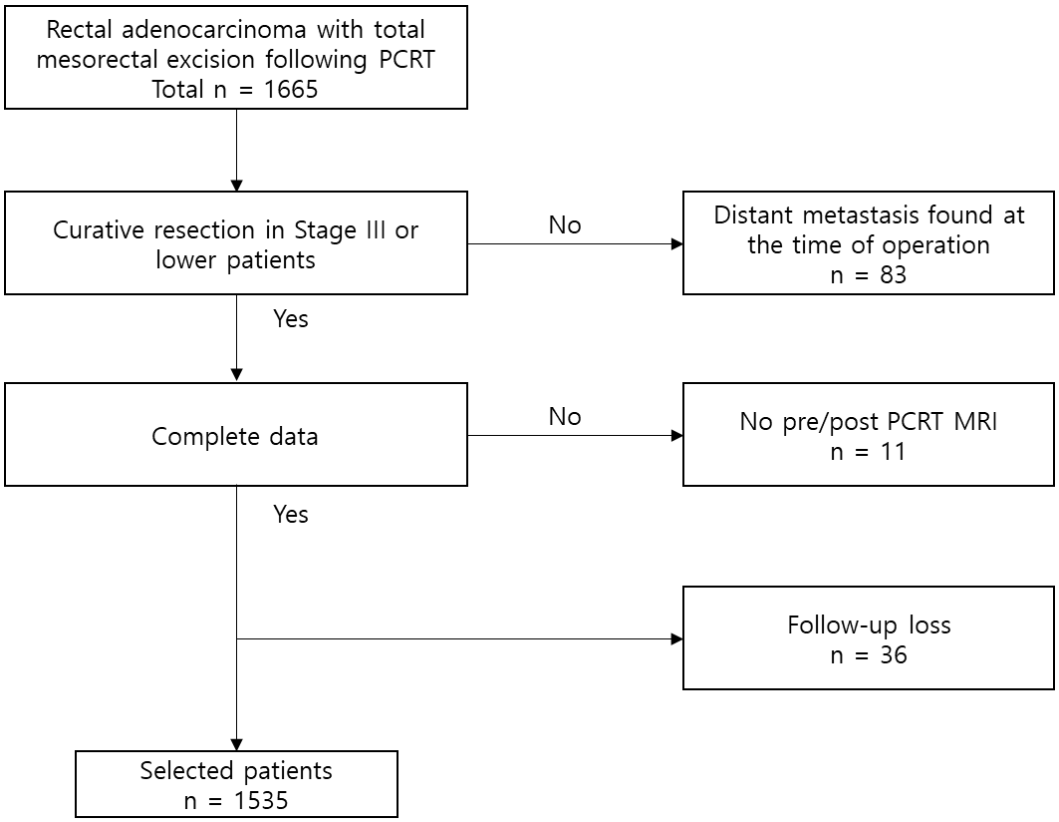


**Figure 1. CONSORT diagram.**

Prior to PCRT, all patients were assessed based on digital rectal examination, blood test including carcinoembryonic antigen (CEA) levels, colonoscopy, and abdomino-pelvic computed tomography (CT) with MRI for staging of disease. mLPLN was defined as enlarged lymph node with short axis (SA)> 5mm in pre- or post- PCRT MRI or radiologic malignant features including round, spiculated, ill-defined margin or heterogenous signal (Figure 2).

A B

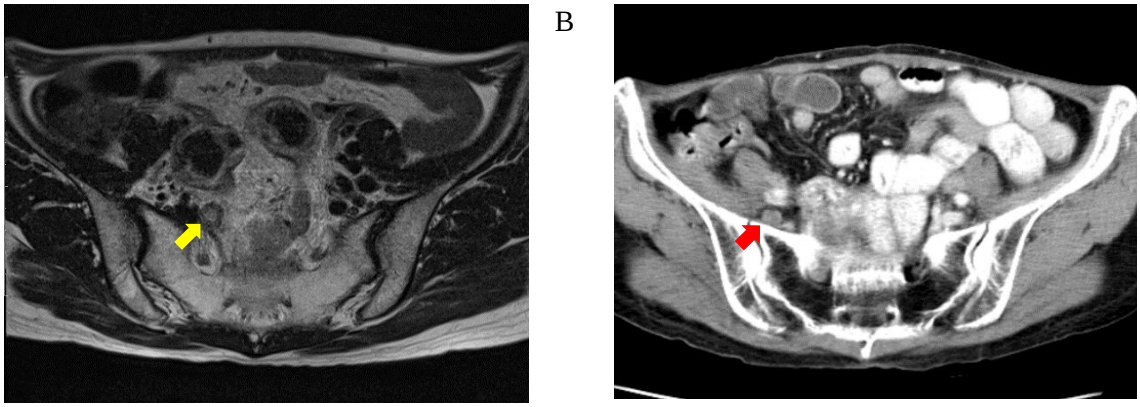

**Figure 2. Imaging study of patient with enlarged right internal iliac lymph node which is suspected as metastasized**

**node. (A) Pre-PCRT magnetic resonance imaging (MRI) showing an enlarged right internal iliac lymph node with heterogenous signal (yellow arrow head) (B) Pre-PCRT computed tomography (CT) showing an enlarged right internal iliac lymph node (red arrow head).**

Patients who had rectal cancer with clinically T3 or clinically node positive without distant metastasis with threatened circumferential resection margin of <1mm on MRI were recommended to receive PCRT. Some patients with low rectal cancer with ≤ cT2 disease received PCRT for shrinkage of tumor field to save anal sphincter. About 4-6 weeks after completion of PCRT, all patients were re-evaluated by colonoscopy or sigmoidoscopy, pelvic MRI, and/or trans-rectal ultrasonography.

### 2-2. Treatment and pathologic evaluation

For PCRT, a dose of 45-50.4 Gy of radiation therapy was given in 25-29 fractions to a target volume including the primary tumor, the perirectal adipose tissue, the lateral pelvis, and the presacral lymph node during the preoperative chemoradiotherapy treatment period. Patients were administered concurrent capecitabine, 5-fluorouracil/leucovorin, or 5-fluorouracil/leucovorin /oxaliplatin (FOLFOX) with radiotherapy. Oral capecitabine (825mg/m2/day) was given twice a day starting from 1 day of radiotherapy and continued during entire radiation period. Intravenous 5-fluorouracil (5-FU, 375mg/m2/day) plus leucovorin (LV, 20mg/m2/day) was given 1$^{st}$ and 5$^{th}$ week of PCRT period.

About 6 to 10 weeks after completion of PCRT, all patients were received curative resection according to TME principle. LPLNs of suspicious metastatic LN was suggested for patients who had suspicious features suggesting mLPLN in pre-/post-MRI. Decision of LPLN sampling was made under discussion between surgeon and radiologist considering primary tumor feature together.

In pathologic evaluation after operation, tumor response was assessed by a pathologist specializing in colorectal malignancy. Tumor regression grading system was used to determine the response of primary tumor according to the proportion of tumor cells and fibrosis. The evaluations were made according to the TRG system from Gastrointestinal Pathology Study Group of the Korean Society of Pathologists [27]. This 4-tier system classifies treatment responses as complete (no residual tumor

cells), near-complete (abundant fibrosis with only a few or scattered tumor cells), partial (easily identifiable residual tumor gland in tumor bed), poor or no (the tumor cells do not demonstrate any response to chemoradiotherapy because abundant residual adenocarcinoma is present) (Figure 3). Pathologic complete/near complete regression was considered as good response, otherwise as poor response.

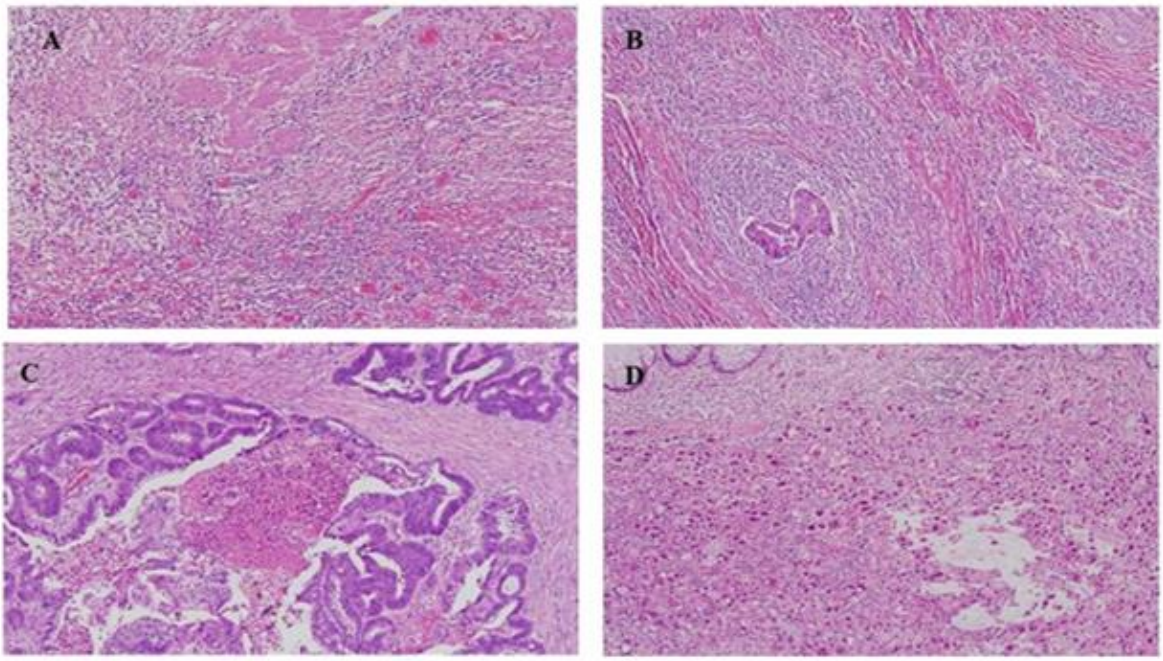


**Figure 3. Pathologic tumor regression grade of primary tumor after PCRT (A) Complete regression (no residual tumor cells) (B) Near-complete regression (abundant fibrosis with only a few or scattered tumor cells) (C) Partial regression (easily identifiable residual tumor gland in tumor bed) (D) Poor or no regression (the tumor cells do not demonstrate any response to chemoradiotherapy because abundant residual adenocarcinoma is present).**

Adjuvant chemotherapy was recommended in all medically fit patients who had undergone PCRT. The recommended adjuvant regimen consisted of four cycles of 5-FU and leucovorin (FL) monthly or six cycles of capecitabine for patients with ypT0-2/N- and eight cycles of FOLFOX for those with ypT3/4 or N+.

**2-3. Surveillance, definition and diagnosis of recurrence**

Patients were followed up every 3-12 months for up to 5 years after surgery. Follow-up evaluations included physical examination, blood tests including CEA levels, and abdomino-pelvic CT and/or chest CT. Patients underwent colonoscopy at 1 year after surgical resection and every 2-3 years thereafter. Patients with preoperative obstructive lesions underwent colonoscopy within 6 months after surgical resection. When suspicious lesions in routine surveillance imaging (Abdominopelvic CT or chest CT) were found, additional imaging such as positron emission tomography (PET)-CT or liver MRI was performed. Local recurrence (LR) was defined as recurrence with clinical, radiologic, or endoscopic evidence of intraluminal tumor in adjacent to primary resection site, or tumor within the mesorectum or rectal wall after primary operation. Distant recurrence (DR) was defined as recurrence in other organs including liver and bone. Pelvic recurrence (PR) was defined as recurrence in pelvic cavity only including common iliac, external iliac, internal iliac, and obturator LNs. PRs were not included in both LR and DR. Distant LNs not included in PR were classified as DR.

Recurrence was diagnosed based on imaging findings and patients with ambiguous imaging findings were continuously observed for serial change. If possible, tissue biopsy is also used to diagnose the recurrence.

**2-4. Statistical analysis**

In this study, primary end point**s** were disease free survival (DFS) defined as the time from operation to recurrence of tumor, local recurrence free survival (LRFS) defined as the time from operation to local recurrence, pelvic recurrence free survival (PRFS) defined as the time from operation to pelvic recurrence and overall survival (OS) defined as the time from operation to any cause of death (not cancer-specific death) or last date of assessment of data. We analyzed DFS, LRFS, PRFS and OS according to mLPLN. The relationships between pre-/post- mLPLN and LR, DR, and PR were also evaluated. Analyses of clinicopathological characteristics of categorical variables and continuous variables were conducted using the chi-square test and t-test, respectively. The Kaplan-

Meier method with log-rank test was used to analyze the DFS, LRFS, PRFS and OS. A multivariable analysis with Cox proportional hazards model was used to compare risk factors associated with OS, DFS, LRFS, PRFS and DRFS including age, sphincter saving resection, initial clinical T staging, lymphovascular invasion, perineural invasion, and pre-/post- mLPLN. P-values < 0.05 were considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics ver 21.0. (IBM Co., Armonk, NY, USA)

# 3. Results

### 3-1. Clinicopathological features of rectal cancer treated with PCRT

Of the 1545 patients, 1022 (66.6%) were male and the mean age was 59.0 (±10.7) years. Sphincter saving resection was done in 1227 (79.9%) patients. Pre-PCRT mLPLN was identified in 317(20.6%) and post-PCRT mLPLN was identified in 264 (17.2%) patients. 96.2% of patients had cT3-4 as initial clinical T stage. LN metastasis was suspected clinically in 1423 (92.7%) patients before PCRT (Table 1). Among included patients, 256 (16.6%) patients showed complete regression for primary tumor.

**Table 1. Clinicopathological characteristics.**

| Characteristics | Value=1535 |
|---|---|
| **Sex** | |
| Male | 1022 (66.6%) |
| Female | 513 (33.4%) |
| **Age(year)** | |
| Mean ± SD | 59.03 ± 10.7 |
| **Sphincter saving resection** | |
| No | 308 (20.1%) |
| Yes | 1227 (79.9%) |
| **pre-PCRT mLPLN** | |
| No | 1218 (79.4%) |
| Yes | 317 (20.6%) |
| **post-PCRT mLPLN** | |
| No | 1271 (82.8%) |
| Yes | 264 (17.2%) |
| **initial clinical T stage** | |
| cT0-2 | 58 (3.8%) |
| cT3-4 | 1477 (96.2%) |
| **initial clinical N stage** | |

| | |
|---|---|
| cN0 | 112 (7.3%) |
| cN+ | 1423 (92.7%) |
| **Pathologic Tumor regression grade** | |
| Complete & near complete | 621 (40.5%) |
| Partial & poor & no | 914 (59.5%) |

### 3-2. Association between pre-/post-PCRT mLPLN and clinicopathological features

Clinicopathological features were compared according to mLPLN (Table 2).

**Table 2. Clinicopathological features according to pre-/post-PCRT pelvic lymph node metastasis (mLPLN).**

| | pre-PCRT mLPLN | | | post-PCRT mLPLN | | |
|---|---|---|---|---|---|---|
| | **No (n=1218)** | **Yes (n=317)** | **P** | **No (n=1271)** | **Yes (n=264)** | **P** |
| **Sex** | | | 0.694 | | | 0.265 |
| Male | 808 (66.3) | 214 (67.5) | | 854 (67.2) | 168 (63.3) | |
| Female | 410 (33.7) | 103 (32.5) | | 417 (32.8) | 96 (36.4) | |
| **Age (years)** | | | 0.106 | | | 0.128 |
| age < 59 | 572 (47.0) | 165 (52.1) | | 599 (47.1) | 138 (52.3) | |
| age≥59 | 646 (53.0) | 152 (47.9) | | 672 (52.9) | 126 (47.7) | |
| **Sphincter saving resection** | | | <0.001 | | | <0.001 |
| No | 214 (17.6) | 94 (29.7) | | 229 (18.0) | 79 (29.9) | |
| Yes | 1004 (82.4) | 223 (70.3) | | 1042 (82.0) | 185 (70.1) | |
| **initial cT** | | | 0.188 | | | 0.291 |
| cT0-2 | 50 (4.1) | 8 (2.5) | | 51 (4.0) | 7 (2.7) | |
| cT3-4 | 1168 (95.9) | 309 (97.8) | | 1220 (96.0) | 257 (97.3) | |
| **initial cN** | | | <0.001 | | | <0.001 |
| cN0 | 113 (9.3) | 0 (0.0) | | 112 (8.8) | 0 (0.0) | |
| cN+ | 1105 (90.7) | 317 (100) | | 1159 (91.2) | 264 (100) | |
| **ypT stage** | | | <0.001 | | | <0.001 |
| ypT0-2 | 656 (53.9) | 135 (42.6) | | 685 (53.9) | 106 (40.2) | |
| ypT3-4 | 562 (46.1) | 182 (57.4) | | 586 (46.1) | 158 (59.8) | |
| **ypN stage** | | | 0.003 | | | <0.001 |
| ypN0 | 887 (72.8) | 204 (64.4) | | 934 (73.5) | 157 (59.5) | |
| ypN+ | 331 (27.2) | 113 (35.6) | | 337 (26.5) | 107 (40.5) | |
| **LVi** | | | 0.022 | | | 0.01 |
| No | 1069 (87.8) | 266 (83.9) | | 1113 (87.6) | 222 (84.1) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Yes | 124 (10.2) | 48 (15.1) | | 131 (10.3) | 41 (15.5) | |
| Indeterminated | 25 (2.1) | 3 (0.9) | | 27 (2.1) | 1 (0.4) | |
| **PNi** | | | 0.006 | | | 0.007 |
| No | 1027 (84.3) | 249 (78.5) | | 1065 (83.8) | 211 (79.9) | |
| Yes | 163 (13.4) | 64 (20.2) | | 175 (13.8) | 52 (19.7) | |
| Indeterminated | 28 (2.3) | 4 (1.3) | | 31 (2.4) | 1 (0.4) | |
| **Pathologic TRG** | | | | | | 0.177 |
| Complete & near complete | - | - | - | 524 (41.2) | 97 (36.7) | |
| Partial & poor & no | - | - | | 747 (58.8) | 167 (63.3) | |

Values in parentheses are percentages unless indicated otherwise
LVi; (Lymphovascular invasion), PNi; (Perineural invasion), cT; (clinical T stage), cN; (clinical N stage), TRG; (Tumor regression grade)

**1) Association between pre-PCRT mLPLN and clinicopathological features**

Sphincter saving resection was more frequently performed in pre-PCRT mLPLN (-) group (1003, 82.4%) than in pre-PCRT mLPLN (+) group (224, 70.4%) ($P < 0.001$). The lymphovascular invasion (LVi) was more identified in pre-PCRT mLPLN (+) groups (15.1%) than in pre-PCRT mLPLN (-) groups (10.2%) ($P = 0.022$). The perineural invasion (PNi) was also significantly more found in pre-PCRT mLPLN (+) group ($P = 0.006$). Patients with less invasive primary tumor (cT0-2) were more identified in pre-PCRT mLPLN (-) groups, but it was not significant statistically (4.1% vs. 2.5%, $P = 0.188$).

**2) Association between post-PCRT mLPLN and clinicopathological features**

There was no significant difference in age between post-PCRT mLPLN (+) groups and (-) groups. Sphincter saving rate was higher in post-PCRT mLPLN (-) groups than (+) groups. (82% vs. 70.1%, respectively) ($P < 0.001$). LVi (15.5% vs. 10.3%, respectively, $P = 0.01$) and PNi (19.7% vs. 13.8% respectively, $P = 0.007$) were significantly more identified in post-PCRT mLPLN (+) group than (-) group. Initial clinical T stage did not show difference between two groups ($P = 0.291$). Distribution of initial clinical N stage was different between groups; post-PCRT mLPLN (-) vs. post-PCRT mLPLN

(+) – N0 (8.8% vs. 0%), N1 (33.4% vs. 26.5%), N2 (57.7% vs. 73.5%) (P < 0.001). The percentage of good responders was not different between post-PCRT mLPLN (-) group and post-PCRT mLPLN (+) group (524, 41.2% vs. 97, 36.7%, P = 0.177).

### 3-3. Recurrences according to mLPLN

Of 1535 patients, 329 (21.9%) patients showed disease recurrence; 71 (4.6%) patients with LR, 25 (1.6%) with PR and 312 (20.3%) with DR. LR rate was significantly higher in pre-PCRT mLPLN (+) than (-) groups (7.3% vs. 3.9%, P = 0.019). DR rate was also higher in pre-PCRT mLPLN (+) than (-) groups (26.5% vs. 18.7%, P = 0.004). Recurrence rates were also different according to post-PCRT mLPLN status. The post-PCRT mLPLN (+) group showed higher LR (8.3% vs. 3.9%, P = 0.004) and DR rate (28.8% vs. 18.6%, P = 0.001) than (-) groups (Table 3).

**Table 3. Recurrence according to pre-/post-PCRT pelvic lymph node metastasis (mLPLN).**

| | pre-PCRT mLPLN | | | post-PCRT mLPLN | | |
|---|---|---|---|---|---|---|
| | **No (n=1218)** | **Yes (n=317)** | **P** | **No (n=1271)** | **Yes (n=264)** | **P** |
| **Local recurrence** | | | 0.019 | | | 0.004 |
| No | 1156 (94.9) | 293 (92.4) | | 1208 (95.0) | 241 (91.3) | |
| Yes | 48 (3.9) | 23 (7.3) | | 49 (3.9) | 22 (8.3) | |
| **Pelvic recurrence** | | | 0.001 | | | <0.001 |
| No | 1191 (97.8) | 304 (95.9) | | 1246 (98.0) | 249 (94.3) | |
| Yes | 13 (1.1) | 12 (3.8) | | 11 (0.9) | 14 (5.3) | |
| **Distant recurrence** | | | 0.004 | | | 0.001 |
| No | 976 (80.1) | 232 (73.2) | | 1021 (80.3) | 187 (70.8) | |
| Yes | 228 (18.7) | 84 (26.5) | | 236 (18.6) | 76 (28.8) | |
| f/u loss | 14 (1.1) | 1 (0.3) | | 14 (1.1) | 1 (0.4) | |

Values in parentheses are percentages unless indicated otherwise

PR occurred in 13 (1.1%) patients in pre-PCRT mLPLN (-) groups and 12 (3.8%) patients in pre-PCRT mLPLN (+) group (P = 0.001). The proportion of PR in post-PCRT mLPLN (+) group is higher than that in post-PCRT mLPLN (-) group (5.3% vs. 0.9%, P < 0.001)

### 3-4. DFS, LFRS, PRFS and OS according to mLPLN

In overall cohort, DFS, LRFS, PRFS and OS were 75.7%, 92.9%, 97.9% and 67.1%, respectively.

#### 1) Association between mLPLN and DFS

The 5- year DFS rate was significantly higher in pre-PCRT mLPLN (-) than (+) group (79.7% vs. 69.9%) (P < 0.001). It was also different according to post-PCRT mLPLN status; DFS was 79.8% in post-PCRT mLPLN (-), and 67.6% in post-PCRT mLPLN (+) group (P < 0.001) (Figure 4).

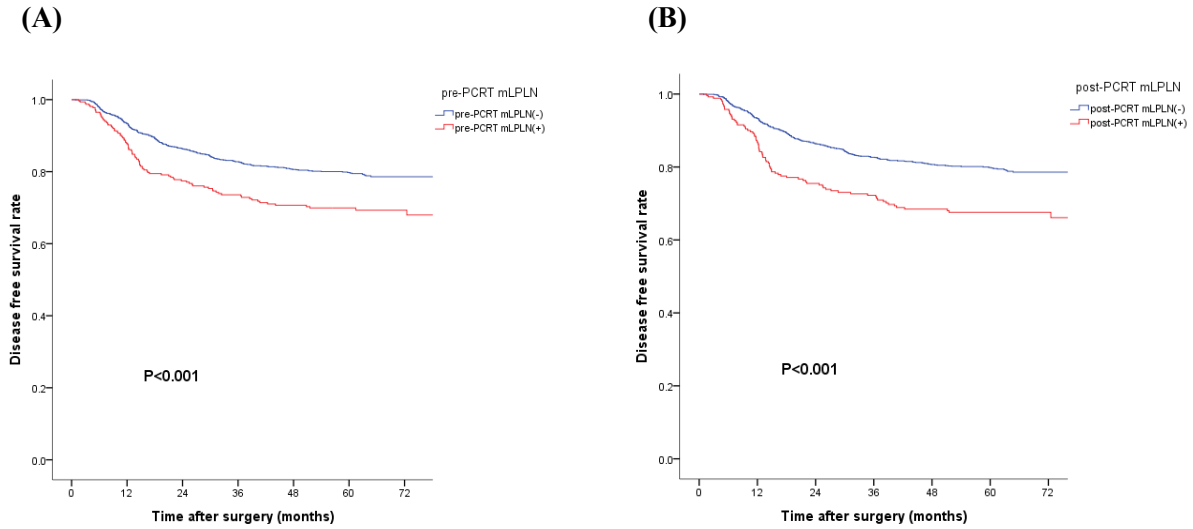


**Figure 4. Disease free survival (DFS) according to pre-/post-PCRT mLPLN. (A) DFS rate was significantly higher in pre-PCRT mLPLN (-) group. (B) DFS rate was significantly higher in post-PCRT mLPLN (-) groups.**

#### 2) Association between mLPLN and LRFS

The 5-year LFS rate was higher in pre-PCRT mLPLN (-) than (+) (96.3% vs. 92.2%, P = 0.008). It was 96.4% in post-PCRT mLPLN (-) group, and 91.6% in post-PCRT mLPLN (+) group (P = 0.002) (Figure 5).

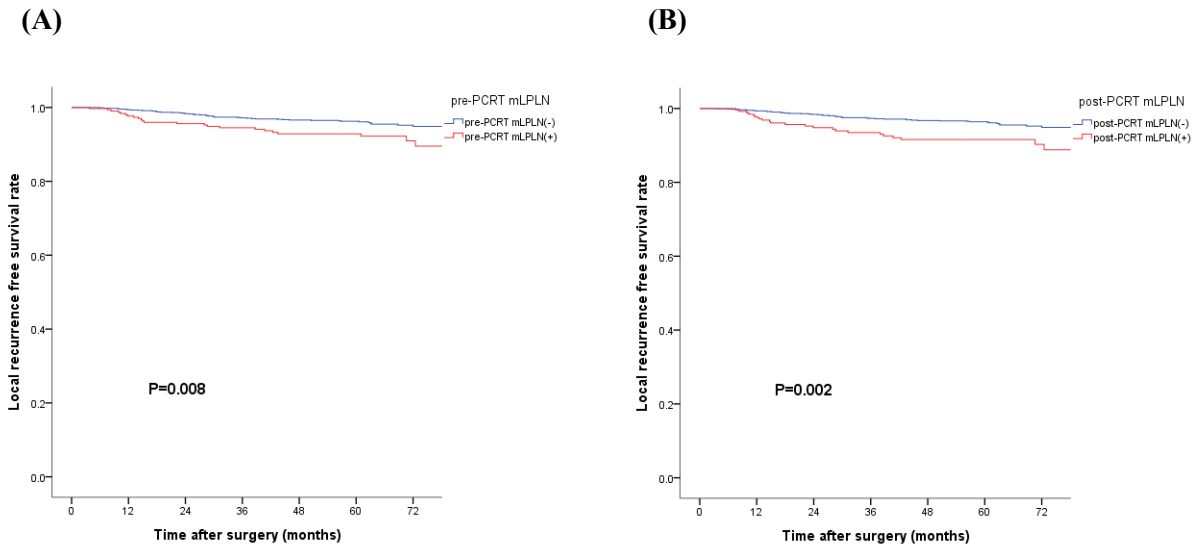


**Figure 5. Local recurrence free survival (LRFS) according to pre-/post-PCRT mLPLN. LRFS rate was different according to mLPLN status and higher in (A) pre-PCRT mLPLN (+) group. (B) post-PCRT mLPLN (+) group.**

### 3) Association between mLPLN and PRFS

The 5-year PRFS rate was 98.9% in pre-PCRT mLPLN (-) group and 96.5% in pre-PCRT mLPLN (+) group ($P < 0.001$). It also showed significant difference according to post-PCRT mLPLN status; It was 94.6% in post-PCRT mLPLN (-), and 81.4% in post-PCRT mLPLN (+) group ($P < 0.001$) (Figure 6).

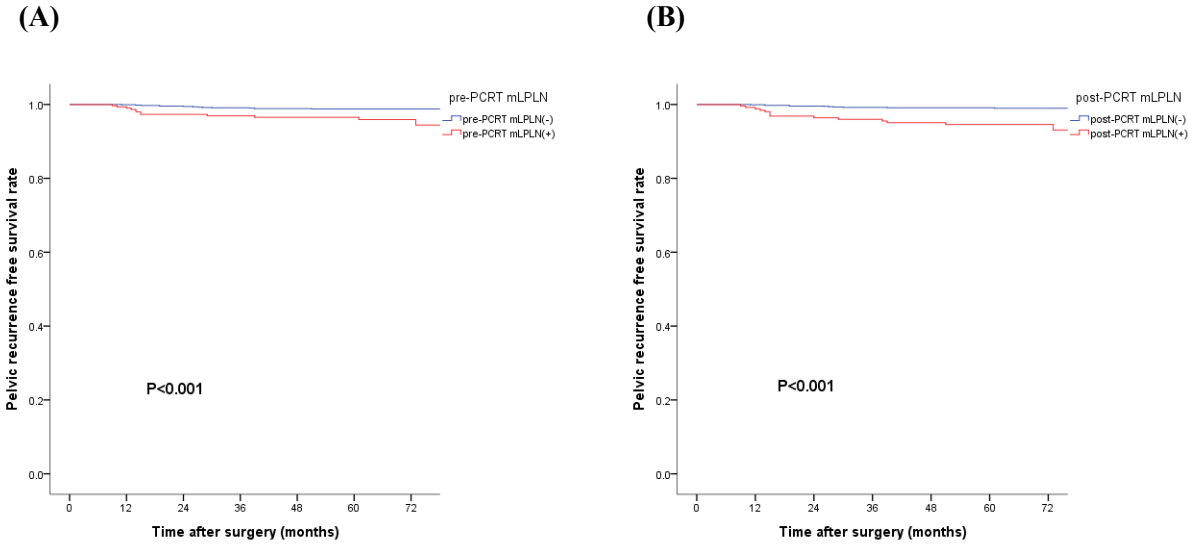


**Figure 6. Pelvic recurrence free survival (PRFS) according to pre-/post-PCRT mLPLN. PRFS rate was**

**different according to mLPLN status and higher in (A) pre-PCRT mLPLN (+) group. (B) post-PCRT mLPLN (+) group.**

#### 4) Association between mLPLN and OS

The 5-year OS rate was 86.1% in pre-PCRT mLPLN (-) group and 77.1% in pre-PCRT mLPLN (+) group (P < 0.001). OS also showed significant difference according to post-PCRT mLPLN status; It was 85.0% in post-PCRT mLPLN (-), and 78.5% in post-PCRT mLPLN (+) group (P = 0.021) (Figure 7).

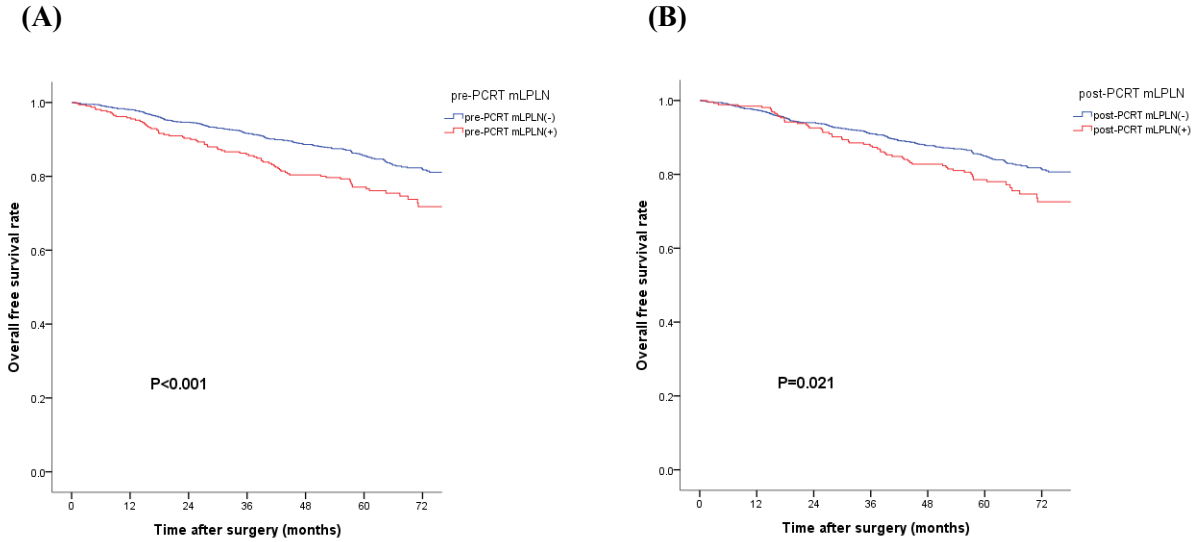


**Figure 7. Overall survival (OS) according to pre-/post-PCRT mLPLN. (A) OS rate was higher in pre-PCRT mLPLN (-) group. (B) OS rate was higher in post-PCRT mLPLN (-) group.**

### 3-5. Pathologic results of lateral pelvic lymph node sampling (LPLNs) and recurrences related with LPLNs

Of 1535 patients, LPLNs was performed in 97 (6.3%) patients. Totally, 412 LNs were harvested. The range of number of harvested LPLN was quite variable with mean – 6.9 nodes (range, 0-23). More than 60% of patients who received LPLNs harvested less than 5 LPLN. Some patients received LPLNs, but no LPLN was identified in pathologic examination. (11 (11.6%) patients) (Figure 8).

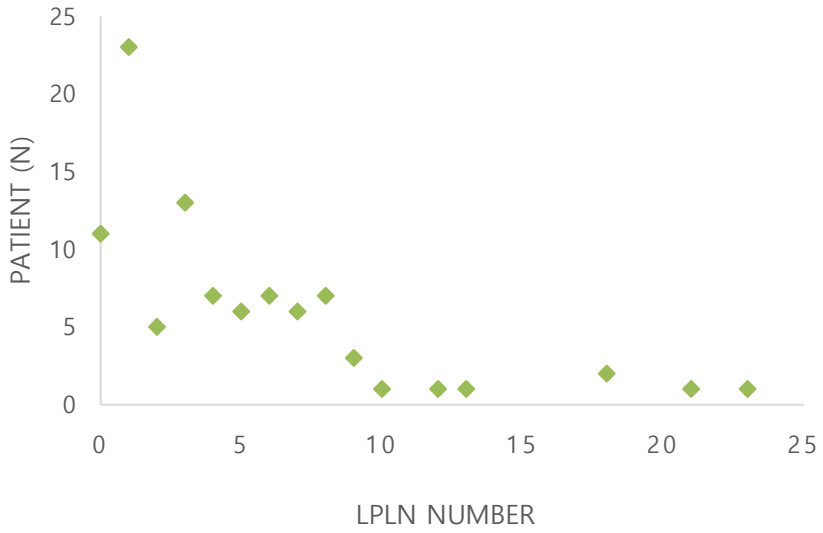


**Figure 8. Distribution of harvested LPLN after LPLNs.**

28 (28.8%) patients had mLPLN confirmed in pathologic examination among 97 patients who was performed LPLNs. Among patients who were categorized as mLPLN (-), 2 patients received LPLNs because of equivocal finding of mLPLN in both pre- and post- PCRT MRI and they were confirmed having mLPLN on final pathologic exam. Patients who had pathologic confirmed LN metastasis did not show difference in OR and DR with patients with no LN metastasis in pathologic examination (OR: 39.3 % vs. 33.3%, P = 0.656, DR: 35.7 vs. 29.0%, P = 0.619, respectively.) However, LR rate was lower in patients with pathologic confirmed LN metastasis (3.2% vs. 6.1%). PR was significantly higher in patients with pathologically confirmed mLPLN (16.1% vs. 3.0%, P = 0.027) (Table 4).

**Table 4. Incidence of recurrence according to pathologic confirm as lymph node metastasis among patients with LPLNs.**

| | **Pathologically confirmed mLPLN** | | |
|---|---|---|---|
| | **No (n=69)** | **Yes (n=28)** | **P** |
| **Overall recurrence** | | | 0.656 |
| No | 45 (65.2) | 16 (57.1) | |
| Yes | 23 (33.3) | 11 (39.3) | |
| **Local recurrence** | | | 0.731 |
| No | 64 (92.8) | 26 (92.9) | |
| Yes | 4 (5.8) | 1 (3.6) | |
| **Pelvic recurrence** | | | 0.027 |
| No | 66 (95.7) | 22 (78.6) | |
| Yes | 2 (2.9) | 5 (17.9) | |

| | | | |
|---|---|---|---|
| **Distant recurrence** | | | 0.619 |
| No | 48 (69.6) | 17 (60.7) | |
| Yes | 20 (29.0) | 10 (35.7) | |
| f/u loss | 1 (1.4) | 1 (3.6) | |

Values in parentheses are percentages unless indicated otherwise

### 1) Recurrences according to LPLNs in pre-PCRT mLPLN (+) group

Among 317 patients with pre-PCRT mLPLN (+), 76 (23.9%) patients underwent LPLNs. 24 (31.6%) patients had pathologically confirmed LPLN metastasis in LPLNs group. OR was higher in LPLNs group: 38.2% (29 patients) in patients with LPLNs and, 26.1% (63 patients) in no LPLND group. (P = 0.024). PR occurred more in LPLNs group ;7.9% vs. 2.5% (P = 0.019). DR also occurred frequently in LPLNs group than no LPLNs group; 34.2%, 24.1%, respectively (P = 0.04). However, LR occurred more in no LPLNs group: 7.5% (18 patients) vs. 6.6% (5 patients), and there was no statistical difference (P = 0.198) (Table 5-1).

**Table 5-1. Incidence of recurrence according to LPLNs in pre-PCRT mLPLN (+) group.**

| | **LPLNs** | | |
|---|---|---|---|
| | **No (n=241)** | **Yes (n=76)** | **P** |
| **Overall recurrence** | | | 0.024 |
| No | 178 (73.9) | 46 (60.5) | |
| Yes | 63 (26.1) | 29 (38.2) | |
| **Local recurrence** | | | |
| No | 223 (92.5) | 70 (92.1) | 0.198 |
| Yes | 18 (7.5) | 5 (6.6) | |
| **Pelvic recurrence** | | | |
| No | 235 (97.8) | 69 (90.8) | 0.019 |
| Yes | 6 (2.5) | 6 (7.9) | |
| **Distant recurrence** | | | |
| No | 183 (75.9) | 49 (64.5) | 0.040 |
| Yes | 58 (24.1) | 26 (34.2) | |
| f/u loss | 0 (0.0) | 1 (1.3) | |

Values in parentheses are percentages unless indicated otherwise,
LPLNs, Lateral pelvic lymph node sampling

### 2) Recurrences according to LPLNs in post-PCRT mLPLN (+) group

Post-PCRT mLPLN (+) group included 264 patients. Among them, 76 (28.7%) patients underwent LPLNs. 24 (31.6%) patients had LPLN metastasis identified in pathologic examination in LPLNs

group. OR occurred in 38.2% in LPLNs and 28.7% in no LPLNs (P = 0.085). LR was less in LPLNs than no LPLNs but it was not statistically significant; 5.3% vs. 9.6%, respectively (P = 0.155). PR was more in LPLNs group; 9.2% vs. 3.7% (P = 0.055) and it was same with DR rate: 32.9% in LPLNs and 27.1% in no LPLNs (P = 0.175) (Table 5-2).

**Table 5-2. Incidence of recurrence according to LPLNs in post-PCRT mLPLN (+) group.**

| | LPLNs | | |
|---|---|---|---|
| | **No (n=188)** | **Yes (n=76)** | **P** |
| **Overall recurrence** | | | 0.085 |
| No | 134 (71.3) | 46 (60.5) | |
| Yes | 54 (28.7) | 29 (38.2) | |
| **Local recurrence** | | | 0.155 |
| No | 170 (90.4) | 71 (93.4) | |
| Yes | 18 (9.6) | 4 (5.3) | |
| **Pelvic recurrence** | | | 0.055 |
| No | 181 (96.3) | 68 (89.5) | |
| Yes | 7 (3.7) | 7 (9.2) | |
| **Distant recurrence** | | | 0.175 |
| No | 137 (72.9) | 50 (65.8) | |
| Yes | 51 (27.1) | 25 (32.9) | |
| f/u loss | 0 (0.0) | 1 (1.3) | |

Values in parentheses are percentages unless indicated otherwise
LPLNs, Lateral pelvic lymph node sampling

### 3-6. DFS, LRFS, PRFS and OS in LPLNs group

#### 1) Association between LPLNs and DFS according to pre-/post-PCRT mLPLN status

Among patients with pre-PCRT mLPLN (+) group, the 5-year DFS rate was higher in no LPLNs group (72.8%) than in LPLNs group (60.7%) (P = 0.035). In patients with post-PCRT mLPLN (+) group, the 5-year DFS rate was also higher in no LPLNs group (70.3%) than in LPLNs group (60.7%), but it was not significant statistically (P = 0.129) (Figure 9).

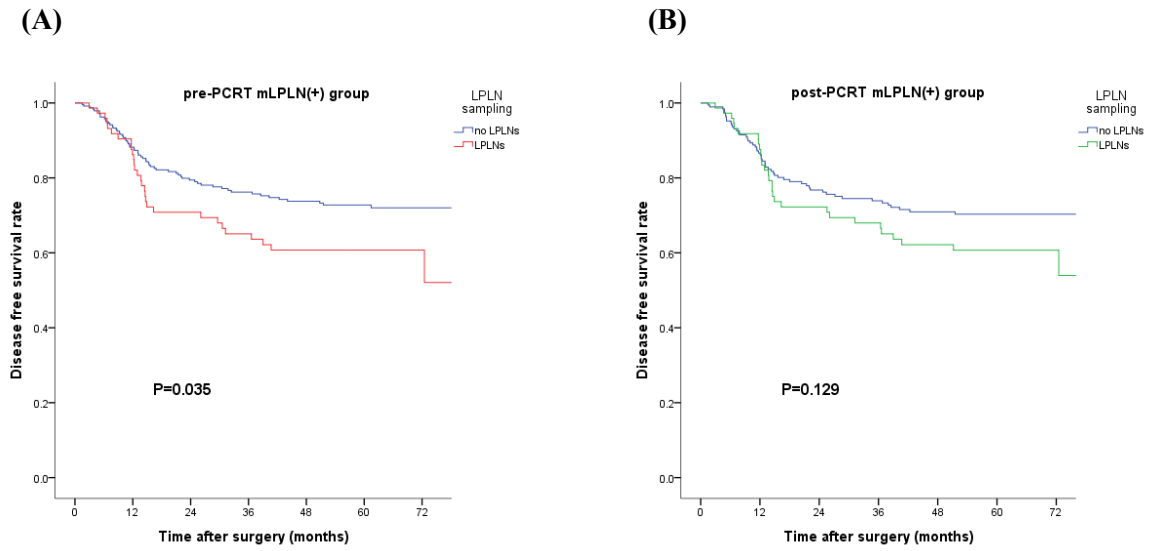


**Figure 9. Disease free survival (DFS) according to LPLNs in (A) pre-PCRT mLPLN (+) and (B) post-PCRT mLPLN (+) group.**

**2) Association between LPLNs and LRFS in pre-/post-PCRT mLPLN (+) group**

In pre-PCRT mLPLN (+) group, the 5-year LRFS rate was 92.6% in no LPLNs group and 93.7% in LPLNs group (P = 0.864). In post-PCRT mLPLN (+) group, the 5-year LFS rate was 90.3% in no LPLNs group and 95.1% in LPLNs group. (P = 0.314). In both pre-PCRT mLPLN (+) and post-PCRT mLPLN (+) group, LRFS was not different according to LPLNs (Figure 10).

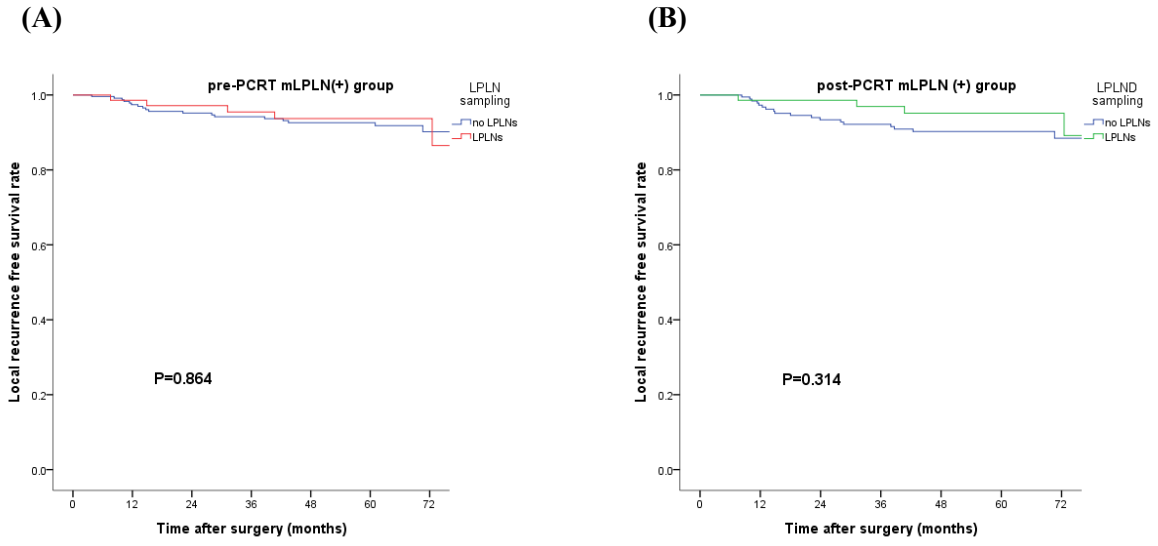


**Figure 10. Local recurrence free survival (LRFS) according to LPLNs in (A) pre-PCRT mLPLN (+) and (B) post-PCRT mLPLN (+) group.**

### 3) Association between LPLNs and PRFS in pre-/post-PCRT mLPLN (+) group

In pre-PCRT mLPLN (+) group, the 5-year PRFS rate was significantly higher in no LPLNs group than LPLNs group (97.7% vs. 92.7%, P = 0.028). In post-PCRT mLPLN (+) group, the 5-year PFS rate was also higher in no LPLNs group, but it was not significant statistically (96.0% vs. 91.0%, P = 0.059) (Figure 11).

**(A)** **(B)**

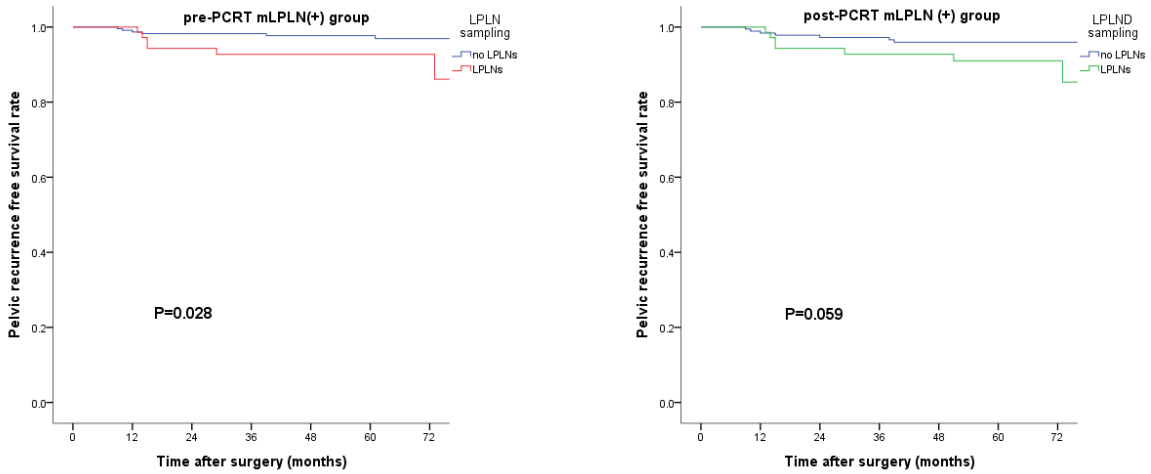


**Figure 11. Pelvic recurrence free survival (PRFS) according to LPLNs in (A) pre-PCRT mLPLN (+) and (B) post-PCRT mLPLN (+) group.**

### 4) Association between LPLNs and OS in pre-/post- PCRT mLPLN (+) group

In pre-PCRT mLPLN (+) group, the 5-year OS rate was higher in LPLNs group than no LPLNs group (79.4% vs. 76.5%, P = 0.283). In post-PCRT mLPLN (+) group, the 5-year OS rate was also higher in LPLNs group than no LPLNs group (82.1% vs. 76.5%, P = 0.228). But, it was not significant statistically (Figure 12).

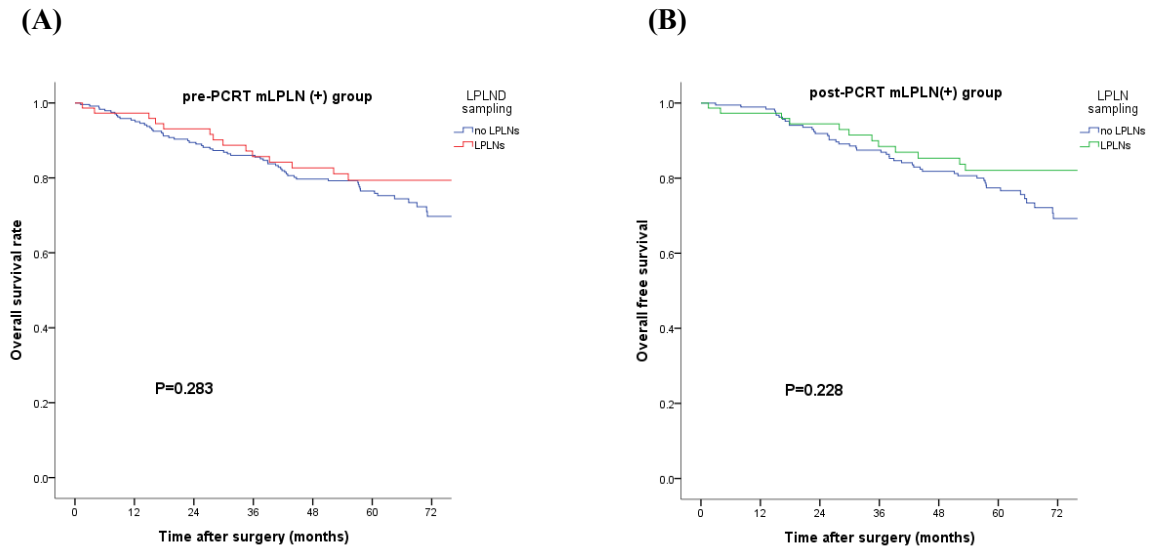


**Figure 12. Overall survival according to LPLNs in (A) pre-PCRT mLPLN (+) and (B) post-PCRT mLPLN (+) group.**

### 3-7. Risk factors associated with oncologic outcomes in rectal cancer treated with PCRT

In multivariable analysis, sphincter saving resection, initial cT, lymphovascular invasion, perineural invasion and pathologic TRG was associated with OS and DFS. Pre-PCRT mLPLN was related with OS (HR 1.39; 95%CI, 1.01-1.92; P = 0.042), whereas, post-PCRT mLPLN was related with DFS (HR 1.36; 95%CI,1.00-1.85; P = 0.048). Post-PCRT mLPLN was also related with PRFS (HR 4.95; 95%CI, 1.83-13.32; P = 0.002). Pathologic TRG was related with OS, DFS, LRFS, DRFS, and PRFS. (LRFS; HR 1.78 95%CI, 0.97-3.28; P = 0.062, DRFS; HR 1.33; 95%CI, 1.01-1.73; P = 0.03, PRFS; HR 6.46; 95%CI, 1.48-28.24; P = 0.013). Poor response to PCRT was confirmed as risk factors of OS, DFS, LRFS, DRFS, and PRFS (Table 6).

**Table 6. Multivariable analysis of risk factors of overall survival (OS) and disease free survival (DFS).**

| | OS | | DFS | |
|---|---|---|---|---|
| | **HR (95%Cl)** | **P** | **HR (95%Cl)** | **P** |
| **Age (years)** | | <0.001 | | NA |
| age < 59 | 1 | | NA | |
| age≥59 | 1.67 (1.30-2.13) | | NA | |
| **Sphincter saving resection** | | 0.001 | | 0.001 |
| No | 1 | | 1 | |
| Yes | 0.57 (0.43-0.74) | | 0.66 (0.51-0.84) | |

| | | | | |
|---|---|---|---|---|
| **initial cT** | | 0.035 | | 0.03 |
| T0, T1, T2 | 1 | | 1 | |
| T3, T4 | 3.41 (1.09-10.67) | | 2.99 (1.11-8.04) | |
| **LVi** | | 0.015 | | 0.014 |
| No | 1 | | 1 | |
| Yes | 1.51 (1.08-2.11) | | 1.45 (1.08-1.94) | |
| **PNi** | | <0.001 | | <0.001 |
| No | 1 | | 1 | |
| Yes | 2.00 (1.49-2.68) | | 2.06 (1.58-2.70) | |
| **Pre-PCRT PLNE** | | 0.042 | | 0.286 |
| No | 1 | | 1 | |
| Yes | 1.39 (1.01-1.92) | | 1.17 (0.87-1.58) | |
| **Post-PCRT PLNE** | | 0.793 | | 0.048 |
| No | 1 | | 1 | |
| Yes | 1.04 (0.74-1.48) | | 1.36 (1.00-1.85) | |
| **Pathologic tumor regression grade** | | 0.029 | | 0.018 |
| Total & near total | 1 | | 1 | |
| Moderate & Minimal & No | 1.37 (1.03-1.82) | | 1.36 (1.05-1.77) | |

Hazard ratio was calculated by multivariable analysis which were significant on univariable analysis
Comparisons that were not significant on univariable analysis did not undergo multivariable analysis
OS, Overall survival; DFS, Disease free survival

## 4. Discussion

We found that patients with pre- or post- PCRT mLPLN (+) had higher LR, PR, DR rate and worse OS, DFS, LRFS, PRFS rate and pre-PCRT mLPLN (+) was risk factor of OS and post-PCRT mLPLN (+) was risk factor of DFS. Patients who underwent LPLNs showed worse OR, PR, DR in pre-PCRT mLPLN (+) group but it did not show difference in LR rate. Based on the result of this study, pre-/post-PCRT mLPLN was poor prognostic factor but LPLN sampling could not add benefit in terms of overall survival as well as disease-free survival, and pelvic recurrence free survival in our cohort.

Although the oncologic outcomes have improved with PCRT, recent studies have shown that rectal cancer patients with LPLN metastasis have poorer outcomes ; moreover, LPLN is the main site of local recurrence, even after PCRT [28]. Lateral pelvic lymph node metastasis is reported in 10-25% of patients with locally advanced rectal cancer [29] [30].

To manage LPLN metastasis which occurred after PCRT, lateral pelvic lymph node dissection (LPLND) had been suggested historically. LPLND is the excision of lymph nodes including both

common and internal iliac, obturator and middle and inferior rectal lymph nodes. Common iliac LN is located along common iliac artery/vein and external iliac LN is located along external iliac artery/vein. Obturator nodes lie lateral to the parietal pelvic fascia, around the obturator neurovascular bundle. Internal iliac group includes lateral sacral nodes (in proximity to lateral sacral arteries), presacral nodes (anterior to sacrum and posterior to the mesorectal fascia), anterior internal iliac nodes (nodes located at the origin of the proximal branches of anterior division of internal iliac arteries), and hypogastric nodes (the most cephalic of the internal iliac nodes) [18]. However, LPLND requires delicate and difficult technique and can cause several morbidities including large volume of blood loss, urinary retention, and sexual dysfunction.

A study by Lee at el. compared the perioperative risk in patients who underwent TME + LPLND (n=37) versus TME alone (n=15) after PCRT [31]. The group that underwent LPLND had significantly longer operating time (562 minutes vs. 436 minutes, P = 0.015), more blood loss (560ml vs. 135ml, P = 0.05), without difference in blood transfusion rates (40.5% vs. 33.3%, P = 0.62) nor postoperative complication rates (37.8% vs. 42.9%, P = 0.74). JCOG0212 showed similar results in terms of short postoperative outcomes of TME + LPLND (n=351) versus TME only (n=350) in patients who did not have neoadjuvant chemoradiotherapy [32]. Patients who had LPLND had significantly longer operating time (360 min vs. 254 min, P < 0.001) and greater blood loss (576ml vs. 337ml, P < 0.001). However, there was no significant difference in rates of grade 3/4 complication, anastomotic leaks, urine retention, postoperative infections, surgical site infection, pelvic abscess, bowel obstructions.

Functional outcome after LPLND also has been a major concern. LPLND involves danger to the nerves in the pelvic sidewall and is obviously resulted in very high rates of sexual impotence and urinary incontinence [33-35]. Therefore, we carefully select the patients who potentially get benefit from LPLND even took a risk of worse short-term surgical outcome and functional outcomes.

However, the prognostic significance of LPLND on LR and survival remains undefined especially in patients with PCRT (Table 7). Because LPLN except internal iliac node has been considered as

distant metastasis and internal iliac node was included in radiation field. Some reported that LPLND resulted in reduction of LR rate and improvement the OS rate [14, 25, 36]. Contrarily, some studies reported that mLPLN showed poor oncologic outcomes even after LPLND because patients with mLPLN had a high distant metastasis rate [37].

**Table 7. Oncologic outcomes according to LPLN dissection status in rectal cancer patients after PCRT.**

| Author | Year | Patients | | Local recurrence, % | | Free of distant metastasis, % | | 5-year overall survival, % | |
|---|---|---|---|---|---|---|---|---|---|
| | | LPLND | No LPLND | LPLND | No LPLND | LPLND | No LPLND | LPLND | No LPLND |
| Watanabe T [38] | 2002 | 53 | 25 | 16.9 | 12 | 50.9 | 68 | - | - |
| Ishihara S [39] | 2016 | 14 | 34 | - | - | - | - | CSS; HR 0.73 95% CI 0.41-1.31 | |
| Ozawa H [40] | 2016 | 193 | 207 | - | - | - | - | 68.9 | 62 |
| Georgiou PA [41] | 2017 | 12 | 19 | 50 | 31.5 | 88.2 | 75 | 60.7 | 75.2 |
| Nagawa H [42] | 2001 | 23 | 22 | 4.3 | 0 | 69.5 | 77.2 | - | - |
| Akiyoshi T [43] | 2014 | 38 | 89 | 2.6 | 7.8 | - | - | 83.8‡ | 74.6‡ |
| Ogura A [14] | 2019 | 71 | 202 | 5.7* | 25.6* | 86.5* | 69.2* | 94.1*† | 79.4*† |
| Matsuda [44] | 2018 | 32 | 13 | 20 | 0 | 74.7 | 78.6 | - | - |

LPLND, Lateral pelvic lymph node dissection; CSS, cancer-specific survival
* Among patients with pretreatment short axis diameter of >7mm, † cancer-specific survival, ‡ 3-year relapse-free survival

JC Kim et al. evaluated outcome between TME and post operative chemoradiotherapy (CRT) (Korean) and LPLND following radical resection without PCRT in rectal cancer patients (Japan). Patients in the LPLND group with stage III low rectal cancer had a locoregional recurrence rate 2.2-fold greater than those in the postoperative CRT group (16.7% vs. 7.5%, P = 0.044). These findings suggest that CRT was eligible for locally advanced rectal cancer without PCRT [45]. Emile et al. also insisted that LPLND was not associated with a significant reduction of recurrence rates or improvement in survival [46].

However, in Japan, Fugita et al. showed that LR were less in TME + LPLND than TME alone group (7.4% vs. 12.6%) [47]. Akiyoshi et al. showed that in patients with LPLN enlargement (short axis at least 7mm), 5-year lateral local recurrence (LLR) rate was significantly low in TME + LPLND

rather than only TME group and suggested that the addition of LPLND following TME results in a lower lateral local recurrence rate [48]. These studies, however, did not include role of chemoradiotherapy.

Kim et al. evaluated oncologic outcome of LPLND based on post-PCRT response. They showed that among patients with suspicious LPNs on pretreatment MRI and good response to PCRT on posttreatment MRI, TME + LPND group showed lower LR than TME along group [25]. National comprehensive cancer network (NCCN) defines lymph nodes outside of the mesorectal lesion should be grouped in distant metastasis. However, Akiyoshi et al. showed that both 5-year OS and cancer-specific survival (CSS) were not significantly different between the N2a and internal-LPLN group. And OS and CSS were significantly better in the external LPLN group than in patients with stage IV. It suggested that LPLN can be considered as regional LNs in low rectal cancer [48]. Kim et al. showed patients with LPLN (+) had a high risk of lateral pelvic recurrence compared with those with LPLN (-) (26.6% vs. 2.3%, $p < 0.001$) and suggested that lateral pelvic recurrence was the major cause of locoregional recurrence [17]. And Atsushi et al. showed LPLN enlargement groups (SA ≥7mm) resulted in significantly higher risk of LLR compared with LLN with a SA <7mm [14].

Selecting optimal patients for LPLND is important for gaining oncologic advantage of LPLND. The LPLN size before PCRT is considered as the main factor for predicting lateral pelvic recurrences and used as one of the criteria for determining LPLND. For the diagnosis of mLPLN, MRI, computed tomography (CT), and positron emission tomography are used. The imaging modalities used to diagnose mLPLN and size criteria varied among studies. In addition, whether LPLN size pre- or post-PCRT would be used as more optimal criteria remains controversial.

Even within one institution, the standard for implementing LPLND changes over time. In Kyungpook national university medical center, patients with persistently suspicious LPLN after PCRT was selected to conduct LPLND before 2010, and after 2011, LPLND was performed in all patients with suspected metastatic pelvic lymph nodes on pretreatment imaging, irrespective of the clinical response shown by post PCRT MRI [25]. The standard for size is different for each center. Recent

data of the largest Western study from MD Anderson Cancer Center proposed that patients with rectal cancer and a post PCRT LPLN SA of ≥5mm need to be considered for LPLN [23] . Among 64 patients who were included, 33 (51.6%) had mLPLN after PCRT and this occurred in all patients with a post PCRT LPLN SA of ≥5mm. Lim et al. showed that the mLPLN was significantly more in patients with LPLN ≥10mm those with <10mm (before CRT ; 59.1% vs. 15.8%, before surgery; 65.5% vs. 22.0%) [26]. The Lateral Node Study Consortium reported that the LPLND significantly the reduced 5-year lateral pelvic recurrence and DR rates in patients with a LPLN SA >7mm on pre-PCRT MRI [14]. In the subgroup analysis, they evaluated the effect of re-staging cancer with MRI in 741 patients who received PCRT and underwent re-staging MRI[32]. Among 741 patients, 651 underwent PCRT with TME and 90 underwent PCRT with TME and LPLND. Compared with PCRT with TME alone, PCRT with TME and LPLND in these unresponsive internal nodes resulted in significantly lower LLR rate of 8.7% (HR, 6.2; 95% CI, 1.4-28.5; P = 0.007) in patients with LPLN SA ≥7mm on primary MRI and >4mm on restaging MRI. They insisted, however, that LPLND can be avoided in patients whose LPLN size decreased, from a SA ≥7mm on primary MRI to SA ≤4mm on restaging MRI, as there was absence of LLR. However, with the same size criteria, Kim et al reported that patients whose short-axis LPLN diameter of ≥7mm on pre-PCRT MRI decrease to <4mm after PCRT was associated with a lower incidence of LR, but the degree of DR risk remained the same in 798 rectal cancer patients treated with PCRT [37]. Akiyoshi et al. evaluated whether post-PCRT change in LPLN size would be an indication for LPLND in 77 patients who had locally advanced low rectal cancer with a long-axis >7mm and received PCRT. After the PCRT, re-staging MRI and LPLND were performed [49]. Before and after PCRT, patients with SA LPLN diameter of >8mm and >5mm, respectively showed higher mLPLN rate. mLPLN was associated with poor 3-year RFS, and the response of LPLN to PCRT was not associated with RFS. In his study, patients with a >60% reduction in the volume of LPLN after PCRT did not show mLPLN. Authors, therefore, concluded that the responsiveness of LPLN after PCRT is not a suitable method for measuring mLPLN. Similar results were also reported by a retrospective, multi-center (three Korean hospitals), cohort study that

analyzed 66 patients who had locally advanced low rectal cancer (below the peritoneal reflection), in which a responsive LPLN would not be a definite indication for LPLND [50].

LPLND is not routine procedure for low rectal cancer with patients having mLPLN radiologic findings in our center. We perform LPLNs of suspected lymph node, however corresponding LPLN is rather hard to find out with LPLNs, in some cases, therefore, there was no harvested LPLN after LPLNs. There are many limitations even in cases of minimally invasive surgery because we have to rely on vision to make all judgments. It is difficult to determine whether there is actually lymph node enlargement and do appropriate sampling. So, recently some centers use fluorescence imaging and indocyanine green (ICG) using a near-infrared camera system to overcome these limitations [51]. However, since this method was not applied at the time in our study, appropriate LPLNs may not have been performed in some patients.

mLPLN is closely related to LR, but is also may be associated with an increase in DR. Recent studies show that LPLND decrease LR, however there is not sufficient evidence that it improves DFS or OS. A multicenter retrospective study involving 12 hospitals in 7 countries, however, reported the beneficial effects of LPLND in the LR, LLR, DR, and 5-year CSS rates (P = 0.042, 0.005, 0.028, and 0.032, retrospectively) compared with the absence of dissection in patients with a SA ≥7mm on pre-PCRT MRI [14].

A 2014 retrospective Korean study by Kim et al. looked at 443 patients with stage II, III rectal cancer, up to 15cm from the anal verge [15]. All patients had PCRT followed by TME dissection, and only 18 patients had LPLND. With 52 months of median follow-up, 107 patients developed a recurrence (23.2%), and LR occurred in 53 patients (11.9%). 12.2% had DR, and 79% had both LR and DR. Among the 53 patients who had a LR, LLR occurred in 20 patients (37.7%), central recurrence in 25 patients (47.2%) and both lateral/central in 8 patients (15.1%) This result shows that PCRT+TME is not enough, and the patients have a high risk of locoregional recurrence rates. Interestingly, this paper found that the size of LPLN was not a significant risk factor of LPLN recurrence (compared <10mm vs. >10mm, P = 0.085). However, this may be because they had set

criteria too high (>10mm), and as will be discussed in the subsequent section, size of >7mm or even 5mm is more appropriate criteria for risk of LPLN recurrence. This paper found that the number of abnormal LPLN (more than 2 vs. less than 2) was significantly associated with recurrence (RR = 0.29, P = 0.01)

Another Korean study from 2015 examined 900 patients with locally advanced (stage II, III) low rectal cancer who had PCRT and TME dissection [16]. The study looked at recurrences in LPLN and examined the risk factors. LR occurred in 65 patients (7.2%) and of these 42 patients (64.6%) had LLR. The 5-year DFS was related with size of LPLN as follows: <5mm: 76.8%, 5-10mm: 72.5% and >10mm: 30.3%. Overall 5-year survival was: <5mm: 86.3%, 5-10mm: 83% and >10mm: 57.5%. Therefore, the study concluded that SA >10mm represents the high-risk group of LR and PCRT/TME is not enough.

A European study based on the United Kingdom and Netherland were published in 2017 based on 127 patients with locally advanced low rectal cancer (up to 8cm from the anorectal junction) treated with PCRT and TME [52]. 14 patients (18.7%) developed LR, of these nine patients of these in the lateral compartment, giving rise to a 5-year LLR of 11.8%. Patients with a SA >10mm had a significantly higher lateral local recurrence rate (33.3% vs. 10.1% 4-year rate, P = 0.03) than in patients with SA <10mm. The paper concluded that PCRT and TME dissection is not enough in patients with enlarged lymph nodes.

In both the European and Korean studies [15, 16, 52], more than half of locoregional recurrences were only in the lateral compartment, and even in patients with recurrent diseases, half did not have distant metastases suggestive that the disease is a localized disease.

In our study, pelvic recurrence is higher in pre-/post-PCRT mLPLN (+). But, DR is also commonly developed in pre-/post- mLPLN (+). LPLNs did not improve both DFS and PRFS in these patients. PR occurred more commonly in patients with pathologically confirmed mLPLN among LPLNs. Based on these results, we could identify pre/post-PCRT mLPLN are definite poor prognostic indicator, LPLNs, however, may be not enough to influence on oncologic outcomes. Considering the

higher DR rate in patients with mLPLN, we need to evaluate the oncologic benefit of LPLND or LPLNs carefully.

In our study, we analyzed the proportion of pathologic TRG groups according to post-PCRT mLPLN and recurrence according to TRG. We expect that if patient has good response at PCRT, mLPLN will decrease although PCRT did not routinely include LPLN area beyond internal iliac LN because internal iliac LN was the most frequently involved site of mLPLN. If so, good responders might be excluded in LPLND criteria.

Among the patients with good response, the patients who had pathologically confirmed mLPLN were significantly lower than those with non-confirmed patients (1.3 vs. 98.7%, respectively). Good responders had low incidence of pathologically confirmed mLPLN (23.5% vs. 76.5%). However, in imaging studies, among poor responders, patients with sustained mLPLN after PCRT are similar in patients with good response to PCRT. Therefore, good response of primary tumor did not guarantee of absence of mLPLN.

This study has some limitations. This study was retrospective and non-randomized design and there could be a selection bias and some data were missing from the medical record. In this study, we did not re-measure LPLN SA because we think it is artificial measurement and it did not really influence on determination LPLNs. We tried to evaluate the real-world practice. And number of patients who performed LPLN sampling is small portion of all selected patients. In this study, LPLNs was performed in about 6% of all patients, which is lower than 12% in other multicenter studies [14].

However, it was a large single center study of a cohort of patients and it reflects the reality in clinical low rectal cancer. And our median f/u month was about 60 months, it was relatively long-term f/u study.

We demonstrate that mLPLN may be a signal of DR as well as risk of PR, and LPLNs may not enough to get oncologic advantage. We have to decide to perfom LPLNs or dissection carefully for this reason considering both advantages and disadvantages and well-designed case control study need to be performed for establishment of criteria for LPLND.

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**국문 요약**

**연구배경 및 목적** 측방 골반림프절은 수술 전 화학방사선치료(PCRT) 후에도 직장암의 주요 국소 재발 부위로 알려져 있다. 측방 골반 림프절 전이를 통한 예후 예측과 직장암에서 측방 골반림프절 절제의 역할에 대한 관심이 높아지고 있다. 그러나, 측방 골반림프절 전이와 관련된 예후 예측과 치료에 관한 증거가 충분하지 않은 것이 현실이다. 본 연구에서는 수술 전 화학방사선치료를 시행 받은 직장암 환자에서 영상학적 검사에서 확인된 측방 골반림프절 전이가 종양학적 결과에 미치는 영향과 측방 골반림프절 샘플링이 향후 예후에 미치는 영향에 대하여 평가하고자 하였다.

**연구 방법** 2008년 1월부터 2016년 12월까지 서울아산병원에서 수술 전 화학방사선치료와 근치적 절제수술을 받은 1535명의 환자 군을 대상으로 연구하였고, 골반 자기공명영상 및 복부 전산화 단층촬영을 시행 받은 환자들을 포함하였다. 측방 골반림프절 전이는 수술 전 화학방사선치료 시행 전후의 영상학적 검사에서 림프절의 단측 길이가 5mm 초과이거나 표면이 뾰족하거나 경계가 불분명하거나 불균일한 신호를 보이는 경우로 정의하였다. 재발 유형은 국소 재발(LR), 원격 재발 (DR), 골반 내 재발(PR)로 분류하였다. 국소 재발은 기존 절제부위에 인접한 관강 내 종양이 임상적, 영상학적, 또는 내시경적으로 재발로 의심되는 경우 또는 첫 수술 후 직장간막 또는 직장벽 내에 위치한 종양이 재발로 의심되는 경우로 정의하였다. 골반 내 재발은 총장골동맥, 외장골동맥, 내장골동맥, 폐쇄동맥의 림프절을 포함한 골반 내 림프절에서의 재발로 정의하였으며, 국소 재발과, 원격 재발 모두에 포함되지 않았다. 측방 골반림프절 전이와 무병생존율, 전체 생존율, 국소재발 없는 생존율, 골반 내 재발 없는 생존율의 연관성에 대하여 분석하였으며 종양학적 결과와 관련된 위험인자도 분석하였다. 추가로, 임상적으로 측방 골반림프절 전이 소견이 있었던 환자들에게 측방 골반림프절 샘플링의 영향에 대해서 분석하였다.

**연구 결과** 1535명의 환자들 중에서 수술 전 화학방사선치료 전에 317명(20.6%), 수술 전

화학방사선 치료 시행 후에 264명(17.1%)이 측방 골반림프절 전이를 보였다. 국소 재발, 원격 재발, 골반 내 재발은 수술 전 화학방사선치료 시행 전 그룹에서 측방 골반림프절 전이 음성 그룹보다 측방 골반림프절 전이 양성 그룹에서 더 높았고 (국소 재발률: 7.3% vs. 3.9%, 원격 재발률: 26.5% vs. 18.7%, 골반 내 재발률: 3.8% vs. 1.1%), 수술 전 화학방사선치료 시행 후 그룹에서도 마찬가지였다 (국소 재발률: 12.1% vs. 4.3%, 원격 재발률: 28.8% vs. 18.6%, 골반 내 재발률: 5.3% vs. 0.9%). 무병생존율, 국소재발 없는 생존율, 골반 내 재발 없는 생존율, 전체 생존율 모두 측방 골반림프절 전이 양성 그룹보다 측방 골반림프절 전이 음성 그룹에서 더 높았고, 이는 수술 전 화학방사선치료 시행 전후 그룹 모두에서 동일하게 나타났다.

수술 전 화학방사선치료 시행에 반응이 좋지 않을수록 전체 생존율, 무병생존율, 국소재발 없는 생존율, 골반 내 재발 없는 생존율 관련 위험도가 높은 것으로 나타났다. 수술 전 화학방사선 치료 시행 전 측방 골반림프절 전이 양성인 경우에는 전체 생존율 관련 위험도가 높았고, 수술 전 화학방사선 치료 시행 후 측방 골반림프절 전이가 양성인 경우에는 무병 생존율 관련 위험도가 높았다. 측방 골반림프절 샘플링을 시행한 환자 군에서는 5년 국소재발 없는 생존율과 5년 전체 생존율이 샘플링을 시행하지 않은 환자 군에 비하여 높았으나 통계학적으로 유의미하지는 않았다.

**결론** 본 연구에서는, 수술 전 화학방사선치료 전후 영상 검사에서의 측방 골반림프절 전이 소견이 확인된 환자에서 국소재발, 골반 내 재발, 원격 재발율이 높고, 전체 생존율, 무병생존율, 국소재발 없는 생존율, 골반 내 재발 없는 생존율이 더 좋지 않다는 것을 확인할 수 있었다. 그리고, 본 코호트 연구에서는 측방 골반림프절 전이가 의심되는 림프절의 샘플링이 종양학적 이득과 관련이 없었다. 그러므로 우리는 장단점을 모두 고려하여 측방 골반 림프절절제 시행 여부를 신중히 결정하여야 한다. 그리고, 광범위한 측방 골반림프절 절제가 종양학적 결과에 미치는 영향은 추가적인 연구를 통해 평가되어야 하며,

이러한 종양학적 이득 여부 및 측방 골반림프절 전이가 예후에 미치는 영향에 근거하여 측방 골반 림프절 샘플링 또는 절제를 결정하여야 한다.