Abstract. Background/Aim: This study evaluated clinico-pathological and molecular features and their prognostic impact on patients with locally advanced rectal cancer (LARC) who received preoperative chemoradiotherapy (CRT). Patients and Methods: We retrospectively gathered data from 284 patients with LARC who underwent total mesorectal excision (TME) after CRT. Results: In the univariate analysis, lower yield pathologic T (ypT) category, yield pathologic N (ypN) category, yield pathologic TNM (ypTNM) stage, as well as the absence of lymphovascular invasion (LVI) and perineural invasion (PNI), were significantly associated with better disease-free survival (DFS) and overall survival (OS). Meanwhile, the expression of Ki-67, p53, and the mismatch repair (MMR) status showed no association with clinical outcomes. A multivariate survival analysis revealed that ypT category and LVI were independent prognostic factors of a worse DFS (HR=3.081, p-value=0.001; HR=2.818, p-value=0.030) and OS (HR=3.158, p-value=0.006; HR=3.837, p-value=0.014). Conclusion: The ypT category and the presence of LVI were found to be prognostic factors for patients with LARC after CRT followed by TME.

Locally advanced rectal cancer (LARC), characterized by invasion of tumors beyond muscle layers or metastasis of regional lymph nodes at diagnosis, shows poor prognosis, and approximately one third of patients eventually experience distant metastases (1). Neoadjuvant chemoradiotherapy (CRT) in LARC is known to have advantages for anal sphincter preservation, preoperative downstaging of the tumor, lower local recurrence rate, and fewer toxicities related to treatment compared with adjuvant CRT (1, 2). Therefore, neoadjuvant CRT followed by surgical excision is recommended as standard treatment for patients with LARC.

Despite the adoption of neoadjuvant CRT in LARC management, the treatment response has remained varied. Around 15% of patients treated with neoadjuvant CRT achieve pathologic complete response (pCR), with the remaining of them exhibiting various pathologic responses from tumor downstaging to distant metastatic disease. The varied treatment responses imply that rectal cancer is a heterogeneous disease, and its unidentified clinicopathological features may be responsible for the different clinical outcomes such as recurrence, metastasis, or survival.

Pathological stages after surgical resection and following neoadjuvant CRT are universally classified by ypStage, which has been considered a robust prognostic indicator of LARC (3, 4). In addition, pathological residual lymph node metastasis and invasion depth of the tumor after neoadjuvant CRT have been confirmed to be major prognostic factors of rectal cancer and are strongly correlated with metastasis and disease-free survival (DFS) (3-6). Previous studies have demonstrated that the presence of lymphovascular invasion (LVI), or perineural invasion (PNI), has a negative impact on clinical long-term outcomes (7). Recently, molecular markers were studied as prognostic factors to predict CRT response and survival outcome in
of clinicopathological features, including pathological and predictive role of MSI after neoadjuvant CRT in rectal molecular characteristics, in patients with LARC treated with neoadjuvant CRT, followed by surgical excision.

However, the patients treated with surgery followed by 5-fluorouracil (5-

negative predictive effect on survival of colon cancer mismatch repair (MMR) function, is known to have a microsatellite instability (MSI) caused by the loss of DNA-

Pathologic M stage, n (%)  
ypStage 0 39 (13.7%)  
ypStage I 51 (18.0%)  
ypStage II 99 (34.9%)  
ypStage III 88 (31.0%)  
ypStage IV 7 (2.5%)  

Patients and Methods

Patients and treatment. We retrospectively reviewed medical records from 284 patients with LARC who underwent neoadjuvant CRT followed by surgical excision at Kyungpook National University Chilgok Hospital (KNUCH, Daegu, Korea) between January 2006 and October 2015. The patients were enrolled in the study if they were (a) pathologically diagnosed with primary rectal cancer, (b) in clinical stage II or III rectal cancer as classified by the seventh edition of American Joint Committee on Cancer staging system (17), and (c) treated with neoadjuvant CRT, followed by surgical excision.

All patients received 45 Gy ~ 50 Gy of radiation delivered in 25 daily fractions over 5 weeks with a concurrent 400 mg/m² intravenous dose of 5-FU and 20 mg/m² of leucovorin on days 1-4 and 29-32, or oral capecitabine (825 mg/m²) twice daily for 5 days per week for 5 weeks. Dose reduction was individualized according to the performance status, toxicities, or medical condition of

Table I. Patient and tumor characteristics.

| Characteristics           | No. of patients (n=284) |
|---------------------------|-------------------------|
| Age                       | 59 (25-88)              |
| Gender, n (%)             |                         |
| Female                    | 86 (30.3%)              |
| Male                      | 198 (69.7%)             |
| Clinical T stage, n (%)   |                         |
| cT2                       | 15 (5.3%)               |
| cT3                       | 228 (80.3%)             |
| cT4                       | 41 (14.4%)              |
| Clinical N stage, n (%)   |                         |
| cN0                       | 44 (15.5%)              |
| cN1                       | 95 (33.5%)              |
| cN2                       | 145 (51.1%)             |
| Clinical Stage, n (%)     |                         |
| Stage II                  | 43 (15.1%)              |
| Stage III                 | 241 (84.9%)             |
| Pathologic T stage, n (%) |                         |
| ypT0                      | 40 (14.1%)              |
| ypT1                      | 8 (2.8%)                |
| ypT2                      | 51 (18.0%)              |
| ypT3                      | 172 (60.6%)             |
| ypT4                      | 13 (4.5%)               |
| Pathologic N stage, n (%) |                         |
| ypN0                      | 195 (68.7%)             |
| ypN1                      | 62 (21.8%)              |
| ypN2                      | 27 (9.5%)               |
| Pathologic M stage, n (%) |                         |
| ypM0                      | 277 (97.5%)             |
| ypM1                      | 7 (2.5%)                |
| Pathologic Stage, n (%)   |                         |
| ypStage 0                 | 39 (13.7%)              |
| ypStage I                 | 51 (18.0%)              |
| ypStage II                | 99 (34.9%)              |
| ypStage III               | 88 (31.0%)              |
| ypStage IV                | 7 (2.5%)                |

CR: Complete remission; TRG: tumor regression grade; LVI: lymphovascular invasion; PNI: perineural invasion; MMR: mismatch repair; MSI-H: microsatellite instability-high; MSI-L: microsatellite instability-low; MSS: microsatellite stable.

LARC. A higher Ki-67 index has been associated with poor CRT response and survival outcomes in several studies (8-10). p53, which has been largely studied as a tumor suppressor in other cancers, has not been verified to have a prognostic impact on survival in LARC (11). In addition, microsatellite instability (MSI) caused by the loss of DNA-mismatch repair (MMR) function, is known to have a negative predictive effect on survival of colon cancer patients treated with surgery followed by 5-fluorouracil (5-FU)-based adjuvant chemotherapy (12, 13). However, the predictive role of MSI after neoadjuvant CRT in rectal cancer remains controversial (14-16).

In this study, we investigated the prognostic significance of clinicopathological features, including pathological and molecular characteristics, in patients with LARC treated with neoadjuvant CRT, followed by surgical excision.
patients. The total mesorectal excision (TME) was performed 6–8 weeks after the completion of neoadjuvant CRT.

Pathological characteristics and molecular pathological features. All surgically resected specimens were examined by pathologists at KNUCH. The pathologic reports included ypT stage, ypN stage, LVI, and PNI. For assessment of tumor regression (TRG), the following Dworak grading system was used: the Dworak regression Grade 0 (TRG 0)=no regression; Grade 1 (TRG 1)=dominant tumor mass with obvious fibrosis and/or vasculopathy; Grade 2 (TRG 2)=dominantly fibrotic changes with few tumor cells or groups (easy to find); Grade 3 (TRG 3)=very few tumor cells in fibrotic tissue with or without mucous substance (difficult to find microscopically); and Grade 4 (TRG 4)=no tumor cells, only fibrotic mass (18). We performed immunohistochemical (IHC) studies for Ki-67 and p53 protein using an autoimmunostainer (Ventana Medical Systems, Tucson, AZ, USA) in accordance with the manufacturer’s instructions. When more than 10% of the tumor cells were stained, the tumor was considered as positive for Ki-67 and p53. Microsatellite instability (MSI) was evaluated by IHC analysis of DNA mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) (19, 20). IHC for MMR protein expression was performed on whole sections using an automatic immunostainer (BenchMark XT, Ventana Medical Systems, Tucson, AZ, USA) according to the manufacturer’s instructions. Tumors displaying loss of expression of one or more MMR proteins were considered to be MSI-high (MSI-H), whereas those with intact MMR proteins were classified as MSI-L/microsatellite stable (MSS) (21).

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statistical analysis. The characteristics of patients were described using proportions and medians. DFS was measured from date of diagnosis to the date of proven local recurrence, distant metastasis, or death by any cause. Overall survival (OS) was calculated from the date of diagnosis to death. Data were censored if patients were free of recurrence or still alive at the last follow-up. We used the Kaplan–Meier method to estimate the DFS and OS, and the log rank test, according to selected prognostic variables, to compare the survival curves. Multivariate survival analyses were carried out using the Cox proportional hazard regression model, and the hazard ratio (HR) and 95% confidence interval (CI) for each variable were estimated. A p-value of less than 0.05 was considered statistically significant. The statistical analysis was performed using SPSS for Windows (version 19.0 SPSS Inc., Chicago, IL, USA).

Results

Patient and tumor characteristics. The patient and tumor characteristics are summarized in Table I. The median age was 59 years (range=25-88 years) at the time of diagnosis. The outcome of patients based on the pathologic stages yielded after neoadjuvant CRT were as follows: ypStage 0 (n=39, 13.7%), ypStage I (n=51, 18.0%), ypStage II (n=99, 34.9%) and ypStage III (n=88, 31.0%). Seven patients (2.5%) were diagnosed with ypStage IV. Among a total of 284 patients, 147 patients were examined for classification according to the Dworak grading system. The rate of patients with TRG 4, which implies complete pathologic regression of the primary tumor, was 27.2% (n=40). The number of patients with the presence of LVI and PNI was 36 (12.7%) and 47 (16.5%), respectively. Local or distant recurrence occurred in 33.4% (n=95) of cases, and 89 patients (31.3%) died during the follow-up period.
Prognostic value of pathological features affecting survival outcomes. The results of the survival analysis are described in Table II. In a median follow-up duration of 60 months (5-151 months), the estimated 5-year DFS and OS were 61.4% and 74.5% for all patients, respectively. In the univariate survival analysis, the ypStage was found to be strongly associated with the survival of LARC patients (p-value<0.001 for both 5-year DFS and OS). Patients with the presence of ypN had significantly inferior DFS and OS compared to those who had negative residual lymph nodes after neoadjuvant CRT (5-year DFS: 71.9% vs. 38.6%, p-value<0.001; 5-year OS: 82.0% vs. 59.0%, p-value<0.001). Tumors penetrating muscle layers and visceral peritoneum, which were categorized as ypT3-4, showed significantly lower survival rates than the ypT0-2 category, in which tumors were confined below the muscle layers (5-year DFS: 81.7% vs. 50.6%, p-value<0.001; 5-year OS: 89.7% vs. 66.8%, p-value<0.001) (Figure 1A and B). Five-year DFS rates of the poor treatment response group (categorized as TRG 2-0) were inferior to the TRG 4-3 category, which was considered a good treatment response group (76.3% vs. 56.5%, p-value=0.015). Pathological characteristics including LVI and PNI were statistically significant prognostic factors for both 5-year DFS (LVI: 65.4% vs. 35.9%, p-value=0.001; PNI: 66.4% vs. 36.9%, p-value<0.001) and OS (LVI: 77.7% vs. 55.6%, p-value=0.001; PNI: 78.8% vs. 52.4%, p-value<0.001) (Figure 2A and B).

Molecular features and survival outcomes. We performed IHC studies for Ki-67 and p53 on the viable tumor cells of
randomized clinical trial that investigated the efficacy of neoadjuvant CRT compared to postoperative CRT in patients with clinical T3-4 or any node-positive rectal cancer (6). Moreover, a number of studies have consistently demonstrated the negative effect of the presence of LVI in rectal cancer survival (7). Lymphatic and vascular structures are considered the main route of spreading of tumor cells. Although it is not fully understood how tumor cells invade lymphatic and vascular vessels, tumor cells that infiltrate lymphatic and vascular structures tend to disseminate to lymph nodes and distant sites (22). This supports the conclusion that the presence of LVI is a potentially unreliable prognostic marker in rectal cancer. Recently, several researchers have attempted to examine whether adjuvant chemotherapy for LARC patients with the presence of LVI and/or PNI after neoadjuvant CRT contributed to favorable survival outcomes. They found that adjuvant chemotherapy resulted in better survival outcomes in the presence of PNI than LVI (23, 24). The strategy of LARC management is moving toward a more tailored treatment that involves stratification of patients according to the possibility to benefit from adjuvant chemotherapy in order to prevent distant metastasis and eventually improving survival. Based on these results, the ypT category and the presence of LVI could be useful indicators for stratifying risk and determining adjuvant chemotherapy in LARC patients who underwent neoadjuvant CRT followed by TME.

The prognostic impact of Ki-67 and p53 expression has already been determined in several cancers (8, 25, 26). In particular, high expression of Ki-67 suggests high sensitivity to radiation, which contributes to a favorable response of radiotherapy in radio-sensitive tumors, such as small-cell lung cancer or cervical cancer (25, 26). However, the prognostic role of Ki-67 and p53 expression in LARC remains controversial (8, 9, 11, 27, 28). In several studies, samples obtained before CRT were used to interpret the degree of expression in IHC (8, 27). However, expression of molecular markers including expression of Ki-67, p53 and the MMR proteins after neoadjuvant CRT were not significantly associated with survival outcomes.

**Multivariate survival analyses.** ypT, ypN, TRG, LVI and PNI, and age were included in the multivariate survival analyses. Among them, depth of tumor invasion, ypT0-2 versus ypT3-4, and the presence of LVI were identified as significant independent prognostic factors for DFS (ypT0-2 versus ypT3-4: HR=3.081, 95%CI=1.593-5.960, p-value=0.001; LVI: HR=2.818, 95%CI=1.108-7.162, p-value=0.030) and OS (ypT0-2 versus ypT3-4: HR=3.158, 95%CI=1.397-7.137, p-value=0.006; LVI: HR=3.837, 95%CI=1.318-11.168, p-value=0.014; Table III).

### Discussion

In the current study, we investigated the prognostic impact of the clinicopathological features including Ki-67, p53, and MSI status in LARC patients who underwent TME after neoadjuvant CRT. Patients in the high ypT category and those with LVI showed significantly poor survival outcomes. Meanwhile, molecular markers including expression of Ki-67 and p53 and the MMR status failed to confirm their prognostic values in LARC patients.

The pathological response after neoadjuvant CRT, including ypT, ypN as well as TRG, has already been reported to be associated with disease recurrence, distant metastasis, and survival in a German multicenter randomized clinical trial that investigated the efficacy of surgical specimens; positive staining was observed in 92.7% (n=178) and 68.1% (n=130) of samples, respectively. In 194 patients who evaluated the loss of MMR proteins expression, 34 (18.2%) patients showed loss of expression of at least one MMR protein, sorting to MSI-H group, and 153 (81.8%) patients without loss of expression of at least one MMR were classified as MSI-L/MSS. The survival analysis showed that the expression of Ki-67, p53 and the MMR proteins after neoadjuvant CRT were not significantly associated with survival outcomes.

|               | DFS          | OS           |
|---------------|--------------|--------------|
| Age           | HR           | 95%CI        | p-Value | HR           | 95%CI        | p-Value |
| Age           | 1.019        | 0.992-1.047  | 0.177   | 1.033        | 0.998-1.069  | 0.064   |
| ypN0 vs. ypN1-2 | 1.390        | 0.682-2.831  | 0.365   | 0.776        | 0.307-1.961  | 0.592   |
| ypT0-2 vs. ypT3-4 | 3.081        | 1.593-5.960  | 0.001   | 3.158        | 1.397-7.137  | 0.006   |
| TRG 4-3 vs. TRG 2-0 | 1.300        | 0.697-2.427  | 0.409   | 1.191        | 0.548-2.589  | 0.659   |
| LVI No vs. Yes | 2.818        | 1.108-7.162  | 0.030   | 3.837        | 1.318-11.168 | 0.014   |
| PNI No vs. Yes | 1.573        | 0.707-3.498  | 0.267   | 1.286        | 0.399-4.139  | 0.673   |

DFS: Disease-free survival; OS: overall survival; CI: confidence interval; TRG: tumor regression grade; LVI: lymphovascular invasion; PNI: perineural invasion.

Table III. Multivariate analysis of disease-free survival and overall survival.
Ki-67 and p53 in this study was examined using operative specimens after neoadjuvant CRT, rather than before treatment. Therefore, there may have been differences in the time of sample acquisition between the specimens used to detect the expression using IHC. In addition, the methodology of IHC will need to be standardized. Furthermore, the correlation between the expression of Ki-67 and sensitivity to radiation was not estimated in the present study.

MSI is a well-known prognostic and predictive biomarker in colon cancer. Its strong association with favorable prognosis and poor response to 5-FU chemotherapy has necessitated adjuvant chemotherapy in low-risk stage II colon cancer (12). However, the role of MSI as a predictive factor in rectal cancer has not been confirmed (29). Some studies have reported that MSI-H was independently associated with poor pCR rates after neoadjuvant CRT (15), and had inferior survival outcomes for rectal cancer (14). In contrast, other studies have reported that patients with MSI-H or dMMR rectal cancer had higher survival rates (16, 30). These contradictory results regarding MSI as a predictive factor may be attributable to the mixed rectal cancer phenotypes with patients harboring various concomitant mutations in different genes such as BRAF, KRAS, or other cancer pathway genes that generally show poor prognosis (15, 29). In the meantime, the MSI status from surgically resected specimens after neoadjuvant CRT was not associated with survival outcomes in the present study. Therefore, further studies are warranted to evaluate the predictive effect of MSI status after CRT in LARC.

In conclusion, the ypT category and the presence of LVI had a significant prognostic impact in patients with LARC. However, the expression of Ki-67, p53, and MMR status had a significant prognostic impact in patients with LARC. Further studies are warranted to evaluate the predictive effect of MSI status after CRT in LARC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Authors’ Contributions

All Authors contributed to the design and implementation of the research, to the analysis of the results, and the writing of the article.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) Grant funded by the Korea government (2014R1A5A2009242).

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Received August 28, 2019
Revised September 21, 2019
Accepted September 23, 2019