The efficacy of hypofractionated preoperative chemoradiotherapy in rectal cancer

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Abstract

Purpose

To evaluate the efficacy and toxicity of hypofractionated preoperative chemoradiotherapy (HPCRT) combined with oral capecitabine in patients with rectal cancer.

Methods

HPCRT was delivered by an intensity-modulated radiotherapy of either 33 Gy to the whole pelvis or 35 Gy in 10 fractions to the primary tumor and 33 Gy to the surrounding pelvis. Surgery was performed 4–8 weeks after HPCRT completion. Oral capecitabine was administered concurrently. Tumor response, toxicity, and survival were analyzed.

Results

Seventy-six patients were eligible for this study. Patients number of clinical stage I, II, III, and IVA were 5, 29, 36, and 6, respectively. Nine patients (11.8%) achieved a pathological complete response. Sphincter preservation was achieved in 23/32 (71.9%) and 44/44 (100%) of patients with a distal extent from anal verge of ≤ 5 cm and > 5 cm, respectively. Twenty-eight patients (36.8%) achieved T-downstaging, and 25 (32.9%) achieved N-downstaging. Five-year disease-free survival (DFS) was 73.6% and overall survival was 90.6%. In the multivariate analysis for DFS, significant prognostic factors were pathologic nodal stage and lymphovascular space invasion. Six patients with stage IVA underwent salvage treatments after HPCRT completion, and all survived to the final follow-up. Three patients experienced grade 3 postoperative complications. No grade 4 toxicities were observed.

Conclusion

HPCRT of 33 Gy or 35 Gy in 10 fractions showed similar results to those of long-course fractionation. This fractionation scheme could be beneficial for patients with early stage disease, locally advanced rectal cancer, simultaneous distant metastasis requiring early intervention, or for patients who wish to avoid multiple hospital visits.

Introduction

Preoperative chemoradiotherapy (CRT) is the standard treatment for locally advanced rectal cancer. It gained popularity from the German CAO/ARO/AIO-94 trial, which reported several advantages of preoperative CRT, such as lower local recurrence, a higher rate of sphincter preservation, and lower acute toxicity than postoperative CRT [1]. Along with the ongoing practice of long-course radiotherapy (LCRT), clinical trials assessing the change in radiotherapy schedule to short-course radiotherapy (SCRT) were
carried out [2, 3, 4], which advocated an excellent local control rate in SCRT compared to that with surgery alone, as well as SCRT being a simpler treatment than is LCRT. It is challenging to compare the two schedules because of the difference in patient selection for each trial. Randomized trials were performed to compare the relative advantages of LCRT and SCRT, which reported no statistically significant difference in oncologic outcomes [5, 6] or health-related quality of life [7, 8]. However, advocates for SCRT emphasize the lower acute toxicity, lower cost, and greater convenience for patients than that of LCRT [5, 9, 10]. Meanwhile, advocates for LCRT highlight higher rates of pathologic complete remission (pCR), a higher sphincter preservation rate, and lower local recurrence (especially in distant tumors) than those with SCRT [11, 12]. Consequently, to optimize the advantages of LCRT and SCRT, a phase II multi-institutional clinical trial was conducted for locally advanced rectal cancer, involving a two-week course of preoperative CRT of 33 Gy in 10 fractions, which included oral capecitabine followed by delayed surgery [13]. This dose prescription had an intermediate biological equivalent dose (BED$_{10}$, assuming $\alpha/\beta = 10$ by linear-quadratic model) of 43.9 Gy, which is between BED$_{10}$ 37.5 Gy of SCRT 25 Gy in 5 fractions and BED$_{10}$ 59.5 Gy of LCRT 50.4 Gy in 28 fractions. This study showed comparable toxicities and tumor responses to the historical LCRT results [13].

In the clinical setting, some patients prefer shorter CRT followed by minimally invasive surgery, such as local excision for clinical T1-2N0 stages. Without compromising the advantages of LCRT, a shorter radiotherapy schedule would be preferable for patients who dislike multiple hospital visits for LCRT or for those with simultaneous distant metastases or double primary cancers who need early intervention. Therefore, we performed hypofractionated preoperative CRT (HPCRT) of 33 Gy or 35 Gy in 10 fractions with an intensity-modulated radiotherapy combined with oral capecitabin in patients with rectal cancer. We analyzed the results of these fractionation schedules to investigate toxicities, tumor response, and survival outcomes in patients at a single institution.

**Materials And Methods**

**Patients**

Patients who were diagnosed with rectal adenocarcinoma and had adequate laboratory data, such as bone marrow, liver, and kidney function, were eligible to be included in this study. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2 and to be aged ≥ 18 years. Pretreatment workups included an estimation of carcinoembryonic antigen, colonoscopy, chest radiography, computed tomography of the abdomen and pelvis, magnetic resonance imaging (MRI), and 18 F-fluorodeoxyglucose positron emission tomography, if required. The study also included patients with distant metastasis (clinical stage IVA) or synchronous additional primary cancers, who preferentially received HPCRT rather than the conventional long-course fractionation for early intervention. The study was approved by our Institutional Review Board (approval number CNUHH-2010-009), and all patients submitted written informed consent upon enrollment.
Treatment

HPCRT was delivered either by a schedule including 1) 35 Gy in 10 fractions to the primary bulky tumor via simultaneous integrated boost (SIB) and 33 Gy to the remaining pelvis with intensity-modulated radiotherapy (IMRT) or 2) 33 Gy in 10 fractions to the whole pelvis with IMRT. In most patients, oral capecitabine was concurrently administered at a dose of 1650 mg/m2/day during radiotherapy. Follow-up examinations were repeated just before surgery. Delayed surgery was performed 4–8 weeks after the completion of HPCRT. After surgery, the pathological tumor stage was determined according to the American Joint Committee on Cancer staging system, 8th edition. Postoperative chemotherapy was recommended approximately 4 weeks after surgery, according to the postoperative pathologic stage and patient performance status.

Response And Toxicity Evaluation

Tumor response was evaluated based on the pathologic downstaging rate and tumor regression grade (TRG). Primary tumor (T) and nodal (N) downstaging was defined as the lowering of the tumor (T) and nodal (N) stage from clinical staging to postoperative pathologic staging respectively. Overall downstaging was defined as overall pathologic stage being lower than the initial clinical stage. TRG was defined as follows: grade 0, no regression; grade 1, minor regression and fibrosis ≤ 25%; grade 2, moderate regression and fibrosis 26–50%; grade 3, good regression and fibrosis 51–99%; or grade 4, total regression and fibrosis 100%. Acute toxicities were assessed from the initiation of HPCRT through three months after surgery. Late toxicities were defined as those that occurred thereafter. Toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

Locoregional recurrence was defined as recurrence within the pelvic cavity and anastomosis site. Distant metastasis was defined as recurrence outside of the pelvis. Locoregional failure-free survival (LRFS) was defined as the interval between the start of HPCRT and the date of locoregional recurrence, censoring the last follow-up case without locoregional recurrence. Disease-free survival (DFS) was defined as the interval between the initiation of HPCRT and the date of any first recurrence, censoring the last follow-up case without any recurrence. Overall survival (OS) was calculated from the initiation of HPCRT to the date of death or last follow-up. Survival for all patients was calculated using the Kaplan–Meier method. Statistical significance between the groups was analyzed using a log-rank test. A Cox proportional hazard regression model was used for multivariate analysis. Statistical analyses were performed using the SPSS statistical software (IBM, Armonk, NY, USA). A \( p \)-value < 0.05 was considered significant.

Results

Patient and treatment characteristics
A total of 116 patients received HPCRT between June 2016 and May 2021. Of these, 40 patients were excluded, because they did not undergo surgery at our hospital for various reasons or they developed new distant metastases after HPCRT but before surgery. The remaining 76 patients were included in the study and patient characteristics are detailed in Table 1. The number of patients with initial clinical stages I, II, III, and IVA were five, 29, 36, and six, respectively. By MRI, the distal extent of the tumor ≤ 5 cm from the anal verge (AV) and > 5 cm from the AV were observed in 32 and 44 patients, respectively. Six patients had initial distant metastasis, three patients had initial lung metastasis and three patients had liver metastasis. Three patients initially had synchronous double primary cancers, two patients had lung cancer and one patient had gall bladder cancer. Treatment characteristics are detailed in Table 1.

Radiotherapy was performed with a daily fraction size of 3.3 Gy and 3.5 Gy in 37 patients (48.7%) and 39 patients (51.3%), respectively, for a median of 14 days (range: 12–23). Concurrent chemotherapy with capecitabine was administered to most patients; however, one patient received Taxol and Cisplatin for the treatment of double primary lung cancer, and one patient received radiotherapy alone due to immune thrombocytopenia. The median interval between HPCRT and surgery was 52 days (range: 16–86). The surgeries performed included low anterior resection in 32 patients (42.1%), laparoscopic abdominal transanal proctosigmoidectomy with coloanal anastomosis in 20 patients (26.3%), ultra-low anterior resection in nine patients (11.8%), and abdominoperineal resection in eight patients (10.5%). Surgical information is detailed in Table 1. Postoperative adjuvant chemotherapy was administered to 52 patients (68.4%) according to the pathological stage or patient performance status.

**Treatment Outcomes**

Nine patients (11.8%) achieved a pCR. Pathologic overall stages were as follows: stage 0 in 9 patients (11.8%), stage I in 13 patients (17.1%), stage II in 30 patients (39.5%), stage III in 18 patients (23.7%), and stage IVA in six patients (7.9%). The median post-CRT distal extent of the tumor from the AV by MRI was 5.75 cm (range: 1.8–10.8), which increased from the pre-CRT extent of 5.5 cm (range: 1.3–9.5). The median post-CRT tumor length by MRI was 2.0 cm (range: 0–4.0), which decreased from the pre-CRT length of 4.2 cm (range: 2.0–6.6). Sphincter preservation was achieved in 24 (75.0%) of 32 patients with an initial tumor distal extent ≤ 5 cm from AV and in all 44 patients with an initial distal extent of > 5 cm. Prior to HPCRT, twenty-seven patients were candidates for abdominoperineal resection (≤ 4 cm from AV and clinical stage T3–4), and 20 of these patients (74.1%) underwent anal sphincter-saving surgery. The overall rate of sphincter preservation was 89.5% (68 of 76 patients). The median postoperative carcinoembryogenic antigen nadir level was 1.73 ng/ml (range: 0.49–10.87), which decreased from the pre-CRT median level of 4.99 ng/ml (range: 0.90–53.70) and post-CRT/preoperative level of 3.17 ng/ml (range: 0.50–35.47). The other outcomes are presented in Table 1. Of the 76 patients, 28 (36.8%) achieved T-downstaging, and 25 (32.9%) achieved N-downstaging. Overall downstaging was achieved in 34 of 76 patients (44.7%). A detailed breakdown of the downstaging is shown in Table 2. According to the 5-cm cutoff of tumor distal extent from the AV or the cutoff of a median 52 days between radiotherapy and surgery, there were no significant differences in TRG or downstaging between the two groups.
Survival And Prognostic Factors

The follow-up period ranged from 3 to 71 months (median: 54). In all patients, 5-year LRFS, DFS, and OS were 90.6%, 73.6%, and 90.6%, respectively (Fig. 1). The results of univariate analyses for LRFS, DFS, and OS are shown in Table 3. The results of multivariate analyses are shown in Table 4. Pathological T-stage was found to be the only significant prognostic factor for LRFS ($p = 0.044$, Fig. 2a). However, there was no statistical significance between pathologic T-stage subgroups because the hazard ratios for pathologic T3 or T4 stage were extremely high compared to those for pathologic T0–T2 stage with no locoregional failure (data not shown). In the multivariate analysis for DFS, significant variables were pathologic N stage (Fig. 2b) and lymphovascular space invasion (LVI, Fig. 2c). Although perineural invasion (PNI) was not significant by multivariate analysis for DFS, the 5-year DFS of patients with both negativity of LVI and PNI (LVI- and PNI-) versus patients with either one or positivity of both LVI and PNI (LVI + and/or PNI+) were significantly higher ($p = 0.015$, Fig. 2d). By multivariate analysis for OS, no significant variables were found. Six patients with initial stage IVA had one or more salvage treatments such as surgery, chemotherapy, or stereotactic radiotherapy, after completion of HPCRT, and all were surviving at the last follow-up. Of the three patients with initial double primary tumors, one patient with lung cancer and one patient with gall bladder cancer underwent surgical resection and the other patient with lung cancer was treated with concurrent CRT. All three patients were followed-up and demonstrated no evidence of disease or stable disease.

Patterns Of Failures And Complications

A local failure occurred in four patients (5.3%), a regional failure occurred in four patients (5.3%), and distant metastasis occurred in 13 patients (17.1%) as a component of failure. The pattern of failure is illustrated in Fig. 3. Sites of distant metastasis are as follows: lung in 10 patients, bone in 2 patients, distant lymph nodes in 2 patients, and liver in one patient. Patients with two or more sites are counted separately. One patient (1.3%) developed an acute grade 3 complication of anastomosis leakage. Three patients (3.9%) experienced late grade 3 complications such as rectovaginal fistula, rectal bleeding, and anastomotic leakage. No grade 4 toxicity was observed.

Discussion

In this study, the rates of T-downstaging, N-downstaging and overall downstaging were 36.8%, 32.9%, and 44.7%, respectively. One of three patients with synchronous double primary cancer achieved overall downstaging of primary rectal cancer. The pCR rate was 11.8%, and the overall rate of sphincter preservation was 89.5%. These results were comparable to those of the historical LCRT studies and similar to the two-week course KROG study. The comparable outcomes of our study could be attributed to dose prescription of 33 Gy ($\text{BED}_{10}$, 43.9 Gy), greater than SCRT ($\text{BED}_{10}$, 37.5 Gy) or 35 Gy ($\text{BED}_{10}$, 47.3 Gy), slightly closer to the LCRT ($\text{BED}_{10}$, 59.5 Gy). Oral capecitabine was prescribed as the concurrent chemotherapy agent, followed by delayed surgery with a median interval of 52 days to allow tumor
regression before surgery. This study showed comparable toxicities to previous LCRT results. Only four patients (5.3%) developed acute or late grade 3 toxicities and there were no grade 4 toxicities in any patients, including the SIB IMRT 35 Gy patient cohort. One patient received 35 Gy and treated with Taxol and Cisplatin concurrently due to synchronous lung cancer and experienced acute grade 2 diarrhea. All patients had one or more weekend rest without receiving HPCRT and received IMRT to limit the radiation dose to normal organs. We performed SIB IMRT of 35 Gy to the gross tumor to improve the pathologic regression. However, in groups of patients with 35 Gy versus 33 Gy, pCR rate was 12.8% vs. 10.8%, sphincter preservation rate was in 87.2% vs. 91.9%, and 5-year DFS was 85.7% vs. 63.9% (p = 0.067), respectively. None of these differences were statistically significant between the two groups.

Five-year LRFS, DFS, and OS were 90.6%, 73.6%, and 90.6%, respectively, in all patients. These survival rates were comparable to previous LCRT results despite our study including patients with synchronous double primary or distant metastasis. We also included five patients with early clinical stages such as T1-2N0. Of these patients, two had synchronous double primary cancers, two preferred HPCRT followed by local excision rather than upfront radical surgery, and one strongly demanded SCRT due to having to travel long-distances to receive CRT. Of these, four patients underwent sphincter preservation surgery. Thus, all our patients had a median radiotherapy duration of 2 weeks, which is 4 weeks shorter than the conventional 6 weeks of LCRT and because of our shorter CRT duration, they could receive surgery 4 weeks earlier than those receiving traditional LCRT.

In the multivariate analysis for LRFS in this study, only pathologic T-stage was an independent prognostic factor. It is well known that patients with sterilized tumors after preoperative CRT have an excellent prognosis with respect to LRFS or DFS [14, 15]. Nine patients who achieved pCR in our study had experienced no recurrence at the last follow-up. In multivariate analysis for DFS, pathologic N stage and LVI were significant prognostic variables. The pathologic N stage is a well-known prognostic factor for survival and is integral to the American Joint Committee on Cancer staging system [16]. The prognosis of patients with remnant lymph node metastasis after CRT is poor, even in cases of complete primary tumor response [17]. Likewise, patients with more advanced pathologic primary tumor (ypT3-4) with pN0 stage showed slightly better recurrence-free survival or OS than did those with ypT0-2 but positive pathologic N [18]. It is well known that the LVI is an independent prognostic factor for survival. Song JH et al. reported that LVI was a significant prognostic factor affecting distant failure-free survival [19]. Saadoun et al. developed a nomogram with eight variables, including pathological stage, LVI, and PNI, which provided individual risk prediction for recurrence [20]. In our study, DFS of patients with both LVI- and PNI- versus that of patients with LVI+ or PNI+ differed significantly, although patients with LVI+ or PNI+ received postoperative adjuvant chemotherapy (often 5-fluorouracil and oxaliplatin) more frequently than did patients who had LVI- and PNI- (18/20 vs. 34/56, p = 0.023). Therefore, more aggressive adjuvant chemotherapy should be considered to improve DFS for these patients.

Some limitations of this study are as follows. First, our study had a small cohort of patients, albeit with a long study duration. We provided this CRT option to selected patients with a preference for HPCRT or even with synchronous distant disease or double primary cancer. Thus, the accrual rate was inevitably
slow. However, the treatment protocol was almost the same throughout the entire study period and treatment consistency was maintained. Second, the patient characteristics in our study were heterogeneous, ranging from the early clinical stage to the advanced clinical stage (IVA) or to synchronous double primary cancer. However, all patients experienced the advantages of HPCRT, which are convenience, low cost, shorter radiotherapy time, and earlier surgical or other radical treatments for distant disease or double primary cancer.

In conclusion, the HPCRT of 33 or 35 Gy in 10 fractions showed comparable results to those of historical conventional LCRT studies. This shorter fractionation scheme may be beneficial without reducing oncologic outcomes for patients with early-stage disease, locally advanced rectal cancer, simultaneous distant metastasis, and other double primary cancer requiring early intervention or for patients who cannot attend the hospital multiple times.

**Declarations**

**Disclosure of potential conflicts of interest:** The authors declare that they have no competing interests.

**Author contributions**

Taek-Keun Nam : the concept and design of the study; Ick Joon Cho, Yong-Hyub Kim, Ju-Young Song, Mee Sun Yoon, Sung-Ja Ahn, Shin Haeng Cho : data acquisition; Ick Joon Cho, Jae-Uk Jeong: statistical analysis; Ick Joon Cho, Jae-Uk Jeong and Taek-Keun Nam : interpreted the results and analyzed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

**References**


**Tables**

Tables are available in Supplementary Files section.

**Figures**
Figure 1

Locoregional failure-free survival (LRFS), disease-free survival (DFS) and overall survival (OS) in entire patients
Figure 2

Disease-free survival (DFS) according to (a) pathologic T-stage, (b) pathologic N-stage, (c) lymphovascular space invasion (LVI), and (d) both status of LVI and perineural invasion (PNI) in entire patients
Figure 3

Venn diagram illustrating the patterns of failure in entire patients

Supplementary Files

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