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Timely tumor response analysis after preoperative chemoradiotherapy and curative surgery in locally advanced rectal cancer: A multi-institutional study for optimal surgical timing in rectal cancer

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ABSTRACT

Background and purpose: The definite surgical timing in rectal cancer after preoperative chemoradiotherapy (CRT) has not yet been fully examined. We assess the tumor response and identify the optimal operation timing after preoperative CRT in rectal cancer.

Methods and materials: The study included data of 1786 patients with locally advanced rectal cancer (cT3-4N0-2M0). They received preoperative CRT followed by total mesorectal excision. Total radiation dose was 50.4 Gy in 28 fractions. Interval time between preoperative CRT and surgery ranged from 2 to 26 weeks, with a median interval of 7.2 weeks. Primary endpoint was to evaluate the period of highest downstaging and pathological complete response (ypCR) rates to determine the optimal timing for curative surgery after CRT.

Results: Downstaging rates peaked between 6 and 7 weeks after CRT and declined afterward. ypCR rates increased from 5 to 6 weeks after CRT and decreased after 9 to 10 weeks. Downstaging rates were similar between the two arms showing 36.9% in the early arm (⩽7 weeks) and 37.0% in the delayed arm (>7 weeks). ypCR rates were significantly higher in the delayed arm, as compared to the early arm (12.3% vs. 8.6%, $p = 0.011$). The delayed arm had higher sphincter preservation rates than the early arm with a marginal significance (92.4% vs. 89.9%, $p = 0.078$). There was no statistically significant difference regarding relapse-free survival and overall survival between the two arms.

Conclusions: ypCR rates increased after 5 weeks and decreased after 10 weeks and the delayed (>7 weeks after CRT) group showed significantly increased ypCR rates than the early arm (⩽7 weeks after CR). The optimal timing for curative surgery in rectal cancer when tumor response is maximal is after 7 weeks and before 10 weeks following preoperative CRT.

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The standard treatment of locally advanced rectal cancer is neoadjuvant chemoradiotherapy (CRT) on the pelvis followed by total mesorectal excision (TME). A milestone study conducted by the German Rectal Cancer Study Group in 2004 reported that preoperative CRT arm had half 5-year local recurrence rates (6% vs. 13%, $p = 0.02$), double sphincter preservation rates in low-lying tumors (39% vs. 19%, $p = 0.004$), and reduced toxicities, as compared with postoperative CRT arm [1]. Several studies have demonstrated that tumor response rate after CRT is time-dependent, showing improved pathological complete response (ypCR) rate in patients who underwent surgery 6–8 weeks after completion of neoadjuvant CRT [2–7]. Other reports showed superior ypCR rate in patients with a time interval of longer than 12 weeks between neoadjuvant concurrent CRT and surgery [8,9]. Since the probability of R0 resection increases with higher ypCR after preoperative CRT, ypCR rate is an important factor for determining the outcomes of the rectal cancer. A pooled analysis by Maas et al. proved that higher ypCR is related to better long-term outcome in rectal cancer

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[10]. However, physicians cannot continue to wait until complete remission of rectal tumor, because when the interval between CRT and surgery elongates, complications by surgical resection will increase due to tissue edema and fibrosis after CRT [9]. Although there is a recent report on positive effects of 'watch and wait' protocol after high-dose chemoradiotherapy and local excision, patients enrolled in this study were in early stage rectal cancer [11]. Tumor with a malignant feature may be left in situ and repopulate or disseminate after radiotherapy. Thus, the National Comprehensive Cancer Network guidelines recommend the radical operation timing between 5 and 12 weeks after preoperative CRT in rectal cancer. However, prospective studies defining the definite time interval between neoadjuvant CRT and curative surgery have not been presented yet.

This multicenter retrospective analysis was conducted by the Korean Radiation Oncology Group (KROG) to evaluate the tumor response and estimate the optimal operation timing after preoperative CRT in rectal cancer.

Materials and methods

Patient eligibility

The study included data of 1804 patients who were diagnosed with locally advanced rectal cancer and received preoperative CRT followed by curative surgery from 2003 to 2014 at eight institutions in Korea. Inclusion criteria were: (1) histologically confirmed adenocarcinoma of the rectum; (2) distal margin of the tumor located $\leqslant$10 cm from the anal verge; (3) clinical T3–4 and N0-2 classification determined by magnetic resonance imaging (MRI); (4) no evidence of distant metastasis at diagnosis; and (5) Karnofsky performance status above 70. Patients with history of malignancy other than non-melanoma skin cancer and patients who had previously received radiotherapy to the pelvis were excluded. In this analysis, medical records of the 1804 patients were retrospectively reviewed and 18 patients with unavailable pathologic or follow-up data were excluded. Thus, 1786 patients were finally evaluated. This study was approved by the institutional review boards of the each participating centers.

Evaluation

For diagnosis and clinical workup, history taking and digital rectal examination were done and complete blood counts, blood chemistry for liver and kidney functions, and carcinoembryonic antigen (CEA) level were checked. Imaging studies included colonoscopy with biopsy, rectum MRI, abdomen and pelvis computed tomography (CT), and chest CT. Liver MRI for suspicious liver metastasis and PET-CT to rule out distant metastasis were done on the clinician's decision. Cancer staging was defined using TNM classification system according to the American Joint Committee on Caner criteria 7th edition.

Neoadjuvant CRT

Radiotherapy simulation was done in prone position. Total radiation dose was 50.4 Gy, delivered as 1.8 Gy per fraction, with 45 Gy in 25 fractions to the whole pelvis followed by 5.4 Gy in three fractions to the gross tumor with margin. The superior border was L5-S1 junction and inferior border was 3 to 5 cm distal to the tumor or the inferior border of the obturator foramen, whichever was inferior. In anterior/posterior fields, the lateral borders were at 1.5–2 cm beyond the medial margins of bony pelvic wall at the widest plane of the pelvis. In lateral fields, the anterior border was the posterior border of the symphysis pubis and the posterior border was 1 cm behind the bony sacrum.

For preoperative concurrent chemotherapy, bolus 5-fluorouracil (5-FU) and leucovorin, continuous 5-FU, or oral capecitabine was administered. 5-FU and leucovorin was delivered in two 5-day courses during the first and fifth weeks of radiotherapy: 5-FU 400 mg/m^2 (intravenous, IV, bolus) 1 h before radiotherapy, and leucovorin calcium 20 mg/m^2 (IV bolus) immediately before each dose of 5-FU. Continuous infusion of 5-FU, 225 mg/m^2/day was also used. Oral capecitabine was prescribed at a dose of 1650 mg/m^2/day, divided into two doses given 12-h apart.

Surgery

All patients received total mesorectal excision. The median interval time between neoadjuvant CRT and surgery was 7.2 weeks (range, 2–26 weeks). Among the 1786 patients, 1108 (62.1%) received laparoscopic surgery and 678 (37.9%) received open surgery. Pathologic specimens were evaluated using the standardized protocol of the College of American Pathologists by specialized colorectal pathologists on tumor size, pathologic cell type, invasion depth, presence of lymph node metastasis, histologic grade, differentiation, resection margin, and tumor response to the neoadjuvant therapy [12]. Low histological grade included well-to-moderately differentiated adenocarcinoma. Poorly differentiated adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma were classified as high histological grade [13].

Downstaging rate was assessed by comparing clinical pre-CRT and pathological post-CRT stages, and downstaging was defined as ypStage 0-I (ypT0-2N0M0). Pathologically complete response (ypT0N0M0) was defined as the complete absence of viable tumor, with only fibrotic tissue in the pathologic specimen.

Statistical analyses

Primary endpoint of this study was to deduce the period of highest downstaging and ypCR rates to determine the optimal timing for curative surgery after neoadjuvant CRT. Secondary endpoints were sphincter preservation rate, relapse-free survival

Table 1
Patient characteristics (n = 1786).

Characteristics – No. (%)	Early arm* (n = 827)	Delayed arm (n = 959)	p-Value
Age, year			0.251
<60	374 (45.2)	401 (41.8)	
⩾60	453 (54.8)	558 (58.2)	
Pre-CRT CEA, ng/mL			0.398
<5	545 (65.9)	613 (63.9)	
⩾5	282 (34.1)	346 (36.1)	
Gender			0.138
Male	554 (67.0)	674 (70.3)	
Female	273 (33.0)	285 (29.7)	
Clinical T classification			0.049
cT3	786 (95.0)	889 (92.7)	
cT4	41 (5.0)	70 (7.3)	
Clinical N classification			
cN0	172 (20.8)	220 (22.9)	0.277
cN1–2	655 (79.2)	739 (77.1)	
Histological grade			0.329
Low	770 (93.1)	904 (94.3)	
High	57 (6.9)	55 (5.7)	
Tumor from anal verge, cm			0.961
<5	300 (36.3)	350 (36.5)	
⩾5	527 (63.7)	609 (63.5)	
Concurrent chemotherapeutic regimen			<0.001
5-FU	647 (78.2)	851 (88.7)	
Xeloda	180 (21.8)	108 (11.3)	

Abbreviations: CEA, carcinoembryonic antigen; CRT, chemoradiotherapy
* Early arm received curative surgery within 7 weeks and delayed arm received curative surgery 7 weeks after preoperative CRT.

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