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Original article

Significance of histologic tumor grade in rectal cancer treated with preoperative chemoradiotherapy followed by curative surgery: A multi-institutional retrospective study

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ABSTRACT

Background and purpose: To evaluate the pre-treatment clinical factors affecting recurrence and survival in rectal cancer patients who receive preoperative chemoradiotherapy (CRT) and curative surgery.

Methods and materials: The clinical data of 1782 patients from 8 institutions in Korea were analyzed. The potential prognostic factors that could be acquired before radical surgery were patient age, gender, clinical T and N stages, tumor size and location, tumor grade, carcinoembryonic antigen (CEA) level, and the concurrent chemotherapy regimen. The relapse-free survival (RFS), overall survival (OS), and cumulative incidence of locoregional and distant recurrence were analyzed according to the clinical factors.

Results: Among the pre-treatment clinical factors, tumor grade, pre-CRT CEA level, tumor location, and clinical N stage were significant prognostic factors affecting the RFS. The high-grade tumor was the hazardous factor for RFS on the multivariate analysis [Hazard ratio (HR), 1.83; 95% confidence interval (CI), 1.29–2.58; $p = 0.001$]. The 5-year RFS rate for high-grade tumors was significantly lower than that for low-grade tumors (63.8% vs. 78.8%, $p < 0.001$). The tumor grade was a significant prognostic factor for distant recurrence (HR, 1.83, 95% CI, 1.29–2.58; $p < 0.001$), but not for locoregional recurrence (HR, 1.49, 95% CI, 0.68–3.26; $p = 0.320$) on the multivariate analysis. The 5-year OS rate for high-grade tumors was significantly lower than that for low-grade tumors (70.6% vs. 85.5%, $p < 0.001$).

Conclusion: The tumor grade is the significant pre-treatment clinical factor for recurrence and survival in rectal cancer patients who receive preoperative CRT and curative surgery.

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The standard treatment of locally advanced rectal cancer is preoperative chemoradiotherapy (CRT) followed by curative surgery on the basis of several randomized prospective studies [1–5]. Although several radiotherapy techniques and various chemotherapy regimens are being investigated, the 5-year progression-free survival is still around 60–80% [2–6]. The rectal cancer recurrence is mainly due to the high rate of distant metastasis rather than locoregional recurrence. With the introduction of total mesorectal excision (TME) after preoperative CRT, the locoregional recurrence rate has dropped to around 10% [7,8].

Several prognostic factors for predicting the recurrence have been reported. Preoperative and postoperative stage [9–11], tumor regression grade [10–12], and carcinoembryonic antigen (CEA) level [11,13,14] are well known prognostic factors. However, the prognostic significance of histologic tumor grade for rectal tumor which could be acquired and interpreted in the biopsy specimen is still controversial [15,16]. In addition, the results of several studies reporting the significance of tumor grade usually include colon cancer for which the treatment modality is different from that of rectal cancer, and the patients in those studies are treated before preoperative CRT and TME era [12,17,18].

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In this multi-institutional analysis, we evaluated the pre-treatment clinical factors affecting cancer recurrence and survival in rectal cancer patients who received the preoperative CRT and TME.

Methods and materials

Patients

The clinical data of 1804 rectal cancer patients who received preoperative CRT with 5-fluorouracil (5-FU) or capecitabine followed by TME surgery were collected from 2003 to 2014, from 8 institutions in the Republic of Korea. The inclusion criteria were as follows; (1) pathologically diagnosed rectal adenocarcinoma; (2) cT3 or cT4 according to American Joint Committee on Cancer (AJCC) criteria (7th edition); (3) no evidence of distant metastasis; and (4) Karnofsky performance status over 70. Twenty-two patients whose pathologic data were incomplete were excluded, reducing the total number of patients analyzed to 1782.

Clinical staging and pathologic evaluation

Before the initiation of preoperative CRT, digital rectal examination, complete blood count, blood chemistry, CEA level, video colonoscopy, chest and abdomen computed tomography (CT), and pelvic magnetic resonance imaging (MRI) with or without endoscopic ultrasound, were performed for the clinical work-up. Tumor location was assessed by digital rectal examination for low to mid rectal cancer or sigmoidoscopy for upper rectal cancer. After curative surgery, the pathologic specimens were evaluated using the standardized protocol of the College of American Pathologists by experienced colorectal pathologists [19]. Information on tumor histology and grade, lymph node metastasis status, the presence of lymphovascular and perineural invasion, tumor regression grade (TRG), and circumferential resection margin (CRM) were evaluated. Each tumor was categorized into one of two groups; low-grade, which represents well or moderately-differentiated tumor, or high-grade, which represents poorly differentiated tumor or mucinous carcinoma or signet ring cell cancer [20]. The CRM was defined as involvement when the tumor had a margin of 1 mm or less. Tumor downstaging was defined as ypT0-2N0M0 which accounts for AJCC stage 0 to I [21].

Treatment

All patients underwent preoperative CRT with conventional fractionation of 1.8 Gy up to a total dose of 50.4 Gy in 28 fractions. The last 5.4 Gy in 3 fractions were delivered as a boost to the gross tumor volume (GTV). The clinical target volume (CTV) was defined as GTV and regional lymphatics including the mesorectal, presacral, internal iliac, and distant common iliac lymph nodes. To cover the CTV properly, the borders of the pelvic fields were as follows: (1) superior: the sacral promontory at the L5-S1 junction level, (2) inferior: 3 to 5 cm distal to the GTV, (3) lateral: 1.5 cm lateral to the widest bony margin of the true pelvic walls, (4) anterior: posterior border of symphysis pubis, and (5) posterior: 1.5 cm behind the anterior bony sacral margin. The concurrent chemotherapy regimens were as follows: (1) two cycles of bolus intravenous 5-FU (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) given at the first and fifth weeks of radiotherapy; (2) oral administration of capecitabine (825 mg/m^2) twice daily; and (3) continuous infusion of 5-FU (225 mg/m^2/day) during radiotherapy. All patients underwent a planned TME surgery 4–8 weeks after the end of CRT. Adjuvant chemotherapy was delivered according to the institutional policy, started 4–6 weeks after curative surgery.

Statistical analysis

The overall survival (OS) was defined as the time interval from the day of surgery to the day of death from any cause. The event of locoregional and distant recurrence was defined as any recurrence inside the pelvis and outside the pelvis. The recurrences were recorded only as first event, not all events during the follow-up period. The relapse-free survival (RFS) was defined as the time interval from the day of surgery to the day of any recurrence or death. Survival analyses were calculated by the Kaplan–Meier method and were compared by the log-rank test. For the multivariate analysis, a Cox proportional hazard model was used to calculate hazard ratios and 95 percent confidence intervals. Gray's test was used to determine whether the difference in cumulative incidence of locoregional and distant recurrence between two arms was significant [22]. Chi-square test was performed to find the associations between the potential prognostic factors. A p value of <0.05 by two-tailed tests was considered statistically significant. All statistical analyses were performed using SPSS version 12.0 (Chicago, IL, USA).

Results

The patient characteristics are shown in Table 1. The median distance of the tumor from the anal verge was 5 cm (range, 0–10 cm), and the median tumor size was 4.0 cm (range, 0.5–14 cm). The tumor grade was classified as high grade in 112 (6.3%) patients and low grade in 1670 (93.7%) patients. Of the 112 patients with high-grade tumors, 63 patients had mucious adenocarcinoma, 3 patients had signet ring carcinoma, and 46 patients had poorly-differentiated adenocarcinoma. Clinical T4 stage was significantly more frequent in the high-grade tumor than the low-grade tumor (12.5% vs. 5.7%, $p = 0.004$). A tumor size of >4 cm was significantly less frequent in the high-grade tumor than the low-grade tumor (38.4% vs. 50.1%, $p = 0.017$). Other characteristics were similar between low and high-grade tumors. The chemotherapy regimen during the CRT was 5-FU with or without leucovorin in 1494 (83.8%) patients, and oral capecitabine in 288 (16.2%) patients. Curative surgery was performed at a median of 7.1 weeks after the end of radiation therapy. All patients underwent TME with a curative aim. However, there were 180 (10.1%) patients whose circumferential resection margin was involved and 11 (0.6%) patients whose distal margin was involved. 1611 (90.4%) of 1782 patients received low-anterior resection and were able to save their anal sphincters. After curative resection, 1516 (85.1%) of the 1782 patients received 4 to 6 cycles of capecitabine (1250 mg/m^2, twice daily, days 1–14, monthly) or 5-FU (400–500 mg/m^2/day, days 1–5, monthly)-based adjuvant chemotherapy.

The pathologic examination after CRT followed by curative surgery showed tumor downstaging (defined as ypT0-2N0) in 660 of 1782 (37.0%) patients and 191 (10.7%) achieved pathologic complete response. Table 2 shows the pathology report according to the tumor grade. The ypT3–4 (74.1% vs. 55.6%, $p < 0.001$) and ypN+ (51.8% vs. 30.2% vs. $p < 0.001$) pathologic classifications were significantly more frequent in high-grade tumors than in low-grade tumors. Positive lymphovascular (32.1% vs. 21.3%, $p = 0.007$) and perineural (27.7% vs. 19.0%, $p = 0.025$) invasion were also significantly more frequent in high-grade tumors than in low-grade tumors. Pathologic complete response (ypT0N0) was achieved in 191 (10.7%) of 1782 patients. The pathologic complete response rate was higher in low-grade tumors than in high-grade tumors with a marginal significance (11.1% vs. 5.4%, $p = 0.058$).

At a median follow-up of 42.4 months (range, 0.5–136.8 months), 352 (19.8%) patients experienced recurrences and 236 (13.2%) deaths occurred. Locoregional recurrence occurred in

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