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Original article

Carcinoembryonic antigen has prognostic value for tumor downstaging and recurrence in rectal cancer after preoperative chemoradiotherapy and curative surgery: A multi-institutional and case-matched control study of KROG 14-12

Jong Hoon Lee [a,*], Dae Yong Kim [b], Sung Hwan Kim [a], Hyeon Min Cho [c], Byoung Yong Shim [d], Tae Hyun Kim [b], Sun Young Kim [b], Ji Yeon Baek [b], Jae Hwan Oh [b], Taek Keun Nam [e], Mee Sun Yoon [e], Jae Uk Jeong [e], Kyubo Kim [f], Eui Kyu Chie [f], Hong Seok Jang [g], Jae-Sung Kim [h], Jin Hee Kim [i], Bae Kwon Jeong [j]

[a] Department of Radiation Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon; [b] Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, Goyang; [c] Department of Surgery; [d] Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon; [e] Department of Radiation Oncology, Chonnam National University Hospital; [f] Department of Radiation Oncology, Seoul National University Hospital, College of Medicine, Seoul; [g] Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [h] Department of Radiation Oncology, Seoul National University Bundang Hospital, College of Medicine; [i] Department of Radiation Oncology, Dongsan Medical Center, Keimyung University School of Medicine, Daegu; and [j] Department of Radiation Oncology, Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Jinju, Republic of Korea

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ABSTRACT

Background and purpose: The Korean Radiation Oncology Group evaluated the significance of carcinoembryonic antigen (CEA) levels both as a predictor of tumor response after CRT and as a prognosticator for recurrence-free survival.

Methods and materials: 1804 rectal cancer patients, staged cT3–4N0–2M0, participated in a multicenter study. The patients were administered preoperative radiation of 50.4 Gy in 28 fractions with 5-FU or capecitabine, followed by total mesorectal excision. Patients with elevated CEA levels (>5 ng/mL) were matched at a 1 (n = 595):1 (n = 595) ratio with patients with normal CEA ($\leqslant$5 ng/mL). The tumor response after CRT and the recurrence-free survival (RFS) rates were evaluated and compared between two arms.

Results: An elevated CEA level ($p < 0.001$) was determined to be a significant negative predictor of downstaging after CRT. The downstaging rate was 42.9% for normal CEA and 23.4% for elevated CEA. A multivariate analysis also revealed that cT ($p = 0.021$) and cN classification ($p = 0.001$), tumor size ($p = 0.002$), and tumor location from the anal verge ($p = 0.006$) were significant predictors for tumor downstaging. The 5-year RFS rates were significantly higher for the normal CEA arm than for the elevated CEA arm (74.2 vs. 63.5%, $p < 0.001$).

Conclusions: Elevated CEA (>5 ng/mL) is a negative predictor of tumor downstaging after CRT and also has a negative impact on RFS in rectal cancer.

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Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision is a standard treatment that has been widely used to cure locally advanced rectal cancer [1,2]. In a German rectal cancer study, good or complete pathologic tumor response after preoperative CRT was associated with an improvement in disease-free survival [3]. If it were possible to identify rectal cancer patients who respond to CRT before treatment, then clinicians would be able to determine the prognosis and assess the optimal treatment strategy for the individual patient.

Carcinoembryonic antigen (CEA) is a glycoprotein member of the immunoglobulin supergene family, and it plays a key role in biological phenomena in tumor cells, including adhesion, immunity, and apoptosis [4]. CEA is a widely accepted tumor marker and may be preoperatively evaluated in patients with colorectal cancer to predict the prognosis. In addition, postoperative serial assays of the CEA levels provide an opportunity for early detection of a recurrent tumor [5]. Some studies have evaluated the clinical significance of CEA levels as a predictor of tumor response in rectal cancer patients who received preoperative CRT followed by surgery [6,7]. However, the optimal cutoff value for the CEA levels

* Corresponding author at: Department of Radiation Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 442-723, 93-6, Ji-dong, Paldal-gu, Suwon, Gyeonggi-do, Republic of Korea.
E-mail address: koppul@catholic.ac.kr (J.H. Lee).

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has yet to be conclusively determined [8]. Previous studies to this end had been performed at a single institution and were retrospective, so the predictive significance of the CEA levels was of limited value. Furthermore, although CEA has been shown to be a prognostic factor after preoperative RT alone in rectal cancer [9], the definite prognostic value of CEA has not yet been fully examined for preoperative CRT. Thus, the Korean Radiation Oncology Group (KROG) designed a multicenter retrospective study and performed case-matched analyses to evaluate the exact predictive role of CEA levels in tumor response and prognosis after preoperative CRT followed by curative surgery for locally advanced rectal cancer.

Materials and methods

Patient enrollment

We conducted a multi-institutional study in the KROG cancer centers to determine the significance of CEA levels as a predictor of tumor response and recurrence in rectal cancer patients who received preoperative radiotherapy with 5-FU or capecitabine followed by total mesorectal excision. The inclusion criteria for the study were as follows: (1) histologically confirmed adenocarcinoma; (2) distal margin of the tumor located $\leqslant$10 cm from the anal verge; (3) cT3–4N0–2 classification, as determined via magnetic resonance imaging (MRI) and/or endorectal ultrasonography (EUS); (5) no evidence of distant metastasis; and (6) no history of malignancy other than non-melanoma skin cancer. Institutional review board approval was obtained at each participating center and at KROG before enrolling the patients, and the data were transferred to the KROG Data Management Center (National Cancer Center, Goyang, Korea). Radiation therapy, pathology, and follow-up records of each patient were reviewed by using a centralized KROG Data Management program.

Evaluation

Clinical staging workups were performed before the preoperative CRT. The staging examinations consisted of a digital rectal examination, carcinoembryonic antigen (CEA) measurements, video colonoscopy, chest and abdomen CT, pelvic MRI with or without EUS. CEA levels were measured in the patient's blood. A CEA level higher than the upper normal limit (>5 ng/mL) was considered to be clinically elevated [7,8]. After the curative surgery, the post-CRT tumor stage was determined according to the TNM classification system, as described by the American Joint Committee on Cancer criteria, 7th edition. Experienced colorectal pathologists used standard methodology to evaluate the pathologic specimens according to the histologic grade, presence of lymph node metastasis, lymphovascular or perineural tumor invasion, tumor regression grade (TRG), and circumferential radial margin (CRM). CRM was defined as an involvement where the tumor was within 1 mm or less of the margin, and TRG after CRT was categorized according to the classification proposed by Dworak et al. [10]. The TRG consisted of 0 (no regression) to 4 (complete regression), and TRG 3 or 4 were considered to be a 'good regression' (3). A 'pathologic complete response' (ypT0N0) was defined as the complete absence of a viable tumor with only fibrotic mass in the pathologic specimen. The downstaging rate was assessed by comparing pre-clinical and post-CRT pathological stages, and 'downstaging' was defined as ypStage 0–I (ypT0–2N0M0) [11,12].

Treatment

Preoperative radiation was delivered to the pelvis at a dose of 45 Gy in 25 fractions, followed by a 5.4 Gy boost to the primary tumor in 3 fractions over a period of 5.5 weeks. One of three chemotherapeutic regimens was delivered concurrently with the radiotherapy: (1) bolus 5-FU and leucovorin (two cycles of bolus intravenous 5-FU [400 mg/m^2/day] and leucovorin [20 mg/m^2/day] during the first and fifth weeks of radiotherapy); (2) capecitabine (oral administration of capecitabine [825 mg/m^2] twice daily during radiotherapy); and (3) continuous 5-FU (continuous infusion of 5-FU [225 mg/m^2/day] during radiotherapy).

All patients underwent a total mesorectal excision, which was scheduled to take place 4–8 weeks after completing the radiation therapy. Patients were considered for postoperative chemotherapy according to the institutional policy, and treatment continued approximately 4–6 weeks after curative surgery.

Statistical analysis

The primary endpoint of the present study was to compare the downstaging rate between the normal CEA (0–5 ng/mL) arm and the elevated CEA (>5 ng/mL) arm, all of whom had been administered preoperative CRT and curative surgery. The secondary endpoints were to compare the recurrence-free survival between the normal CEA (0–5 ng/mL) arm and the elevated CEA (>5 ng/mL) arm. We hypothesized that the patients with elevated CEA levels before preoperative CRT would exhibit a worse downstaging rate than the patients with normal CEA levels. We set a 40% pathologic downstaging rate after preoperative radiotherapy with 5-FU or capecitabine in locally advanced rectal cancer [11,12]. The trial was designed to have 90% power to detect at least 10% difference in terms of the primary endpoint, that is, the downstaging rate of the elevated CEA arm versus the normal CEA arm by using a two-sided test at the 5% level of significance. A sample size of 954 patients was required. Since we assumed that 10% of the patients would not be assessable, we planned to enroll at least 1050 patients for this study.

We performed a controlled propensity-score matching analysis to compensate for the difference in the baseline characteristics of age, gender, clinical T and N stage, histologic grade, tumor location, and concurrent chemotherapy regimen between the two arms. The univariate analysis consisted of a Chi-square test to compare the categorical variables. A logistic regression model was used for a multivariate analysis to develop the prediction nomogram for estimating the downstaging rate. The discrimination and calibration of the predictive model were assessed through the use of the receiver operating characteristic technique and the Hosmer–Lemeshow test, respectively. The discrimination was evaluated by using the c-index.

Locoregional relapse was defined as a recurrence within the pelvic cavity and the anastomosis site. The recurrence-free survival time was defined as the interval starting from the date of the surgery to the date of recurrence, the final follow-up, or death. The Kaplan–Meier method was used to determine the recurrence-free survival rates of the two arms. For the univariate analysis, the log-rank test was used to evaluate the association between the recurrence-free survival time and the prognostic factors. For the multivariate analysis, a Cox proportional hazards regression model was used to estimate the hazard ratio of the prognostic factors for recurrence-free survival. All statistical tests were two-sided, and p-values <0.05 were considered to be statistically significant. Data analyses were performed with R software version 2.15 (Alcatel-Lucent, Murray Hill, USA).

Results

We initially enrolled 1804 patients at 8 institutions in Korea between March 2003 and June 2014. The patients had been

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