Use of sequential endorectal US to predict the tumor response of preoperative chemoradiotherapy in rectal cancer

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Background and Aims: Accurate prediction of the response to preoperative chemoradiotherapy (CRT) potentially assists in the individualized selection of treatment. Endorectal US (ERUS) is widely used for the pretreatment staging of rectal cancer, but its use for preoperatively predicting the effects of CRT is not well evaluated because of the inflammation, necrosis, and fibrosis induced by CRT. This study assessed the value of sequential ERUS in predicting the efficacy of preoperative CRT for locally advanced rectal cancer.

Methods: Forty-one patients with clinical stage II/III rectal adenocarcinoma were enrolled prospectively. Radiotherapy was delivered to the pelvis with concurrent chemotherapy of capecitabine and oxaliplatin. Total mesorectal excision was performed 6 to 8 weeks later. EUS measurements of primary tumor maximum diameter were performed before (ERUS1), during (ERUS2), and 6 to 8 weeks after (ERUS3) CRT, and the ratios of these were calculated. Correlations between ERUS values, tumor regression grade (TRG), T down-staging rate, and pathologic complete response (pCR) rate were assessed, and survival was analyzed.

Results: There was no significant correlation between ERUS2/ERUS1 and TRG. The value of ERUS3/ERUS1 correlated with pCR rate and TRG but not T down-staging rate. An ERUS3 value of 6.3 mm and ERUS3/ERUS1 of 52% were used as the cut-off for predicting pCR, and patients were divided into good and poor prognosis groups. Although not statistically significant, 3-year recurrence and survival rates of the good prognosis group were better than those of the poor prognosis group.

Conclusions: Sequential ERUS may predict therapeutic efficacy of preoperative CRT for locally advanced rectal cancer. (Clinical trial registration number: NCT01582750.) (Gastrointest Endosc 2017;85:669-74.)

Preoperative chemoradiotherapy (CRT) combined with total mesorectal excision (TME) is the standard treatment for locally advanced rectal cancer, with a pathologic complete response (pCR) rate of 8.1% to 20.9%.[1-8] Improved long-term outcomes are possible in patients with pCR after preoperative CRT.[9-11] Accurate prediction of the response to preoperative CRT potentially assists in the individualized selection of treatment; however, using a diagnostic imaging system as a method to predict the effects of CRT is still under investigation.

Sequential assessment of diagnostic imaging, such as magnetic resonance imaging (MRI) and positron emission CT, before and after preoperative CRT has been proved to be a validated systematic approach for predicting treatment sensitivity in patients with rectal cancer.[12,13] Endorectal US (ERUS) enables the high-resolution examination of

Abbreviations: AUC, area under the curve; CRT, chemoradiotherapy; ERUS, endorectal ultrasonography; MRI, magnetic resonance imaging; pCR, pathologic complete response; ROC, receiver-operating characteristic; TME, total mesorectal excision; TRG, tumor regression grade.

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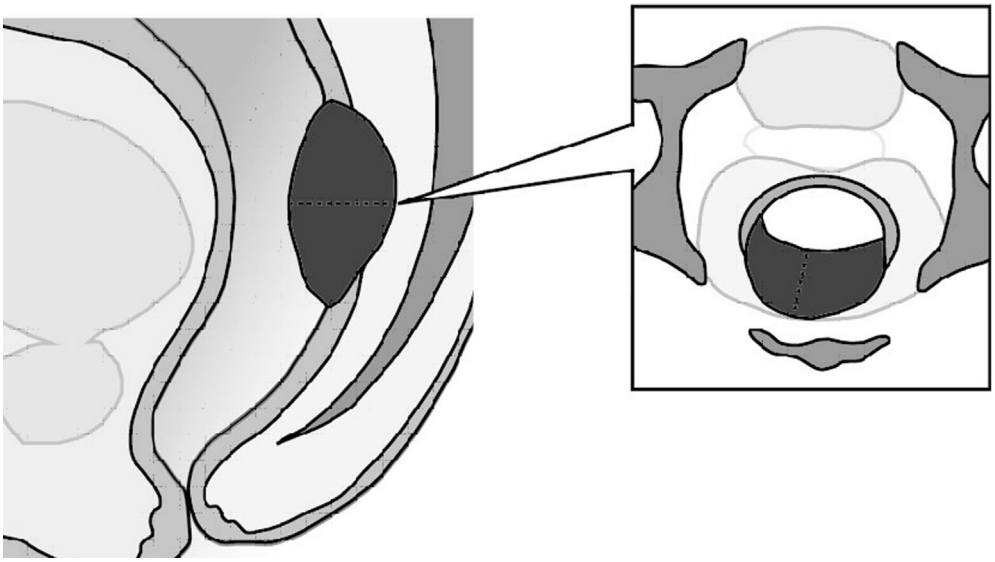

Figure 1. Measurements on the maximum thickness slice by endorectal ultrasonography.

rectal wall layers. In addition to the circumference and depth of penetration of the primary tumor, ERUS shows the peripheral rectum lymph nodes. Currently, ERUS is widely used for the pretreatment staging of rectal cancer, but its use for preoperatively predicting the effects of CRT is not well evaluated. Because of the inflammation, necrosis, and fibrosis induced by CRT, the diagnostic accuracy is between 38.3% and 75%.[14-17] The application of sequential ERUS provides the possibility to evaluate the response and long-term outcome of CRT in esophageal cancer.[18] The purpose of this study was to assess the capability of sequential ERUS in predicting the response of rectal cancer to preoperative CRT to inform personalized treatment.

METHODS

Patients

Eligible patients were those with the following characteristics at the point of selection: histologically confirmed rectal adenocarcinoma, with the lower borders within 15 cm of the anal verge; Karnofsky performance status score not less than 70; age between 18 and 75 years; previously untreated; eligible according to hematologic criteria; and diagnostic imaging–confirmed stage II/III (American Joint Committee on Cancer)[19] by physical examination, chest radiograph, abdominal and pelvic CT scans, conventional MRI, and ERUS. Eligibility criteria of hematologic examinations were white blood cell count not less than 4.0×10^9/L, platelet count not less than 100×10^9/L, creatinine and total bilirubin levels not more than 1.5 times the upper limit of normal range, alanine and aspartate aminotransferase levels not more than 2.5 times the upper limit of normal range, and alkaline phosphatase level not more than 5 times the upper limit of normal range.

Study design

This prospective study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was registered on the www.ClinicalTrials.gov website. The institutional review board and ethics committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences, approved the study. Each selected patient gave written informed consent.

Whole pelvic 3-dimensional conformal (intensity-modulated) radiotherapy with concurrent chemotherapy was administered to each patient within 5 weeks of diagnosis and selection for the study at a dose of 50 Gy/25 fractions for 5 weeks. The clinical target volume included the primary tumor, mesorectal region, presacral soft tissue and internal iliac, partial external iliac, and obturator and presacrum lymph drainage regions. The concurrent chemotherapy regimen was administered as capecitabine 1650 mg/m^2 daily and oxaliplatin 50 mg/m^2 weekly. TME surgery was performed 6 to 8 weeks after CRT. Postoperative pathologic specimens were taken and evaluated by experienced pathologists. Adjuvant chemotherapy criteria and regimen were not specific. According to long-term follow-up results, the patients were divided into good and poor prognosis groups by cut-off points of ERUS data.

ERUS was performed 1 week before CRT (ERUS1) and repeated 2 weeks after the start of CRT (ERUS2) and 6 to 8 weeks after CRT but before surgery (ERUS3), using a GF-UM2000 radial echo endoscope (5 MHz and 20 MHz) and a UM-DP-25R 20 MHz miniature probe (water immersion method) (Olympus, Tokyo, Japan). This enabled