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Assessment of the value of carcinoembryonic antigen reduction ratio as a prognosis factor in rectal cancer

Chih-Sheng Huang, M.D.[a,b], Jen-Kou Lin, M.D., Ph.D.[a,b], Ling-Wei Wang, M.D.[b,c], Wen-Yih Liang, M.D.[b,d], Chun-Chi Lin, M.D.[a,b], Yuan-Tzu Lan, M.D., Ph.D.[a,b], Huann-Sheng Wang, M.D., Ph.D.[a,b], Shung-Haur Yang, M.D., Ph.D.[a,b], Jeng-Kai Jiang, M.D., Ph.D.[a,b], Wei-Shone Chen, M.D., Ph.D.[a,b], Tzu-Chen Lin, M.D.[a,b], Shih-Ching Chang, M.D., Ph.D.[a,b,*]

[a]*Division of Colon and Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital, No. 201, Section 2. Shih-Pai Road, Taipei 11217, Taiwan;* [b]*School of Medicine, National Yang-Ming University, Taiwan;* [c]*Cancer Center, Taipei Veterans General Hospital, Taiwan;* [d]*Department of Pathology, Taipei Veterans General Hospital, Taiwan*

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CEA reduction ratio

Abstract

BACKGROUND: Carcinoembryonic antigen (CEA) is the most widely used tumor marker for colorectal cancer. This study aimed to investigate the role of CEA reduction ratio after preoperative chemoradiotherapy (CRT).

METHODS: We enrolled 284 patients who underwent preoperative CRT followed by radical surgical resection. Patients were divided into 3 groups: serum CEA levels before CRT (pre-CRT CEA) less than 5 ng/mL (group 1); pre-CRT CEA of 5 ng/mL or more with CEA reduction ratio of 50% or more (group 2); and pre-CRT CEA of 5 ng/mL or more with CEA reduction ratio less than 50% (group 3).

RESULTS: The 5-year disease-free survival (DFS) rate was not different between groups 1 (71.8%) and 2 (69.4%) but was significantly lower in group 3 (49.5%). CEA group, lymph node status after CRT (ypN) stage, and histologic type were independent prognostic factors for DFS on multivariate analysis.

CONCLUSIONS: CEA reduction ratio might be an independent prognostic factor for DFS in rectal cancer patients treated with preoperative CRT and radical surgery.

Serum carcinoembryonic antigen (CEA) is the most widely used tumor marker for patients with colorectal cancer. Although serum CEA is a poor marker for the diagnosis of primary colorectal cancer, preoperative CEA values are of prognostic significance. Preoperative CEA levels of 5.0 ng/mL or more have an adverse impact on survival that is independent of tumor stage.[1] Besides, elevated preoperative CEA levels that do not normalize after surgical resection imply the presence of persistent disease and the need for further evaluation.[2] Most published guidelines, including those from National Comprehensive Cancer Network and American Society of Clinical Oncology, recommend that postoperative CEA testing be performed every 3 to 6 months.[2,3]

C.-S.H. and J.-K.L. contributed equally to this article.

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* Corresponding author. Tel.: +886-2-2875-7544; fax: +886-2-2875-7639.
E-mail address: changsc@vghtpe.gov.tw

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Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the gold standard of treatment for locally advanced rectal cancer. This procedure can produce tumor down staging, resulting in a reduced rate of postoperative local recurrence and a higher preservation rate of the anal sphincter.[4–7] The advantage of administering radiotherapy before as opposed to after surgery is that the tissues are better oxygenated; this is proposed to enhance the efficacy of radiotherapy.[8] Other advantages of preoperative radiotherapy include the treatment of smaller volumes, less small bowel in the field (which can fall into the pelvis after surgery), avoidance of directly irradiating the healing anastomosis (which could cause an anastomotic leak), and better anorectal function postoperatively.[4] Patient compliance with treatment is also greater when radiotherapy is given before surgery.[9]

The 5-year survival of patients with recurrent disease is less than 7% with a mean life expectancy of 7 months. Therefore, determination of factors predicting pathologic tumor response is of considerable importance, in that it may suggest tailored treatment options and also indicate how individual prognosis should be assessed. Previous studies have suggested that clinical factors, such as the tumor volume,[10,11] pretreatment CEA level,[12,13] distance from the anal verge,[13] and treatment interval between radiation and surgical resection,[14] correlate significantly with clinical response. In addition, reduction of CEA levels after CRT may be an independent prognostic factor for disease-free survival (DFS) after preoperative CRT and surgery in rectal cancer patients.[15–17]

In this setting, the aim of this study was to identify pretreatment clinical factors that may predict DFS after preoperative CRT.

Methods

Patients

From January 1, 2000, to December 31, 2010, 474 patients diagnosed with rectal adenocarcinoma received preoperative CRT and surgical treatment at the Taipei Veterans General Hospital. Of these, 190 patients were excluded because of the presence of stage IV disease (n = 114), tumor located within the upper rectum (n = 5), transanal excision (n = 7), or a lack of complete data regarding CEA (n = 64). Thus, 284 patients remained eligible for the study. The computerized database at Taipei Veterans General Hospital was constructed prospectively and updated constantly. The recording variables included the demographic data of the patients; major comorbidities; family history of cancers; location, number, gross, and microscopic pathological characteristics and staging of the tumor; and status of the patient at their last follow-up visit. Tumor staging was classified using the tumor node metastasis system published by the International Union Against Cancer/American Joint Committee on Cancer, Seventh Edition.[18]

Evaluation

All patients were evaluated with staging workups, including digital rectal examination, complete blood count, liver function test, serum CEA level, colonoscopy, chest radiography, computed tomography (CT) scan of the abdomen, and pelvic MRI. In the context of an abdominal CT scan or MRI, lymph node involvement was regarded as positive when the lymph node was 5 mm or more in size in the short axis. Serum CEA levels were measured in a single laboratory using an immunoassay, with a recommended upper normal limit of 5 ng/mL. Serum samples were obtained from all patients up to 2 weeks before the initiation of preoperative CRT. Postoperative CEA was checked 1 week after surgery.

Response to preoperative CRT was evaluated using a tumor regression grade (TRG) system proposed by Dworak et al.[19] TRG definitions were as follows: TRG 0, no regression; TRG 1, dominant tumor mass with obvious fibrosis and/or vasculopathy; TRG 2, dominant fibrotic changes with few tumor cells or groups (easy to find); TRG 3, very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; and TRG 4, no tumor cells, only a fibrotic mass (total regression or response). TRG 4 was defined as "complete response," TRG 3 was defined as "good response," and TRG 1 or 2 were defined as "poor response." There was no TRG 0 in this study.

Treatment

The details of CRT in the protocol were described in our previous publication.[19] The prescription dose to the whole pelvis was 45 Gy in 20 fractions for a period of 4 weeks. For primary T4 disease only, a boost of 5.4 Gy in 3 fractions to the gross rectal tumors with a margin of 1.5 cm was administrated after pelvic irradiation. The median radiotherapy duration was 26 days. Oral chemotherapy agents, tegafur–uracil (UFUR; TTY Biopharm, Taipei, Taiwan), 200 mg/m^2/d, and leucovorin (Wyeth Lederle Laboratories, Taipei, Taiwan), 45 mg/d, were concurrently administered with RT. The total daily doses of both drugs were divided into 3 doses/d. The oral chemotherapy was continued after RT with a dose of 250 mg/m^2/d in another 28-day cycle on days 36 to 63. The patients were monitored with an interview, physical examination, and complete blood count every week.

Radical surgical resection by experienced colorectal surgeons was performed at 6 to 8 weeks after completion of RT. Pathological staging was available in these patients and was compared with the initial clinical stages.

Postoperative adjuvant chemotherapy was considered for those patients with pathologic stage III disease. Of these 71 patients, 11 did not receive adjuvant chemotherapy owing to patient refusal or poor performance status. 5-Fluorouracil (5-FU)/leucovorin was administrated to 34 patients, FOLFOX (5-FU/leucovorin/oxaliplatin) to 18 patients, oral