Biomarkers and Genomic Medicine (2013) 5, 18–22

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.j-bgm.com

REVIEW ARTICLE

# Predictors of response in locally advanced rectal cancer following concurrent chemoradiotherapy

**Hsiang-Lin Tsai** [a,b,c,d], **Jaw-Yuan Wang** [a,c,e,f,g,h,*]

[a] *Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[b] *Division of General Surgery Medicine, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[d] *Program of Bachelor of Health Beauty, School of Medical and Health Sciences, Fooyin University, Kaohsiung, Taiwan*
[e] *Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[f] *Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[g] *Division of Gastroenterologic and General Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[h] *Department of Medical Genetics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*

Received 9 April 2013; received in revised form 7 May 2013; accepted 10 May 2013
Available online 22 June 2013

**KEYWORDS**
locally advanced rectal cancer;
predictive factors;
preoperative chemoradiotherapy

**Abstract** Colorectal cancer (CRC) is one of the most common malignancies and the third major cause of cancer-related deaths in Taiwan. In 2011, more than 13,000 new cases of CRC were diagnosed and more than 4921 Taiwanese died from CRC. Standards of rectal cancer diagnosis and treatment have changed considerably during the past decade. Although surgery is still considered the cornerstone of rectal cancer treatment, high rates of local recurrence and unsatisfactory survival rates (40–55% at 5 years) have remained significant problems, even in patients subjected to curative resection. Preoperative chemoradiotherapy (CRT) is currently considered the standard treatment for locally advanced rectal cancer, and oncological outcomes using this approach are encouraging, with rates of local and distant recurrence at the five-year mark being 6–9% and 33–36%, respectively. The peculiar aspects of this approach are related to clinical over-staging, which may result in unnecessary neoadjuvant treatment in almost 18–20% of cases as proven in a trial conducted in Germany. This article focuses on the results of studies assessing the predictors of responses for locally advanced rectal cancer patients following CRT. The ability to predict response to preoperative CRT can prevent unnecessary treatment and protect poorly responding patients from the side effects of neoadjuvant treatment.


* Corresponding author. Department of Surgery, Kaohsiung Medical University Hospital, Number 100, Tzyou 1st Road, Kaohsiung 807, Taiwan.
*E-mail addresses:* cy614112@ms14.hinet.net, jawyuanwang@cc.kmu.edu.tw (J.-Y. Wang).


http://dx.doi.org/10.1016/j.gmbhs.2013.05.002

## Introduction

Colorectal cancer (CRC) is one of the most common types of cancer in Asian countries, and its incidence and mortality have significantly increased in the past several decades.[1,2] In addition to being one of the most common malignancies in Taiwan, CRC is also the third major cause of cancer-related deaths in Taiwan. In 2011, more than 13,000 new cases of CRC were diagnosed and more than 4921 Taiwanese died from CRC.[3]

Standards for the diagnosis and treatment of rectal cancer have changed considerably during the past decade. Although surgery remains the cornerstone of rectal cancer treatment, high rates of local recurrence and unsatisfactory survival rates (40—55% at 5 years) continue to pose significant problems, even in patients subjected to curative resection.[4] Recent prospective randomized studies with large sample sizes and long-term follow-up have demonstrated that multimodal treatment strategies [such as neoadjuvant radiotherapy and chemoradiotherapy (CRT)] are superior to surgery alone or surgery with postoperative CRT in terms of local control, feasibility, and toxicity.[5,6] Preoperative CRT for locally advanced rectal cancer (LARC) provides several potential advantages, including reduction in radiation-induced toxicity, decrease in tumor volume, introduction of downstaging, increase in the possibility of R0 resection, enhanced probability of anal sphincter preservation by shrinking large distal tumors, reduction in local recurrence, and increase in survival rates.[7,8] Preoperative CRT is currently considered the standard treatment for LARC. The oncological outcomes using this approach are encouraging, with rates of local and distant recurrence at 5 years being 6—9% and 33—36%, respectively.[6,9,10] However, only a subgroup of patients treated with preoperative CRT respond to treatment.[6,11] The other subgroup consists of nonresponders who do not benefit from the therapy and who may be treated using alternative means. The peculiar aspects of this approach are related to clinical over-staging, which may result in unnecessary neoadjuvant treatment in almost 18—20% of cases, as proven in a trial in Germany.[6] Currently, patient selection for preoperative neoadjuvant therapy depends mainly on clinical parameters, including the stage of the disease. However, most of these parameters do not have a predictive impact on therapy response. Thus, the implication of potential factors predicting histopathological response to treatment is a major issue.

This article reviews updated information regarding the prognostic and molecular aspects of LARC patients who have received preoperative CRT, and evaluates the significance of such aspects in neoadjuvant therapy and their impact on therapeutic strategies.

## Conventional predictive factor in LARC with preoperative CRT

### Carcinoembryonic antigen

Given its reliability and cost-effectiveness, serum carcinoembryonic antigen (s-CEA) is currently the most widely used tumor marker, especially in CRC.[12] Most s-CEA studies in CRC patients have focused on the prognostic effect of preoperative s-CEA concentration, and elevated preoperative s-CEA levels have been correlated with high recurrence rates. Furthermore, postoperative s-CEA monitoring has been valuable for the early detection of recurrence after curative surgery and the assessment of responses to chemotherapy in patients with metastatic CRC.[13] Increased preoperative and early postoperative s-CEA concentrations after curative resection are associated with more frequent systemic failure and poorer survival rates in rectal cancer patients.[13] In general, elevated CEA levels measured during treatment indicate disease progression, but with some exceptions. An increase in CEA alone should not be considered as evidence of disease progression, especially immediately after chemotherapy is recommended, because chemotherapy may transiently elevate CEA levels.[14]

Several studies have investigated the utility of pre- and post-CRT s-CEA concentrations as predictors of response to preoperative CRT.[15,16] In 2011, Kim et al[17] evaluated 333 rectal cancer patients who received preoperative CRT followed by surgery, and assessed the clinical significance of a reduction in s-CEA concentration ratio prior to and after preoperative CRT. They demonstrated that the reduction ratio of pre- to post-CRT s-CEA concentrations may be an independent prognostic factor for disease-free survival following preoperative CRT and surgery in rectal cancer patients with initial s-CEA $>$ 6 $\mu$g/L.[17] In LARC, CEA levels are of potential clinical value as a predictor of response to preoperative CRT and as an independent prognostic factor after preoperative CRT and curative surgery.

## Molecular (biological) markers

Several molecular markers have been proposed for measuring the radio- and chemo-sensitivity of rectal cancer. We categorized the surrogate biomarkers into six subgroups.

(1) Resistant to chemoradiotherapy: CD133 and cyclooxygenase-2

CD133 can be used to identify colon cancer-initiating cell populations in human tumors.[18,19] Increasing evidence suggests that cancer stem cells are more resistant to chemotherapy and radiotherapy than other types of cancer cells.[20,21] In addition, the administration of a selective cyclooxygenase-2 (COX-2) inhibitor can significantly increase tumor susceptibility to radiation by reducing prostaglandin release.[22] Therefore, COX-2 is a potential predictor of tumor response to radiotherapy.

Shinto et al[23] investigated whether the overexpression of CD133 and COX-2 can be used as predictive markers of tumor response to preoperative CRT in LARC patients. Results of both univariate and multivariate analyses indicated that CD133 and COX-2 are independent predictors of tumor regression grade (TRG) after preoperative CRT. Patients lacking both CD133 and COX-2 expression have an extremely high histopathological response rate to CRT. The combination of CD133 and COX-2 expression is highly associated with pathological response, which indicates the radioresistant properties of cancer cells with putative stem cell marker CD133 overexpression and supports the hypothesis that the number of cancer stem cells in a tumor may serve as a predictive marker of CRT resistance.