

# Genomic predictor of complete response after chemoradiotherapy in rectal cancer

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A multimodal approach to locally advanced (cT3, 4 and/or N+) rectal cancer, based on the use of concurrent chemo-radiotherapy followed by radical surgery with total mesorectal excision, has led to a significant improvement in oncologic outcomes (1,2). This therapeutic approach also improves tumor resectability and increases the chance to preserve anal sphincter (3,4). For these reasons, neoadjuvant chemoradiotherapy (nCRT) followed by surgery has become the standard treatment for locally advanced rectal cancer.

However, the response to nCRT varies substantially in each individual patient, which is considered as an important prognostic factor (5-8). Currently, there is no definite method to predict a tumor response to nCRT. Determination of factors predicting tumor regression after nCRT is important, which would permit tailored treatment strategies that include fewer invasive surgical approaches or intensified neoadjuvant treatment in patients with a lower likelihood of responding (9,10).

To date, multiple factors have been suggested as a putative predictive factor for tumor regression. Clinical factors include performance status, tumor stage, tumor mobility and circumference of the rectal wall involved by tumor (11). Treatment factors include radiation dose and time elapsed from radiation to surgery (12,13). Additionally, there are various biologic factors that may be involved in the tumor response process such as specific gene or protein expression and genetic mutation (14).

As a biologic factor, genetic polymorphisms have been investigated to reveal the association with tumor regression after nCRT. In the previous study, patients with specific thymidylate synthase (TS) single nucleotide polymorphism (SNP) showed significantly greater downstage of rectal cancer after nCRT (15). Also, polymorphisms in the *EGFR* gene have been investigated but the results were not confirmed as predictive markers of response (16).

A recent *The Pharmacogenomics Journal* paper entitled “EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer” investigated the association between tumor response to capecitabine-based nCRT and polymorphism in genes involved in the fluoropyrimidine metabolism (TS), the DNA repair (*ERCC1*, *XPD*, *XRCC1*) and the *EGFR* pathway (*EGFR*, *EGF*, *AREG* and *EREG*). A total of 84 patients with rectal cancer underwent capecitabine-based nCRT were included. Analyzing SNPs in the selected genes from blood samples by means of genotyping, the associations of pathological response to nCRT with each SNP were investigated. This study showed significant associations of two SNPs with pCR; rs11942466 C>A polymorphism in *AREG* gene and rs11615 C>T in *ERCC1* gene. Authors suggested these SNPs as a potential biomarker for pCR after capecitabine based chemoradiation.

The *EGFR* pathway and DNA repair mechanism were revealed to involve in the resistance to radiotherapy (17).

Several studies have found a relationship between the expression of these genes and tumor response after nCRT in rectal cancer (18). However, limited data are available on the polymorphisms in *AREG* or *ERCC1* genes and the radiotherapy response (19). Furthermore, in the field of specific haplotypes and genetic polymorphisms, the data for SNPs is limited and only a few genes have been the candidate for genotyping such as TS and EGFR. In this context, the result of this study has substantial clinical importance.

Genetic polymorphisms are promising predictive biomarker because drug resistance or severe toxicity might be related to genetic variations in tumor cells and/or to the genetic background of each patient. However, it requires higher levels of evidence before they can be considered clinically useful. Thus retrospective studies on large numbers of samples with detailed clinical data, and prospective pharmacogenetic-guided clinical trials, albeit challenging, are needed. These gene polymorphisms could be candidate markers for such further studies.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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