# Complete Clinical Response after Neoadjuvant Chemoradiation for Distal Rectal Cancer

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• Clinical response • Neoadjuvant chemoradiation
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Multimodality treatment of rectal cancer, with the combination of radiation therapy, chemotherapy, and surgery has become the preferred approach to locally advanced rectal cancer.[1–4] The considerably high local recurrence rates observed after radical surgery alone has led to the use and recommendation for additional therapy either before or after surgery for T3/T4 or N+ tumors.[5] In this setting, to avoid overtreatment of patients with early-stage disease, preoperative treatment with radiation therapy with or without concomitant chemotherapy requires optimal radiological staging because there is no pathologic confirmation of exact TNM parameters. However, there is a theoretic benefit of exposing unscarred tissue with optimal oxygen delivery to both radiation and chemotherapy as opposed to postoperative treatment. The results from randomized controlled trials suggest that the neoadjuvant approach seems to be superior for local disease control, even in the setting of appropriate surgical technique (total mesorectal excision).[1] The use of neoadjuvant chemoradiation therapy (CRT) has resulted in additional benefits such as reduced toxicity rates, significant tumor downsizing and downstaging, better chance of sphincter preservation, and improved functional results (compared with postoperative CRT).[1,6] In a multicenter study of patients undergoing

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neoadjuvant CRT for clinically stage II disease (staged by either endorectal ultrasound or magnetic resonance imaging), more than 20% of the patients staged as N0 were found to harbor lymph node metastases in their tumors on pathologic examination. Considering that these patients underwent neoadjuvant CRT, even greater rates of nodal disease underestimation might be expected. The investigators concluded that radiological inaccuracy (particularly for nodal disease) may justify, and possibly warrant, overtreatment of patients with rectal cancer by the use of neoadjuvant CRT.[7] There is a subset of patients with early-stage disease (particularly T2N0) who may also benefit from neoadjuvant CRT despite there having been no demonstration of improved local disease control in randomized trials. Patients with distal T2N0 rectal cancers are at higher risk for developing local disease recurrence compared with the mid- and upper rectal locations.[8] In addition to the potential benefits in terms of local disease control in this high-risk group of patients, neoadjuvant CRT could also improve the chance for sphincter preservation in these patients, allowing for ultralow or even intersphincteric resections.[9]

## RATIONALE FOR THE INVESTIGATION OF A NONOPERATIVE APPROACH

Radical surgery with total mesorectal excision remains the mainstay of treatment of distal rectal cancer and is considered by many to be necessary regardless of tumor response to neoadjuvant CRT. However, it has been associated with high rates of immediate morbidity and mortality. For immediate morbidity, an anastomotic leak is one of the most important complications and may occur in up to 12% of cases.[1,10] Overall, perioperative mortality may reach 2% to 3% in patients managed by radical surgery. Perioperative mortality is significantly higher, reaching up to 13% of patients with anastomotic leaks, when temporary diversion is not performed.[11,12] The requirement for a temporary stoma may add additional morbidity related to stoma closure and should be considered in the cumulative morbidity of rectal cancer management.[13] Preoperative radiation may lead to a significant increase in the risk of leaks; however, prospective randomized trials have failed to demonstrate the differences described in previous retrospective analysis.[1,11,12]

Tumor regression after neoadjuvant CRT may be observed not only in the primary tumor (within the rectal wall) but also in perirectal metastatic lymph nodes. This finding has been supported by the observation of a shift toward earlier disease staging in patients treated preoperatively with CRT, for whom the rates of stage II or III disease are markedly decreased compared with patients managed by surgery and postoperative CRT.[1,6]

Tumor regression after neoadjuvant CRT may be complete, leading to an absence of residual neoplasia in the resected specimen, known as complete pathologic response or ypT0N0M0 (ypCR).[14]

Therefore, the rationale for a nonoperative approach to patients with rectal cancer is to avoid a significantly morbid procedure in patients with complete tumor regression after neoadjuvant CRT.

## FACTORS INFLUENCING TUMOR REGRESSION

In a review of phase II and phase III studies including variable regimens of neoadjuvant CRT, several factors were found to be associated with higher rates of ypCR after radical surgery. The use of fluorouracil (5-FU) by continuous venous infusion, the delivery of a radiation therapy dose higher than 45 Gy, and the use of an additional drug combine with 5-FU have all been associated with increased rates of ypCR.[15]

Another factor that has frequently been associated with complete tumor regression is the interval between CRT completion and surgery. Radical surgery has traditionally