

# Current Controversies in Neoadjuvant Chemoradiation of Rectal Cancer

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## KEYWORDS

- Rectal cancer • Neo-adjuvant chemoradiation • Short course • Long course
- Complete pathologic response

## KEY POINTS

- Total mesorectal excision with preoperative radiation and chemotherapy provide the lowest local recurrence rates for rectal cancer.
- Timing of surgery after preoperative chemoradiation is being increased to optimize tumor downstaging.
- Permissive observation of complete clinical response is investigational at present.
- Preoperative and postoperative radiation provides improved local cancer control for superficial cancers removed by local excision.
- Good prognostic tumor characteristics are being investigated with the aim of selecting patients for whom preoperative radiation may be avoided.

## BACKGROUND

In the history of rectal cancer surgery, outcomes have previously been less favorable than for colon cancer, with local recurrence rates on the order of 25% versus 5% and 5-year survival rates on the order of 30% versus 50%. To improve on rectal cancer surgery outcomes, postoperative (adjuvant) combination radiation and chemotherapy regimens were recommended, based on trials conducted by the US North Central Cancer Treatment Group (NCCTG),<sup>1</sup> the Gastrointestinal Tumor Study Group (GITSG),<sup>2</sup> and the National Surgical Adjuvant Breast and Bowel Project (NSABP).<sup>3</sup> However, outcomes of rectal cancer remained less favorable despite this standard adjuvant treatment.<sup>4</sup>

A remarkable improvement in outcomes of rectal cancer was reported by Heald and Ryall<sup>5</sup> using the technique of total mesorectal excision (TME). The report on Heald's surgical results without adjuvant treatments by MacFarlane and colleagues<sup>6</sup> showed

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local recurrence outcomes to be superior to non-TME surgery with adjuvant treatments, 7% versus 19%.

The second remarkable improvement in outcomes of rectal cancer was preoperative (neoadjuvant) radiation, introduced in the Swedish rectal cancer trials.<sup>7</sup> Local recurrence and survival were improved in a randomized trial using short-course preoperative radiation versus surgery alone. However, surgery in this study was not based on TME technique. Outcomes with short-course preoperative radiation plus non-TME surgery remained suboptimal, stressing the importance of TME surgery as the main standard treatment of rectal cancer.

The first randomized trial using TME was reported by Dutch investigators,<sup>8</sup> who demonstrated that TME surgery could be learned and adopted by general surgeons, with good results. Norway has also adopted TME surgery on a national basis, with national local recurrence rates of 8%.<sup>9</sup> Furthermore, the main finding of the Dutch trial was that the combination of short-course preoperative radiation plus TME had the lowest local recurrence rate.<sup>10</sup> This large multicenter study provided new outcomes standards for rectal cancer that approach outcomes for colon cancer.<sup>11</sup> The protocol of preoperative short-course radiation and TME surgery has also been used for populations in Sweden, Denmark, and British Columbia in Canada.<sup>10–12</sup>

Preoperative radiation was demonstrated to be superior to postoperative radiation in a German randomized trial,<sup>13</sup> which also used TME as the standard surgery technique. Preoperative radiation reduced local recurrence by half compared with postoperative radiation (6% vs 13%). Moreover, the downstaging effect of preoperative radiation resulted in increased sphincter-preserving resection with less permanent colostomies in patients preoperatively judged to require abdominoperineal resection (39% vs 19%). This sphincter-preserving effect from downstaging by preoperative long-course chemoradiation was also seen in a Korean trial.<sup>14</sup> The NSABP also conducted a trial of preoperative versus postoperative chemoradiation. Though unable to complete its full study because of incomplete recruitment, the NSABP did report trends toward improved disease-free survival with preoperative treatments, 64% versus 52% at 7 years.<sup>15</sup>

On this basis, preoperative radiation combined with chemotherapy has been adopted as the standard protocol for rectal cancer management by the National Institutes of Health (NIH) and the National Comprehensive Cancer Network (NCCN) in the United States and Canada.

## CONTROVERSIES: OUTLINE

The evolution of the management of rectal cancer provides a background for controversies over preoperative radiation in current management. Controversies to be discussed here include:

- The protocol of preoperative radiation (short vs long course): efficacy and toxicity
- Whether chemotherapy is used in combination with radiation, and which chemotherapy drugs are used
- The optimum timing of surgery after radiation to achieve maximum downstaging
- Whether radiation is used for all rectal cancers or on a selected basis only
- The preferred radiation protocol for treating superficial rectal cancer being considered for local excision
- Whether endocavitary radiation can be used as an effective treatment

**Table 1** lists randomized trials for each of the topics.

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