

Practical Issues in Adjuvant Therapy for Rectal Cancer

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Abstract

Introduction: While the standard adjuvant therapy for rectal cancer includes radiation therapy (RT) and chemotherapy (CT), the optimal treatment combination and sequencing have yet to be determined. In recent years, a large number of clinical trials have been reported in this rapidly evolving field. **Materials and Methods:** A review of pivotal trials in rectal cancer was undertaken with a focus on the important recent literature that has determined the current approach to adjuvant treatment. **Results:** Multiple well-conducted, randomised studies have demonstrated that, for patients with stage II and III rectal cancer, the combination of adjuvant CT and RT reduces the risk of local recurrence (LR) and distant recurrence, improves overall survival and should form part of the standard treatment. Due to the reduced risk of LR, the absolute benefit from adjuvant RT is less if optimal oncologic surgery has been performed. Theoretical advantages and preliminary clinical results suggest that delivering part of the adjuvant therapy preoperatively will produce superior results. Ongoing randomised trials will define the relative merits of long-course RT (with CT) and short-course RT alone as preoperative therapy. Preoperative combined modality therapy might increase the rate of sphincter preservation, although definitive data supporting this is still being awaited, whereas RT alone does not facilitate sphincter preservation. **Conclusion:** Management of patients with rectal cancer is complex and requires ongoing close collaboration between the colorectal surgeon, medical oncologist and radiation therapist in order to achieve the best possible outcomes. The optimal combination of CT and RT will be defined by current clinical trials.

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of the significance of these results, particularly when compared to more recent trials.

In earlier studies, the demonstrated benefit, in terms of reducing LR rates, is in the context of LR rates in the control group (25%,⁴ 24%⁵ and 30%⁶) that are considered unacceptably high by modern standards using TME techniques. However, reports of LR rates less than 10% following surgery alone are potentially misleading.^{1,2} Such low LR rates are reported in series that include many early stage patients and have not yet been reproduced in any mature prospective clinical trial. As level 4 evidence these series cannot be used as justification to alter the current standard approach. The best results in a prospective series were those achieved in the recently reported National Surgical Adjuvant Breast and Bowel Project (NSABP)-R02 study,⁷ where postoperative RT significantly reduced the cumulative locoregional relapse from 13% to 8% at 5 years follow-up ($P = 0.02$). However, in this NSABP study, there was no beneficial effect on disease-free or overall survival, irrespective of the CT used. The authors cautioned the reader that “whether the 5% absolute decrease in the cumulative incidence of locoregional relapse is sufficient to justify the routine use of postoperative radiotherapy is a decision that must be made by the clinician”. In discussions on postoperative adjuvant therapy, such as in a review in 2002,⁸ undue emphasis is placed on the results from earlier small studies, with little regard for the more recent and much larger NSABP-R02 trial. The absolute benefit from adjuvant therapy, not the percentage change in a particular endpoint, is critical when deciding whether a particular patient should be offered adjuvant treatment.

Comparisons between studies, with respect to LR rates, are potentially misleading. There are several reasons to believe that preoperative treatment may prove superior to postoperative therapy, including improved oxygenation in a vascularised presurgical environment⁹ and the reduced potential for tumour seeding with surgical handling. However, a higher rate of LRs would be expected in studies where patients are treated postoperatively, rather than preoperatively, regardless of the surgical technique or adjuvant therapy. This is because all patients in postoperative series have at least T3 tumours, whereas preoperative studies due to limitations of current diagnostic modalities will include a significant percentage of patients with earlier stage disease (in the Dutch preoperative study,¹ about 30% of patients had T2 lesions), where the risk of LR is much lower.

The intensity of follow-up and the thoroughness with which adverse events are documented also vary considerably between studies. These are factors that will significantly influence the reported LR rates. Also, patients

may be censored after they have a distant relapse documented, meaning any subsequent local relapse is not included in the outcome figures. Some series may also categorise patients into “curative” and “non-curative” resections,⁶ or simply not state if some poor-prognosis patients have been excluded, another factor that can confound data analysis. The standard of reporting of patients suffering LR has recently been critically reviewed.¹⁰ Of the 21 studies included in this analysis, only 3 of the 21 studies scored more than 11 out of 26 criteria regarding the adequacy of methodology (a score of 26 being perfect).

While considerable attention remains focused on the incidence of LR, there is a virtual absence of data on the impact this has on overall quality of life, or how often this occurs in the context of advanced metastatic disease and remains asymptomatic. While every surgeon has had personal experience of a patient who suffered greatly as a result of LR, these experiences reinforce the importance of this endpoint. For many patients, this may be an incidental occurrence or one successfully managed with further appropriate therapy. Such data are critical to a balanced interpretation of the risks and benefits of adjuvant RT and need to be sought in future studies.

Preoperative Radiotherapy

In a recent meta-analysis of studies that included more than 8000 patients,¹¹ preoperative RT was found to reduce the risk of LR by about 50%, independent of fractionation schedules or the underlying rate of LR. While not directly comparable, the results from postoperative RT suggest a slightly lower (37%) reduction in LR.

Preoperative therapy is potentially less toxic as a lesser amount of small bowel will prolapse into the pelvis to fall within the radiation field¹² and the absence of treatment to the perineal scar (which must be irradiated following an abdominoperineal resection¹³). Despite these considerations, it has largely been economic and practical considerations that have driven preoperative short-course RT. Two landmark randomised controlled studies^{1,14} have recently been published (Table I) and are worthy of detailed analysis.

In the Swedish rectal cancer trial,¹⁴ 1168 patients with clinically resectable rectal cancer were randomised to receive either short-course RT (25 Gy in 1 week), followed by surgery 1 week later or surgery alone. This study demonstrated that, at a median follow-up of 5 years, short-course RT reduced the risk of LR from 27% to 12% and improved overall survival from 48% to 58%. The Dutch rectal cancer trial¹ is similar in design but with the important exception that the TME operative technique was mandated. Preliminary data from this study showed that with preoperative RT, the 2-year LR rate improved from 8.2% to 2.4% ($P < 0.001$). With this absolute improvement of

TABLE I: TWO MAJOR STUDIES ON PREOPERATIVE SHORT-COURSE RADIATION THERAPY (SCRT)

Study	Treatment arms	Median follow-up (years)	LR rates (%)	P value	Overall survival (%)	P value
Swedish ¹⁴ (n = 1168)	SCRT + surgery	5	11	<0.001	58	0.004
	Surgery alone		27		48	
Kapiteijn et al ¹ (n = 1805)	SCRT + TME	2	2.4	<0.001	82.0	ns
	TME alone		8.2		81.8	

LR: local recurrence; ns: not significant; TME: total mesorectal excision

5.8% in the 2-year LR rate, 17 patients were treated to prevent 1 LR. Thus, better techniques for case selection are needed. In addition, overall survival for the almost 400 patients that had reached 3 years of follow-up was very similar for patients undergoing a TME with or without prior RT. This is relevant as the maximum survival advantage was reached at 3 years in the Swedish rectal cancer trial. While more mature survival data from the Dutch trial are being awaited, the data suggest that with optimal surgery preoperative RT is unlikely to yield any survival advantage.

In the Swedish study,¹⁴ an increased frequency of postoperative fistulas, femoral neck/pelvic fractures and altered sphincter function were reported. Patients that received preoperative RT also reported a greater dissatisfaction with bowel function, including a greater number of bowel movements, urgency and incontinence. Of some concern is the fact that 5% of the patients in the RT group died from intercurrent disease within 6 months of treatment, mainly of cardiovascular origin, compared with 1% of the patients in the non-irradiated group ($P = 0.02$).

In the Dutch trial,¹⁵ the total number of complications was higher in the RT group ($P < 0.01$). These included cardiac deaths ($P = 0.04$), intraoperative blood loss ($P < 0.001$) and perineal wound complications after abdominoperineal resection ($P = 0.0008$). Sexual function was analysed in 991 patients,¹⁶ with the results suggesting that RT had little or no effect on sexual function, which was impaired overall due to the effect of surgery.

Data from both the studies are consistent with that reported in the meta-analysis of preoperative RT by Camma et al,¹⁷ who noted an increased rate of sepsis ($P < 0.001$) and overall postoperative adverse events ($P < 0.001$) in patients receiving RT.

Preoperative Combined Modality Therapy

In many centres outside Europe, this has been adopted as standard treatment, despite a lack of randomised trials demonstrating that this approach is as effective or more effective than postoperative treatment, or that this approach results in less toxicity. The explanation is that many have been convinced by the theoretical advantages of

preoperative treatment along with the impressive data produced in single-arm studies, where high clinical tumour response rates, in the order of 70%, and high rates of pathological complete responses, in the order of 10% to 20%, have been consistently reported.¹⁸⁻³⁵ There is also the suggestion that an increased number of patients may be able to undergo sphincter sparing surgery,³³⁻³⁵ and that toxicity is less than that experienced with postoperative administration.²⁹ The potential impact of preoperative combined modality therapy (CMT) on sphincter preservation rate is an area of major interest and more data are keenly awaited.

Patients who achieve a response to preoperative therapy appear to have a significantly improved prognosis. In a series of 77 patients with locally advanced rectal cancer (fixed or tethered T4), the response to preoperative treatment was correlated with patient outcomes.³⁶ No patients with a pT0-T2 tumour experienced a local or distant recurrence, compared to a recurrence rate of 13% in patients with pT3-4N0 tumours and 16% in those with node-positive tumours. A more recent series of 165 patients with rectal cancer, who received preoperative combined modality therapy, has also reported that tumour response and pathological response are closely correlated with outcomes.³⁷

Fortunately, the lack of data from existing randomised trials is being addressed in several studies that have recently been completed or, are about to be completed, accrual (Table II). The most important of these is a large German study³⁸ where patients are randomised to either preoperative or postoperative combined modality treatment. Over 800 patients have now been entered, with the first results on survival for all the patients due in March 2003.³⁸ In the initial analysis, a lower than expected rate of pathological complete response was achieved with preoperative therapy (8%) which the investigators attributed partly to a meticulous pathological review of the total specimen. Toxicity data were in keeping with phase II data, with preoperative therapy resulting in less diarrhoea, nausea and vomiting, skin toxicity and leukopaenia. There was no difference in anastomotic leakage, postoperative bleeding, intestinal obstruction or fistulas. There was, however, a significant increase in the incidence of delayed wound healing in

TABLE II: CURRENT STUDIES ON ADJUVANT THERAPY FOR RECTAL CANCER

Study	Arms	Status
NSABP-R03 ⁷	5-FU/CMT/5-FU => Surgery Surgery => 5-FU/CMT/5-FU	Closed prematurely
German ³⁸	5-FU/CMT/5-FU => Surgery Surgery => 5-FU/CMT/5-FU	Completed accrual
Polish ³⁹	SCRT => Surgery CMT => Surgery	Ongoing accrual
EORTC 22921	SCRT => Surgery => 5-FU CMT => Surgery => Observation SCRT => Surgery => Observation CMT => Surgery => 5-FU	Ongoing accrual
Australian Intergroup	SCRT => Surgery => 5-FU CMT => Surgery => 5-FU	Ongoing accrual

5-FU: 5-fluorouracil; CMT: combined modality therapy;
EORTC: European Organisation Research and Treatment of Cancer;
NSABP: National Surgical Adjuvant Breast and Bowel Project;
SCRT: short-course radiation therapy

patients who have received preoperative therapy.

Of the patients receiving postoperative therapy, 18% of patients determined to require an abdominoperineal resection, prior to randomisation, underwent a sphincter saving procedure instead. This contrasted with a rate of sphincter saving operations of 35% in patients receiving preoperative treatment, suggesting that treatment prior to surgery might significantly impact on the type of operation performed. To date, there are no significant differences with respect to locoregional recurrences or overall survival, but obviously this data is currently very immature.

Some data are also available from the NSABP-R03⁴⁰ study, where the study design is similar to the German study. Unfortunately, this study was closed after only 267 patients had been enrolled due to poor accrual. Another American study (INT1047) was closed early for the same reason and no data were available from this trial. In a preliminary report on the NSABP-R03 study,⁴⁰ there was a trend toward increased sphincter sparing surgery in patients receiving preoperative combined modality therapy, with equivalent disease-free survival at 1 year (83% for preoperative versus 78% for postoperative, $P = 0.29$). There was, however, an unexpected trend for increased toxicity in patients receiving preoperative treatment, with the largest difference being in the rate of grade III and grade IV diarrhoea.

Substantial early and mid-term toxicity data are available from centres treating patients with combined modality therapy as part of single-arm trials. For example, in a series by Tjandra et al⁴¹ grade III or IV toxicity occurred in 45% of patients and quality of life was impaired on all subscales assessed. Some longer-term toxicity data are available

from other single-arm studies. Two published retrospective surveys^{42,43} reported an increase in the number of bowel movements, clustering of bowel actions, nocturnal bowel movements and occasional incontinence in patients receiving preoperative therapy compared to surgery alone controls.

Preoperative RT versus Preoperative Combined Modality Therapy

There are 3 major studies that the authors are aware of where patients are randomised to receive either short-course preoperative RT or long-course RT with concurrent CT. In one of these, being conducted by the European Organization for the Research and Treatment of Cancer (EORTC), another important question is being addressed as patients are also being randomised to receive either postoperative CT or no postoperative treatment. A 2-arm Australian study is not expected to complete accrual for another 2 years. The third study, performed by Polish investigators,³⁹ is the most advanced.

A preliminary report on the first 316 patients entered into the Polish study was recently presented in abstract form.³⁹ This study enrolled patients with clinically staged T3 and resectable T4 tumours, with surgeons declaring before treatment the patients who are likely to require an abdominoperineal resection. Only 2% of such patients receiving short-course RT went on to a sphincter saving procedure, compared with 17% in the long-course RT and CT arm. This is a potential advantage of CMT as short-course regimens do not lead to tumour downstaging and have no role in patients with bulky or fixed tumours. Significant differences in tumour responses were also demonstrated, with the mean maximum diameter of tumours in the short-course RT group being 48 mm compared to 29 mm in those patients treated with combined modality therapy. Further outcome data from this important study are eagerly awaited.

While we await the results of the many ongoing clinical trials, the authors would consider that preoperative combined modality therapy, postoperative combined modality therapy and short-course preoperative RT (with postoperative chemotherapy in selected patients) could all be considered standard care.

Adjuvant Therapy-related Toxicity

We have already discussed some of the toxicity data from the various approaches, but several further comments are worthwhile. Importantly, documentation of complications with adjuvant therapy is often incomplete, thus making overall analysis difficult. Objective assessment of bowel function and quality of life satisfactory scoring systems have only recently been developed and popularised.^{44,45}

Until recently, sexual functioning has largely been ignored. Also, older studies reporting RT-related toxicity data have complication rates well in excess of that expected when modern multiple field techniques are applied.

The largest deficit in current knowledge relates to data on longer-term morbidity, as late toxicity might potentially decrease a patient's quality of life for many years, such as the effect on rectal/sphincter function. The incidence of ongoing faecal urgency, frequency, bleeding, incontinence and other toxicities are infrequently documented in the literature. For some late toxicities, such as the risk of second malignancy, there is even less information although data on the treatment of prostate cancer provide some insights into this critical endpoint. Brenner et al⁴⁶ reported that patients who received RT for prostate cancer had a greater increased rate of second malignancies, increasing to 1 in 70 after 10 years.

Conclusion

Improvements in surgical technique and the use of adjuvant therapy have led to considerable improvements in the prognosis of patients with rectal cancer. Close collaboration between the treating surgeon, medical oncologist and radiation therapist will remain essential to delivering the best possible outcome. The outcomes will continue to be improved with ongoing research into the optimal timing and combination of CT and RT. While a number of approaches can currently be considered as standard, preliminary evidence indicates that preoperative combined modality therapy may provide the best outcome for patients. This hypothesis is being tested in several ongoing clinical trials and the results from these studies are being eagerly awaited.

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