

## CHAPTER 16 ADJUVANT THERAPY FOR RECTAL CANCER

Adjuvant therapy is any treatment that is given in addition to a standard cancer treatment. For early rectal cancer, the standard treatment is surgery to remove the cancer. Radiotherapy and chemotherapy have both been extensively studied to see if they may reduce the risk of cancer recurrence. They may be used alone or in combination, preoperatively or postoperatively.

### 16.1 Radiotherapy

Radiotherapy uses ionising radiation to kill cancer cells. Only those tissues within the treatment beam are affected. Radiotherapy achieves high cell kill but only within the treatment field. It may also affect the normal tissues within the field. It aims to reduce the incidence of recurrent cancer within the pelvis. Recurrent pelvic cancer is nearly always incurable and often causes pain, bleeding and sometimes ureteric obstruction. It is associated with a significant deterioration in quality of life.

### 16.2 Chemotherapy

Chemotherapy is cytotoxic drug treatment. Systemic chemotherapy affects the entire body, and is given with the aim of killing circulating cancer cells that may grow in distant organs such as the liver and lungs. Distant recurrence is almost always fatal. The addition of chemotherapy may also have some radio-sensitising action when used in combination with radiation.<sup>1</sup>

### 16.3 Benefits of adjuvant therapy

Patients whose tumours have penetrated the wall of the rectum and/or have metastasised to regional lymph nodes are at increased risk of recurrent cancer in the pelvis or at distant sites. There is also a higher risk of local recurrence when the surgical resection margins (either radial or longitudinal) are close or positive.<sup>2</sup> The optimum strategy to improve the outcome of patients with rectal cancer must address the problems of local and distant recurrence.

### 16.4 Can the results of international trials be applied in the Australian setting?

Patients enrolled in clinical trials have to be fit enough to withstand further treatment in addition to major surgery. A review of the entry criteria of combined modality therapy (CMT) (radiotherapy and chemotherapy) studies have not shown them to be restrictive. For patients who received surgery alone as the control group in the NSABP randomised study of CMT versus surgery alone,<sup>3</sup> the five-year survival data are comparable to a large cohort study performed by an Australian colorectal unit.<sup>2</sup> For lymph node positive patients, the five-year survivals for the NSABP and Concord groups were 35% and 32% respectively. Corresponding survival for tumours that had penetrated through the bowel wall were 57% and 62%.

### 16.5 The role of combined chemotherapy and radiotherapy

The current recommendations are based on a review of randomised trials. There have been ten randomised studies of CMT. Postoperative CMT has been most extensively studied. The Gastro-Intestinal Tumour Study Group (GITSG)<sup>4</sup> performed a study in which the four arms were: surgery, surgery and postoperative radiotherapy, postoperative chemotherapy with semustine and 5-FU, or postoperative CMT.

Disease-free survival was improved in the CMT arm versus surgery alone (67% versus 45%). However, overall survival was not significantly different between the arms. This study has been criticised because of the small numbers in each treatment arm (about 50).

Only one other study has compared CMT with surgery alone.<sup>5</sup> In this study, 144 patients were randomised to receive postoperative radiotherapy and synchronous bolus chemotherapy, or no further treatment. Local recurrence in the CMT arm was 12% compared with 30% in the surgery alone arm. Survival was also significantly increased (64% vs 46%,  $p = 0.01$ ).

Krook et al<sup>6</sup> randomised 204 patients with high-risk rectal cancer to postoperative radiotherapy alone or CMT. The CMT arm experienced lower recurrence rates, both locally and distantly. The rates of cancer-related deaths and deaths from any cause were also significantly reduced with the combined modality treatment.

Five further studies have addressed refinements of chemotherapy when used in combination with radiotherapy. The GITSG<sup>7</sup> randomised 210 patients to postoperative radiotherapy with either semustine and 5-FU or 5-FU alone. There was no survival advantage to the addition of semustine and, given its known leukemogenic activity, they recommended that 5-FU alone be used.

O'Connell et al<sup>8</sup> examined the effectiveness of alternative schedules of chemotherapy and different delivery methods in 660 patients with high-risk rectal cancer. Patients were randomised to receive 5-FU as a bolus or by protracted venous infusion during radiotherapy. They were also randomised to receive systemic 5-FU chemotherapy with and without semustine. Protracted venous infusion conferred a significant advantage in time to relapse and survival. When compared with bolus 5-FU, there was a 10% absolute increase in survival at four years for the infusion patients. Again, semustine gave no benefit over 5-FU alone.

Intergroup 0114<sup>9</sup> was a four-armed study of adjuvant postoperative chemoradiotherapy that compared 5FU alone against modulation of 5-FU with levamisole, leucovorin or levamisole plus leucovorin. There were no differences in the different regimens on final analysis in terms of disease-free or overall survival.<sup>10</sup> The Hellenic Cooperative Oncology Group<sup>11</sup> also found no advantage from adding chemotherapy with 5-FU plus leucovorin into a schedule of combination bolus 5-FU plus concomitant radiotherapy.

The preliminary results of a Korean study<sup>12</sup> in 308 patients suggest that early radiotherapy with concurrent chemotherapy (commencing with the first cycle of chemotherapy) after resection of rectal cancer has an advantage in terms of disease-free survival compared to late radiotherapy (commencing with the third cycle of chemotherapy). The PAR Cooperative Study Group,<sup>13</sup> in a trial of 218 Dukes B and C patients, found no difference in 5-year disease-free survival and overall survival when sequential bolus five-day monthly 5-FU with levamisole fortnightly was given in addition to postoperative radiation therapy. The study was, however, underpowered and there was a low (59%) compliance with the chemotherapy due to toxicity.

NSABP R02<sup>14</sup> randomised 694 Dukes B and C patients to receive either postoperative chemotherapy (MOF or 5-FU plus LV) alone or postoperative chemotherapy with radiotherapy. Although radiotherapy conferred no advantage in disease-free or overall survival it reduced the cumulative incidence of locoregional relapse.

Three studies have examined the use of preoperative CMT, and compared it with preoperative radiotherapy alone. In a European Organization on Research and Treatment of Cancer (EORTC) trial<sup>15</sup> there was a non-significant trend to better survival in the RT/S 59% versus 46% CMT ( $p = 0.06$ ) at five years. The radiotherapy in both arms of the study covered the para-aortic region and the pelvis, with opposed anterior and posterior portals. Such a technique has been shown in subsequent randomised studies to be associated with an excessive risk of late small-bowel damage.<sup>16,17</sup> The Polish Colorectal Study Group<sup>18</sup> trial using modern techniques enrolled 316 patients, and compared conventional long-course 50.4Gy RT combined with bolus 5-FU plus LV to short-course radiotherapy (25Gy in 5) before TME. There was more acute toxicity in the long course CMT that was associated with a higher pathological shrinkage but not an increased sphincter preservation rate. Preliminary results from the EORTC 22921 trial comparing the addition of two cycles of 5-FU plus LV to

preoperative RT 45Gy over 5 weeks show that the chemotherapy significantly reduced the tumour size and pathological TN staging as well as the incidence of lymphatic, venous or perineural invasion.<sup>19</sup> Acute diarrhoea was increased but compliance with radiation and feasibility of surgical resection were not affected.<sup>20</sup>

No direct comparison between long-course and short-course preoperative radiation has been published. This question is currently being addressed in a Trans Tasman Radiation Oncology Group (TROG)/Australasian Gastrointestinal Trials Group (AGITG) study.

NSABP R03 (closed early by poor accrual) has been completed and compares pre- versus post CMT.<sup>21</sup> Early results of this trial suggested that a larger proportion of the preoperative patients had sphincter-sparing surgery, but also experienced higher toxicity from the treatment.

The recently reported CAO/ARO/AIO-94 trial also compares pre and postoperative CMT<sup>22</sup> and 823 patients were accrued. Grade 3 or 4 acute toxic effects were less in the preoperative (27%) as compared with postoperative (40%) treatment group ( $p = 0.001$ ). A higher sphincter preservation rate was also seen for the preoperative group. Post operative morbidity was not increased by preoperative CMT. The corresponding rates of long-term toxic effects were 14% and 24%, respectively ( $p = 0.01$ ). Chronic anastomotic stenosis rate was seen less following preoperative CMT than postoperatively (4% versus 12%,  $p = 0.003$ ). Five-year pelvic and distant recurrence rates were 6% versus 13% ( $p = 0.006$ ) and 36% versus 38% ( $p = 0.84$ ) respectively. Disease-free and overall survivals are not significantly different. The conclusions of this well-performed RCT was that 'preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local control and was associated with reduced toxicity, but did not improve overall survival.'

A similar trial, the Intergroup 0147, has also recently closed due to poor accrual.<sup>23</sup>

## **16.6 The role of adjuvant radiotherapy without chemotherapy**

The best evidence of the value of radiotherapy alone comes from five meta-analyses of more than 8000 patients randomised to receive radiotherapy and surgery, or surgery alone.<sup>24-28</sup> Radiotherapy alone significantly reduces local relapse and also deaths related to rectal cancer, but the impact on overall survival is counterbalanced by early non-cancer deaths. Recent studies suggest a survival benefit from using modern techniques. Even without a survival improvement, the use of radiotherapy can be justified, based on the avoidance of the morbidity and costs associated with local recurrence of rectal cancer. However, radiotherapy itself has certain morbidity.

## **16.7 Preoperative radiotherapy without chemotherapy**

The Colorectal Cancer Collaborative Group overview analysed individual patient data on over 8000 patients from 14 trials, comparing preoperative radiotherapy with no preoperative therapy for rectal cancer.<sup>26</sup> In this analysis, radiotherapy significantly reduced the proportional risk of local recurrence by 46% ( $p = 0.00001$ ) and the absolute risk of death from rectal cancer by 5% (45% vs 50%,  $p = 0.003$ ). Early non-cancer deaths (within a year), however, were increased from 4% to 8% ( $p < 0.0001$ ). This counterbalanced the overall survival benefit. A statistically significant correlation ( $p = 0.02$ ) of decreasing benefit of preoperative radiotherapy on mortality was seen with increasing age. The proportional mortality reduction in rectal cancer deaths did not vary by stage. The absolute benefits, however, are larger for the patients with Dukes C cancer as they are at a higher risk of recurrence. In studies where biologically effective doses of  $\geq 30$  Gy were used, the reduction in risk of local recurrence was 50%. No significant reductions were seen in those with a dose that was of low or intermediate biological effect ( $< 20$  Gy and 20–20.9 Gy).

Two recent studies<sup>29,30</sup> employing modern short-course three- or four-field radiotherapy techniques and included in the above meta-analysis have shown a significant survival advantage. In a Swedish

study, 1168 patients less than 80 years of age with rectal cancer were randomised to receive either 25 Gy in five fractions followed by surgery, or surgery alone. Postoperative mortality was equal in each arm. Local recurrence was reduced from 27% to 11% ( $p < 0.001$ ) and survival at five years was significantly increased in the radiotherapy arm (58% vs 48%,  $p = 0.004$ ). This improvement was found across all stages of cancer. The Stockholm II trial<sup>30</sup> of 557 patients at a median of 8.8 years follow up found pelvic recurrence rates reduced from 25% to 12% and overall survival improved from 39% to 46% ( $p < 0.03$ ). Cardiovascular death was found to be the main cause of intercurrent death. The toxicities of preoperative radiotherapy are discussed in detail in Section 16.11.1.

The Lyon R90-01 trial examined the interval between completion of pelvic radiotherapy (39 Gy in 13 fractions) and surgery<sup>31</sup>. A long interval (6–8 weeks) was found to be associated with a higher clinical and pathological downstaging compared with a shorter interval (two weeks). No effect was seen on toxicities, local recurrence, anal function or survival after median follow up of six years.<sup>32</sup> The local recurrence rate following anal sphincter preserving surgery was, however, 15% higher than if adominoperineal surgery was carried out. In the Swedish study, no downstaging effect was seen if the interval between radiotherapy and surgery was not more than ten days.<sup>33</sup>

## **16.8 Postoperative radiotherapy without chemotherapy**

There have been eight trials of surgery and postoperative radiotherapy versus surgery alone. The Colorectal Cancer Collaborative Group meta-analysis shows that postoperative radiotherapy significantly reduces local recurrence by about one third ( $p = 0.0002$ ).<sup>26</sup> There is no evidence, however, that overall survival is improved by postoperative radiotherapy alone.

## **16.9 Preoperative versus postoperative radiotherapy**

The Colorectal Cancer Collaborative Group meta-analysis shows the reduction in rectal cancer mortality is greater for preoperative radiotherapy (22%,  $p = 0.00002$ ) than for postoperative radiotherapy (9%,  $p = \text{NS}$ ). The better results seen in preoperative radiotherapy studies may be due to the selection of clinically-staged patients with earlier tumours than those pathologically staged before entry into a postoperative radiotherapy trial.

One direct comparison was performed between 25 Gy in one week preoperatively or 60 Gy in 7-8 weeks postoperatively.<sup>34</sup> There were significantly fewer local recurrences in the preoperative radiotherapy arm (13% vs 22%,  $p = 0.02$ ), but no difference in overall survival. Late radiotherapy complications were reported by treatment given and were higher with postoperative radiotherapy than with either preoperative radiotherapy or surgery alone (41%, 20% and 23% respectively). After accounting for the effect of different fraction size, the postoperative biological dose was about 50% higher than the preoperative dose,<sup>35</sup> and a much greater rate of late effects would be expected. However, when the results are analysed by intention-to-treat, the rate of complications in the postoperative arm falls to 31%, which is not significantly different from the preoperative rate.

The 2004 randomised controlled German rectal trial (CAO/ARO/AIO-94) by Sauer et al<sup>22</sup> of over 800 patients revealed no difference in survival rates. However, the five-year local recurrence was 6% for preoperative chemoradiotherapy and 13% in postoperative ( $p = 0.06$ ). Grade 3 or 4 acute toxic effects were less (27% preoperative as compared with 40% postoperative treatment group,  $p = 0.001$ ) The conclusions of this well-performed RCT was that 'preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local control and was associated with reduced toxicity but did not improve overall survival'.

As already mentioned in Section 16.5, the German rectal trial<sup>22</sup> also showed that preoperative long-course chemoradiotherapy, when compared with postoperative chemoradiation, improved local control without affecting overall survival. Acute and long-term toxicities were also less with preoperative therapy.

This suggests that a policy of preoperative radiotherapy for all patients with rectal cancer would yield a similar absolute number of complications to a policy of selective postoperative radiotherapy. Better selection of preoperative patients by endorectal ultrasound or MRI may improve this ratio to clearly favour preoperative radiotherapy.

Preoperative radiotherapy may be preferred over postoperative radiotherapy if radiotherapy alone were to be used, because of the higher rate of local control. This may not be feasible in some circumstances, such as emergencies due to obstruction or perforation. The United Kingdom MRC CR07 study is currently comparing preoperative radiotherapy with postoperative selective chemoradiotherapy.

#### When should adjuvant therapy be considered for rectal cancer?

Guideline — Adjuvant therapy for rectal cancer	Level of evidence	Practice recommendation	Refs
Adjuvant preoperative or postoperative radiotherapy is recommended for high-risk (T3/4 or N1) rectal cancer.	I	Strongly recommend	26

#### Does preoperative therapy reduce late morbidity compared with postoperative?

Guideline — Adjuvant therapy for rectal cancer	Level of evidence	Practice recommendation	Refs
Preoperative therapy may lower the incidence of late morbidity.	II	Recommend	22, 34

#### What postoperative chemotherapy should be administered if radiotherapy is indicated?

Guideline — Adjuvant therapy for rectal cancer	Level of evidence	Practice recommendation	Refs
Where postoperative radiotherapy is indicated, 5-FU-based chemotherapy should be administered.	II	Recommend	6

### 16.10 Role of chemotherapy without radiotherapy

Postoperative adjuvant chemotherapy alone for rectal cancer has been tested in several studies. The underpowered study GITSG 7175 compared chemotherapy using 5-FU plus semustine with surgery alone, surgery plus radiotherapy, and surgery plus CMT.<sup>4</sup> There was a non-significant trend to higher cancer-free survival for patients receiving chemotherapy compared to surgery alone. NSABP R-01 compared chemotherapy with MOF (Mitomycin C, Oncovin, 5-FU) to surgery alone or radiation alone in 555 subjects.<sup>3</sup> A significant overall improvement in disease-free and overall survival was found with chemotherapy. A Japanese trial used oral 5-FU combined with mitomycin C for a year and detected a decrease in local failure. A CCOPGI pooled analysis of these trials found a mortality odds ratio of 0.65 ( $p = 0.0006$ ) in favour of chemotherapy, but no significant impact on local recurrence.

A subgroup analysis of rectal patients within a Japanese meta-analysis of three randomised trials of adjuvant oral fluoropyrimidine chemotherapy in Colorectal Cancer following surgery has been reported. This analysis found a mortality risk reduction of 0.86 ( $p = 0.05$ ) and disease free survival risk of 0.77 ( $p = 0.0003$ ) in favour of oral chemotherapy.<sup>36</sup>

In an interim analysis at 3.5 years, the Netherlands Adjuvant Colorectal Cancer Project found no significant difference in disease-free or overall survival for chemotherapy with 5-FU plus levamisole versus surgery alone in a rectal cancer subgroup.<sup>37</sup>

There is an extensive body of evidence examining the role of chemotherapy in colon cancer. Some of these studies may have included rectal cancer patients. This evidence is reviewed elsewhere in these guidelines (see Chapter 15). There is a significant survival benefit from 5-FU-based chemotherapy for patients with lymph-node positive colon cancer. Data from studies of patients with metastatic disease from these sites would support this. Chemotherapy alone does not appear to affect local recurrence.

### **16.11 Complications of adjuvant therapy and how they may be reduced**

All radical anti-cancer treatments are associated with specific morbidities.<sup>38</sup> These must be weighed up against the morbidity and risk of death associated with cancer persistence or recurrence. This balance will be different for each patient and will also need to include an assessment of his or her preferences and general condition.

Overall quality of life has not been directly assessed in any published randomised trial of adjuvant therapy for rectal cancer, but it is being addressed, along with functional endpoints, in current studies. An indirect assessment of quality of life using Q-TWIST methodology supports adjuvant therapy.<sup>39</sup>

#### **16.11.1 Radiotherapy**

Short-term (acute) complications of pelvic radiotherapy include lethargy, mild nausea, diarrhoea, tenesmus, urinary frequency, and skin erythema or desquamation. These acute effects develop in most patients to some degree during the treatment, and usually resolve within weeks of completion.

Long-term (late) side effects affect only a small number of patients, but are usually permanent. They include small bowel damage (bleeding, stricture, perforation and malabsorption) and rectal damage (reduced reservoir capacity, urgency, frequency, bleeding, incontinence and fistula formation). These effects are seen in 3–11% of cases.<sup>34</sup> Persisting lumbosacral plexopathy was seen in six patients in the Swedish Rectal Cancer Trial, but this may have been due to incorrect placement of dorsal shields. The Dutch Colorectal Cancer Group preoperative radiotherapy study<sup>40</sup> (to be discussed below) recorded 53 patients as experiencing acute neuropathic symptoms from short-course radiotherapy. With careful evaluation of treatment fields, shielding with adjustments as necessary plus selective treatment interruption, none of these patients had long-lasting symptoms at two years of follow up. Early quality of life data based on 991 Dutch patients indicate that at 1-year post operation, 63% of the radiotherapy group who were sexually active before the operation were still sexually active, compared to 74% for the surgery-alone arm ( $p > 0.001$ ). Sexual satisfaction and dyspareunia were worse in the radiotherapy group.<sup>41</sup> All premenopausal women receiving pelvic radiotherapy will undergo a premature menopause. Fertility may be affected in men.

Preoperative radiotherapy has been associated with an increase in postoperative complications in some studies.<sup>28,29</sup> A follow up of patients in the Swedish Rectal Cancer Trial revealed an increase in median bowel frequency, incontinence and urgency as well as emptying difficulties for the irradiated group.<sup>42</sup> Thirty per cent of the irradiated group reported impairment of social life because of bowel dysfunction, as compared to 10% with surgery alone ( $p < 0.001$ ). Long-term data from the Stockholm II trial demonstrated an increased risk of death within six months of surgery (5% vs 1%), deep vein thrombosis, cardiovascular events, bowel damage and incontinence in those who had preoperative radiotherapy.<sup>30</sup> The recent toxicity report from the Dutch Colorectal Cancer Group trial of TME with or without preoperative short-course radiotherapy found that irradiated patients that underwent abdominoperineal resection had more blood loss and more complications in perineal wound healing.<sup>40</sup>

Mortality from non-cancer causes was greater in the radiotherapy arms of older studies and those that used two field techniques (see above). Recent series using modern techniques report postoperative mortality rates of 2–4%.<sup>38</sup> Long-term morbidity and mortality are significantly increased in patients over 75. Technique is important and multiple fields are mandatory. Manoeuvres that reduce the amount of small bowel in the treatment volume are associated with lower morbidity. These include the prone treatment position, belly boards, and infrequently-used surgical procedures such as omental slings or dextron meshes.<sup>17</sup>

### **16.11.2 Chemotherapy**

Acute complications of 5-FU-based chemotherapy are mouth ulcers, diarrhoea and nausea. Marrow suppression is typically mild, but significant myelo suppression is seen in a small number of patients. Uncommonly, palmar plantar erythema or skin photosensitivity may develop. Complete alopecia is very uncommon.

### **16.11.3 Combined modality therapy**

Both acute and late morbidity are increased with CMT. In the management of individual patients, this should be considered when discussing treatment recommendations. In the GITSG study,<sup>4</sup> severe non-haematological toxicities occurred in 35% of patients with CMT, compared to 16% for radiotherapy alone, or 15% for chemotherapy alone. Leucopenia (white cell count <2000/ml) occurred in 26% of the CMT group, compared with 2% for radiotherapy alone and 13% for chemotherapy alone.

Krook et al<sup>6</sup> also found haematological toxicity to be increased when CMT was compared with radiotherapy alone. Protracted venous infusion was associated with significantly more diarrhoea (24%) than bolus 5-FU (14%,  $p < 0.01$ ), but less leucopenia (2% vs 11%,  $p < 0.01$ ).<sup>8</sup>

Rectal function may also be adversely affected by CMT. In a survey of patients entered into the Mayo randomised trial,<sup>43</sup> those who received CMT had significantly higher rates of occasional and frequent incontinence (39% vs 7% and 17% vs 0% respectively). There was also an increased frequency of bowel motions, loose stools and urgency. Future studies of adjuvant therapy should include quality of life and rectal function in the trial endpoints.

## **16.12 Costs of adjuvant therapy**

Simulation methods have been used to model the costs and benefits associated with adjuvant chemotherapy for Colorectal Cancer. In general, these studies demonstrate favourable cost-utility for adjuvant chemotherapy. Cost estimates per quality adjusted life year (QALY) gained vary from A\$370/QALY to A\$17,500/QALY for the one Australian study.<sup>44</sup>

There are two cost-effectiveness studies that address adjuvant radiotherapy for rectal cancer. The marginal cost of postoperative radiotherapy and 5-FU was US\$8700 per life year gained, and the extra cost for infusional chemotherapy was US\$950 per life year gained.<sup>45</sup> Cost analysis over eight years of 98 patients enrolled onto the Swedish Rectal Cancer trial of short-course preoperative radiotherapy found the cost of a life-year saved was US\$3654.<sup>46</sup> With sensitivity analysis for different rates of recurrence and costs related to complications, this figure could vary up to US\$15,228. These compare favourably with many widely accepted health care interventions.

## **16.13 Is adjuvant therapy necessary with optimal resectional surgery?**

The body of randomised trials covers a long period in which both surgical and adjuvant techniques have evolved considerably. It has been suggested that very low local recurrence rates can be achieved by optimum expert surgery with clear resection analysis,<sup>47,48</sup> including those series employing total mesorectal excision.<sup>49,50</sup> Analysis of the effect of surgeon variation was performed on patients entered

into the randomised Stockholm study.<sup>51</sup> They found that even for some centres that had lower rates of recurrence, these rates of recurrence and survival could be further improved by the addition of preoperative radiotherapy.

The Dutch Colorectal Cancer Group has published the early results of a randomised study of perioperative short-course radiotherapy combined with total mesorectal excision in rectal cancer. The study enrolled 1805 subjects.<sup>52</sup> In the 1748 patients where a macroscopic complete local resection was carried out, radiotherapy was associated with a local recurrence rate at two years of 2.4% compared to 8.2% with surgery alone ( $p < 0.001$ ). This implies treatment of 17 patients to prevent a recurrence. A recent update at three and a half years found respective recurrence rates at 3.4% compared to 10.1%.<sup>41</sup> The preoperative radiotherapy did not compensate for margins less than 1 mm, but for margins greater than 2 mm, the local recurrence rates were 0.4% versus 5.8%. The radiotherapy did not appear to benefit high rectal cancers more than 10 cm from the anal verge. Preoperative radiotherapy reduces the risk of local recurrence in patients with rectal cancer who undergo a total mesorectal excision. “The Dutch trial” included patients with high risk as well as low risk rectal cancer (stages I, II, III and up to 15 cm from anal verge). The benefit of adjuvant therapy is less with better surgery. No differences in distant recurrence rate or overall survival have yet been seen at this interval of follow up.

#### **16.14 Conclusions and future directions**

For patients with high-risk rectal cancer there are clear benefits in having adjuvant therapy. The nature of the optimum treatment is still uncertain. Postoperative chemotherapy and radiotherapy significantly improves survival and local control by about 10% in absolute terms. The major area of improvement with protracted venous infusion has been a reduction in deaths from metastases. Any postoperative adjuvant therapy program should include radiotherapy and chemotherapy. Currently, there are good data only for postoperative CMT. Preoperative radiotherapy alone using modern techniques at biologically effective doses may also improve survival. Data directly comparing this with postoperative CMT are pending. These studies are continuing, as are others integrating the use of new chemotherapy agents such as the oral fluoropyrimidines, raltitrexed, oxaliplatin and irinotecan into the radiation protocols.

## References

1. Fu KK. Interactions of chemotherapeutic agents and radiation. In: Meyer JL, Vaeth JM (eds.) Radiotherapy/chemotherapy interactions in cancer therapy. Front Radiation Therapy Oncology. 26 edn. Basel: Karger, 1992.
2. Bokey EL, Chapuis PH, Dent OF, et al. Factors affecting survival after excision of the rectum for cancer: a multivariate analysis. *Dis Colon Rectum* 1997; 40: 3–10.
3. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 1988; 80: 21–9.
4. Gastrointestinal Tumor Study Group (GSTG). Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 1985; 312: 1465–72.
5. Tveit KM, Guldvog I, Hagen S, et al. Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer. Norwegian Adjuvant Rectal Cancer Project Group. *Br J Surg* 1997; 84: 1130–5.
6. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991; 324: 709–15.
7. Gastrointestinal Tumor Study Group (GTSG). Radiation therapy and fluorouracil with or without semustine for the treatment of patients with surgical adjuvant adenocarcinoma of the rectum. *J Clin Oncol* 1992; 10: 549–57.
8. O’Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994; 331: 502–7.
9. Tepper JE, O’Connell MJ, Petroni GR, et al. Adjuvant postoperative fluorouracil-modulated chemotherapy combined with pelvic radiation therapy for rectal cancer: initial results of intergroup 0114. *J Clin Oncol* 1997; 15: 2030–9.
10. Tepper JE, O’Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control — final report of intergroup 0114. *J Clin Oncol* 2002; 20: 1744–50.
11. Fountzilas G, Zisiadis A, Dafni U, et al. Postoperative radiation and concomitant bolus fluorouracil with or without additional chemotherapy with fluorouracil and high-dose leucovorin in patients with high-risk rectal cancer: a randomized phase III study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol* 1999; 10: 671–6.
12. Lee JH, Lee JH, Ahn JH, et al. Randomized trial of postoperative adjuvant therapy in stage II and III rectal cancer to define the optimal sequence of chemotherapy and radiotherapy: a preliminary report. *J Clin Oncol* 2002; 20: 1751–8.
13. Cafiero F, Gipponi M, Lionetto R. Randomised clinical trial of adjuvant postoperative RT vs. sequential postoperative RT plus 5-FU and levamisole in patients with stage II–III resectable rectal cancer: a final report. *J Surg Oncol* 2003; 83: 140–6.
14. Wolmark N, Wieand HS, Hyams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst* 2000; 92: 388–96.

15. Boulis-Wassif S, Gerard A, Loygue J, Camelot D, Buyse M, Duez N. Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Trial of the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *Cancer* 1984; 53: 1811–8.
16. Haie C, Pejovic MH, Gerbaulet A, et al. Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. *Radiother Oncol* 1988; 11: 101–12.
17. Smalley S, Evans R. Radiation morbidity to the gastrointestinal tract and liver. In: Plowman P, McElwain T, Meadows R (eds.) *Complication of cancer management*. Oxford: Butterworth Heinman, 1991; Ch.18.
18. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. *Radiother Oncol* 2004; 72: 15–24.
19. Bosset JF, Calais G, Mineur L, et al. Does the addition of chemotherapy (CT) to preoperative radiotherapy (preopRT) increase the pathological response in patients with resected rectal cancer: Report of the 22921 EORTC phase III trial. *Proc Am Soc Clin Onco* 2004; 23: Abstract 3504.
20. Bosset JF, Calais G, Daban A, et al. Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group. *Eur J Cancer* 2004; 40: 219–24.
21. Hyams DM, Mamounas EP, Petrelli N, et al. A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of National Surgical Breast and Bowel Project Protocol R-03. *Dis Colon Rectum* 1997; 40: 131–9.
22. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; 351: 1731–40.
23. Roh M, Petrelli N, Wieand Sea. Phase III randomized trial of preoperatives versus postoperative multimodality therapy in patients with carcinoma of the rectum (NSABP R03). *Proc Am Soc Clin Oncol* 2001; 20: Abstract 490.
24. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer. Why we still don't know. *JAMA* 1988; 259: 3571–8.
25. Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. *JAMA* 2000; 284: 1008–15.
26. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001; 20;358: 1291–304.
27. Figueredo A, Germond C, Taylor B. Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer. *Cancer Care Ontario Practice Guidelines Initiative* 2000; Practice Guideline No.2–3.
28. National Health Service Executive. *Improving outcomes in colorectal cancer: the research evidence*. Weatherby, United Kingdom: Department of Health, 1998.

29. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; 336: 980–7.
30. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. *Cancer* 2001; 92: 896–902.
31. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol* 1999; 17: 2396–402.
32. Glehen O, Chapet O, Adham M, Nemoz JC, Gerard JP. Long-term results of the Lyons R90-01 randomized trial of preoperative radiotherapy with delayed surgery and its effect on sphincter-saving surgery in rectal cancer. *Br J Surg* 2003; 90: 996–8.
33. Marijnen CA, Nagtegaal ID, Klein KE, et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001; 19: 1976–84.
34. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993; 36: 564–72.
35. Barton M. Tables of equivalent dose in 2 Gy fractions: a simple application of the linear quadratic formula. *Int J Radiat Oncol Biol Phys* 1995; 31: 371–8.
36. Sakamoto J, Hamada C, Kodaira S, Nakazato H, Ohashi Y. Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomized trials. *Jpn J Clin Oncol* 1999; 29: 78–86.
37. Zoetmulder F, Taal B, van Tinteren H. Adjuvant 5FU plus levamisole improves survival in stage II and III Colonic cancer, but not in rectal cancer. Interim analysis of the Netherlands Adjuvant Colorectal Cancer Project (NACCP). *Proc Am Soc Clin Onco* 1999; 18.
38. Ooi BS, Tjandra JJ, Green MD. Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. *Dis Colon Rectum* 1999; 42: 403–18.
39. Gelber RD, Goldhirsch A, Cole BF, Wieand HS, Schroeder G, Krook JE. A quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis of adjuvant radiation therapy and chemotherapy for resectable rectal cancer. *J Natl Cancer Inst* 1996; 88: 1039–45.
40. Marijnen CA, Kapiteijn E, van de Velde CJ, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2002; 20: 817–25.
41. Marijnen CA, Kapiteijn E, van de Velde CJ, et al. Side effects after preoperative radiotherapy followed by TME surgery. *Proc Euro Soc Ther Radio Oncol* 2002; 21.
42. Dahlberg M, Glimelius B, Graf W, Pahlman L. Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study. *Dis Colon Rectum* 1998; 41: 543–9.
43. Kollmorgen CF, Meagher AP, Wolff BG, Pemberton JH, Martenson JA, Ilstrup DM. The long-term effect of adjuvant postoperative chemoradiotherapy for rectal carcinoma on bowel function. *Ann Surg* 1994; 220: 676–82.

44. Smith RD, Hall J, Gurney H, Harnett PR. A cost-utility approach to the use of 5-fluorouracil and levamisole as adjuvant chemotherapy for Dukes' C colonic carcinoma. *Med J Aust* 1993; 158: 319–22.
45. Lee JHA. Cost-effectiveness analysis of adjuvant therapies for resected adenocarcinoma of the rectum. *Int J Radiat Oncol Biol Phys* 1997; 39: Abstract 235.
46. Dahlberg M, Stenborg A, Pahlman L, Glimelius B. Cost-effectiveness of preoperative radiotherapy in rectal cancer: results from the Swedish Rectal Cancer Trial. *Int J Radiat Oncol Biol Phys* 2002; 54: 654–60.
47. Killingback M, Baron P, Dent OF. Local recurrence after curative resection of cancer of the rectum without total mesorectal excision. *Dis Colon Rectum* 2001; 44: 473–86.
48. Bokey EL, Ojerskog B, Chapuis PH, Dent OF, Newland RC, Sinclair G. Local recurrence after curative excision of the rectum for cancer without adjuvant therapy: role of total anatomical dissection. *Br J Surg* 1999; 86: 1164–70.
49. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; 20;341: 457–60.
50. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Arch Surg* 1998; 133: 894–9.
51. Holm T, Johansson H, Cedermark B, Ekelund G, Rutqvist LE. Influence of hospital- and surgeon-related factors on outcome after treatment of rectal cancer with or without preoperative radiotherapy. *Br J Surg* 1997; 84: 657–63.
52. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345: 638–46.

