Locally Advanced Rectal Cancer: What Is the Evidence for Induction Chemoradiation?

ROB GLYNNE-JONES, MARK HARRISON

Centre for Cancer Treatment, Mount Vernon Hospital, Northwood, Middlesex, United Kingdom

Key Words. Rectal cancer • Neoadjuvant • Chemoradiation • Sphincter-sparing surgery
Circumferential resection margin • Pathological complete response

Disclosure: R.G.-J. has received honoraria for lectures and advisory boards and has been supported in attending international meetings by Merck, Pfizer, Sanofi-Aventis, and Roche. He has also received unrestricted grants for research from Merck, Sanofi-Aventis, and Roche. M.H. has received honoraria for lectures and advisory boards and has been supported in attending international meetings by Merck, Astra-Zeneca, Pfizer, Sanofi-Aventis, and Roche.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Interpret the results of the relevant randomized trials of neoadjuvant induction chemoradiation from Europe and the U.S.
2. Explain why induction chemoradiation is preferred over postoperative adjuvant chemoradiation.
3. Discuss the rationale for using neoadjuvant induction chemoradiation in rectal cancer.

ABSTRACT

The concept of spatial cooperation in neoadjuvant chemoradiation (CRT) for locally advanced rectal cancer is attractive. Chemotherapy may, as a component of CRT, not only act as a radiosensitizing agent but also potentially eradicate distant micrometastases. Recent trials have demonstrated that the addition of concurrent 5-fluorouracil (5-FU)-based chemotherapy to radiation increases the pathological complete response rate, and reduces local recurrence, but as yet, a survival advantage has not been observed.

Aims. This review aims to examine the evidence for induction CRT in locally advanced rectal cancer. The endpoints of pathological complete response, a negative circumferential margin, sphincter-sparing surgery, local control, disease-free survival (DFS), and overall survival (OS) are examined, as are acute and late morbidity, surgical complications, and late functional results.

Methods. The information to produce this review was compiled by searching PubMed and MEDLINE for English language articles published until April 2007. The search term included “induction, neoadjuvant, chemotherapy, radiotherapy, chemoradiation, combined modality” in association with rectal cancer.

Conclusions. CRT in the European randomized trials of rectal cancer improves tumor downstaging, pathological complete response, and local control over radiotherapy alone, but does not translate into a benefit in terms of longer DFS or OS, or a higher chance of sphincter preservation. Metastatic disease remains a significant problem, which provides a strong rationale for the integration of a second cytotoxic drug, or biologically targeted agents. The Oncologist 2007;12:1309–1318
INTRODUCTION
The potential for a curative surgical resection is the most important component of the multimodality management of rectal cancer. Techniques to improve or allow surgical resection are of increasing importance. Recent randomized trials have endorsed the role of short-course preoperative radiotherapy (SCPRT) and long fractionation chemoradiation (CRT) in resectable rectal cancer [1–5].

Systematic reviews/meta-analyses have examined the role of radiotherapy (RT) in resectable rectal cancer [6–8]. These meta-analyses concluded that the data favored preoperative RT, rather than postoperative RT, and that a biologically equivalent dose of >30 Gy is more effective in reducing local relapse. A recent Cochrane review [9] further supported these findings, but it did not confirm a lower mortality rate or a sphincter-sparing benefit from preoperative RT, and it highlighted the risks of more pelvic and perineal infections, and worse late rectal and sexual function.

Patients with rectal cancer can be divided into three main groups. Most patients have easily resectable cancers. Patients in the next category have borderline resectable disease, that is, “threatened” or minimally breached circumferential margins as predicted by magnetic resonance imaging (MRI). Finally, there are patients with fixed unresectable cancers, for whom surgery is not possible without leaving tumor within the pelvis. This group may, after CRT, become resectable in the future.

In clinically resectable cancers, residual microscopic disease after surgery can persist either at or beyond the surgical resection margins, within lymph nodes, or in distant metastatic sites. In locally advanced rectal cancer (LARC), lymph node involvement and positive resection margins are common, leading to local recurrence and metastatic disease. Both RT and chemotherapy have been advocated as adjuvant strategies to eradicate cells at the margins or in discontinuous areas of tumor within the pelvis, in nodes, or in distant metastatic sites to improve both local control and also overall survival (OS).

In borderline unresectable rectal cancers, a high risk for local recurrence and poor survival have been reported with preoperative RT alone [10, 11]. This finding illustrates the need for combining therapies that integrate concurrent chemotherapy, RT, and surgery. Chemotherapy may, as a component of CRT, both act as a radiosensitizing agent and also potentially eradicate distant micrometastases. This strategy has been investigated with different agents in a number of phase I/II and III trials of preoperative neoadjuvant CRT.

In the 1980s, preoperative assessment and clinical staging in rectal cancer were limited to digital rectal examination and surgical assessment of tumor “fixity.” There was no widely accepted and validated imaging method of defining either LARC or unresectable disease. Postsurgical histopathological review offered the best prediction of outcome. Consequently, most randomized trials tested chemotherapy, RT, and CRT in the postoperative adjuvant setting. The efficacy of this approach was then extrapolated to the preoperative setting. The advent of MRI now allows an accurate prediction as to whether the surgical resection margin will be clear or involved by tumor [12]. MRI also appears to be the most accurate method of categorizing tumor (T) stage preoperatively in LARC. This permits selection of patients who should benefit from preoperative CRT.

Sequential dose-finding studies from France [13] and the U.S. [14] confirmed the optimum dose of 5-fluourouracil (5-FU) and both low-dose folinic acid and high-dose folinic acid in combination with RT. Others integrated a prolonged venous infusion of 5-FU [15], which, in later studies, appeared to have higher efficacy [16]. The use of infusional 5-FU allows both RT and chemotherapy to be delivered near their individual maximum doses with regard to acute and late toxicities. However, recently, the oral fluoropyrimidines have been compared with 5-FU in these regimens [17, 18] and are likely to replace i.v. schedules [19].

In randomized phase III studies, the addition of 5-FU to preoperative RT produces a higher pathological complete response (pCR) rate over RT alone [20], and there is evidence for better locoregional control [4, 5], but no improvement in disease-free survival (DFS) or OS has been demonstrated. Distant metastases occur in at least 30% of cases [4, 5, 21]. Nevertheless, because of the better pCR and locoregional control rates, 5-FU–based preoperative CRT followed by total mesorectal excision has become the standard of care in patients with LARC.

More recently, oxaliplatin and irinotecan have been explored within a CRT schedule to increase tumor shrinkage prior to surgery and potentially mirror the success of oxaliplatin in dealing with distant micrometastases in colon cancer [22].

Current CRT schedules have been empirically developed. There is no widely accepted optimal schedule, sequence, and timing, either in terms of the drugs or RT dose. Radical pelvic RT at doses of 55–60 Gy is associated with high levels of normal tissue damage, including small bowel injury, rectal bleeding, impaired sphincter function, vaginal stenosis, nerve dysfunction, and sacral fractures. Lower RT doses, 40–50 Gy in 1.8- to 2.0-Gy fractions, are associated with a good tumor response and with more acceptable levels of late morbidity. These doses have become established
as the current standard in rectal cancer, but hyperfractionation with acceleration or concomitant boost techniques have also been considered [23, 24].

This review aims to examine the evidence for induction CRT in LARC. In total, 162 phase I/II or retrospective studies and 12 phase III trials were identified. The endpoints of pCR, a negative circumferential margin, local control, DFS, and OS are scrutinized, as are acute and late complications, surgical complications, and late functional results.

MATERIALS AND METHODS
The information used to produce this review was compiled by searching PubMed and MEDLINE for English language articles published until April 2007. The search term included “induction, neoadjuvant, chemotherapy, radiotherapy, chemoradiation, combined modality” in association with rectal cancer. Papers highlighted by the search were reviewed and prioritized according to relevance of content. Full articles were obtained, and references were checked for additional appropriate references.

RESULTS
Unresectable Rectal Cancer: RT Appears Insufficient
For those patients in whom MRI suggests that the surgical resection margin is involved with tumor, or resection margins are “threatened” or “unsafe,” preoperative RT, either alone or ideally in combination with chemotherapy, is recommended. Preoperative RT without chemotherapy for such locally advanced tumors using doses of 45–50 Gy was reported [25] to be capable of downstaging 79% of patients, which resulted in high resection rates being achieved. This assessment was based on digital rectal examination and fixation, and lacks the accuracy of MRI scanning. Despite complete resection, the 5-year survival rate was only 18%, and these patients continued to have a high risk for local failure. Patients who remain unresectable after RT have an even poorer overall median survival duration of 8–10 months [25, 26].

Unresectable Rectal Cancer: Randomized Trials of CRT Versus RT Alone
Historical randomized studies of RT versus CRT in unresectable rectal cancer in general used poor methodology, were poorly controlled, and were inadequately reported [27–29]. Within the last decade, a single small phase III study [11] randomized only 70 patients with fixed inoperable rectal cancer. The CRT delivered an alternating hyperfractionated split-course regimen to a total dose of 40 Gy over 8 weeks in combination with methotrexate, 5-FU, and folinic acid. The trial established an advantage in terms of resectability and local control for the CRT arm. The local recurrence-free survival rates at 5 years were 35% versus 66% (p = .03) and the 5-year survival rates were 18% versus 29% (nonsignificant) for RT versus CRT, respectively. These data lend support to the view that CRT is more effective than RT. A recent abstract also supports the use of 5-FU–based CRT in this setting [30].

However, intensification of the CRT component for patients with T3N0 or T2N0 rectal cancer may achieve a higher pCR rate without a longer OS [5]. If we are achieving very low levels of local recurrence in this group of patients, the risk for metastatic disease will almost certainly predominate.

Facilitating Sphincter-Sparing Procedures
The low position of some rectal cancers (3–6 cm from the anal verge) and bulky anterior tumors in obese men with a narrow pelvis render surgery technically demanding if sphincter-sparing surgery (SPSS) is the aim. Long-course CRT followed by a planned delay prior to surgery, may result in shrinkage back from the distal margin, and enable SPSS. Impressive results appear to have been achieved in phase II studies with CRT [31, 32], and long-term follow-up has confirmed an excellent outcome if marked shrinkage of the distal tumor margin is demonstrated [33]. Subset analysis of randomized trials suggests that preoperative CRT offers a 10% [34] or even a 20% [2] higher chance overall of achieving SPSS. Whether a surgeon attempts SPSS depends on many factors, including tumor size, location, and accessibility, surgical experience and training, and the individual’s philosophy regarding risk. Interestingly, a randomized trial investigating SCPRT against preoperative CRT with the endpoint of SPSS showed no difference [3]—surgeons did not change their initial decision. A further recent randomized study, presented in abstract form [35], demonstrated a high rate of conservative surgery for low rectal cancers within 2 cm of the levator ani whether RT with a high dose rate boost or 5-FU–based CRT (45 Gy in 25 daily fractions) was administered. A systematic review of randomized trials of RT or CRT failed to confirm that anterior resection was more likely even after downsizing [36]. In conclusion, the validity of the concept that neoadjuvant CRT allows more downstaging and facilitates SPSS remains unproven, and data on the late function of the sphincter mechanism following CRT remain elusive.

When CRT is used to downstage a rectal tumor and facilitate SPSS, a surgical distal margin of ≤1 cm has been suggested to be quite safe [37]. However, a recent paper,
using patients from a Polish trial, showed that approximately 10% of rectal cancers have distal intramural spread of >5 mm following either RT or CRT. The Polish study demonstrated that discontinuous spread is more frequent following CRT than following SCPR. This reflects tumor response following CRT and an interval of 6 weeks to definitive surgery. A consequence of this is that discontinuous cancer foci could reside in the distal rectal stump beyond the tissue donuts used to establish clear lateral margins [38]. For those patients who fail to respond to CRT but still proceed to have SPSS, there is a much higher risk for recurrence [39].

Randomized Trials in Resectable Rectal Cancer

Preoperative CRT Versus Postoperative CRT

A common randomized trial design compares preoperative CRT with postoperative CRT. There are three trials in this setting—the National Surgical Adjuvant Breast and Bowel Project (NSABP) R03, the Intergroup trial INT-0147, and the German CAO/ARO/AIO-94 trial.

NSABP R03. The NSABP R03 trial was initiated in 1993 with the primary endpoint of OS. It closed early because of poor accrual after randomizing only 267 patients. The trial mandated an RT dose of 45 Gy, and included a neoadjuvant chemotherapy component delivered weekly for 6 weeks until the start of the CRT. Few details are published [34, 40, 41], but a greater proportion of patients who had SPSS and were disease free at 1 year was reported in the preoperative arm. This advantage was at the expense of more frequent acute toxicity.

Intergroup trial INT-0147. The Intergroup INT-0147 trial also closed early because of poor accrual, after randomizing only 53 patients. The planned RT dose was 50.4 Gy.

The German CAO/ARO/AIO-94 Trial. The German CAO/ARO/AIO-94 study was initiated in 1995 to investigate preoperative 5-FU–based CRT versus postoperative combined-modality treatment for stage II/III resectable rectal cancer. The primary endpoints were OS and relapse-free survival and locoregional and distant control. The secondary endpoints included the rates of curative (R0) resections, SPSS, toxicity, and surgical complications. Published data show no greater surgical morbidity for CRT [2].

The locoregional failure rate was lower with preoperative CRT—6%, compared with 13% for the postoperative arm. However, neither the DFS nor OS rate, nor the overall abdominoperineal excision of the rectum (APER) rate, was greater in the preoperative arm. On subset analysis, a slightly higher SPSS rate was noted for those patients in whom the surgeon initially felt that an APER was inevitable. Interpretation of the results of this trial is complicated by their use of the Zelen method of randomization, which may have biased the borderline resectable patients to be withdrawn from the postoperative arm. In addition, compliance was low for the postoperative arm, and only 54% received the full RT dose, compared with 92% in the preoperative arm. Both acute and late toxicities appeared to be less frequent in the preoperative arm, but it should be noted that a 5.4-Gy radiation boost was mandated in the postoperative arm [42]. Patients in the postoperative arm would have received a 10% higher RT dose. RT dose escalation has rarely been evaluated in rectal cancer because of the constraints of acute and late toxicities. The Lyon R96–02 study used contact therapy to boost external beam RT with an extra 85 Gy in three fractions [43]. Despite a higher complete clinical response rate, and a higher SPSS rate, there was no difference in terms of locoregional failure or OS at 2 years. Dose escalation prior to surgical resection seems an illogical strategy to improve local control. If surgery can achieve a good quality mesorectal excision, then recurrences are likely to lie outside this volume. Consequently, dose escalation of RT to the primary tumor seems unlikely to achieve much more than a higher rate of acute toxicity.

Preoperative CRT Versus RT Alone

The second strategy has been to randomize between preoperative neoadjuvant CRT and an identical schedule of preoperative RT alone. One historical and two other recent larger studies have used this design.

Boulis-Wassif et al. (1984) [44]. This European Organization for Research and Treatment of Cancer (EORTC) study randomized 339 patients with resectable rectal cancer between preoperative RT alone followed by surgery and preoperative RT combined with 5-FU followed by surgery [44]. Only 247 patients were eligible for analysis. The primary endpoint was OS. The RT protocol used large, parallel opposed “chimney” fields, which would not be acceptable today. There was an imbalance in the T staging in favor of the RT group. No difference was observed in local recurrence or DFS. Patients who received the addition of 5-FU actually fared worse, and had a lower 5-year OS rate of borderline significance (p = .06) However, little information relevant to contemporary staging, planning, and techniques to reduce toxicity can be gleaned from this study.
EORTC 22921 Trial. The EORTC 22921 trial was initiated in 1993 and enrolled 1,011 patients with T3/T4 resectable rectal cancer over 11 years, with endpoints of OS and DFS. That study examined the role of the timing and duration of 5-FU–based chemotherapy both in combination with preoperative RT, and in the postoperative adjuvant setting. In a two-by-two factorial design, patients were randomized to receive preoperative RT (45 Gy in 25 fractions) or RT and an additional two courses of 5-FU and folinic acid. A second randomization allocated four courses of postoperative chemotherapy with 5-FU and folinic acid or observation alone.

The trial stratified according to T stage, distance to the anal verge, sex, and institution. Total mesorectal excision (TME) was only recommended in 1999. Compliance with the preoperative chemotherapy was high, but only 42.9% adhered to the postoperative component of chemotherapy. Not surprisingly, the toxicity was higher in the CRT arm [45].

The pCR rate was significantly higher in the CRT arm and it appeared to offer a marginal benefit in terms of a higher SPSS rate (55.6% versus 52.4%; p = .05). The loco-regional failure rates at 5 years were 17% with RT and 8% with CRT. With a median follow-up of 5.4 years, no significant difference was seen in DFS or OS between groups that received RT or CRT and those who received further adjuvant chemotherapy postoperatively (p = .12). A major conclusion of the study and an intriguing finding is that if RT is given, then 5-FU–based chemotherapy, whether administered concurrently with RT prior to or following surgery, confers a significant advantage in terms of local control.

Fédération de Francophone de Cancérologie Digestive FFCD 9203 Trial. The FFCD 9203 trial randomized 762 patients with T3/T4 resectable rectal cancer between preoperative RT and preoperative CRT to a dose of 45 Gy. The same chemotherapy regimen as in the EORTC trial (5-FU, 350 mg/m², and folinic acid) was combined with the same dose of RT (45 Gy in 25 fractions). The primary endpoint was OS. In contrast to the EORTC study, patients were mandated to receive postoperative adjuvant chemotherapy, but compliance was poor and only 70% of patients received it.

Compliance in the preoperative CRT arm was 93%. The rate of grade 3 or 4 acute toxicity was significantly higher in the chemotherapy arm (14.6%, versus 2.7% for RT alone; p < .05). Surgical complications, including anastomotic leaks, were similar in the two arms. Similar to the EORTC trial, the pCR rate was higher with CRT, 11.4%, versus 3.6%. There was no impact of CRT on sphincter preservation. A lower local recurrence rate was observed, 8.1%, versus 16.5%. Again, neither DFS nor OS was significantly different in the two groups. A similar number of patients in each arm developed metastatic disease (99 following RT and 107 following CRT). Interestingly, this trial claims that, from 1999, the majority of patients were treated with TME style surgery and the local recurrence rate was reduced to 14% for RT alone and 5% for CRT.

The Polish Trial. The Polish study [3] randomized 316 patients between preoperative long fractionation CRT (50.4 Gy in 28 daily fractions with 5-FU and folinic acid) and SCPRT. The trial aimed to evaluate whether long course CRT with an interval to allow response could facilitate SPSS when compared with five fractions of short-course RT and immediate surgery. SPSS was the main endpoint, but this trial is important in that it is the first time that a long fractionation CRT regimen has been directly compared with SCPRT. The pCR rate was 15% in the CRT arm, compared with only 1% in the SCPRT arm, but this did not impact sphincter preservation—61% in the SCPRT arm versus 58% in the CRT arm (p = .57). Crucially, this trial reported a difference in curative resection rates for the two strategies. A circumferential resection margin of ≤1 mm was observed in 4%

---

**Table 1.** pCR, LRC, rate of metastases, and OS rate from the chemoradiation arms of recently published randomized trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>n of patients</th>
<th>pCR</th>
<th>5-Yr LRC</th>
<th>Metastases</th>
<th>5-Yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAA/ARO/AIO-94, Sauer et al. (2004) [2]</td>
<td>394</td>
<td>8%</td>
<td>6%</td>
<td>36%</td>
<td>4-yr, 74%</td>
</tr>
<tr>
<td>Polish trial, Bujko et al. (2004) [3]</td>
<td>157</td>
<td>16%</td>
<td>4-yr, 15.6%</td>
<td>34.6%</td>
<td>4-yr, 66%</td>
</tr>
<tr>
<td>FFCD 9203, Gerard et al. (2006) [4]</td>
<td>375</td>
<td>11.4%</td>
<td>8%</td>
<td>36%</td>
<td>66%</td>
</tr>
<tr>
<td>EORTC 22921, Bosset et al. (2005, 2006) [5, 20]</td>
<td>505</td>
<td>13.4%</td>
<td>8.7%</td>
<td>34%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; FFCD, Fédération de Francophone de Cancérologie Digestive; LRC, locoregional control; OS, overall survival; pCR, pathological complete response rate.
of patients after CRT versus 13% of patients after SCPRT. The local failure rate was 11% after SCPRT versus 16% in the CRT arm, although these are not significantly different. There was no difference in DFS and OS.

Recent published randomized trials of CRT appear to have remarkably homogeneous populations, which have led to strikingly similar outcomes (Table 1).

**Trials in Progress.** The Trans Tasman Oncology Group (TROG 01–04) completed a study in 2006 that randomized 326 patients with T3 clinically resectable cancers between preoperative short fractionation RT (25 Gy in five fractions over 5 days) and CRT (50.4 Gy in 28 fractions with continuous infusion 5-FU). The primary endpoint is local recurrence. Results are awaited.

A summary of trial results is appended in Tables 2–4.

**Preoperative Toxicity**
The acute side effects of pelvic RT are self-limiting and usually resolve within 4–6 weeks of completing treatment. In addition, CRT is associated with both toxic deaths and a small but significant higher rate of death from noncancer causes [40, 46]. Acute toxicity should therefore be rigorously assessed using validated instruments that can distinguish small but clinically relevant differences in toxicity. We are not aware of such an instrument in rectal cancer, although this approach has been successfully adopted for CRT trials in head and neck cancer [47].

**Rectal Function After CRT**
Few nonrandomized studies provide mature follow-up data [48, 49]. Despite a median follow-up of 54 and 38 months, respectively, these studies offer no information on late bowel, bladder sphincter, and sexual function. Hence, data are sparse regarding the late radiation effects on anal sphincter function, compliance of the rectal reservoir, fashioned colonic pouches, and other soft tissues within the pelvis. Functional outcome in rectal cancer following sphincter-sparing treatment is determined by surgical parameters such as the height of the anastomosis and the type of reconstruction. The predicted late complications of pelvic RT depend on the volume, radiation field, overall treatment time, fraction size, total dose, and technique, but the most crucial factor is the volume of the small bowel in the radiation field.

**Surgical Complications: Anastomotic Leaks/Pelvic Sepsis/Wound Healing**
There is no universally accepted definition of anastomotic leaks [50], and the majority of studies seem to use a combination of both the clinical features and radiological inves-
### Table 3. Unresectable rectal cancer: trial design, preoperative radiation versus chemoradiation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>n of patients</th>
<th>Randomization</th>
<th>n</th>
<th>TME</th>
<th>Primary endpoint</th>
<th>Local recurrence</th>
<th>Metastases</th>
<th>OS</th>
<th>DFS</th>
<th>pCR</th>
<th>Pathology (CRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frykholm et al. (2001) [11]</td>
<td>1988-2001, 13 yrs</td>
<td>70</td>
<td>46 Gy (23 fx) versus 5-FU/MTX + split</td>
<td>27 versus 29</td>
<td>No/No</td>
<td>Curative resection</td>
<td>12/27 = 17% versus 5/29 = 44%</td>
<td>Not stated</td>
<td>18% versus 29% (NS)</td>
<td>Not stated</td>
<td>1/27 (4%) versus 5/29 (12%)</td>
<td>36% versus 26%; not Quirke</td>
</tr>
<tr>
<td>Braendigen et al [30]</td>
<td>1996-2003</td>
<td>208</td>
<td>50 Gy RT versus 50 Gy CRT</td>
<td>94 versus 88</td>
<td>Yes/Yes</td>
<td>71 (65%) versus 78 (81%)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>7 (6%) 19 (19%)</td>
<td>?Yes</td>
</tr>
</tbody>
</table>

**Abbreviations:** 5-FU, 5-fluorouracil; CRM, circumferential resection margin; CRT, chemoradiation; DFS, disease-free survival; fx, fractions; MTX, methotrexate; NS, not significant; OS, overall survival; pCR, pathological complete response; RT, radiotherapy; TME, total mesorectal excision.

### Table 4. Resectable rectal cancer: trial design, preoperative versus postoperative chemoradiation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>n of patients</th>
<th>Randomization</th>
<th>n</th>
<th>TME</th>
<th>Primary endpoint</th>
<th>Local recurrence</th>
<th>Metastases</th>
<th>OS</th>
<th>DFS</th>
<th>pCR</th>
<th>Pathology (CRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter 147 (No data)</td>
<td>5 yrs</td>
<td>53</td>
<td>Preop 50.4 Gy + FUFA versus postop 50.4 Gy + FUFA</td>
<td>No data</td>
<td>No</td>
<td>OS</td>
<td>No data, closed early</td>
<td>74% versus 66% at 5 yrs</td>
<td>64% versus 53% at 5 yrs</td>
<td>16% versus 0%</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>NSABP R03, Hyams et al. (1997) [40], Roh et al. (2001), (2004) [34, 41]</td>
<td>1993-2003, 10 yrs</td>
<td>267</td>
<td>Preop 45 Gy + FUFA versus postop 45 Gy + FUFA</td>
<td>130 versus 137</td>
<td>No</td>
<td>OS</td>
<td>5% versus 0% at 5 yrs</td>
<td>Not stated</td>
<td>74% versus 66% at 5 yrs</td>
<td>64% versus 53% at 5 yrs</td>
<td>16% versus 0%</td>
<td>No data</td>
</tr>
<tr>
<td>CAO/ARO/AIO-94, Sauer et al. (2004) [2]</td>
<td>1995-2004, 9 yrs</td>
<td>823</td>
<td>Preop 50.4 Gy + 5-FU versus postop 50.4 Gy + 5-FU</td>
<td>405 versus 394</td>
<td>Yes, in later yrs</td>
<td>OS</td>
<td>6% versus 13% at 5 yrs</td>
<td>36% versus 38% at 5 yrs</td>
<td>76% versus 74% at 5 yrs</td>
<td>68% versus 66% at 5 yrs</td>
<td>8% versus 0%</td>
<td>2% versus 3%; not Quirke</td>
</tr>
</tbody>
</table>

**Abbreviations:** 5-FU, 5-fluorouracil; CRM, circumferential resection margin; DFS, disease-free survival; FUFA, 5-fluorouracil plus folinic acid; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; pCR, pathological complete response; RT, radiotherapy; TME, total mesorectal excision.
tigations. Randomized studies have shown no statistical difference in anastomotic leaks [51] whether the patient received preoperative CRT (11%) or surgery alone (12%). Infections relating to wound healing in the sacral cavity and in the perineal areas following APER remain one of the most frequent postoperative complications. Perineal postoperative wound healing is reported to range between 7% and 63%. Preoperative RT poses an additional risk for pelvic infection [9].

**DISCUSSION**

There is a consistent trend that the addition of concurrent 5-FU–based chemotherapy leads to a higher pCR rate in LARC. This ranges from <10% with RT alone to 15%–30% with CRT, and is a consistent finding both from single-center series and randomized trials. As yet, a survival advantage has not been observed. Clinical trials are mainly in the phase II setting, and there are no published meta-analyses examining CRT in rectal cancer.

The optimum timing of chemotherapy has not been established in rectal cancer. In other settings, for example, head and neck cancer, neoadjuvant chemotherapy appears to reduce the risk for micrometastases but does not impact locoregional control. In contrast, synchronous chemotherapy with radiotherapy impacts locoregional control but not the subsequent risk for metastatic disease. Hence, in early resectable rectal cancers, the impact of CRT is low but the relative impact of chemotherapy may be high. In contrast, for locally advanced, unresectable, or borderline rectal cancers, both systemic chemotherapy and CRT schedules play a role.

Preoperative CRT has a major impact on local control compared with long fractionation RT alone. However, there is no evidence that CRT improves the chance of SPSS, and there has been no impact on DFS or OS. The optimal chemotherapy, total dose fractionation, and clinical target volumes remain a matter of debate. A review [52] suggested that the use of continuous infusion 5-FU (p = .01), the addition of a second drug to 5-FU, and the total radiation dose (p = .02) were associated with a higher rate of pCR. It is not clear whether the high biological activity of SCPRT is equivalent to that of 50 Gy of CRT, but the Australian TROG study will clarify this when it is published.

Other more recent strategies include the intensification and prolongation of neoadjuvant chemotherapy [46]. The role of induction chemotherapy alone in shrinking these tumors remains experimental, with little in the form of definitive evidence to support better local control or survival.

The majority of patients in CRT trials did not undergo TME. There is rather poor compliance with postoperative adjuvant chemotherapy following surgical resection (50%–66%). It remains unclear how much the observation of higher compliance with chemotherapy and RT contributes to the advantages attributed to preoperative CRT compared with postoperative CRT, because the German AIO study demonstrated a compliance rate of only 54% for postoperative CRT. Preoperative treatment has a higher therapeutic ratio over postoperative therapy, but whether this reflects compliance or the fact that higher doses are often used in the postoperative setting remains unclear. Because the majority of recurrences are extrapelvic, more impact is likely from improving adjuvant chemotherapy or the introduction of biologically targeted drugs.

**CONCLUSIONS**

In most tumor sites, concurrent chemotherapy and RT, rather than sequential, is the most effective way to achieve local control and OS. The addition of 5-FU–based chemotherapy to neoadjuvant RT in the recent European randomized trials of rectal cancer led to significantly better tumor downstaging, pCR, and local control than with RT alone, but it does not translate into a benefit in terms of longer DFS or OS, nor a higher chance of sphincter preservation. Metastatic disease remains a significant problem. Adding a second drug (mitomycin C, oxaliplatin, or irinotecan) results in a higher pCR rate, and could be more effective in killing micrometastases, but this strategy has not yet been demonstrated to result in longer DFS or OS. Randomized studies are in progress (the NSABP R-04 trial and the Pan-European Trials in Alimentary Tract Cancer PETACC 6 trial); however, no radiation dose, schedule, or fractionation is superior to any other if CRT is employed, and there is no evidence of a dose–response relationship above 45 Gy.

The site of the tumor and MRI staging define high-risk patients. The choice of not using preoperative 5-FU–based CRT represents a positive decision to forego effective neoadjuvant treatment. If the surgical histopathology subsequently reveals positive lymph nodes, or—even worse—a positive circumferential margin, the optimal window for treatment may have been lost.
REFERENCES


16 Crane CH, Skibber JM, Birnbaum EH et al. The addition of continuous infusion 5-FU to preoperative radiation therapy increases tumour response, leading to increased sphincter preservation in locally advanced low rectal cancer. Int J Radiat Oncol Biol Phys 2003;57:84–89.


35 Rouanet P, Rivoire M, Leong B et al. Sphincter preserving surgery after...


