Improving Chemoradiotherapy in Rectal Cancer

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Key Words. Capecitabine · 5-FU · Rectal cancer · Radiotherapy · Chemoradiotherapy

ABSTRACT

The optimal management of rectal cancer remains a major challenge for oncologists. The treatment of stage II/III rectal cancer has historically been associated with a high risk of local recurrence and poor survival, which led to the development of adjuvant treatments in the hope of improving outcomes. The approach to adjuvant therapy for rectal cancer currently varies widely between Europe and the U.S. Postoperative adjuvant chemoradiation is the standard of care in the U.S. In contrast, in Europe, because there is a greater emphasis placed on preoperative imaging, meticulous surgical technique, and accurate pathologic reporting of the circumferential or radial margin, preoperative treatment (radiotherapy and chemoradiation) is used widely. The aims of preoperative radiotherapy and chemoradiation are to facilitate a curative resection (R0) and to increase the chance of performing sphincter-sparing procedures, and, therefore, to improve both survival and quality of life.

INTRODUCTION

The optimal management of rectal cancer remains a major challenge for oncologists. Currently, the 5-year survival rate for patients with stage II and III rectal cancer ranges from 33% to 70%. Prognosis correlates with both the degree of penetration through the rectal wall and nodal involvement. Surgical resection of primary rectal cancer has typically been associated with a high rate of locoregional recurrence in 10%-60% of patients, with a median time to recurrence of approximately 12 months. Total mesorectal excision is now accepted as the optimal surgical approach, although the availability of this technique differs from country to country and hospital to hospital.

The development of adjuvant treatments to improve outcome began in 1969, when a landmark, retrospective review of 830 patients with well-documented follow-up showed that 5-year survival rates were 79%, 25%, and 6% for patients with Dukes’ A, B, and C rectal cancer, respectively [1]. Other nonrandomized studies in the 1970s defined both clinical and histopathological features that predicted a high risk of local and systemic recurrence. These very poor survival data for Dukes’ B and C disease led to the initiation of several randomized trials in Europe and the U.S. The strategies subsequently adopted for the management of rectal cancer have tended to differ between the two continents, with preoperative chemoradiotherapy preferred in Europe and postoperative chemoradiotherapy predominant in the U.S.

This article reviews the clinical trials that led to these diverging standards of care. An interesting new approach in chemoradiation is the use of the oral fluoropyrimidine capecitabine as a combination partner for radiotherapy. Preclinical studies have demonstrated that the combination of capecitabine and radiotherapy has highly enhanced antitumor activity. This is most likely attributable to the upregulation of thymidine phosphorylase (the rate-limiting enzyme needed to convert capecitabine to 5-fluorouracil [5-FU]) in tumor cells following radiotherapy. A phase I study has consequently been performed to establish a feasible chemoradiotherapy combination. Capecitabine has the potential to replace bolus or continuous infusion 5-FU as the standard treatment for rectal cancer and offers a potentially enhanced therapeutic ratio. Oral chemotherapy has the additional advantage of simplifying chemoradiation and providing a treatment that is more appealing to patients. The Oncologist 2001;6(suppl 4):29-34
POSTOPERATIVE CHEMORADIOThERAPY

In the U.S., a series of well-designed, randomized trials clearly demonstrated that adjuvant 5-fluorouracil (5-FU)-based chemotherapy administered with postoperative radiotherapy significantly reduced rates of local recurrence and improved overall survival compared with surgery alone or surgery plus postoperative radiotherapy [2-4]. These studies led to the National Institutes of Health (NIH) consensus statement of 1990 that recommended adjuvant therapy for rectal cancer of tumor/node/metastasis (TNM) stages II and III, which was to be initiated within 6 weeks of surgery. In addition, the NIH consensus recommends chemoradiation therapy, in particular, 5-FU-based chemotherapy and a radiation dose of 45-55 Gy, as the most effective adjuvant therapy [5].

Several approaches to improving the efficacy of chemoradiation have been investigated, including the coadministration of agents such as leucovorin (LV), levamisole, or nitrosourea, and/or 5-FU schedule modulation. Most of these strategies failed to significantly improve outcomes compared with standard 5-FU-based chemoradiation. However, a large, randomized trial by O’Connell et al., conducted in 660 patients with TNM stage II or III rectal cancer, demonstrated that continuous infusion of 5-FU (225 mg/m2/d) for the 5-week duration of radiotherapy (total dose 45 Gy plus a 5.4 Gy boost) resulted in significantly improved overall survival (Fig. 1; \( p = 0.005 \)) and disease-free survival (\( p = 0.01 \)) compared with bolus 5-FU administration (500 mg/m2 on days 1-3 during weeks 1 and 4 of radiotherapy) [6]. Patients in the two groups received identical pre- and postradiation therapy, consisting of i.v. bolus 5-FU 500 mg/m2 (or 350 mg/m2 plus semustine 130 mg/m2 on day 1) on days 1-5 and 36-40, and i.v. bolus 5-FU 450 mg/m2 (or 400 mg/m2 plus semustine 100 mg/m2 on day 134) on days 134-138 and 169-173.

The incidence of distant metastases was also significantly decreased with infused versus bolus 5-FU. Moreover, the treatment was well tolerated. There was more grade 3/4 diarrhea associated with infused 5-FU (24% versus 14%) but less grade 3/4 leukopenia (2% versus 11%). This study was very influential in the U.S., where postoperative chemoradiotherapy with infused 5-FU is now widely considered as the standard of care.

A recently published study by the National Surgical Adjuvant Breast and Bowel Project (NSABP), protocol R-02, confirmed that at the 5-year follow-up, postoperative radiotherapy plus 5-FU/LV achieves a small but significant reduction in the rate of local relapse from 13% to 8% (\( p = 0.02 \)) [7]. However, in this study, the incidence of distant relapse was not significantly improved and the addition of radiotherapy to chemotherapy did not confer a survival advantage. It should be noted, however, that the chemoradiotherapy administered in the chemoradiotherapy arm (bolus 5-FU for 3 days) was inferior to the control arm of the O’Connell study (bolus 5-FU for 4 days). The local recurrence rates are probably underreported in this study because only the first site of relapse is documented, and regular pelvic computerized tomography scans were not mandated.

Nevertheless, these data prompted the question whether all patients with resected rectal cancer should receive postoperative chemoradiation. In the U.S., the standard has been for patients to receive such treatment; in Europe, however, this has tended not to be the case.

PREOPERATIVE RADIOThERAPY/ChemoradioTherapy

In Europe, the current enthusiasm is for preoperative neoadjuvant therapy. There is greater emphasis on better patient selection using preoperative imaging. The aim is to maximize the potential for a histologically confirmed complete resection and sphincter-sparing procedures. Huge advances have been achieved through improvements in surgical technique, pathologic staging, and tumor downsizing.

Randomized trials have provided evidence that preoperative radiotherapy is more dose effective and achieves more effective local control than postoperative radiotherapy [8, 9]. Compliance with therapy is also improved. For example, in the Swedish Rectal Cancer Trial [10], 1,168 patients with resectable rectal cancer were randomized to either a short regimen involving five large fractions of 5 Gy over 5 days followed by immediate surgery or surgery alone.

With the Swedish schedule, chemotherapy cannot be integrated into these large fractions of radiation without excessive toxicity. Furthermore, radiation of the anal sphincter with the same schedule is associated with poor bowel function [11]. Another disadvantage is that high
doses per fraction may increase the incidence of late effects such as injury to the small bowel. Furthermore, with a short interval between radiotherapy and surgery, neither tumor regression nor an increased ability to perform sphincter-sparing surgery were achieved. In the Swedish study, however, the regimen was associated with a substantial reduction in local recurrence (27% to 11%; \( p < 0.001 \)), and also improved the 5-year survival rate (48% to 58%; \( p = 0.004 \)).

The findings of this study have been confirmed by a meta-analysis of 3,722 patients comparing preoperative radiotherapy with surgery alone [12]. The analysis demonstrated that preoperative radiotherapy was associated with a small but significant improvement in 5-year survival (odds ratio [OR] = 0.49; \( p = 0.03 \)) and drastically reduced local recurrence (OR = 0.49; \( p < 0.001 \)). However, the occurrence of distant metastases was not reduced (OR = 0.93; \( p = 0.54 \)).

Further points in favor of preoperative radiotherapy include the lower incidence of side effects with preoperative versus postoperative radiotherapy, although the recently reported results of the NSABP R-03 study contradict this approach [13]. In addition, the improved local control achieved with postoperative radiotherapy is not always matched by a convincing benefit in terms of survival [7].

A key question is whether all patients with resectable cancer (pathologic stages T1/2N1 and T3N0/1) should receive preoperative radiation. The answer is almost certainly not. The meta-analysis [12] demonstrated only a small survival benefit with preoperative radiotherapy, and a potential risk to anal function. Only those patients at risk of local recurrence are likely to benefit from preoperative radiation. Negative prognostic markers for local recurrence include nodal involvement, penetration through the rectal wall, and positive circumferential margins, and these should be used to identify those patients at high risk of local recurrence who are most likely to benefit from preoperative radiation. Improved magnetic resonance imaging techniques may enable the identification of patients who will benefit from preoperative chemoradiation, as they may improve clinical staging and accuracy in pathologic staging [14, 15].

Developments in surgical techniques (total mesorectal excision) are especially important and contribute, with the factors described above, to improving outcomes for patients with rectal cancer. Numerous clinical trials are being conducted to elaborate on pre- versus postoperative chemoradiation, combined chemoradiation versus radiation, and selection of subgroups through improved clinical staging.

**Rectal Chemoradiation with Capecitabine**

Another important advance in the care of patients with rectal cancer is the potential integration of more convenient, oral alternatives to 5-FU into standard chemoradiotherapy. Currently, chemoradiation using 5-FU as a radiosensitizer is the standard therapy for rectal cancer in the (neo)adjuvant setting. However, as an oral fluoropyrimidine that mimics continuously infused 5-FU, capecitabine has the potential to replace i.v. 5-FU and simplify chemoradiation. In addition, its unique mechanism of activation may further enhance efficacy and tolerability, offering the potential for an enhanced therapeutic ratio. Capecitabine generates 5-FU preferentially at the tumor site by exploiting the higher activity of the enzyme thymidine phosphorylase (TP) in tumor tissue compared with healthy tissue [16, 17]. Furthermore, radiotherapy has been shown in preclinical studies to selectively increase the activity of TP in tumor tissue but not in healthy tissue [18]. Preclinical studies also demonstrated that capecitabine/radiotherapy combination treatment achieves highly enhanced antitumor activity compared with either agent alone, whereas 5-FU/radiotherapy combination treatment shows no clear additive effect (Fig. 2).

These characteristics provided the rationale for a phase I dose-finding study [19]. The primary objective of the study was to determine the maximum tolerated dose of twice-daily capecitabine administered for the duration of standard radiotherapy. The maximum tolerated dose was defined as the twice-daily dose of capecitabine with radiotherapy causing dose-limiting toxicities, during treatment or in the 6-week period following treatment, in at least one-third of a six-patient cohort. Dose-limiting toxicities were defined as any clinically relevant grade 3/4 adverse event/laboratory abnormality (except grade 3 vomiting, grade 3 neutropenia without fever, or grade 3 hyperbilirubinemia) or any adverse event causing capecitabine treatment interruption for more than seven single doses or for >10% of the total scheduled dose. Secondary objectives of the study included assessment of the safety profile and antitumor efficacy of the combination.

In this study, patients received a total irradiation dose of 45 Gy plus a boost of 5.4 Gy to the presacral area, delivered as 1.8 Gy daily fractions over a period of approximately 6 weeks. Capecitabine was administered continuously twice daily at doses of 250-1,000 mg/m² for the entire duration of radiotherapy, without interruption at weekends. The first daily dose was administered approximately 2 hours before radiotherapy, with the second dose given approximately 12 hours after the first.

To date, 32 patients have been treated at six dose levels (250, 375, 500, 650, 825, or 1,000 mg/m²). All patients had histologically confirmed rectal adenocarcinoma and were scheduled for conventional pelvic radiotherapy following resection of primary or recurrent rectal cancer, or for a primary inoperable tumor. Nineteen patients were treated in
in the adjuvant setting, 10 in the neoadjuvant setting, and three in the palliative setting.

The maximum tolerated dose was reached at capecitabine 1,000 mg/m² twice daily. Two of six patients treated at this dose level experienced dose-limiting grade 3 hand-foot syndrome on days 22 and 30, respectively. The only other case of hand-foot syndrome occurred at grade 1 intensity in one patient treated at the capecitabine 650 mg/m² twice daily dose level. The recommended dose for further evaluation is capecitabine 825 mg/m² twice daily in combination with radiotherapy. No grade 3/4 toxicities have occurred in the eight patients treated at the 825 mg/m² twice daily dose level to date, and four additional patients are currently being treated at this dose to confirm the feasibility of the recommended regimen.

Overall, the most common toxicities were leukopenia (57%), local skin toxicity (43%), and diarrhea (33%) (Fig. 3). Most adverse events (related and unrelated to treatment) were mild to moderate in intensity. There were no grade 4 adverse events, and grade 3 adverse events besides the two dose-limiting toxicities were rare: rash/itch (at capecitabine 375 mg/m²), local skin toxicity (at capecitabine 650 mg/m²), and diarrhea (at capecitabine 1,000 mg/m²), which each occurred in one patient. The trial protocol specified that grade 3 diarrhea was not defined as dose limiting unless it failed to resolve to grade 1/2 within 2 days of symptomatic treatment.

There was no clear increase in toxicity with escalating doses of capecitabine, suggesting that the occurrence of toxicities was probably influenced predominantly by administration of radiotherapy and the predisposition of individual patients rather than the administration of capecitabine.

In addition to its favorable safety profile, capecitabine/radiotherapy combination treatment showed promising antitumor activity. Among seven patients treated in the neoadjuvant setting who were evaluable for response by surgery, tumors were downstaged in five patients, and there was one pathologically confirmed complete response.

The encouraging results of this study suggest that in combination with radiotherapy, capecitabine has the potential to replace bolus or continuous infusion 5-FU as the standard treatment for rectal cancer. As an oral agent, capecitabine is easy to administer and convenient for the patient, thus simplifying chemoradiation and providing a treatment that is more appealing to the patient. Phase II evaluation of the recommended capecitabine/radiotherapy regimen as neoadjuvant therapy for patients with rectal cancer is ongoing. The NSABP is considering incorporating this regimen into a randomized, phase III trial (NSABP R-04) evaluating preoperative chemoradiation in rectal cancer.

**CONCLUSIONS**

In the U.S., postoperative chemoradiation is likely to play a continuing role in the management of rectal cancer.
It remains apparent that few surgeons in the U.S. practice total mesorectal excision and few pathologists comment on the circumferential margin. It, therefore, remains necessary for most patients with pathologic stage T1/2N1 and T3N0/1 rectal cancer to continue to receive postoperative chemoradiation. However, preoperative therapy has been accepted by some large American institutions [20, 21]. The high rate of radical abdominoperineal resection seen in randomized trials in the U.S. suggests that more might be achieved by optimizing surgery rather than using radiotherapy to compensate for inadequate surgery.

In contrast, in Europe there is a greater emphasis placed on optimal surgical technique, and accurate radiological, clinical, and pathologic staging. There is a growing interest in chemoradiation and the possibility of tumor downstaging to facilitate curative (R0) resection and sphincter-sparing procedures. These factors are likely to fuel the increasing use in Europe of preoperative chemoradiation, particularly for subgroups of patient most likely to benefit from this approach. On both continents, a number of large trials are ongoing or planned to further evaluate the optimal chemoradiation strategy for patients undergoing surgery for rectal cancer.

A potential future advance in chemoradiation may be the replacement of i.v. 5-FU as a combination partner for radiotherapy with convenient, oral fluoropyrimidines. A phase I dose-escalation study demonstrated that capecitabine 825 mg/m$^2$ twice daily in combination with standard radiotherapy is feasible with promising antitumor activity. This regimen simplified chemoradiotherapy and is highly appealing to patients. In combination with radiotherapy, capecitabine offers the potential to replace bolus or continuous infusion 5-FU as the standard treatment for rectal cancer.

**REFERENCES**


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