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# Current Controversies in Cancer

# Is There a Standard Adjuvant Treatment for Rectal Cancer?

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### BACKGROUND

One of the major controversies in oncology today, among oncologists as well as surgeons, is adjuvant treatment for rectal cancer. The current practice differs from Europe to the U.S.A., between countries in Europe, and even between institutions within the same country. The question of whether or not to give adjuvant treatment and what regimen should be used is extremely important, as rectal cancer is one of the most frequent cancer types [1]. Thus, an improvement of 5-year survival from, for example, 50 to 60%, corresponds to approximately 100 lives saved in a small country like Norway and approximately 5,000 lives saved in the U.S.A. In addition, successful adjuvant treatment may reduce suffering from painful recurrences and the need for resource demanding palliative treatment. Establishing an optimal treatment for rectal cancer should, therefore, be a high priority in modern medicine.

I will focus on adjuvant treatment for resectable rectal cancer (Dukes' A, B and C) and will only briefly consider primarily unresectable locally advanced cases. The discussion of standard adjuvant treatment is largely influenced by the fact that so far no standard surgery has been defined. Surgeons have resected rectal cancer for cure for decades, and with large variations in results, in terms of local recurrence rate, survival and complications [2, 3]. The surgical techniques employed differ, and it is well known that the experience of individual surgeons has a major impact on treatment results [2–5]. Recently, surgeons in many countries made an effort to standardise surgery. This change in surgical approach will also have a major impact on the question of a standard adjuvant treatment. So, what is standard adjuvant treatment today and what will be the standard tomorrow?

What is standard? The introduction of a standard adjuvant treatment for rectal cancer (as with other standard treatments) should, in general, be based on available documentation from at least two or three high quality independent randomised trials (or a meta-analysis). Moreover, the benefit of the treatment should be clinically significant in terms of survival, recurrence rate or quality of life, the side-effects should be tolerable and the costs acceptable. On this background, I will discuss adjuvant treatment for rectal cancer.

### STANDARD TREATMENT: POSTOPERATIVE RADIOTHERAPY PLUS CHEMOTHERAPY

The NIH Consensus Conference in 1990 [6] concluded that patients with rectal cancer Dukes' B and C (Astler Coller B2 and C) should receive postoperative radiotherapy combined with chemotherapy. Since then, this combination has been considered the standard in the U.S.A., within and outside clinical trials. In Europe, however, this conclusion has in general not been accepted and, with a few exceptions, most institutions give either no adjuvant treatment, pre-operative radiotherapy or chemotherapy alone.

How strong is the evidence for postoperative radiotherapy plus chemotherapy? Theoretically postoperative radiotherapy *per se* is attractive, as it does not postpone surgery and it is possible to select the high risk patients (Dukes' B and C) without overtreatment of good prognosis patients (Dukes' A) or patients with disseminated disease. However, it seems to be less effective and also gives more postoperative complications than pre-operative radiotherapy [7]. Postoperative radiotherapy without chemotherapy may reduce the local recurrence rate, but no significant improvement of survival has been documented [8–10].

In contrast, the combination of postoperative radiotherapy and 5-fluorouracil-based chemotherapy has now been shown in several randomised trials to reduce the local recurrence rate and improve recurrence-free survival and overall survival compared with surgery alone or surgery plus postoperative radiotherapy. Thus, the Gastrointestinal Tumor Study Group (GITSG) demonstrated [10, 11] an improvement in disease-free and overall survival by combining postoperative radiotherapy with 5-fluorouracil and methyl-CCNU for 18

months compared with surgery alone. However, this regimen was not well tolerated, as only 65% of the patients completed the treatment as scheduled, and the toxicity was considerable. In the Mayo/NCCTG trial [12], in which patients were randomised between a more optimal radiation regimen (45–50.4 Gy with 1.8 Gy per fraction, multiple fields) in one arm and the combination of radiotherapy and chemotherapy for 6 months in the other arm, the combined treatment reduced the local and distant recurrence rate and improved survival significantly compared with radiotherapy as adjuvant treatment. Approximately 20% of patients in the combination group had severe diarrhoea and leucopenia.

In a more recent report on a NCCTG/intergroup trial, O'Connell and colleagues [13] demonstrated that combined chemoradiotherapy can be improved with respect to both relapse-free survival and overall survival by administering 5-fluorouracil continuously during the radiotherapy period, with a moderate increase in the incidence of severe diarrhoea. Moreover, methyl-CCNU (semustine) was found not to be of any importance, as was also indicated by GITSG [14]. Recently, a Norwegian randomised trial [15, 16] showed that a month-long regimen of postoperative radiotherapy (46 Gy with 2 Gy per fraction, three fields, prone position, full bladder) combined with bolus 5-fluorouracil 30 min before radiotherapy fractions 1, 2, 11, 12, 21 and 22 reduced the cumulative local recurrence rate from 30 to 12% and improved 5-year recurrence-free and overall survival from 46 to 64%, and from 50 to 64%, respectively, compared with surgery alone. The relative death risk was reduced by 44% by the combined therapy. The regimen was well tolerated with no increase in small bowel obstruction. The 5-fluorouracil administration 30 min before radiotherapy was chosen in order to optimise inhibition of sublethal irradiation damage.

Together, the trials of combined postoperative radiotherapy and 5-fluorouracil-based chemotherapy, given partly to obtain radiosensitisation and partly to affect micrometastases, show a reduced local recurrence rate and improved disease-free and overall survival. Two of the trials [10, 11, 15, 16] had surgery alone as the control group, whereas the third [12] had surgery plus postoperative radiotherapy and the fourth [13] had postoperative radiotherapy and bolus chemotherapy as the control arm. It should be noted that in all trials 'conventional' surgery was applied with relatively high local recurrence rates with surgery alone (approximately 30%) or surgery plus radiotherapy (approximately 20%). Whether the regimen [13] with continuous 5-fluorouracil during radiotherapy plus bolus 5-fluorouracil after radiotherapy (6 month regimen) or the 1 month regimen [15, 16] with time-scheduled 5-fluorouracil is the most optimal, has still to be tested. However, the principle of postoperative radiotherapy combined with 5-fluorouracil is so far the best documented for adjuvant treatment. Moreover, in Dukes' B and C rectal cancer, the magnitude of the reduction of the local recurrence rate is relatively high (from approximately 30 to 12%), and the magnitude of the improvement in overall survival is also relatively high (risk of death is reduced by approximately 40%).

Some scepticists have claimed that the survival effect shown by combined radiotherapy and chemotherapy is a chemotherapy effect only. I do not think this is the case, as the combination also has a significant effect on local recurrences, and since chemotherapy alone has so far not been shown to improve survival in the rectal cancer group.

The important components of a standard radiotherapy/chemotherapy regimen are as follows:

1. Total irradiation dose 45–50 Gy, with 1.8–2.0 Gy per fraction in 4.5–5.5 weeks.
2. Three- or four-field technique with the posterior part of the pelvis as the clinical target volume, with the upper border at L5/S1 intervertebral disc, and the lower border at perineum (at least after abdominoperineal resection).
3. Patient treated in the prone position and with attempts to reduce the volume of the small bowel in the target volume.
4. Chemotherapy based on 5-fluorouracil during radiotherapy (continuously or bolus 30 min before radiotherapy fractions). Chemotherapy for some months after the radiotherapy period is probably optimal, preferably combined with folinic acid. The maximum treatment period should be 6 months.

Which patients should be offered postoperative radiotherapy and 5-fluorouracil? The answer depends on the results obtained by surgery alone, whether 'conventional' surgical techniques are used or whether a 'standardised modern' technique is employed:

1. All patients aged < 75 years with rectal cancer Dukes' B and C, if 'conventional' surgery is performed and the institution has a high local recurrence rate by surgery alone (> 10–15%).
2. If a modern surgical procedure is used [3] (total mesorectal excision) and the institution, in general, has a low local recurrence rate with surgery alone (< 10–15%), the combined treatment is justified only in subgroups of patients. These subgroups are patients with increased risk of local recurrence, such as patients with positive lateral resection margins, patients with perforation during surgery and probably other groups of patients which have to be identified during the next years of total mesorectal excision practice in Europe. These groups may be patients with low tumours, abdominoperineal resection, Dukes' stage C, neural infiltration, etc.

## INVESTIGATIONAL AND STANDARD TREATMENT: PRE-OPERATIVE RADIOTHERAPY

Theoretically, pre-operative radiotherapy is attractive as it may have a downstaging effect and reduce the risk of tumour cell spillage. A certain dose seems to be more effective if given pre-operatively compared with postoperatively, and pre-operative treatment also seems to give fewer side-effects than postoperative treatment [7]. However, pre-operative radiotherapy usually postpones surgery considerably, it usually represents a real organisational problem, and patients with Dukes' stage A or disseminated disease will often receive an unnecessarily harmful and expensive treatment.

In resectable rectal cancer, low-dose pre-operative radiotherapy has not shown a significant effect on the local recurrence rate or survival [17]. Several trials with moderate/high-dose radiotherapy have shown a reduction in the local recurrence rate [17–20], but until recently no trial has shown a significant survival improvement. The large Swedish rectal cancer trial, published recently [21], employing 25 Gy in 5 Gy fractions during 1 week immediately before surgery, and a

modern multiple field technique to avoid complications, found a reduction in the local recurrence rate from 27 to 11% and an improved 5-year survival from 48% by surgery alone to 58% by addition of pre-operative radiotherapy. Corrected for Dukes' stage, the relative death risk was reduced by 19% by the adjuvant treatment. These results obtained by a low cost radiotherapy regimen are interesting, and current European trials employing this regimen will hopefully give confirmational data. Although the large fractions are of considerable concern with respect to late side-effects, the regimen is so far reported to be tolerable, although some problems occurred with postoperative mortality, delayed perineal wound healing [21, 22], and sphincter function problems [21]. Using the standardised total mesorectal excision technique there should be no reason to employ pre-operative radiotherapy routinely in resectable cases. A much more attractive approach is to select the high risk patients at the operation and give these postoperative radiotherapy and chemotherapy.

In contrast, in the primarily unresectable locally advanced cases, pre-operative radiotherapy with a dose of 45–50 Gy with 1.8–2.0 Gy fractions is to be considered as standard treatment, followed by attempts of radical surgery 4–6 weeks after the end of radiotherapy. An important downstaging may be obtained, permitting radical surgery with a curative intent [23].

## INVESTIGATIONAL SYSTEMIC TREATMENT

5-Fluorouracil-based chemotherapy has a proven role together with postoperative radiotherapy in rectal cancer Dukes' B and C. However, so far chemotherapy alone as adjuvant treatment has not been shown to improve survival in rectal cancer, except for a subgroup in the NSABP R-01 trial [9]. Several Scandinavian trials and a Dutch trial are investigating adjuvant chemotherapy without radiotherapy in Dukes' B and C rectal cancer and data from these trials will soon be available.

In primarily unresectable cases, chemotherapy is often included together with pre-operative radiotherapy and attempts of radical surgery. There are indications of an increased downstaging by adding chemotherapy [24]. A Scandinavian randomised trial is currently being performed to investigate a possible survival benefit in this group of patients.

The study by Riethmuller and colleagues [25] of the antibody 17-1A in colorectal cancer Dukes' C showed a survival benefit over surgery alone. However, so far it is not known whether this antibody treatment improves survival in rectal cancer *per se*. Current and future trials will hopefully clarify this point.

## INVESTIGATIONAL LOCAL TREATMENT

Intra-operative radiotherapy, brachytherapy and hyperthermia are used as additional treatments in a multidisciplinary approach in locally advanced rectal cancer. Several institutions employ these modalities on a routine basis, although they have still to be considered as investigational. Randomised trials are being run in Europe.

## CONCLUSIONS

In rectal cancer Dukes' B and C postoperative radiotherapy with 45–50 Gy (1.8–2.0 Gy per fraction), using a multiple field technique, combined with 5-fluorouracil during the radiotherapy period and probably for some months thereafter, should be a standard regimen. If the institution has a high local recurrence rate (> 10–15%), all patients younger than 75 years of age should be offered the treatment, if the patients cannot be operated on in another hospital with a low local recurrence rate. If surgery is more optimal with a low local recurrence rate, the treatment should only be given to patients at high risk for local recurrence. In primarily unresectable cases, pre-operative radiotherapy with 45–50 Gy should be given. In resectable cases, the regimens with pre-operative 25 Gy with 5 Gy fractions, as well as pre-operative radiotherapy combined with chemotherapy, are particularly interesting. The role of these regimens will be ruled out in current trials. A change in surgical technique may have a major impact on the future standard adjuvant treatment.


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ONLY HALF the patients who undergo surgery for rectal adenocarcinoma can be cured. Many attempts at improving the results of treatment have been made. Although for many years rectal cancers were considered resistant to radiation therapy, the biology of tumours and the effects of radiation and chemotherapy on locoregional spread and distant metastases are now better understood. Surgical resection which remains the principal curative tool for rectal cancer has benefited in recent years from different progresses leading to a better control of cancer and improved functional results. Adjuvant therapy, using radiation to improve local control and chemotherapy to prevent distant relapses, has been studied in many trials. Although most experts agree on analysis of the data, quite different conclusions have been reached: ''The best current adjuvant therapy for rectal cancer involves *post-operative treatment* with both chemotherapy and radiotherapy'' (NIH Consensus Conference, 1990) [1]; ''The benefits observed with pre-operative radiation incite to test *pre-operative treatment* with radiotherapy and chemotherapy'' (Paris Consensus Conference, 1994) [2]. Are we closer to a consensus in 1998?

Searching for an optimal treatment means reviewing progress in: surgical procedures used for resection of rectal adenocarcinoma, the progress of which cannot be separated from that of adjuvant treatment; radiation therapy before and after surgery; chemotherapy; combined radiation and chemotherapy.

## SURGICAL RESECTION FOR RECTAL CARCINOMA

The two goals of surgical excision for rectal cancer are to ensure control of cancer spread whilst preserving anorectal function. Many advances have been made in these two directions over the last decade. Better understanding of distal cancer spread has allowed the widespread acceptance of sphincter saving operations, anterior resection with colorectal or colo-anal anastomosis for most rectal cancers, thus preserving continence and acceptable bowel function. Preservation of autonomic pelvic nerves is possible in most cases and reduces the risk of postoperative sexual and urinary dysfunction.

For many years, surgical resection alone had been somehow disappointing for local control of stage B2 and C rectal cancers, as shown by recurrence rates ranging from 20 to 40% observed in the control arms of most multicentric randomised trials [3, 4]. Better knowledge of distal microscopic lymphatic spread within the mesorectum, usually undetected by routine histological examination, has led some surgeons to propose the systematic use of total mesorectal excision for mid or low rectal cancer. In their first report in 1982 Heald and colleagues had not observed pelvic recurrences in a consecutive series of 50 rectal resections for cancer after a mean follow-up of 2 years [5]. In 1993, the same group reported a 5% local recurrence rate and a 22% overall recurrence rate at 5 years in a series of 135 consecutive Dukes' B2 and C rectal tumours located within 12 cm from the anal verge [6].

Two recent series have confirmed the excellent results achieved by surgery alone with low recurrence and good survival rates [7, 8]. Total mesorectal excision requires specific surgical expertise and strengthens the case for specialised referral patterns. The meticulous dissection of the pelvis increases operating time and is also associated with an increased rate of anastomotic leaks, although permanent stomas are rare [9]. Similar local recurrence rates below 10% have also been observed in institutions where several surgeons of different ages are performing rectal surgery but with the same principles [10]. These data suggest that nerve

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