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Contra:

B. Nordlinger and C. Penna

Department of Surgery, Hôpital Ambroise Paré, 9 avenue Charles de Gaulle, 92104 Boulogne, France

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

Correspondence to B. Nordlinger.

sparing total mesorectal excision should be the gold standard for resection of mid and low rectal tumours and should be used as the reference in prospective trials of adjuvant therapy for rectal cancer.

ADJUVANT CHEMOTHERAPY FOR RECTAL CARCINOMA

Until recently, data on the efficacy of postoperative chemotherapy alone for the adjuvant treatment of rectal cancer were difficult to analyse because rectal and colon cancers were mixed in many trials, in others the number of patients were insufficient to draw valid conclusions, patients were not stratified according to prognostic factors and end-points were not clearly defined. Even a meta-analysis of the worldwide published experience, which demonstrated a significant benefit of adjuvant chemotherapy in rectal cancer patients (38% decrease in the mortality rate) was not considered completely convincing for many physicians [11]. NSABP study R01 included a total of 555 patients with B2 or C rectal cancer randomised to one of three arms: postoperative observation, postoperative pelvic radiation therapy of 4700 cGy of MOF chemotherapy (methyl CCNU, vincristine, 5-fluorouracil). After a 64 month mean follow-up period, there was a statistically significant disease-free survival advantage for MOF chemotherapy and an overall survival improvement for selected subsets of patients receiving MOF [12]. The recently published results of the NSABP study R02 including 741 patients showed that addition of radiotherapy to adjuvant MOF chemotherapy had no impact in disease-free survival or survival when compared with MOF alone, but decreased locoregional recurrence [13].

ADJUVANT RADIATION THERAPY

Radiation therapy can be administered either before, after or during surgery. Few studies have concerned intra-operative radiotherapy. Several trials have compared pre-operative radiotherapy and surgical excision of rectal cancer with surgery alone. The results of 12 studies have been published. No obvious benefit was observed after administration of relatively low-doses below 20 Gy [14]. After administration of higher doses (25–40 Gy) of pre-operative radiation, a benefit over surgery alone was observed in five studies [3, 15–18].

In these five studies, the risk of local recurrences was reduced as compared with the control group receiving surgery alone. However, in the control group of these studies, pelvic recurrences were observed in 20–30% of patients. This rate is much higher than that observed recently in retrospective non-randomised studies with rectal resection and total mesorectal excision.

The group from Uppsala compared pre-operative irradiation with 25 Gy in 1 week with postoperative radiotherapy (60 Gy in 8 weeks) and concluded that pre-operative radiotherapy was superior both for the rate of local recurrences and tolerance [19].

In a meta-analysis of 7,925 patients included in 24 trials in which they received surgery and radiation therapy, before or after surgery, Gray observed a risk of local recurrences of 36% after surgery alone, reduced to 18% when radiotherapy was also administered. The rate of local failures was reduced by 42% by pre-operative radiotherapy and by 25% by post-operative radiotherapy [20].

Whether the beneficial effect of pre-operative radiotherapy on the risk of local failure is maintained after up-to-date technically well done surgical excision with total mesorectal excision remains to be proven. This question is addressed in a trial which started recently in The Netherlands. The answer may be either that pre-operative radiotherapy associated with surgery with total mesorectal excision offers the best local control for patients with rectal cancers or that radiation therapy does not add any benefit to surgery with total mesorectal excision and is useful only in patients who have not received ideal surgery. Two recently published studies also demonstrated an improved survival rate after adjuvant radiation therapy over surgery alone [16, 17]. One inconvenience of pre-operative radiotherapy is that it is administered before the surgical specimen is analysed and, thus, the precise stage of the tumour is unknown. One advantage is that it is usually better tolerated than postoperative irradiation. Long term ileitis is less frequent, and pre-operative radiation therapy does not seem to compromise anal sphincter function after sphincter saving surgery.

Alternatively, the studies using postoperative radiation therapy did not show any statistically significant benefit on local control or survival [12, 21–23]. One problem associated with postoperative radiotherapy is the long term detrimental effect on bowel function. In a retrospective analysis at the Mayo Clinic, the group of patients that had received post-operative chemotherapy for rectal cancer had more long term intestinal morbidity than those who had received surgery alone [24].

ADJUVANT CHEMORADIATION FOR RECTAL CARCINOMA

If radiation and chemotherapy, when used alone, have failed to prolong survival in most studies, combined modality seems attractive in order to reduce the rates of recurrence both at the primary tumour site and outside the pelvis. To date, most of the randomised trials have tested postoperative adjuvant combined modality therapy. GITSG study 7,175 included 227 patients with B2 or C completely resected rectal tumours in one of four treatment arms. After 80 months' median follow-up, the recurrence rate was 55% in the control group and 33% in the radiation (4,000–4,400 cGy) plus concomitant 5-fluorouracil and methyl CCNU group ($P < 0.009$) [22]. A subsequent analysis at a median follow-up of 94 months showed an even larger margin of benefit for the combination therapy with an approximate 20% superiority in survival rates at 6 years for the 96 patients at risk [25]. The NCCTG study 79-47-51 randomly assigned 204 Dukes' B2 and C patients with rectal cancer to receive postoperative radiation alone (4500 cGy) or in combination with 5-fluorouracil and methyl CCNU (sandwich therapy). After a median follow-up of more than 7 years, there were 62 recurrences in the radiation alone group and 40 among the patients treated with combination therapy ($P < 0.0025$). After adjustment for known prognostic factors, the risk of relapse of patients treated by combination therapy was reduced by 47% as compared with radiation alone. The risk of cancer related death was reduced by 36% and the overall death rate by 29% [26]. Significant haematological toxicity was observed in both trials probably associated with methyl semustine (CCNU). These studies led to the conclusion that combined postoperative radiation and chemotherapy was superior to surgery alone. However, several questions remained unanswered. An ECOG trial, where 5-fluorouracil was not given concurrently with radiation, failed to demonstrate any advantage of the

combination over one or other of the adjuvant modalities alone, suggesting that drug administration and radiotherapy should be given simultaneously [27]. Two studies [28, 29] failed to demonstrate any advantage for the addition of methyl CCNU in the chemotherapy regimen, suggesting that 5-fluorouracil alone was sufficient. One study [30] showed that patients who received a protracted infusion of 5-fluorouracil during radiation had a significantly increased time to relapse and improved survival compared with those receiving bolus 5-fluorouracil during radiation. In contrast, a recent study conducted by the NSABP including a total of 741 patients with Dukes' B and C rectal cancers showed that the combination of postoperative chemotherapy and radiotherapy had no impact on disease free survival or survival when compared with postoperative chemotherapy alone [13].

Combined postoperative chemoradiation is also associated with deleterious consequences on the small bowel, and on anal sphincter functions in patients who received a low colorectal anastomosis. Acute or severe toxicity was observed in 35–41% of patients in the GITSG and NSABP studies. Kollmorgen and colleagues reviewed retrospectively 100 patients with B2 or C rectal cancers who had received curative anterior resections, 41 of whom had received postoperative chemoradiotherapy. Stool frequency, clustering of bowel movements, incontinence, liquid stools and inability to defer defecation were significantly more frequent after chemoradiotherapy [31].

In summary, two randomised trials have shown that postoperative combined chemoradiation therapy could reduce the risk of recurrence and prolong survival when compared with surgery alone. However, the rate of recurrence in control groups was close to 20% and is much higher than that now observed after rectal excision with total mesorectum excision. Significant toxicity was associated with the regimen. Haematological toxicity can be reduced by omission of methyl CCNU without compromising efficacy. Deleterious intestinal effects remain a major problem at a moment when surgery allows a better preservation of anal sphincter function.

IS THERE A CONSENSUS FOR A STANDARD TREATMENT?

New data have been collected and progress has been made both in Europe and U.S.A. since the last consensus conferences. Clearly it would be premature to say that a general consensus on the curative treatment of rectal cancers has now been reached.

Surgery of rectal cancer is probably the treatment modality which is closer to a consensus. After total mesorectal excision performed by skilled surgeons local recurrence rates are below 10%. Except in very low rectal cancers, the anal sphincter can usually be preserved. In some countries it has been suggested that this difficult surgery should be reserved for specially trained colorectal surgeons. Clearly, isolated local recurrence rates above 20% after curative resection of rectal adenocarcinoma are no longer acceptable.

Pre-operative radiation therapy can reduce the risk of local recurrences when compared with control groups where this risk is in the range of 20–30%. Whether this benefit will persist if local failures after surgery and mesorectal excision are reduced to 5–10% remains unknown. Adjuvant radiotherapy may appear to be effective only after less than perfect surgery.

To improve not only local but also distant control of rectal cancer, chemotherapy should be added to radiotherapy. The benefits of radiochemotherapy on survival and recurrences have been demonstrated only with postoperative combined treatment. Haematological toxicity observed in the first trial has been reduced by omitting methyl CCNU in the regimen, but intestinal toxicity remains a major concern.

Radiotherapy when administered alone was shown to be more effective and better tolerated if given before surgery than after. It is conceivable that the same might be true for radiochemotherapy. Several ongoing trials are studying preoperative chemoradiation. The comparison of radiochemotherapy before and after surgical resection of rectal adenocarcinomas will be very important.

Maybe then, a consensus can be reached.

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Arbiter:

H.-J. Schmoll

Department of Internal Medicine, Department of Haematology and Oncology, Martin Luther University Halle, Ernst-Grube Strasse 40, 06120 Halle, Germany

IN CONTRAST to the situation in resectable colon cancer, where there exists a common sense concerning the indication, type and overall efficacy of adjuvant chemotherapy, in resectable stage II and III rectal cancer the situation is much more complicated. Despite the clear recommendation by the NIH Consensus Conference 1990 [1] that postoperative chemotherapy plus radiotherapy should be standard, within Europe a wide range of treatment options is performed—from no treatment or postoperative radiotherapy alone, to radiation plus 5-fluorouracil (5-FU)-based chemotherapy given either pre-operatively or postoperatively or both. This situation is further complicated since, recently, surgical oncologists have developed the method of 'total mesorectal excision', a so-called 'optimal surgery' which seems to reduce the locoregional failure rate from 25% to less than 10%. This modern surgery, which is only performed by relatively few specially skilled surgical oncologists, furthermore challenges the value of pre- or postoperative radiation for the improvement of local control and probably even survival.

In the light of this scenario, it is not surprising that K.M. Tveit, as a medical oncologist, and B. Nordlinger and C. Penna, as surgical oncologists, express different views regarding standard treatment for resectable rectal cancer. A third contribution from a radiation oncologist would probably have complicated this matter even further.

However, there is at least one very sound congruence, which regards the standard approach for primarily irresectable rectal cancer. Both papers clearly state that pre-operative combined chemotherapy and radiotherapy is the treatment of choice. But what is the treatment of choice and, therefore, what should be standard treatment in resectable rectal cancer stage II and III (B2 and C according to the Dukes' classification)?

WHAT SHOULD BE STANDARD TREATMENT: RADIOTHERAPY, CHEMOTHERAPY, COMBINED CONCURRENT OR SEQUENTIAL CHEMORADIATION?

As mentioned by both authors, adjuvant radiotherapy, either pre- or postoperative, reduces the locoregional recurrence rate after 'standard' surgery from 36% to 18%. These data have been derived from a meta-analysis of adjuvant trials in rectal cancer [2]; the rate of locoregional relapses was reduced by 42% with pre-operative radiotherapy and by 25% with postoperative radiotherapy. Whereas this reduction in locoregional recurrence with postoperative radiotherapy is too low to have a demonstrable effect on survival, the effect of pre-operative irradiation seems to be high enough to increase the overall survival, as has been demonstrated at least in the more recent studies using modern radiation techniques and good trial methodologies [3]. The value of postoperative