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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

irradiation in increasing survival is also challenged by the preliminary results of the recent NSABP rectal cancer adjuvant trial [4], where the combination of adjuvant radiotherapy plus effective systemic 5-FU-based chemotherapy showed a significant but small benefit in terms of locoregional recurrence, and had no influence on survival. Also, the value of pre-operative irradiation is challenged by the method of total mesorectal excision which reduces the locoregional recurrence rate to at least the same dimension as pre-operative irradiation plus or minus chemotherapy. However, even if in the ongoing trial in The Netherlands which is looking at the value of total mesorectal excision with respect to locoregional recurrence and survival, an advantage for the use of mesorectal excision in terms of a reduced locoregional relapse and perhaps prolonged survival would be demonstrated, this method would presently not apply to the majority of patients with rectal cancer. Although stated by Nordlinger and Penna, it is a matter of fact that the exact method of total mesorectal excision is available only at relatively few centres for colorectal cancer surgery, and not in the majority of the hospitals usually treating and operating upon these patients.

It is unclear whether adjuvant chemotherapy alone improves survival in stage II and III rectal cancer given after surgery or pre-operative radiotherapy followed by surgery. There is, however, clear evidence that systemic chemotherapy at least contributes to the survival benefit of the combination of postoperative adjuvant radiation and chemotherapy. The following observations suggest this conclusion:

1. in comparison with postoperative radiation alone, the combination of postoperative adjuvant radiation and systemic chemotherapy has been proven to increase survival significantly in comparison with untreated control (GITSG study [5, 6]), as well as in comparison with postoperative radiation alone (Mayo Clinic/NCCTG trial [7]);
2. in the more recent NCCTG/Intergroup trial comparing adjuvant radiotherapy plus either standard bolus 5-FU or continuous infusional 5 FU with the time of radiation, a significant survival benefit has been achieved by infusional 5-FU, without difference in locoregional relapse rate [8]. These data indicate that infusional 5-FU, which is supposed to be a more effective chemotherapy than bolus 5 FU, contributed to an improved survival due to a systemic effect against micrometastases and not by an improvement in the locoregional relapse rate.

In conclusion, what should be the standard treatment in stage II and III rectal cancer out of clinical trials today?

In the paper by Tveit, there are somewhat clear recommendations with a plea for postoperative combined radiation and chemotherapy—a recommendation which is also highly accepted in the U.S.A. Dose, fractionation and size and location of fields are also clearly indicated in this paper, according to the NIH Consensus Conference recommendations [1]. The description of the type of chemotherapy in the paper by Tveit is very imprecise and seems to allow any type of either 5-FU or 5-FU/folinic acid. However, since there are no clear data from clinical trials using the combination of 5-FU/folinic acid, the best recommendation should be either to follow the guidelines as outlined in the NIH Consensus Conference with respect to 5-FU bolus application or to apply the 5-FU bolus plus infusion schedule as used in the more recent NCCTG trial and described by O'Connel and colleagues [8]. Since both schedules derive from published, relatively large multicentre trials, these schedules should be the recommended standard out of clinical trial. Since infusional 5-FU with radiation was superior in terms of survival in comparison with bolus 5-FU, without increase of toxicity, this could argue in favour of 5-FU continuous infusion. However, this positive result has been achieved in only one study so far.

WHICH PATIENTS SHOULD GET ADJUVANT CHEMORADIATION?

Both authors recommend combined adjuvant treatment for patients of less than 75 years with stage II and III rectal cancer who have conventional surgery. If total mesorectal excision is applied, in particular by a skilled surgeon in an experienced institution, both authors recommend the application of adjuvant radiotherapy only to subgroups of patients with increased risk of local recurrence, e.g. patients with positive lateral resection margins, perforation during surgery, low tumours, abdominoperineal resection, stage III or neural infiltration. However, the authors also remark that it is unclear which patient belongs to the group with higher risk for relapse after 'optimal' surgery and claim that these factors still have to be identified, e.g. in the ongoing clinical trials investigating total mesorectal excision. This means that at present it is unclear what should be the standard for patients who will or did undergo 'optimal' surgery.

WHAT IS BETTER: PRE- OR POSTOPERATIVE ADJUVANT TREATMENT?

As mentioned in the contra by Nordlinger and Penna, preoperative radiotherapy without systemic chemotherapy seems to have the same benefit and survival as postoperative combined chemoradiation. In fact, pre-operative radiation according to the dose and fractionation used in the recent Swedish study with only five large fractions over 1 week, in contrast to the 28 fractions over 6 weeks in the conventional schedule, is tolerable, is costly and effective in terms of decrease in local relapse rate and increase of survival [3]. However, as stated in an editorial to this paper by Minsky [9], this type of pre-operative radiation might create more acute postoperative toxicity, including up to 4% mortality, perhaps also late toxicities due to the high single fractionation chosen, and does not allow enough time for tumour shrinkage before surgery, which leads to a higher rate of abdominoperineal resection in comparison with standard pre-operative radiation techniques. Indeed, particularly in rectal cancer, besides an improvement in survival, the increase of the rate of sphincter preserving surgery is also of nearly equivalent importance. Therefore, presently, pre-operative radiation alone cannot generally be recommended as standard treatment; this needs to be improved further by: (i) combination with chemotherapy either concurrent with the pre-operative radiotherapy; or (ii) by administration of systemic chemotherapy after completion of both pre-operative radiation and surgery; or (iii) both modalities together, pre-operative radiotherapy as well as postoperative chemotherapy.

This highly interesting question is investigated in a current EORTC study on adjuvant treatment of rectal cancer performed by the EORTC Radiotherapy Group and the Gastrointestinal Tumor Study Group. It is strongly recommended that all patients should be treated within such a

prospective randomised study which alone can help to clarify a new and common treatment standard for a patient with stage II and III rectal cancer. Such innovative studies are presently highly relevant for several reasons, in particular due to the following reasons:

1. the survival benefit presently achieved with post-operative adjuvant combined chemoradiation is relatively small and needs to be improved further;
2. the best chemotherapy with postoperative radiation as well as the optimal systemic chemotherapy after adjuvant chemoradiation has not been defined;
3. the optimal mean of pre-operative radiation ± chemotherapy is still unclear and presently under investigation;
4. the contribution of optimal surgery (total mesorectal excision) in terms of final outcome in patients with stage II and III rectal cancer and the relative contribution of pre- or postoperative adjuvant radiation to this 'optimal' surgery are still not defined;
5. the type of chemotherapy—5-FU bolus or continuous infusion or 5-FU/folinic acid—and, more importantly, the emerging role of additional agents, e.g. oxaliplatin or irinotecan, need to be clarified.

There is in fact one standard adjuvant treatment presently available which could have been generally agreed upon. However, it seems very likely that we have several means in our hands which have the potency to improve the outcome of patients with resectable stages of rectal cancer. Future prospective trials must include many more patients within a shorter time than in the past to prove the value of the best surgery, pre- or postoperative radiation and highly active chemotherapy and hopefully define a better standard for the beginning of the new Millenium.

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