porting this theory. First, the patient received the transplant 16 years before the development of renal failure. Graft survival after the first year declines logarithmically out to at least 10 years, and probably longer. Therefore, the chance of chronic rejection occurring at 16 years is fairly high (i.e., approximately 36%). Second, his patient had a serum creatinine value of 2.0 mg/dl 5 years after completion of cisplatin therapy; this value rose in the sixth year after treatment. Cisplatin nephrotoxicity most often becomes evident during therapy or within 6 months after therapy and then stabilizes once therapy is discontinued. Therefore, although cisplatin nephrotoxicity cannot be entirely ruled out in this case, it does not represent a classic presentation.

We do not believe that the study by Bajorin et al. precludes the use of carboplatin in these patients because no significant difference in survival or remission duration was demonstrated. Their study compared a regimen of carboplatin plus etoposide with a regimen of cisplatin plus etoposide in patients with metastatic germ cell tumors. Recently, Horwich et al. concluded that a combination of carboplatin, etoposide, and bleomycin was an effective and less toxic alternative to cisplatin-based chemotherapy in patients with metastatic nonsemionomatous germ cell tumors with a good prognosis. We believe that carboplatin may yet prove to be a valid treatment option for renal transplant recipients who require platinum-containing compounds.

We strongly agree that measures for prevention of nephrotoxicity, including hydration and mannitol, must be taken in all patients receiving cisplatin. We also agree that all renal transplant patients who require therapy with cisplatin should be described in the literature because this is a subject of growing concern.

References


Postoperative Radiation Therapy for Rectal Cancer: An Interim Analysis of a Prospective, Randomized Multicenter Trial in The Netherlands

The Dutch multicenter group recently published a first analysis of a prospective, randomized trial. The aim of the trial was to assess the impact of adjuvant postoperative radiation therapy in rectal cancer Stage BII, CI, and CII. Patient accrual was stopped as soon as 172 patients had entered the study.

Eighty-eight patients were entered in the treatment arm. Eighty-four patients were entered in the control arm. There was a slight imbalance favoring the control arm concerning prognostic factors such as histologic differentiation (poorly differentiated tumors, 17% in the treatment arm versus 6% in the control arm) and tumor location (more lower tumors in the treatment arm).

Sixty-four of the 88 patients designated at random to the radiation therapy arm received the adequate dose according to protocol prescription (50 Gy in 5 weeks). In ten cases there was a dose reduction. Moreover, 14 patients did not receive radiation therapy at all (Table 1).

The local control seems to be better in the treated group. However, this difference does not reach a statistically significant level. The authors were looking for a 50% difference. The alpha and beta risks are not mentioned in the current publication.

We analyzed the difference in crude local recurrence as a function of whether the patients received the prescribed dose in the radiation therapy arm (chi-square, 4.61; P < 0.05). Together with the imbalance in prognostic factors, these protocol violations could be at the origin of the lack of significant impact on local control. Assuming that treatment according to protocol results in the correct figures concerning recurrence rate, the total expected incidence of local recurrence should be 10/88. Moreover, the exclusion of 16 patients (14 who did not receive radiation therapy according to protocol and 2 who received radiation therapy although they were not members of the control arm) results in a marginal significant reduction of the actuarial local relapse rate.

The increased number of poorly differentiated and lower tumors in the radiation therapy group results in an increased incidence of distant metastatic disease (26% versus 39%). This imbalance in prognostic factors and the high number of local recurrences in those patients designated to receive 50 Gy who did not (14 of 24) favor the radiation therapy arm having a higher actuarial relapse-free survival rate than the surgery alone arm.

We do not understand why this trial has been closed, knowing the high incidence of protocol violations. The argument that it is difficult to understand why refusal of therapy would imply a higher chance of recurrence does not hold looking at the imbalance in prognostic factors between the treatment arms.

The assessment that rectal cancer could be radioresistant if only 50 Gy was applied is not based on hard data. There are no large series of in vivo measurement of intrinsic radioresistance. According to Malaise and Fertil, the alpha value for
correlate colorectal cancer is an intermediate value considering different established cell lines of human origin. Moreover, biologic efficacy of a treatment depends not only on intrinsic radiore sistance, but also on reoxygenation, redistribution, repair, and repopulation. Concerning repopulation, recently published data yield low values for potential doubling time in colorectal cancer, especially for poorly differentiated tumors. This could indicate the need for accelerating treatment in subgroups of patients with extremely rapidly proliferating tumors, rather than increasing total dose.

These data cannot be considered evidence of lack of impact on local control or survival of adjuvant postoperative radiation therapy in rectal cancer.

<table>
<thead>
<tr>
<th>No.</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment according to protocol</td>
<td>64 (73%)</td>
</tr>
<tr>
<td>Treatment not according to protocol</td>
<td>24 (27%)</td>
</tr>
<tr>
<td>Total</td>
<td>88 (100%)</td>
</tr>
</tbody>
</table>

References


Reply to Coucke

We object to the figures produced by Dr. Coucke regarding 64 patients. We did not provide recurrence rates for ten patients who received a lower dose of radiation.

In a randomized trial, one considers a large number of factors of imbalance and one might expect 1/20 factors to have a statistically significant difference (P < 0.05). In this study, the imbalance between arms with respect to grade of differentiation and location was not statistically significant.

Moreover, multivariate Cox regression analysis showed only moderate associations between grade of differentiation or site of disease and failure rate, and this association was far from being statistically significant. The major and statistically significant factor is Dukes' Astler Coller stage; with respect to this factor, the treatment arms are balanced. We object to the suggestion that an imbalance of prognostic factors would explain the lower relapse-free survival rate in the radiation therapy arm.

Regarding the closing of the trial, there is a decrease in accrual in any trial after a number of years. One can hope that the combination of results in meta analysis will strengthen conclusions.

The interpretation of the radioresistance is difficult. However, the success of a lower preoperative dose suggests a role of oxygenation.

Treurniet-Donker et al.1 reported the results of an interim analysis of a prospective trial on postoperative radiation therapy for rectal adenocarcinoma. They concluded that postoperative radiation therapy alone cannot be justified as a routine procedure in the primary management of resectable rectal cancer. In our opinion, this conclusion is highly preliminary and unsupported by their data for several reasons.

First, the relatively small number of patients suggests that at least some preselection by the participating centers could have taken place before randomization.

Second, the radiation therapy arm consisted of only 88 patients, of which 14 (16%) did not receive irradiation for various reasons. Another ten patients (11%) received a total dose of 4000 cCy or less. In the control group, two patients received radiation therapy. Notwithstanding the fact that only 73% of the patients in the radiation therapy group received treatment as prescribed, the so-called "intention-to-treat principle" was applied in the statistical analysis of the results in the two arms of the trial. Doing so introduced an important bias. It is well known that more than 20% protocol violations make any comparison in any trial unreliable. We think these patients should have been excluded from the analysis.

Third, the 16 patients who did not receive treatment according to randomization did rather badly, with only 3 alive and disease-free at the time of analysis. A separate analysis excluding these patients showed a statistically significant lower local relapse rate in the radiation therapy group. The ten patients who received a suboptimal dose of 4000 cCy or less were included in this separate analysis. However, no specific information concerning those ten patients was provided by the authors.

Fourth, in the calculation of disease-free survival, death was regarded as an event or a failure, even if the patients died intercurrently without evidence of disease (7 of 37 in the radiation therapy group and 5 of 29 in the control group). No disease-specific survival results were mentioned. The incidence
of metastasis was higher in the radiation therapy arm (39% versus 26%), resulting in a higher death rate. This difference was, for this relatively small population, attributed to chance fluctuation. It might, as stated by the authors, indeed mask any influence of improved local control on survival. We think that the influence on disease-specific survival rates would be even more important. The same conclusions can be drawn concerning the higher incidence of poorly differentiated adenocarcinoma in the radiation therapy arm (17% versus 6%). Further proof of the imbalance in patient distribution is the predominance of the abdominoperineal resection in the irradiated group (56% versus 46%).

Finally, Table 2, which summarizes relapse and survival numbers, contains, in our opinion, three mistakes in the column "Received RT." After reconstructing the table using the numbers of events mentioned in Table 2 and in the text, the differences between the two groups in terms of sites of recurrence (local versus distant) are highlighted.

The two groups are not truly comparable because of the limited number of patients, the differences in patient characteristics, and the large number of patients who did not receive treatment according to randomization. However, a definite trend (according to the analysis of the authors this trend was statistically significant!) toward a reduction of the local recurrence rate in the irradiated group (excluding the patients who were not irradiated, but including ten patients who received a suboptimal dose of radiation remains).

Local recurrence constitutes a major threat to the quality of life of our patients. This study has strengthened our opinion that every patient who received radical surgery for rectal cancer, Stages B2 and C or International Union Against Cancer Stages III and IV, should be offered a full course of postoperative radiation therapy to reduce the probability of a local relapse.

Recent publications suggest the addition of chemotherapy to postoperative radiation therapy, using the cytotoxic drugs as radiosensitizers and/or as adjuvant therapy. This causes a remarkable shift in the discussion on postoperative radiation therapy from the former "to irradiate or not to irradiate?" to the current "to irradiate in combination with what?" question.

References


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Reply to Poortmans

When this trial was started it was the intention of most of us not only to prove the value of postoperative radiation therapy in rectal cancer, but also to quantify this value to be able to make it a standard therapy. Other investigators (Gastrointestinal Tumor Study Group, National Surgical Adjuvant Breast Project, Balslev [Denmark], Medical Research Council [MRC], and European Organization for Research and Treatment of Cancer [EORTC]) started similar studies in the past decade. All except EORTC have published their results so far and they reinforce our conclusions.

As for point 1 in the criticism by Poortmans and Hamers, 172 is not a large number of patients and is identical to the EORTC achievement. Preselection cannot be proven or completely avoided in any large multicenter project, but randomization eliminates the weight of this point. In this study there is no reason to assume that the selection process may affect the ability to generalize the results.

Point 2 is the most important issue raised because it concerns the basis of randomization, which is the production of comparable groups of patients to test the effect of a certain treatment. Application of the intention-to-treat principle does not introduce an important bias; on the contrary, this principle is the only way to prevent a bias. Refusal is regrettable, but can happen in any treatment offer. In the National Surgical Adjuvant Breast Project study of Fisher et al. there were 22 refusals among 184 patients in the treatment arm. They should not be (and were not) excluded from the analysis. Patients who could not fulfill the complete course of treatment can never be excluded because they would not have been able to complete the treatment even if it were standard therapy. Exclusion would have created a serious bias.

Regarding points 3 and 5, we did our analysis after excluding 16 patients who did not receive treatment according to the arm of randomization. Table 2 shows detailed data beyond the randomization on request of one of the reviewers of Cancer. Thus, one can analyze separately as Poortmans and Hamers have done after excluding patients not treated according to protocol. However, this expresses unwillingness to accept the rules regarding randomized trials and statistical interpretation when the outcome does not reinforce long held beliefs in some standard practice.

Concerning point 4, it is becoming standard practice to separate the cancer-related death rate from the total death rate figure. However, this should be viewed with caution because data regarding actual cause of death tend to be unreliable. Furthermore, there is treatment-related death that should not be hidden. We covered disease-specific end points sufficiently by the analysis of local relapse and distant relapse-free survival data. The slight difference between the groups of patients regarding histologic type and type of surgery is not of major importance.

A definite trend toward a reduction of the local relapse rate is not enough of an argument for standardizing a treatment that has toxic effects (two deaths!) and implies, at least in 85% of patients, overtreatment at high cost. Recently, some
data came forth suggesting that preoperative radiation therapy may be more effective than postoperative radiation therapy.

The value of radiation therapy in primary treatment of rectal cancer has not been sufficiently investigated to make final recommendations on standard treatment.

References


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