## Reviewer's report

**Title:** The Use of Preoperative Radiotherapy in the Management of Patients with Clinically Resectable Rectal Cancer: A Practice Guideline


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**Reviewer:** Lars Pahlman

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This is an interesting systematic review, where the authors have tried to evaluate the use of preoperative radiotherapy in resectable rectal cancer and at the end try to find some guidelines of practice.

It is more or less obvious that the authors are already biased due to the statement that postoperative radiotherapy combined with chemotherapy is better than preoperative or postoperative radiotherapy in terms of survival. Of course, this is a fact if all radiotherapy alone trials are bunched together with pre- and postoperative radiotherapy, and especially if the low dose preoperative trials are in the same group. However, if only trials using preoperative radiotherapy to a dose high enough to give a likelihood of killing micrometastases are taken into consideration, the figures are different for preoperative radiotherapy alone and data are as good as or sometimes even better than postoperative chemo-radiotherapy. Therefore, I have problems with the statement given by the authors on page 3; 'patients who choose preoperative radiotherapy as a treatment option instead of postoperative combined radiotherapy and chemotherapy need to be aware that because pathological stage is unknown until surgery is performed, many patients, who will not benefit from treatment, will be exposed to the risk of radiation-induced morbidity and mortality'. Such a statement is, of course, in one way correct but with modern imaging it is definitely wrong. Most patients with a favourable rectal cancer, where additional radiotherapy could be questioned are possible to depict preoperatively. Moreover, what is not mentioned at all in all trials using postoperative radiotherapy is that many of the patients who are not fit for radiotherapy due to an unexpected course with postoperative complications or fatigue will never ever be given radiotherapy despite that radiotherapy should benefit for the treatment. Such considerations would never be a problem among patients having preoperative radiotherapy.

Another statement indicating that the authors are biased by guidelines is stated on page 5. The authors claim that postoperative radiotherapy and chemotherapy is the preferred treatment for resected stage II and III rectal cancer and that 'the same guidelines discouraged the use of radiotherapy alone'. However, there are several countries in the world where the guidelines are written in the opposite direction, indicating that preoperative radiotherapy is the treatment of choice. This is true for many European countries.

Another very important thing when comparing pre- and postoperative radiotherapy is, of course, the selection bias. The authors are correct when they state that many patients having preoperative radiotherapy might have this treatment in vain due to unknown liver metastases and advanced disease. All those patients can be omitted from postoperative radiotherapy since they are not considered to have curative surgery. In the preoperative setting, those with minor metastases will alter the outcome, indicating that an analysis based upon intention to treat will not favour the preoperative treatment group compared to patients treated with postoperative radiotherapy. That could be one reason why the survival figures are as good with postoperative chemo-radiotherapy as with high-dose preoperative radiotherapy alone.

Another bias in this report is the way patients have been selected for evaluation. As given in paragraph 1 in the chapter "Synthesizing the Evidence" all deaths at the time of reporting, regardless the course, were included in the survival calculation. 'Patients with local failure included those with non-resected as well as those with recurrent disease'. Again, this is unfavourable for preoperative radiotherapy since patients submitted for postoperative radiotherapy have all R0 resection and R1 and R2 are considered not curatively treated.

As in all other meta-analysis regarding radiotherapy there is a confusion regarding the Swedish Rectal Cancer Trial and the Stockholm Rectal Cancer Study II. The true story is that in 1987 the Swedish Rectal Cancer Trial was started. This trial was a multicentre independent trial, where randomisation was done at all six Swedish health-care region and data were pooled into the Swedish Rectal Cancer Study organisation. After the recruitment number of patients was reached regions stopped the randomisation except the Stockholm area. The Stockholm Group continued to randomise patients according to the Swedish Rectal Cancer Trial protocol. In total almost 2/3 of the patients (316 patients) in Stockholm II trial were randomised to and reported in the Swedish Rectal Cancer Trial as well. Therefore, the genuine study was the Swedish Rectal Cancer Trial and the Stockholm II trial is just a subgroup analysis adding some more patients. Again, based upon this knowledge it is confusing to notice that the authors have graded the quality of study design different for the Swedish Rectal Cancer Trial and Stockholm II trial. Both reports are based upon the same protocol and data management, and subsequently should the scores be the same.

Another confusing phenomenon is that in the Stockholm II trial a non-standardised radiotherapy was used. The described increased risk of morbidity and mortality in the Stockholm II trial has not been found in the Swedish Rectal Cancer Trial. When data from the Swedish Rectal Cancer Trial are analysed without the Stockholm patients there is no difference at all regarding early and late complications due to radiotherapy in those having had preoperative radiotherapy or surgery alone.

Another very important thing which differ this meta-analysis from the one by the Colorectal Cancer Collaborative Group (CCCG) review is the way data have been analysed. The CCCG research group found 19 trials where individual data from all patients have gathered and scrutinised by the statisticians in the CCCG group. With such an approach exactly the same criteria for resection, survival and recurrences have been used for all trials indicating a more appropriate approach than the one which has been used in this report.

Another difficult part with this paper is the external review. It is very odd to ask radiotherapists and surgeons from an area having used postoperative radiotherapy and chemotherapy for many years of advice how to use this treatment in a normal setting. It is obvious that the answer will be that postoperative radiotherapy is as good as preoperative although most data actually do support the superiority with preoperative radiotherapy in terms of local disease control and also survival figures. The addition of chemotherapy can always be argued but those data are based upon three very small trials with just 250-300 patients.

It is also interesting to notice that all the respondents in this special survey have stated that 'postoperative radiotherapy combined with chemotherapy should remain the standard treatment'. If

such a question has been asked in Europe, and especially in the northern and western European countries the answer would be totally the opposite, indicating that selective preoperative radiotherapy is the treatment of choice. The cultural difference between the European continent and the North American continent is very difficult to interpret. It is obvious that in health care systems where each treatment session will cost money for the patient and increase the salary for the doctor a prolonged treatment is the treatment of choice. In health care systems, where physicians have no benefit of expanding the treatment, the short course 5x5 Gy is more accepted. Those main differences are interesting and will reflect the way doctors and physicians actually are acting.

A more important thing is actually not the use of radiotherapy in a pre- or postoperative setting but merely a matter of toxicity. It is obvious from many data that postoperative radiotherapy is theoretically more toxic than preoperative radiotherapy. An interesting phenomenon is that the best data about toxicity to radiotherapy in rectal cancer are coming from the Scandinavian countries, where the health care system easily can trace all individuals and analyse them for toxicity. As most 5x5 Gy preoperative radiotherapy trials have been run in the Scandinavian countries, the results of toxicity may be biased due to more and better reports from those studies than from studies given postoperative radiotherapy. This publication bias has to be taken into decision when the choice of radiotherapy is considered.

In summary, this is a nice report although it is rather biased in my opinion, favouring postoperative chemo-radiotherapy. Based upon all knowledge today I think the treatment of rectal cancer has been more or less solved in terms of local regional cure. With good surgery and radiotherapy given pre- or postoperatively the local failure rate should be more or less gone. There are several data supporting that in terms of reducing the local recurrence rate preoperative radiotherapy is better than postoperative radiotherapy. Therefore, with good imaging technique, preferably MRI, it is possible to preoperatively divide rectal cancer patients in three main groups according to the extent of local disease; good, bad and ugly. For the 'good' ones, with a clear circumferential margin based upon preoperative MRI, there is no need for any radiotherapy at all. The 'bad' ones are those having a tumour growing close to the circumferential margin and in such cases preoperative short-course (5x5 Gy) or long-course (25x2 Gy) radiotherapy is justified. In the third group, the 'ugly' ones, the likelihood of an involved circumferential margin is substantial. In this group of patients preoperative radiotherapy with prolonged course and preferably combined with chemotherapy is probably the treatment of choice to diminish the tumour size and to make a curative procedure possible.

**Competing interests:**

None declared.