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Current Controversies in Cancer

Is Radiochemotherapy Necessary in the Treatment of Rectal Cancer?

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INTRODUCTION

SURGERY IS the main treatment option in patients with rectal cancer. Only in very early stages, can treatment modalities such as endoanal radiotherapy be discussed, but for the majority of patients surgery is necessary.

The local recurrence rates after surgical excision of a rectal cancer varies enormously in reported series. Figures less than 5% after curative surgery contrast with figures of more than 50% [1, 2]. This huge difference in local recurrence rate reported from different series can be explained by patient selection, definition of radicality, definition of local failure, follow-up routines and/or the skill of the surgeon. A relatively appropriate figure which reflects standard surgery is a local recurrence rate of approximately 30%, which is reported from most randomised trials (Table 1). Most of these trials were recruiting patients during 1970–1990 indicating that the high local recurrence rates found in these trials are not an old phenomenon, but merely a result of todays standard surgery.

The best figures reported in literature are mostly institutional series probably from devoted and enthusiastic surgeons [3, 4]. In some of the series a more radical procedure has been used, such as extended pelvic lymph adenectomy [5]. All surgeons reporting good results have emphasised the importance of the surgical technique. However, in the latter study where a more aggressive dissection has been used [6], there is a clear risk of increased morbidity, especially regarding sexual and bladder function. None of the above mentioned studies with specific surgical techniques have been randomised. All series have been compared with historical controls and the figures can therefore be questioned.

Heald and associates have presented the best data, and have proposed total mesorectal excision and the initial report shows very low recurrence rates [1]. This technique is a more precise resection of the whole mesorectum including the rectal fascia. As proposed, the dissection starts posteriorly where the mesorectum is dissected in the embryological plane surrounding the rectum by the rectal fascia and fascia Denovillier. By following the embryological plane laterally and anteriorly, the whole mesorectum can be excised. The importance of this approach has recently been highlighted since involvement of the lateral margins is an important prognostic factor regarding development of local recurrences [7]. However, lymph nodes and metastatic deposits even more laterally, i.e. among the inferior mesenteric artery and the foramen obturatorium, are not excised with the technique proposed by Heald and associates. But those areas are cleared with a more extended pelvic adenectomy proposed by the Japanese surgeons [5, 6].

RADIOTHERAPY

The use of radiotherapy can be divided into adjuvant radiotherapy, where radiotherapy probably is not necessary, but will improve the results in some cases; and treatment where the addition of radiotherapy to surgery is more or less mandatory.

TREATMENT

In patients with a huge non-mobile or fixed tumour, the tumour stage is at least Dukes' stage B, but most often Dukes' stage C. Whether or not the fixity is caused by tumour overgrowth or just fibrosis, is sometimes extremely difficult to determine. With the assumption that most cases with a fixed tumour have locally advanced disease, they should have preoperative radiotherapy to achieve tumour shrinkage and if possible an operable tumour. In cases like this, radiotherapy should be given with a prolonged schedule with 1.8–2.0 Gy daily during a 5 week period. After another 3–4 weeks, the patient should be operated upon. This treatment option will not be discussed in this paper since most surgeons accept a concept such as this.

Table 1. *Pelvic recurrence after a combination of surgery and radiotherapy in rectal carcinoma (controlled trials with a surgery alone group)*

Study	Iradiation Dose (Gy) Number of fractions	Surgery alone Number of local recurrences/total (%)	Surgery + radiotherapy Number of local recurrences/total (%)	Reduction in recurrences (%)
Pre-operative				
St Marks [10]	15/3	51/210 (24)	31/185 (17)	29
Bergen [11]	31.5/18	31/131 (24)	24/138 (17)	29
North-West [12]	20/4	58/141 (41)	26/143 (18)	56
EORTC [13]	34.5/15	49/175 (28)	24/166 (14)	50
MRC2* [14]	40/20	50/132 (38)	41/129 (32)	16
Stockholm [15]	25/5	120/485 (28)	61/424 (14)	50
SRCT [16]	25/5	150/557 (27)	63/553 (11)	58
Postoperative				
Odense [17]	50/25	57/250 (23)	46/244 (19)	17
MRC3 [18]	40/20	69/235 (29)	46/234 (20)	31
GITSG [19]	40–48/22	27/106 (25)	15/96 (16)	36
NSABP [20]	46.5/26	45/184 (24)	30/184 (16)	33
EORTC [21]	46/23	30/88 (34)	25/84 (30)	12
Rotterdam [22]	50/25	28/84 (33)	21/88 (24)	27

*Only tethered tumours.

One important question is whether this prolonged pre-operative treatment should be combined with chemotherapy or not. No trial has shown a benefit from combined treatment in terms of resectability or survival benefits, although there are experimental data indicating that such a concept will have a better effect on tumour cell kill [8, 9]. We also know that toxicity is increased substantially if chemotherapy is added to pre-operative radiotherapy. However, in a patient with a locally advanced cancer where the cure rate can be very low, more toxicity can often be accepted due to the severity of the disease. There are several ongoing randomised trials, where radiotherapy alone is being compared with a combined radiochemotherapy treatment in this group of patients, but the results are not yet available.

ADJUVANT TREATMENT

The use of adjuvant radiotherapy in rectal cancer surgery has been discussed for more than 30 years and has been used in several well-conducted randomised trials and we know that the local recurrence rate will decrease substantially and a slight effect on survival has been shown. Despite this, there are still many controversies regarding the benefit of this type of treatment. Questions on dose levels, timing, should it be used pre- or post-operatively and to which group of patients should this treatment be recommended?

In my opinion, too many surgeons have taken a wrong attitude to all these questions. They say, ''since so many questions have to be answered, I will wait for the right answer, and meanwhile, I will just operate upon my patients''. They do not even send their patients into a trial to rule out some of the questions.

Radiotherapy—alone, effect on local recurrence rate

According to Table 1, it is obvious that the reduction in local recurrence rates is dose dependent. It is also clear that pre-operative radiotherapy is more effective than post-operative in reducing local recurrence rates. Since a local recurrence is a dreadful disorder for the patient and almost always an incurable situation, all efforts should be made to reduce it. As can be seen in Table 1, if standard surgery alone is used, the recurrence rate will be approximately 30%, which means that one third of all patients will suffer from this condition. If appropriate radiotherapy is added to standard surgery the recurrence rate will be reduced to 15%. Data from the Swedish Rectal Cancer Trial also show that the recurrence rate is reduced with 58% in all situations after pre-operative radiotherapy, which means that in hospitals where the recurrence rate after surgery alone is 30%, it will fall to 15% with radiotherapy [16]. At those hospitals reporting low recurrence rates (approximately 5%) almost all local recurrences have occurred in the surgery alone arm and very few in the radiotherapy arm, indicating that a combination of optimal surgery and radiotherapy will more or less eradicate a local recurrence.

Radiotherapy plus chemotherapy

There are experimental data which indicate that a combined pre-operative radiochemotherapy schedule could be better [8, 9]. This was tested in randomised settings in The Netherlands and Denmark in the early 1980s. Both trials had to be closed due to toxicity [23, 24]. As mentioned above, radiochemotherapy has been used in patients with locally advanced disease. These patients accept more toxicity and are more motivated for having this combined treatment, but in cases where the treatment is an adjuvant setting, it can be too tough.

The American experience has shown a survival benefit when chemotherapy is combined with radiotherapy [19, 20, 25]. The three trials which reported a survival benefit when chemotherapy was added to postoperative radiotherapy, have also shown almost the same magnitude in terms of survival figures if chemotherapy is used alone, indicating that those promising data merely reflect the effect of chemotherapy rather than radiotherapy [19, 20, 25].

Effect on survival

The concept which has been accepted in the U.S. with post-operative chemoradiotherapy in cases with Dukes' stage

B and C is a result of the survival figures from the American trials. It is interesting to note that the latest data from the Swedish Rectal Cancer Trial, where 25 Gy in 1 week used pre-operatively, has shown an overall survival benefit to the patients who have had pre-operative radiotherapy. 58% of all patients who had received pre-operative radiotherapy were alive after a minimum follow-up of 5 years. In the surgery alone group this figure was 48%, a highly statistically significant difference [16]. Why have those good results not been reported before? The reason is the dose-level and the size of the trial. The dose used in Sweden, 25 Gy (5×5 Gy in 1 week), is probably a very high-dose. The exact correlation to a more conventional treatment using 1.8–2 Gy daily is not known. 25 Gy in 1 week is probably equivalent to 50–55 Gy with conventional fractionation. Moreover, in the Swedish Rectal Cancer Trial, 1168 patients were included. Similar good results on survival has been noted in the North-West trial from U.K. [12]. In this trial, where 20 Gy (4×5 Gy in 1 week) were used, a significant effect on cancer specific survival was demonstrated [12], despite a low number of patients in the trial.

It is not likely that adjuvant radiotherapy will have an impact on occult liver metastases. However, the reduction in local recurrence rate which has been demonstrated in all trials using preoperative radiotherapy (Table 1) indicates that adjuvant radiotherapy will have an impact on survival. According to the studies from Erlangen by Professor Hermanek, there is a clear correlation between survival and the number of local recurrence rate [26]. This can be explained by the fact that, in 20–30% of all patients with a recurrent rectal cancer, the disease recurs locally first and then disseminates to other organs. It is also interesting to see that the effects on survival in the Swedish Rectal Cancer Trial are of the same magnitude as the figures shown in the American trials, indicating that pre-operative treatment will have a similar good effect on survival as postoperative radiochemotherapy. For me, it is more logical to use pre-operative radiotherapy alone and add the best postoperative chemotherapy regimen in cases with Dukes' stage B and C. Another option is of course to use pre-operative chemoradiotherapy. This schedule has not been properly tested in an adjuvant setting and we know that the toxicity is very high. To use such an adjuvant treatment may be questionable.

WHY SHOULD WE USE ADJUVANT RADIOTHERAPY?

It is interesting to discuss rectal cancer surgery among surgeons. Several surgeons propose that adjuvant radiotherapy is of no use. They quote figures from Heald and associates and Enker and colleagues and claim that radiotherapy is not necessary. However, if we look at all randomised trials (Table 1), we know that the recurrence rate in the surgery alone arm is much higher. The main question is, of course, whether all surgeons can be as good as Mr Heald or Dr Enker. I think that surgeons are fooling themselves by quoting exemplary data in the literature. The only way to know their own figures is to have an appropriate audit from all rectal cancers. After having seen those data, I am willing to discuss whether radiotherapy should be used or not. Data from Uppsala have been reviewed and during the last 8 years we have not seen a single local recurrence after pre-operative short term radiotherapy in operable cases. Unfortunately, our first recurrence in 7 years was diagnosed in November 1995, out of 230 cases. Those figures have been achieved with proper surgery, but all patients have had pre-operative radiotherapy, again indicating that local recurrences can be more or less eradicated if optimised surgery is performed after pre-operative radiotherapy.

The main problem is to predict the group of patients who will develop a local recurrence. Such a prognostic prediction is not possible today and therefore most patients have to be sent for pre-operative radiotherapy. There is a group of patients with a tumour confined to the bowel wall, who have a very little risk of having a local recurrence after proper radical surgery. That group of patients can be disclosed with pre-operative ultrasound, which should be used in this group of patients [27].

SAFETY WITH RADIOTHERAPY

We have to admit that by using adjuvant treatment several patients will receive overtreatment. Therefore, such treatment must be as non-toxic as possible. Postoperative complications after pre-operative radiotherapy can be minimised if radiotherapy is optimised [28]. There is no risk of postoperative mortality, anastomotic dehiscences or other complications. The only adverse effect which has consistently been noticed in all trials using pre-operative radiotherapy is an increased risk of having a perineal wound infection in patients operated upon with an abdomino-perineal excision. This risk is increased from 10% without radiotherapy to 20% with radiotherapy [16].

In the long run very little has been done to evaluate late adverse effects to radiotherapy. According to our own experience in Uppsala it looks like pre-operative radiotherapy has the same complication rate in the long run as surgery alone, whereas postoperative radiotherapy will double the risk of late adverse effects like small bowel obstruction, perineal fibrosis and urinary disorders [28].

CONCLUSIONS

To me it is obvious that pre-operative radiotherapy should be used in patients with rectal cancer. It is not ethical to perform a more aggressive surgery as proposed by the Japanese surgeons, with a very high risk of impotence and bladder dysfunction, when you can achieve exactly the same effect with adjuvant radiotherapy. I also believe that surgeons have to question themselves as to whether or not they are a new Bill Heald. We must admit that his results are extremely good, an effect of several years working on the most perfect solution to this problem. Of course, it would be wonderful if surgeons all around the world could improve their surgery to that level so that radiotherapy is superfluous, but unfortunately I do not believe this.

My recommendation is that all surgeons use pre-operative radiotherapy in resectable rectal cancer and try to adopt the mesorectal excision. Moreover, an aggressive audit is mandatory. If the local recurrence rate is more or less eradicated with this treatment schedule, it indicates that surgery is good and radiotherapy is appropriate. After such an experiment, it might be advisable to postpone radiotherapy in selected favourable cases and see what happens. If the recurrence rate is still very low, it may be possible to change the situation even more, but for most of the patients I think pre-operative radiotherapy is necessary. This is even more important for the very low tumours, where an abdominoperineal excision is the surgical option. In this group of patients, we know that radi-

cal surgery can be doubtful due to difficulties in dissection. This is especially true for men, when the tumour is growing anteriorly. Therefore all patients, despite the size of the tumour, should have pre-operative radiotherapy if it is known in advance that the patient will have an abdominoperineal excision.

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THE DEVELOPMENT of a locoregional recurrence of a rectal carcinoma has a substantial influence on the overall prognosis [1–5]. An earlier analysis involving our own patients showed that, following an RO resection (and leaving out consideration of all other criteria), the 5-year survival rate for patients with no local recurrence was 85%. Otherwise, the 5-year survival rate was only 23% [6]. It has also been shown that, as the global local recurrence rate over the last three decades has declined from more than 40% to just under 10% today, so the 5-year survival rate has increased from 50 to 71% [7]. A review of the results reported in the literature also confirms this direct association [8–14] as does the evaluation of the German Study Group Colorectal Carcinoma (SGCRC) with respect to the individual surgeon (Figure 1). Finally, in a multivariate analysis based on data of the SGCRC, curative

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