150 The role of radiotherapy in rectal cancer treatment in 2007.

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Introduction

The most important part in treating patients with rectal cancer is surgery, although the overall treatment policy has changed during the last three decades. Surgery has become more precise with a specific attention to a locally more aggressive and meticulous technique. Moreover, local excision has become a realistic alternative in some patients. The value of concomitant radiotherapy as well as the use of chemotherapy given pre– or postoperatively, has been studied extensively in many trials showing the benefit of adding chemotherapy and radiotherapy to surgery.

Based upon the modern treatment philosophy, with a multidisciplinary approach, every single patient must be offer the best and most appropriate treatment based upon a correct local staging as well as evaluating eventual spread of the disease to distant

organs. After the local and distant staging process the next step is to decide how to use adjuvant radiotherapy and/or chemoradiotherapy but also how to use different types of surgical approaches, i.e., local excision or an abdominal procedure.

Surgery

The decision making between a local excision and an abdominal resection is based upon estimating the risk of lymph node metastases in the mesorectum. This estimation is done with a proper preoperative T-staging, and to reach this endorectal ultrasound is necessary, since no other staging technique (CT or MRI) can with high accuracy evaluate whether or not the tumour is growing into the m. propria or not. A T1 tumour, i.e., not growing into m. propria has 1-15% risk of having involved lymph nodes in the mesorectum dependent upon how deep into the subserosal tissue the tumour is penetrating [1,2].

If a local excision is planned the TEM-technique (Transanal Endoscopic Microsurgery) is to be preferred due to a better visualisation of the tumour area with a much better chance of having a local radical excision. Based upon the final pathological report a proper risk analysis can be done regarding possible lymph node metastases, based upon the SM 1-3 classification proposed by Kukuchi et al [1].

If, based upon digital examination, it is obvious that the tumour cannot be excised locally an abdominal procedure must be consider. In this group, adjuvant radiotherapy must be considered and therefore a proper staging with MRI (Magnetic Resonance Image) is essential. With a high resolution technique the distance from the bowel wall to the rectal fascia can be estimated as well as whether or not the fascia is involved indicating that the circumferential resection margin will not be free at surgery [3-5]. If the margin is involved neo-adjuvant radiotherapy should be considered.

The abdominal part of the procedure has changed dramatically during the last 3 decades. The more precise dissection technique following the rectal fascia leaving the mesorectum intact as proposed by Mr Heald is essential, i.e., the TME-technique (Total Mesorectal Excision) [6]. The most challenging part of rectal cancer surgery is the perineal part of the abdominoperineal resection. With the patient in the prone position and excise the pelvic floor cylindrically a waste will be avoided leading to a radical procedure [7].

Radiotherapy

The indication for radiotherapy in the treatment of rectal cancer can be divided in four main topics.

1. To lower local recurrence rates and improves survival in resectable rectal cancer.
2. To allow surgery in non-resectable rectal cancer.
3. To facilitate sphincter-preserving procedures in low lying rectal cancer.
4. A totally curative procedure without major surgery.

To lower the local recurrence rate and improve survival in resectable rectal cancer.

Radiotherapy has been used for more than 30 years as a neo-adjuvant (given preoperatively) or adjuvant (given postoperatively) treatment and both settings has been used in combination with chemotherapy. According to the three published meta-analyses there are no doubt that neo-adjuvant treatment is superior in terms of reduction in local failures rate and cancer specific survival [8-10]. This is supported by the results from the three trials that specifically have studied pre- vs. postoperative radiotherapy. The first report was the Uppsala Trial where short-course preoperative radiotherapy to all patients was compared with postoperative prolonged course only till patients with advanced cancers (stage II and III) [11]. The other two trials have compared neo-adjuvant chemoradiotherapy with adjuvant chemoradiotherapy with same schedules and doses. The NSABP R-03 trial, which closed prematurely because of poor accrual, showed that 44% of patients having undergone preoperative chemoradiation were disease-free at one year, compared with 34% of patients who had received postoperative chemoradiation [12]. The German CAO/ARO/AIO-94 trial was randomizing patients with T3-4 N0-1 rectal cancer to neo-adjuvant chemoradiation followed by surgery and additional postoperative chemotherapy or postoperative chemoradiation. The local recurrence rate was halved in the preoperative setting and the survival was superior although not statistically significant in the neo-adjuvant arm [13].

Neo-adjuvant therapy: radiation alone versus chemoradiation

The advantages of neo-adjuvant therapy include increased tumour radiosensitivity with decreased small bowel toxicity, decreased overall radiation, and decreased tumour seeding. The main disadvantage of neo-adjuvant therapy is the risk for overtreatment in patients with early-stage disease. However, with appropriate imaging with endorectal ultrasound [14] and magnetic resonance imaging (MRI) [3-5] preoperative identification of patients with T2 and T3 tumours will be identified, thus minimizing the number of patients who would be overtreated.

Neo-adjuvant radiation alone has been used with to main techniques, i.e., the short preoperative course, 25 Gy given during one week (most commonly used), or as a long-course treatment of 45-55 Gy given over 5-6 weeks. Both schedules have an equivalent biological effect on the tumour. In 1996, the Swedish Rectal Cancer Trial (SRCT) demonstrated that short course (25 Gy) of preoperative radiotherapy with surgery within the next week significantly reduced local recurrence from 27% to 12%, and improved 5-year survival rates from 48% to 58% when compared to surgery alone [15]. In new follow-up more than 10 years, the beneficial effect of radiotherapy dose exist [16]. The main objection to all trials published during the 80's and early 90's, including the SRCT, is that surgery was not optimal. The average local recurrence rate in the „surgery alone"-arm in all trials dis-

cussed in the meta-analyses was 29-30% [8-10]. Although the undisputed major benefits of preoperative radiotherapy remain loco-regional tumour control with a decreased local recurrence rates, several reports have shown that the same low local recurrence rates have been achieved in specialized centres with surgery alone using a more meticulous surgery [17-19]. Several reports from different countries have demonstrated that surgical skill is of outmost importance, and the use of radiotherapy can be discussed if surgery is optimized [20-23].

In the Dutch trial short-course neo-adjuvant radiotherapy followed by surgery in one week was tested against surgery alone but it was mandatory that surgeons had adopted the TME-technique before entering patients. A total of 1861 patients were included and a significantly improved 2-year local recurrence rates from 8.2% to 2.4% was noticed if preoperative radiation was given [24]. The improvement in local recurrence rate after five years follow-up is 11.4% to 5.6% but now advantage in overall 5-years survival has been demonstrated in this trial [25].

There are several theoretical reasons to combine chemotherapy to preoperative radiation. The addition of 5-FU based chemotherapy may theoretically act as a radiosensitizer and has therefore been used in advanced rectal cancers (see below). However, in patients with advanced but resectable tumour (T3-4, N2) two randomized phase III study comparing neo-adjuvant radiotherapy versus neo-adjuvant chemoradiotherapy have failed to demonstrate an survival effect although the local recurrence rate have been halved from 11% to 5% [26,27].

Postoperative adjuvant therapy: radiation alone versus chemoradiation.

The rational of reserving adjuvant treatment for the postoperative setting is to restrict its use to patients who are at identified risk for failure, based on their histopathologic staging. Disadvantages include a higher incidence of radiation-related complications, particularly to the small bowel and a higher number of patients unable to complete the entire course of therapy because of treatment side effects.

Several trials using postoperative radiotherapy alone was conducted during the 80's and did report decreased local recurrence, although not to the same extent as neo-adjuvant treatment, and but this reduction did not improve survival [28-30]. If radiotherapy was combined with 5-fluorouracil based chemotherapy an increased local control and significantly improved survival by 10-15% [31,32]. All those trials were heavily under-powered, but despite this, these findings prompted the National Cancer Institute Consensus Conference of 1990 to recommend combined modality chemoradiotherapy as the standard postoperative adjuvant treatment for patients with stage II and stage III rectal cancer [33]. Although a recently published Norwegian trial confirmed [34] these findings, many countries, especially in Europe, did not follow those recommendations manly due to the fact that neo-adjuvant radiotherapy was proven to be more efficacious. Other reasons are the relative radioresistance of the hypoxic surgical bed and the risk for re-population of tumour cells from surgery to the start of radiotherapy.

To allow surgery in non-resectable rectal cancer.

A non-resectable rectal cancer is by definition a tumour not possible to excise without a very high risk of a local recurrence, indicating that the tumour has an involvement with the rectal fascia. Accordingly, there is a high risk of having a positive circumferential resection margin on the surgical specimen. These are the tumours which are tethered or fixed but it is difficult to know whether or not the fixity is due to cancer overgrowth or fibrosis. From the literature it is obvious that there is no uniform definition of a non-resectable rectal cancer but based upon available data, patients with such a large tumour do benefit from a preoperative radiotherapy with the aim to downsize the tumour. Approximately 10-15% of all patients with a rectal cancer do have an advanced cancer, which could be considered non-resectable and half of those patients have no metastases, indicating that there is a potential possibility for a curative procedure [35]. Surgery alone is likely to cure very few and therefore it is more or less mandatory to offer those patients radiotherapy. The question is whether this should be combined with chemotherapy. However, in this specific setting short-course radiotherapy is not a valid option. The rationale for using radiotherapy in this group of patients is the down-sizing effect and therefore a prolonged treatment with conventional radiotherapy (25x2 Gy) over a five weeks period is used. After a waiting time for up to 6-8 weeks the tumour shrinkage will make it possible to do a curative procedure.

The evidence for chemoradiotherapy based upon randomised trials is very poor with only one old positive trial published in 1969 [36] and two negative trials with increased toxicity published in the late 80's [37,38]. One Swedish trial in which patients was randomised to long-course radiotherapy alone or to long-course chemoradiation was published in 2001 showed a beneficial effect on both local recurrence rate and survival. Unfortunately, that trial was under powered [39]. However, several phase II trials have reported a good reduction in local recurrence rate and these data are also very impressive regarding survival [40,41]. The problem with all different reports is the case-mix making it almost impossible to really interpret the trials since the definition of 'non-resectability' differs enormously. One recently finished Nordic trial, the LARCS trial, where patients were randomised to either 50 Gy preoperatively or 50 Gy and chemotherapy preoperatively. The trial has just been closed and preliminary data supports the advantage of chemoradiation in this group of patients [42]. Despite lack of good evidence-based data the movement is strong and many patients will be offered chemoradiotherapy, and probably no more trials with a radiotherapy arm will start.

Although no strong evidence-based data support the use of chemo-radiotherapy in patients with advanced rectal cancers, most radiotherapists and medical oncologists use this combined treatment to improve the effect of radiotherapy. The newer chemotherapeutic agents currently in use or under study for treatment of locally advanced and metastatic colon cancer (e.g. irinotecan,

capecitabine, and oxaliplatin) will doubtlessly be evaluated for their usefulness in neo-adjuvant treatment of rectal cancer in the near future and several phase-II trials are ongoing [43].

To facilitate sphincter-preserving procedures in low-lying rectal cancer.

It has been claimed from several series that preoperative radiotherapy and preferably chemoradiotherapy will downsize the tumour to that extent that it is possible to increase the number of patients where the sphincters could be preserved [44-48]. Moreover, there is one group who has reported a series of patients with complete response to chemoradiotherapy (including T4 tumours), where surgery has been postponed with several long-term survivors and those patients are alive and doing well despite no surgery has been done [49].

However, the problem with all those phase II trials is that all authors are comparing the results with historical controls from their own unit. Since surgery has change the last two decades with acceptance of a much less distal margin of 5-10 mm margin it is difficult to interpret all trials [50-51]. Therefore, randomised comparisons with patients treated having different radiation options have to be done. In one French trial, were sphincter preservation was an endpoint, patients with T2 and T3 tumours had preoperative 39 Gy (13 x 3 Gy) and were randomised to immediate surgery or surgery 5 weeks after irradiation. The surgeons were asked before any treatment to evaluate the possibility to preserve the sphincters. There is a slight increase in numbers where the sphincter could be preserved if surgery was delayed [52]. However, the overall recurrence rate was 9%, which is considered a rather high figure today, but more importantly, the local recurrence rate among those patients where the surgeon change the procedure to a sphincter sparing one was 12% [52].

A sub-group analysis from the German trial (CAO/ARO/AIO-94) where patients were randomised to pre- or postoperative chemoradiotherapy, revealed an increase in sphincter preservation if preoperative chemoradiotherapy was used (35% vs. 18%). However, it is not possible, based upon the report to interpret the figures and the overall sphincter preservation was the same in both arm, and no data on local recurrence rate from this sub-group is reported [13].

Another very important trial is the Polish trial, where patients were randomised to short-course radiotherapy with immediate surgery vs. a long-course chemoradiotherapy and delayed surgery. The inclusion criterion in this trial was a tumour possible to be reached by a digital examination but no sphincter infiltration. It should be a T3 or a resectable T4 tumour and 1 cm microscopic distant margin was sufficient. This trial was conducted to see whether chemoradiotherapy and delayed surgery would have an impact on sphincter preservation and this was primary end-point in the trial together with local recurrence rate. More than 300 patients were randomised and after closure of the trial the percentage of preserved sphincters was identical in both groups, 61% in the short-course radiotherapy with immediate surgery vs. 59% in the prolonged chemoradiotherapy course and delayed surgery [53].

The results from the Polish trial are important and underlines that there is still no good evidence supporting that a prolonged course radiotherapy combined with chemotherapy with delayed surgery will have an impact on sphincter preservation. A very important draw-back of having too many sphincters preserved is actually the poor function. In some reports up to 20% of all patients are incontinent for solid stools [47]. This cannot be a good quality of life! Moreover, there are data supporting that, as a group, patients with a stoma has a better quality of life compared to those with an anterior resection [54].

In summary, there are rather vague data supporting that chemoradiotherapy will reduce more preserved sphincters than radiotherapy alone. Probably, an important factor is the waiting time from end of radiotherapy to surgery to achieve good downsizing and this might improve the number of sphincters preserved.

Conclusion

Based upon available literature the use of radiotherapy can be summarised as followed:

Provided the preoperative staging indicates a high risk of having a local recurrence after surgery alone (> T3 tumours) preoperative radiotherapy should be considered. Data do support that preoperative short-course radiotherapy is as good as long-course radiotherapy. If the preoperative staging indicates an involved margin, preoperative long-course chemoradiation should be considered. There is still no evidence supporting that radiotherapy or chemoradiation will increase sphincter-preservation.

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