Long-term outcome of rectal cancer treatment

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CHAPTER 10

Discussion and future perspectives

Curative rectal cancer treatment has been performed for more than 100 years. It was initiated by Miles, who established the focus of attention on the importance of local tumour spread and lymph node involvement. In 1908 he introduced radical tumour resection by abdominoperineal resection (APR). In the subsequent century rectal cancer treatment has tremendously progressed. Rectal cancer surgery turned from destructive amputative surgery to restorative surgery by changing surgical technique from conventional blunt dissection to total mesorectal excision (TME) with sharp dissection.[1] Sharp dissection in the avascular plane between the mesorectum and surrounding tissues led to improved overall survival (from 48 percent to >60 percent), reduced local recurrence rates (from >20 percent to <10 percent), higher incidence of sphincter preservation and reduced peroperative blood loss and autonomic nerve damage.[2-5] The addition of radiotherapy further improved outcome of rectal cancer treatment. In the Dutch TME trial five-year local recurrence risk of patients undergoing a macroscopically complete local resection was significantly reduced in case of short-course preoperative radiotherapy (PRT; 5x5 Gy over 5 days) compared to patients undergoing surgery alone (5.6 *versus* 10.9 percent; $p<0.001$).[6] However, PRT was shown to be ineffective in case of incomplete tumour resection.[7] Involvement of the circumferential resection margin (CRM) remained the most important prognostic factor.[8] Reducing the risk of CRM involvement was recognized to be a matter of team work. Standardised pathological examination of the surgical specimen has become an important tool to evaluate surgical quality and provide feedback to the individual surgeon. Furthermore, the MERCURY-study group demonstrated that high-resolution magnetic resonance imaging (MRI) is accurate in predicting whether the CRM will be affected by tumour.[9] In that case, radiation and medical oncologists decrease tumour burden by administering prolonged chemoradiotherapy (CRT), increasing the likelihood that the surgeon can perform a radical (R0) resection. Burton *et al.* showed that multidisciplinary team discussion of MRI and implementation of a preoperative treatment strategy result in significantly reduced positive CRM rates in rectal cancer patients.[10] In this manner rectal cancer treatment has evolved into a multidisciplinary treatment with standardised surgical, pathological and radiotherapeutical procedures.

Today rectal cancer treatment continues to develop explicitly. First of all, an increasing role of adjuvant chemotherapy is to be expected. In contrast to the amazing achievements with respect to locoregional control, the rates of distant metastasis have not changed since the early eighties.[11] Distant metastases are accountable for mortality and frequently occur, regardless of radiotherapy (25.8 percent *versus* 28.3 percent).[4] Adjuvant chemotherapy might approach micrometastatic disease early, trying to control it and by this, curing more patients and prolonging survival over

locoregional therapies alone. The development of effective adjuvant chemotherapy for rectal cancer is a priority issue. In the past adding adjuvant chemotherapy to long-course PRT (45-55 Gy in 1.8 Gy fractions over 4-6 weeks) has been proven to be ineffective for improving survival of rectal cancer patients, however this was in the era of conventional surgery.[12] In the more recent EORTC 22921 and FFCD 9203 trials, adjuvant chemotherapy did not improve survival either.[13,14] Furthermore, in the Polish study survival of patients treated with long-course CRT was similar to survival in patients treated with short-course PRT only.[15] However, in these studies surgical quality control was not performed. Currently, the SCRIPT (Simply Capecitabine in Rectal Cancer after Irradiation Plus TME) trial randomises stage II/III rectal cancer patients who have had 5x5 Gy plus TME between oral capecitabine and observation.

Another purpose of chemotherapy in the multimodality approach of rectal cancer is enhancing the efficacy of radiation. Due to the modulating effect of chemotherapy on tumour cells and therefore increased sensitivity for radiation damage, CRT was expected to be superior to radiotherapy alone with respect to local control. Buijko *et al.* reported similar local recurrence rates in patients treated with short-course PRT compared to patients treated with long-course CRT.[15] However, the addition of chemotherapy to long-course PRT in the EORTC 22921 and FFCD 9203 trials resulted in a significant reduction of local recurrence rates.[13,14] Furthermore, higher rates of tumour eradication (pathologic complete response, pCR) were found. The sterilisation effect of CRT would significantly reduce the risk of lymph node metastases, which may reach rates over 13 percent even in T1 rectal cancer.[16] Therefore, patients with early rectal cancer after neoadjuvant treatment (ypT1 and ypT2) might be considered candidates for local excision by means of transanal endoscopic microsurgery (TEM), which has shown disappointing local recurrence rates of 15-30 percent in patients treated without neoadjuvant treatment.[17] In case of pCR, which has been reported in 10–30 percent of patients treated with preoperative CRT, surgery might even be omitted.[18,19] Rutten *et al.* recently stated that treatments that keep surgical trauma to a minimum and optimise the use of radiotherapy might be more suitable for elderly patients with diminished physiological reserves and comorbid conditions.[20] The development of rectum saving treatment is further encouraged by our finding that surgery is the main cause of functional morbidity after rectal cancer treatment. However, discrepancy exists between clinical complete response (cCR) and pCR.[21] In case of cCR cancer cells are found in 40-75 percent of postoperative specimens.[18,21-24] Moreover, following preoperative CRT, the incidence of residual mesorectal lymph node involvement remains significant.[25] Nevertheless, the study of Habr-Gama *et al.* in which patients with sustained cCR were managed by observation alone has shown excellent results.[26] However, results of patients with cCR who did

not receive surgical treatment and developed a recurrence within one year were not provided. Furthermore, as local recurrences after CRT tend to occur late, follow-up was too short. Therefore, long-term follow-up of prospectively conceived multicentre data concerning safety and functional outcome are needed.

The overall aim of clinical research in rectal cancer should be to develop a range of multidisciplinary treatment strategies that can be tailored to the requirements of individual patients, taking into consideration disease factors and patient factors, such as the presence of comorbidities and risks of suffering treatment-related complications. Improved imaging techniques and translational research are required for the identification of patients groups which will gain the maximum benefit from each treatment option. Magnetic resonance imaging with lymph node specific contrast enhancement may be the most promising modality for distinguishing between the lower risk N0 rectal cancer patients, for whom TEM or TME might suffice and higher risk N1 and N2 rectal cancer patients, which should be treated with PRT followed by TME. New MRI contrast agents, like ultrasmall superparamagnetic iron oxide (USPIO) and MS 325 may help radiologists to solve the problem of lymph node identification in the near future.[27] A cohort study in which 322 patients were stratified into different treatment groups after USPIO-MRI has shown promising results (95 percent complete resections). Furthermore, translational research will contribute to tailored treatment based on individual tumour profiles in the near future. Genomics and proteomics enable identification of biomarkers which may be used to predict prognosis and response to treatment. For example, local recurrence can be predicted by detection of tumour apoptosis-levels through measurements of caspase-3 activity.[28] Research on cancer biology and the discovery of a number of molecular pathways has also led to the development of molecular targeted treatments. Bevacizumab, the monoclonal antibody targeting the vascular endothelial growth factor, as well as cetuximab, which is a monoclonal antibody against epidermal growth factor receptor, have recently been approved to be used against advanced colorectal cancer. The optimal use of these agents, as well as their combined administration, are currently the focus of several ongoing studies.[29]

In the progress of rectal cancer treatment during the upcoming century, surgeons will remain the key characters. Several aspects of surgical performance are to be improved. Firstly, anastomotic leakage remains a frequently reported complication after low anterior resection (LAR) and is associated with postoperative mortality and increased recurrence rates.[30] At present, temporary defunctioning stomas are often created as it has recently been shown to limit the consequences of anastomotic leakage.[31] However, den Dulk *et al.* showed that a substantial proportion of these stomas are never reversed (19 percent).[32] Therefore, the chance of stoma reversal

should be estimated preoperatively and an individualized decision should be made on resection type by counterbalancing the possible loss of quality of life (QoL) in case of a definitive colostoma created during APR, which depends on the patient's preferences and socio-demographical characteristics, with the patient's comorbidity, which might limit successful reversal of a temporary stoma after LAR. Furthermore, vascular ligation technique might influence anastomotic healing. Although data are not conclusive, Chapter 2 suggests that high tie ligation, which is the most popular technique, might be less preferable than low tie ligation.[33] However, a change of practice is unlikely to occur. As anastomotic leakage will probably remain a problem in the upcoming decades, it is important to control the consequences in case anastomotic leakage occurs. Currently, a standardised postoperative surveillance is being introduced in The Netherlands to reduce delay in the diagnosis of anastomotic leakage and mortality.[34]

Secondly, APR resection technique needs to be improved. At present, APR is associated with worse local control and a 10 percent reduction in overall survival.[35-37] Positive CRM rates are 26.5 percent after APR *versus* 12.6 percent after LAR ($p<0.001$), which indicates that the quality of the surgical procedure is a crucial factor contributing to the poor results after APR.[36] In this respect preoperative CRT is suggested. Chemoradiotherapy and delayed surgery has been shown to downstage and downsize tumours.[23,38] However, downstaging and downsizing are not the only contributors to free CRM. In the EORTC 22921 trial, it was shown that no significant difference in CRM involvement was obtained after preoperative CRT despite an impact on tumour stage and size.[39] Therefore, improvement in surgical technique remains necessary to reduce CRM involvement. Wider perineal and pelvic floor resections for low rectal cancers will improve results after APR in the upcoming decade.[35,36,40]

Upgrading surgical performance also implies reducing variability among surgeons. Total mesorectal excision is a difficult and technically demanding operation and the skills of the surgeon are of major importance in achieving good results.[41] Surgical trainee programmes can have a major impact. The national Scandinavian and Dutch surgical initiatives have shown lasting effects of training of surgeons in resection technique.[34] Also case volume appears to be related to variability in patient outcome.[41] In order to improve results in the future all patients should be offered cure by a well educated, multidisciplinary team in high-volume centres. In addition, CRM involvement should be determined in daily practice as it is an important parameter of outcome and essential for feedback to the individual surgeon.[41] A recent study evaluating the rate of reported CRM in the pathology report, found an increase from 37 to 70 percent after feedback to the regional pathology working group.[42] This illustrates the importance of registration to assess and improve quality of rectal cancer treat-

ment. From January 1st 2009 a Multidisciplinary Quality Assurance Program will be started under the initiative of the European Society of Surgical Oncology (ESSO) implicating outcomes registry which will enable assessment of structure and process of care, identification and implementation of best practices and subsequent confirmation of improvement of rectal cancer treatment. In this manner, reliable treatment evaluation becomes within reach for individual centres and individual surgeons. In case of suboptimal performance, treating teams can be encouraged either to improve their treatment results by seeking additional training or to stop treating rectal cancer patients. This will reduce variability and contribute to improved clinical outcome. When counterbalancing this against expensive chemotherapy regimens and universal leukocyte depletion of transfused blood products, both beneficial to only a minority of patients, one has to conclude that upgrading the surgical performance is cheap and definitely cost effective.[43,44]

Given the increasing number of treatment alternatives in rectal cancer treatment, it will become increasingly important to accurately capture the impact of different treatment regimens on QoL. This would help in making difficult decisions, in which modest changes in survival or local control must be balanced against effects on QoL, from chemotherapy and radiotherapy toxicities to permanent colostomies. Understanding the impact of various treatment alternatives on postoperative QoL will help to choose a plan optimising both oncologic outcome and function. Therefore, QoL is now regarded as a key measurement in assessing outcomes of interventions.[45,46] However, as patients adjust to the functional changes after having survived cancer, their perception of QoL might shift and might not accurately reflect postoperative functional differences.[46-49] Interestingly, QoL of rectal cancer patients is comparable to that of the same aged general population, despite significant problems with respect to anorectal and urogenital functioning.[46,50-52] Therefore, QoL measurements, such as the EORTC C-30 and CR-38 are not suitable to detect functional differences and thus to determine the optimal treatment strategy.[53,54] More data concerning specific organ dysfunction before and after rectal cancer treatment are required. This may help patients set realistic expectations for their postoperative life. More realistic expectations may, in turn, help patients to adapt to functional alterations postoperatively, resulting in a better QoL. Next to informing patients, it has been suggested that patients need to be involved in treatment decision making. Especially when a patient presents with a serious illness, different treatment options exist, the gains of treatment should be weighed against possible adverse effects, or outcomes are uncertain, patient involvement is required.[55] This is supported by the fact that both individual patients and individual oncologists greatly vary in their perception of how tumour control, survival and functional outcome should be weighed in decid-

ing upon the most preferable treatment.[56,57] At present, patients are often informed through internet and prefer a more active role in decision making. However, there is considerable evidence suggesting that patients do not wish to be involved in decisions regarding their own care and instead prefer a more paternalistic approach in which their physicians make the decisions for them.[58] An ongoing project is investigating to what extent patients and oncologists believe that patients should also participate in decision making regarding therapy.

To adequately balance benefits and costs of each treatment alternative and to elucidate etiology for prevention and treatment of postoperative organ dysfunction, systematic registration of preoperative and long-term postoperative pelvic organ dysfunction is needed. In this respect the Dutch TME trial has been exceptional. This study, which was a surgical initiative conducted by the Dutch Colorectal Cancer Group (DCCG) organised rectal cancer treatment for the first time and realised specialisation of surgeons in TME surgery and nerve preservation and pathologists in assessment of the quality of resected specimens. High compliance of patients, radiotherapists, surgeons and pathologists has generated a unique set of long-term data, among which different aspects of QoL. Through the current thesis the Dutch TME trial has provided insight in the incidence and etiology of long-term pelvic organ dysfunction after rectal cancer treatment. Poor functional outcome appears to occur commonly: about one third of patients reported urinary dysfunction, half of patients suffered from faecal incontinence and more than half of patients experienced deterioration of sexual functioning. Significant adverse effects of short-course PRT on long-term anorectal and urogenital functioning were observed, which is supported by the Stockholm trials.[52,65,68] This has resulted in criticism against short-course PRT. However, reliable data concerning late side-effects of other regimens are lacking. In a study of Buijko *et al.* short-course PRT was compared with preoperative CRT and no increased toxicity was observed after short-course PRT.[15] Furthermore, the addition of chemotherapy might result in even more dysfunction, as it has been shown to induce nerve damage.[72] Long-term functional outcome of long-course CRT should be evaluated extensively.

In this thesis, it has been shown that despite the additional effect of PRT, anorectal dysfunction seems to be mainly caused by surgical damage, as even without PRT faecal incontinence occurs in 40 percent of patients.[50,73] In addition, in Chapter 4 we found only a minor effect of PRT on sexual dysfunction . Moreover, no contribution of PRT in the development of urinary dysfunction was shown in Chapter 5.[51] Therefore we conclude that pelvic organ dysfunction is mainly caused by surgical factors. First of all, surgical resection of rectal cancer inevitably results in a decrease in maximum tolerated volumes, as the neorectum has a relatively low capacity.[71] Moreover, the rich network of nerve endings to the anal canal, sensitive to pain, temperature and

touch differentiating solid or liquid stool from flatus and allowing selective passage is removed. This also explains why patients with a small neorectum after resection of a distal tumour are at increased risk of faecal incontinence. Other surgical factors influencing functional outcome, which were identified in our study, include anastomotic leakage and excessive peroperative blood loss. Inflammation and haemostasis by diathermic coagulation and numerous sutures may cause nerve damage. Surgical nerve disruption during dissection is also believed to be a cause of pelvic organ dysfunction.[74-76] Some authors support the idea that specific identification of the pelvic autonomic nerves is not essential during TME surgery.[77] By following the concept of the TME procedure, the pelvic autonomic nerves would be automatically preserved. However, the data presented in this thesis do suggest that avoiding pelvic autonomic nerve damage during TME surgery might be more troublesome than it seems. In a quarter of the cases the surgeon stated that the pelvic autonomic nerves had or might have been disrupted. We found an association between damage to the parasympathetic nerves (pelvic splanchnic nerves and inferior hypogastric plexus) and difficulty in bladder emptying in addition to an association between damage to the sympathetic nerves (superior hypogastric plexus and hypogastric nerves) and ejaculatory dysfunction.[51] The parasympathetic nerves may be disrupted during deep dissection of the lateral planes. The sympathetic nerves are at risk during presacral and ventrolateral dissection of the mesorectum. Regarding the dysfunction rates, it seems probable that the surgeons have underreported nerve damage. Moreover, damage to the levator ani nerve was not reported, as this nerve was not addressed at during the Dutch TME trial. However, the levator ani nerve is responsible for the innervation of the main body of the pelvic floor muscle, which is of major importance for the urinary and faecal continence system.[78,79] The levator ani nerve has been neglected so far, but we have shown this nerve might be involved in the etiology of incontinence after rectal cancer treatment. It is interesting that such a new concept can be developed after rectal resection has been performed for more than 100 years. Although the levator ani nerve has been illustrated in detail as early as in the 19th century (Hirschfield), in current anatomy textbooks it is hardly ever mentioned. Anatomy, as well as surgery, is still developing, and cooperation of anatomists and surgeons may be an effective tool for further progress in the future. Besides the superior and inferior hypogastric plexuses, the hypogastric and pelvic splanchnic nerves, the levator ani nerve also would not be disrupted during a correctly performed TME. However the surgical 'margin' is so small that any deviation from the surgical plane easily results in nerve damage. Differences among individuals in the running patterns of the nerves and variations in the volumes of nerve fibres in each region of the pelvis make appropriate identification difficult. Especially when excessive peroperative blood loss hinders sight in the pelvis, in most cases due to disruption of

the presacral venous plexus, nerve sparing is virtually impossible.[63,64,80] The use of a nerve stimulating device might facilitate preservation of the pelvic autonomic nerves during TME in the future.[81] Data concerning nerve disruption during laparoscopic TME should be awaited. Theoretically, the magnified view of the pelvis afforded by the laparoscope might facilitate nerve identification and thus prevent nerve injury.

In conclusion, this thesis indicates that nerve preservation during rectal cancer surgery needs to be more emphasised in daily practice. In this respect systematic registration of identified crucial structures (superior and inferior hypogastric plexuses, hypogastric and pelvic splanchnic nerves, levator ani nerve) during surgery is needed. Additionally, structured education in pelvic neuroanatomy and training as a prerequisite for certification as a rectal cancer surgeon, would be the key to improvement of functional outcome.

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