Chapter 12

General discussion

Summary

Nederlandse samenvatting
GENERAL DISCUSSION

Colorectal cancer is the cancer with the second highest cancer incidence in Europe. Roughly, one out of three patients with a colorectal malignancy has a rectal carcinoma. Surgery is the cornerstone in the curative treatment of rectal cancer. In the 1980s with conventional surgery, the 5-year local recurrence rate was over 20% and the 5-year overall survival rate around 50%. In the Swedish Rectal Cancer trial in which 1168 patients were included, preoperative radiotherapy in addition to conventional surgery resulted in a reduction of more than 50% in the 5-year local recurrence rate in comparison to conventional surgery alone (11% versus 27%; $P < 0.001$). Besides, the 5-year overall survival rate improved from 48% to 58% if patients were treated with preoperative radiotherapy in addition to conventional surgery ($P = 0.004$). With the total mesorectal excision (TME), by which the rectum with its mesorectum and visceral fascia are dissected sharply and under direct vision, local recurrence rates dropped and overall survival improved. In the Dutch TME trial, 5 x 5 Gy preoperative radiotherapy in combination with TME surgery was compared to TME surgery alone (1861 patients). In this trial, the 5-year local recurrence rate for patients treated with TME surgery alone was similar to patients treated in the Swedish Rectal Cancer trial with blunt dissection in combination with preoperative 5 x 5 Gy radiotherapy (11%). If preoperative radiotherapy was added to TME surgery, 5-year local recurrence rate was reduced to 5.6%. The overall survival rate at 5 year was 64% for both patients treated with TME surgery alone and patients treated with preoperative radiotherapy followed by TME surgery, compared to 48% for patients treated with blunt dissection alone in the previously mentioned Swedish trial. TME surgery is now considered the standard surgical procedure for rectal cancer. However, even if TME surgery is performed, surgical quality varies. First, these results indicate that improvements in the surgical procedure itself can result in major progress regarding long-term oncological outcome such as decreased local recurrence rates and improved overall survival. Second, it illustrates that variation in surgical quality could lead to large differences in outcome. Recently, it was shown that surgical variation is not only important for patients with rectal cancer, but also plays an important role for the outcome of patients with colon cancer.

SURGICAL QUALITY ASSURANCE

In 1991, McArdle and Hole wrote that “some surgeons perform less than optimal surgery... If by meticulous attention to detail the results of surgery could be improved, and our results suggest that this would not be difficult, the impact on survival might be greater than that of any of the adjuvant treatment therapies currently under study”.
Quality assurance aims at reducing variability and can be defined as the systematic measures required to achieve a treatment result that meets a certain standard. These measures include training of all participating surgeons to reduce the variation in skill level, presence of an instructor surgeon during the first procedures of each surgeon, and pathological quality control of the resected specimen on, for example, the number of resected lymph nodes or circumferential resection margin involvement.

Several studies showed that circumferential resection margin involvement is a risk factor for increased local recurrence and reduced overall survival. Some even consider circumferential resection margin involvement as an early (surrogate) end-point. Furthermore, it has been shown that preoperative radiotherapy could not compensate for circumferential resection margin involvement. The predictive value of the circumferential resection margin for local recurrence is significantly higher if preoperative therapy has been applied compared to no preoperative treatment (hazard ratio 6.3 versus 2.0, respectively; $P < 0.05$). Consequently, circumferential resection margin involvement is not only prognostic for oncological outcome, but also influences the studied effects of the (neo)adjuvant treatment. This illustrates the necessity to document circumferential resection margin involvement in randomised trials. Feedback from the pathologist to the surgeon on, for example, circumferential resection margin involvement could eventually improve the number of radical resections. In the MRC CR07 trial, which compared short course preoperative radiotherapy with selective postoperative chemoradiotherapy in case of involvement of the circumferential resection margin, quality of the resection specimen was prospectively assessed and reported to the surgeons. During this trial, the frequency of involved circumferential resection margins decreased. Furthermore, both this trial and the Dutch TME trial showed that poor quality of surgery, defined as resection in the muscularis plane, was associated with poor local control and disease-free survival. This feedback could also improve the surgical resection quality in the daily clinical practice: distance of the tumour to the circumferential resection margin should be a standard parameter in the pathology report of a rectal resection specimen.

**Considerations after the introduction of TME surgery**

Although in general the outcome for patients improved since the introduction of the TME procedure, outcome for some groups of patients improved less than for others. In the Netherlands, TME surgery was nationwide introduced during the TME trial (1996-1999). For patients under 75 years, the population-based 5-year overall survival rate in the Netherlands was 60% in the period before the TME trial, 67% in the period of the trial and 70% in the period after the TME trial. However, in the same study, patients aged ≥ 75 years had a 5-year overall survival rate of respectively 41%, 40% and 43% in these periods. In the elderly patients, the 1-month and 6-month postoperative mortality rates are much higher compared to the rates of younger patients. Treatment
related mortality is probably an important competitive risk factor, which obscures the positive effects of TME surgery in patients aged ≥ 75 years.\textsuperscript{21,22} Another group of patients who used to have a worse outcome, is the group of patients treated with an abdominoperineal resection compared with the group of patients treated with a low anterior resection. These patients have higher rates of circumferential resection margin involvement, worse local control, and a reduced overall survival rate.\textsuperscript{24} At the beginning of the 1990s, it became clear that the distal margin of 5 cm from the tumour could be safely reduced to 2 cm or less.\textsuperscript{25} Simultaneously, the TME technique was introduced as standard treatment.\textsuperscript{4,26} Consequently, the frequency of abdominoperineal resections decreased, whereas more low anterior resections were performed.\textsuperscript{27} Marr and colleagues studied the abdominoperineal resection before and after the introduction of the TME procedure in Leeds.\textsuperscript{24} They found that patients treated with an abdominoperineal resection had more involved circumferential resection margins, an increased local recurrence rate, and a reduced overall survival rate.\textsuperscript{24} Interestingly, since the introduction of the TME technique the frequency of involved circumferential resection margins after an abdominoperineal resection did not change: 43% involved margins between 1997 and 2000 compared to 36% in the period 1986 to 1997.\textsuperscript{24} Over time less patients were treated with an abdominoperineal resection compared to a low anterior resection.\textsuperscript{24} This difference in patient selection could have influenced the results, as nowadays only the more difficult, distal tumours are treated with an abdominoperineal resection. Nevertheless, also in the Dutch TME trial, high rates of circumferential resection margin involvement were found after an abdominoperineal resection.\textsuperscript{9} In general, with TME surgery overall survival is still 10% worse for patients treated with an abdominoperineal resection in comparison to patients treated with a low anterior resection.\textsuperscript{9,28,29}

The above mentioned examples are indicating the importance of performing continuous research and quality monitoring to identify the areas where treatment results are not as expected. The findings for the elderly patients question the benefit of the “standard” TME procedure for some frail elderly patients with a limited tumour: neoadjuvant treatment in combination with a smaller surgical procedure might be a good alternative for these patients.\textsuperscript{22} The results of the abdominoperineal resection did also lead to a change in practice in several institutes, where a wider, cylindrical resection is performed instead of the traditional conic excision.\textsuperscript{30,31}

**National cancer plans**

In several countries, the importance of continuous research and quality assurance for improving oncological care has been recognised. In the United Kingdom, the National Health Service (NHS) Cancer Plan was formulated in 2000, which gave cancer services high priority. The plan aimed to reduce death rates and improve prospects of survival and quality of life for patients with cancer and to guarantee high quality treatment and
care throughout the country. Also in France, a national cancer plan was introduced (2003). As a result the French National Cancer Institute was founded in 2004. Its mission is to direct the course of cancer care policy, to provide a network hub for research, and to act as a catalyst for European and international cooperation. In several other countries, including Australia, New Zealand and Canada, similar national cancer plans have been formulated. These plans emphasize the improvement of quality of care for the patient with cancer. Nevertheless, to structurally gain insight in the nationwide improvements of cancer care, and more importantly in the short and long-term results of the provided care, an audit is necessary.

**AUDITS ON RECTAL CANCER**

Several countries have organised a national audit, such as Norway and Sweden. Recently, a national colorectal audit was also implemented in the Netherlands. In Norway, a national audit for the period 1986-1988 was performed. It was found that the 5-year local recurrence rate was 28% with a 5-year overall survival rate of 55% for patients aged younger than 75 years. The Norwegian Rectal Cancer Group was founded and established a national rectal cancer registry. Each department regularly received its own results together with the national average for comparison and quality control. From November 1993 until December 1999, 5382 patients with rectal cancer were included. TME surgery was rapidly implemented: 96% of patients were treated with this surgical technique in 1998. For patients younger than 75 years, the local recurrence rate was 8% after a mean follow-up of 39 months, and the 5-year overall survival was 71%. Wibe and colleagues conclude the following: "The Rectal Cancer Registry has provided the opportunity for monitoring treatment standard in each department, and the routine reports of results to the departments are also believed to encourage every surgeon and pathologist to do his or her best. Moreover, it provides data which allow comparison of the results of individual units to the national average." In Sweden, an audit for all patients with rectal cancer was launched in 1995: the Swedish Rectal Cancer Registry. According to the Swedish healthcare system it is obligatory for pathologists and surgeons to report cancer diagnoses to the Swedish Cancer Registry. All departments of surgery agreed to provide clinical data to the registry. Feedback is given to all centres on treatment outcome. Between 1995 and 2003, 13434 patients were documented in the Swedish Rectal Cancer Registry. The 5-year survival rate for rectal cancer improved significantly from 36.1% in the period 1960-1964 to 57.6% in the period 1995-1999. The survival rates for colon cancer were not included in the national audit and improved from 39.6% to 57.2% in these periods. These results indicate that in Sweden, survival for both rectal cancer and colon cancer have improved. Similar to the
Swedish results, in the regional database of the Dutch Comprehensive Cancer Centre West was found that, historically, patients with colon cancer had a better survival rate than patients with rectal cancer: hazard ratio 0.84; $P = 0.001$ for patients with colon cancer compared to patients with rectal cancer in the period 1990-1995, adjusted for age, gender, and TNM stage (unpublished data). However, due to the focus on rectal cancer in the last decade, the survival rate for patients with rectal cancer is now similar to patients with colon cancer. The concentration of patients with rectal cancer to a specialised hospital, the nationwide introduction of TME surgery, and the implementation of preoperative radiotherapy have probably contributed to these improvements.

The EUROCARE collaboration is an example of a collaboration between more than 83 cancer registries across 23 countries. The data are obtained from some national registries, which cover 100% of the cases, and also from many regional registries. For colorectal cancer, the 5-year relative survival in the EUROCARE-4 study was 56.2% for patients diagnosed in the period 2000-2002. In general, the countries in Northern and Central Europe had the best survival rates, whereas countries in Eastern Europe, such as Poland and Czech Republic, had a 10% lower overall survival rate compared to the average. Furthermore, also the survival rate of the United Kingdom, a country with a Cancer Plan since 2000, was below the average survival rate in the EUROCARE study. A limitation of the EUROCARE study is that for some nations only regional registries were available and only a proportion of all cases was included in the database: for example in Poland and the Czech Republic respectively only 9% and 8% of the national population is covered by the used registries. Nevertheless, the results indicate that large differences exist in survival rates of rectal cancer between nations. It is important to realise that not only survival differences between nations are present, but also within a nation due to different outcome in different centres. An audit such as the EUROCARE study helps to identify where the quality of care should and could be improved. However, interesting questions, such as why these differences exist and how the survival rate can be improved, cannot be answered by the EUROCARE database.

**An European audit on colorectal cancer treatment outcome**

In Europe, international initiatives for collaboration to improve cancer care outcome are limited. In the early 1980s, the Federation of European Cancer Societies (FECS) was founded, based on the vision that treating cancer is an effort of a multidisciplinary team. The European Society of Surgical Oncology (ESSO) took with support of the European Society for Therapeutic Radiology and Oncology (ESTRO) the initiative to officially disband and replace the FECS in 2007 by the European CanCer Organisation (ECCO), which aims at taking an even wider approach to oncology. One of the goals of the ECCO is to uphold the right of all European cancer patients to the best possible treatment and care. The ECCO supported a recently initiated, European audit on colorectal cancer, which is
an outcome-based quality improvement project. The following outcomes will be considered: morbidity, mortality, loco-regional control, and survival. The aims of the audit are first to improve outcome for patients with cancer in Europe by quality assurance measures, and second to decrease the use of unproven treatments, which might cause side-effects without improving outcome. Regularly, collected data will be analysed to identify areas where further improvements in the quality of care are possible or necessary. Additional data, such as TNM stage and other confounders, are collected so the analyses can be adjusted for confounders such as patient case-mix.

Furthermore, the audit could be used to identify centres which have the best (adjusted) outcome for colorectal cancer treatment: the "centres of excellence". Studies why these centres have better results will contribute to the understanding of factors that influence colorectal cancer outcome. Apart from that, the audit could give insight in the actual number of procedures that are performed within each centre and by an individual surgeon each year. This could be important as Birkmeyer and colleagues showed that hospital volume was associated with operative mortality for colectomy in the United States (6.5% in hospitals with less than 33 resections per year compared to 4.5% for hospitals with more than 124 resections per year, \( P < 0.001 \)).\(^{39}\) Besides, several groups showed that surgical caseload was associated with oncological outcome for rectal cancer.\(^{38,40}\) Surprisingly, in the Swedish Uppsula trial was found that 50% of patients were operated by surgeons who performed less than one rectal cancer operation per year.\(^{28,41}\) As a consequence of above mentioned findings rectal cancer care in Sweden was eventually concentrated to centres with specialised surgeons. In the future, the outcome-based European audit for colorectal cancer could also result in reorganisation of colorectal cancer care in other countries in Europe: concentration of colorectal cancer care in the centres with the best outcome. It could be that these centres are high volume centres, but the decision should be based on outcome parameters and not solely on caseload.

**Costs of quality improvement**

Every treatment costs money. Chemotherapeutic agents are relatively expensive, and the effects on outcome in the treatment of rectal cancer are currently limited. An example in which systemic treatment is used is metastatic colorectal disease. Due to the chemotherapeutic agents, the prognosis has improved from a median survival of eight months to more than 21 months (regimen including bevacizumab or cetuximab).\(^{42}\) Although the progress is commendable, we should remember that these treatments costs over US$ 21,000 for the initial 8 weeks.

In the last decade, the largest improvements in survival of patients with rectal cancer resulted from a change in surgical technique: due to a change from blunt dissection to TME surgery the survival rates in several countries have improved.\(^{5,20,43}\) Professor Wibe showed during the Colorectal Conference 2007 in St. Gallen that the National Rectal
Cancer Audit in Norway, which started in 1993, costed €120,000 per year including the costs of two secretaries and one statistician (50%). Until 2007, more than 14,000 patients were included in a country with 4.6 million inhabitants. During the audit each department was monitored. Feedback and, if necessary, counselling was given. The local recurrence rate decreased and the overall survival rate improved from 55% in the period 1986-1988 to 71% in the period 1993-1999. Wibe estimated that since the introduction of the audit 2,500 patients have been saved due to improved treatment. As the audit has cost around 1.6 million euros since 1993, the costs per saved life were around 700 euros. This does not implicate that radiotherapy or chemotherapy should not be used. Rather, it indicates that quality assurance projects such as an audit have been shown to be very cost effective.

Although the costs of an audit are relatively low, it still has to be financed. One of the parties who could contribute towards the costs is the government: an audit fits within the national cancer plans as it helps to improve cancer care outcome. Consequently, an European audit might be supported by both the national government and the European Union. Moreover, an audit could result in reduction of the incidence of (expensive) complications and a decreased use of unproven treatments, which could eventually result in a reduction of total expenses. Therefore, it is also interesting for medical insurance companies to invest in an outcome based audit. Finally, independent, grant-giving institutes such as cancer foundations might be willing to contribute to quality improving initiatives.

**Considerations for the audit**

A registration project in which only data is collected for documentation purposes, will not lead to an improved quality of care. First of all, an audit should be an interactive system in which regularly feedback is given on performance, mirrored to the regional, national and European average. Besides, recommendations where further improvements can be made should be given at least annually to the participants. Second, if only dedicated treatment teams register their data, a bias of the results will exist, eventually resulting in a failure to improve overall treatment outcome. Therefore, participation to the audit should be mandatory.

**CONCLUSIONS**

Variability results in differences in outcome. Surgical variability can be minimised by extensive quality assurance. In several surgical randomised trials, the importance of quality assurance measurements are shown. However, the majority of patients is treated outside the framework of a trial. For patients treated in the daily clinical practice, quality
assurance by means of auditing is necessary. Registration of outcome-based quality measurements is cost effective and provides transparency, benchmarking, and internal feedback which will rapidly lead to improvements in cancer care.
Summary

In the last decade the surgical procedure for rectal cancer has been changed. At the end of the 1980s, a blunt dissection was performed. Several studies have shown that a total mesorectal excision (TME), which is a sharp removal under direct vision of the complete rectum with its intact mesorectum and visceral fascia with preservation of the autonomic nerves, resulted in better local control and overall survival. In the same period as the introduction of TME surgery, it became clear that the distal margin of 5 cm from the tumour could be safely reduced to 2 cm or less. Consequently, fewer abdominoperineal resections were performed.

In the Netherlands, the TME trial introduced the TME technique nationwide. In this trial, radiotherapy, surgery, and pathology were extensively quality controlled. For the surgical procedure, several workshops were organised, videotapes with the procedure produced, trainings at the dissection table were given, and the first procedures of each participating surgeon were supervised by an instructor surgeon. This thesis focuses on quality assurance of rectal cancer treatment, in particular on the surgical treatment.

In chapter 1 the general introduction and outline of the thesis are described.

The effect of the introduction of TME surgery on population-based overall survival in the Netherlands is studied in chapter 2. In this study the cancer registries of the Comprehensive Cancer Centres South and West are used. In total 3179 patients were included. Three periods were studied: before, during and after the TME trial. Overall survival was respectively 56%, 62% and 65% in the pre-trial, trial and post-trial period (P < 0.001). Overall survival, adjusted for the confounders gender, age, pT-stage, lymph node involvement, and (neo)adjuvant treatment, improved in the trial period (P < 0.001), suggesting that the introduction of TME surgery was successful. Preoperative radiotherapy was increasingly used over time. In the period of the TME trial, overall survival was similar for patients treated with preoperative radiotherapy and without (neo)adjuvant treatment (P = 0.315). In the post-trial period, preoperative radiotherapy was significantly related to improved overall survival compared with no (neo)adjuvant treatment (P = 0.002). The results indicate that population-based overall survival improved since the nationwide introduction of TME surgery. Besides, with standardised TME surgery, preoperative radiotherapy resulted in an improved overall survival rate, whereas withholding preoperative radiotherapy was associated with a poorer prognosis.

Although chapter 2 showed that in general overall survival increased since the introduction of TME surgery, in chapter 3 and 4 it was studied whether the outcome for the elderly patients with rectal cancer also improved. In most rectal cancer trials patients...
aged over 75 years are underrepresented due to exclusion based on age or comorbidity. However, rectal cancer is a disease predominately occurring in the elderly patient. For both chapters 3 and 4, the Dutch TME trial and the cancer registries of Comprehensive Cancer Centres South and West were used. In chapter 3 it was shown that the 5-year overall survival was 60% before the introduction of TME surgery, 67% during the TME trial, and 70% after the TME trial in patients aged younger than 75 years \( (P < 0.0001) \). The survival for older patients did not improve and remained at 41%, 40%, and 43% at 5 years in the respective periods. Furthermore, mortality during the first 6-month period after treatment is significantly raised compared to younger patients: 14% in the elderly patients, compared to 3.9% in the younger TME study patient \( (P < 0.0001) \). In the database of the Comprehensive Cancer Centres these figures were confirmed at 16% and 3.9% \( (P < 0.0001) \). In chapter 4, the association between age, morbidity and 6-months mortality is shown. Treatment related mortality is probably an important competitive risk factor which obscures the positive effects of TME surgery in patients aged ≥ 75 years. It is discussed that for elderly patients who retain a good physical and mental condition, treatment that is given to younger patients is regarded to be appropriate, whereas for those with diminished physiological reserves and comorbid conditions, alternative treatments that keep surgical trauma to a minimum and optimise the use of radiotherapy might be more suitable.

Another group of patients who had a worse outcome is the group of patients treated with an abdominoperineal resection compared with those treated with a low anterior resection. In chapter 5 it is studied which of the following is associated with circumferential resection margin involvement, local recurrence, overall survival, and cancer-specific survival: the abdominoperineal resection itself or the factors resulting in the decision to perform an abdominoperineal resection. Patient and treatment related variables of the Swedish Rectal Cancer trial, Dutch TME trial, CAO/ARO/AIO-94 trial, EORTC 22921 trial and Polish Rectal Cancer trial were combined (5187 patients). A propensity score was calculated, which indicated the predicted probability of undergoing an APR given gender, age, and distance of the tumour to the anal verge. The results showed that an abdominoperineal resection was associated with an increased risk of circumferential resection margin involvement (odds ratio 2.52; \( P < 0.001 \)), increased local recurrence rate (hazard ratio 1.53; \( P = 0.001 \)), and a decreased cancer-specific survival rate (hazard ratio 1.31; \( P = 0.002 \)), whereas the propensity score was not. The results suggest that the abdominoperineal resection itself is a significant predictor for nonradical resections and is associated with an increased risk of local recurrence and death due to cancer for patients with advanced rectal cancer.

Chapter 6 focuses on patients treated with an abdominoperineal resection in the TME trial, to identify tumour and patient related risk factors associated with positive
circumferential resection margins, local recurrence, and overall survival. A positive circumferential resection margin was found in 29.6% of all patients: 44% for anterior, 21% for lateral, 23% for posterior, and 17% for (semi)circular tumour location ($P < 0.001$). In a multivariate analysis, T-stage, N-stage, and tumour location were independent risk factors for circumferential resection margin involvement. If a (partial) resection of the vaginal wall was performed in women, 47.8% of patients still had a positive circumferential resection margin. T-stage, N-stage, and circumferential resection margin were risk factors for local recurrence and age, T-stage, N-stage, circumferential resection margin, and distance of the tumour to the anal verge for overall survival. The results indicate that the surgical treatment should primarily be aimed at adequate resection margins. To further improve the outcome of patients treated with an abdominoperineal resection, tumours should be properly preoperatively staged, including an assessment of the circumferential resection margin (mesorectal fascia). For patients with a threatened circumferential resection margin preoperatively, 5 x 5 Gy radiotherapy alone is insufficient and treatment should preferentially consist of chemoradiotherapy and/or extended resection.

The EORTC 22921 trial studied the addition of pre- and/or postoperative chemotherapy to preoperative radiotherapy followed by surgery in T3 or resectable T4 rectal cancer. The trial ran from April 1993 to March 2003. In 1999, an addition to the trial protocol was made in which it was recommended to perform a TME procedure. Circumferential resection margin involvement, local recurrence, overall survival, and disease-free survival in patients treated with a long schedule of (chemo)radiotherapy are studied in chapter 7. Circumferential resection margin involvement was associated with the period of treatment: less circumferential margin involvement was found after 1999. Although preoperative chemoradiotherapy resulted in more downstaging and downsizing in comparison to preoperative radiotherapy alone in a previous analysis, the preoperative treatment did not significantly affect circumferential resection margin involvement. A positive circumferential resection margin was associated with a higher risk of a local recurrence and a decreased disease-free and overall survival rate. Although downstaging might be helpful in the treatment of these advanced tumours, the results suggest that the ultimate aim of the treatment should be to perform a radical operation.

In chapter 8, the data of EORTC 22921 trial are further explored, to study which patients might benefit from the addition of postoperative chemotherapy to a preoperative schedule of long (chemo)radiotherapy. Although there was no statistically significant impact of postoperative chemotherapy on disease-free survival for the whole group ($P > 0.05$), the treatment effect differed significantly between the patients showing downstaging (ypT0-2) and the patients that did not show downstaging after preoperative therapy (ypT3-4): only the ypT0-2 patients seemed to benefit from postoperative
chemotherapy \((P = 0.013)\). The same pattern was observed for overall survival. These results indicate that predictive factors such as tumour responsiveness to preoperative treatment must be taken into account in the design of future trials studying postoperative treatments. Besides, tumour sensitivity for the primary treatment might be considered to tailor postoperative therapy and prevent ineffective treatments, which might cause addition burden and toxicity.

One of the feared complications after a low anterior resection is anastomotic leakage. In chapter 9, the data of the Swedish Rectal Cancer trial, Dutch TME trial, CAO/ARO/AIO-94 trial, EORTC 22921 trial, and Polish Rectal Cancer trial were used to study the association between anastomotic leakage and long-term outcome. In total 2726 patients with a low anterior resection were selected. Anastomotic leakage occurred in 9.7\% of patients. The presence of a diverting stoma was negatively associated with anastomotic leakage \((P = 0.002)\). After exclusion of patients with early postoperative mortality, anastomotic leakage was independently associated with overall survival (HR 1.29; 95\% CI 1.02-1.63; \(P = 0.034\)), but not with cancer-specific survival (HR 1.12; 95\% CI 0.83-1.52; \(P = 0.466\)). These data indicate that patients who survived their anastomotic leakage still have a decreased long-term overall survival rate.

In the early postoperative period, anastomotic leakage is feared for its associated morbidity and mortality. In chapter 10 is focused on this period. First, historical data of 3 regional hospitals were collected (1066 patients). These data revealed that 7.0\% of patients developed a symptomatic anastomotic leakage. The mortality rate of patients diagnosed with anastomotic leakage was 39\%. It was considered that delay in the diagnosis of anastomotic leakage might have contributed to these findings: the diagnosis was made with a median delay of 4 days after the first symptoms were observed. As a result a protocol for standardised postoperative surveillance was made, using easily accessible clinical parameters such as temperature, heart rate, and physical examination of the abdomen. This protocol was then prospectively tested between August 2004 and August 2006 (223 patients). The anastomotic leakage rate was 9.4\% in this period. Compared to the historical controls, the delay between the first symptoms and the diagnosis of anastomotic leakage decreased significantly from a median of 4 days to 1.5 days \((P = 0.01)\). The mortality rate dropped, but this difference was not statistically significant. The results indicate that standardised postoperative surveillance for anastomotic leakage could result in a shorter delay between the first signs and symptoms to the confirmation of anastomotic leakage. At present a multicentre registration project is performed, to further improve and validate the scoring list and decision model (DUtch LeaKage score).

In chapter 9 and in other studies it was shown that the presence of a diverting stoma is associated with a lower rate of anastomotic leakage. However, part of the stomas constructed with temporary intent are never removed. In chapter 11, the data of the
Dutch TME trial were used to study the rate of stoma reversal and to identify factors that limit stoma closure. In 19% of patients, the stoma was never reversed. Postoperative complications and secondary constructed stomas, for example after anastomotic leakage, were associated with a higher likelihood of a permanent stoma. The results show that temporary stomas should be created as if they are permanent stomas; correct placement that helps life-long handling is of utmost importance.

In Chapter 12 this thesis is placed in a wider context. The importance of quality assurance is illustrated, using the results of the TME trial. To continuously improve the outcome of the oncological care it is necessary to monitor structurally. Quality assurance should not only be used within randomised clinical trials, but be a part of the daily clinical practice. In several countries the efficiency of audits has been shown before. Recently, an European outcome-based audit was initiated, supported by the European CanCer Organisation (ECCO). Eventually, feedback of the audit will result in an improved outcome of the oncological treatment.
REFERENCES


Summary


NEDERLANDSE SAMENVATTING

In het laatste decennium is de chirurgische behandeling van het rectumcarcinoom veranderd. Aan het einde van de jaren 80 van de vorige eeuw werd er een stompe dissectie verricht. Verschillende studies hebben aangetoond dat een operatie waarbij het complete rectum met een intact mesorectum en viscerale fascie onder zicht en middels een scherp resectie werd verwijderd, resulteert in betere lokale controle en algehele overleving: de totale mesorectale excisie (TME).1,2 In dezelfde periode als de introductie van de TME procedure werd duidelijk dat de distale marge van 5 centimeter van de tumor gereduceerd kon worden tot (minder dan) 2 centimeter.3 Dit leidde ertoe dat er minder abdominoperineale resecties werden verricht.4 In Nederland werd met de TME studie de TME techniek landelijk geïntroduceerd.5 In deze studie naar rectumcarcinoom werd de kwaliteit van radiotherapie, chirurgie en pathologie uitgebreid gecontroleerd: kwaliteitsborging of “quality assurance”. Het doel van deze kwaliteitscontrole was te garanderen dat radiotherapie, chirurgie en pathologie aan een bepaalde standaard voldeden. Voor de chirurgische kwaliteitsborging werden onder andere verschillende workshops georganiseerd, videobanden van de procedure verspreid, trainingen in de snijzaal gegeven en de eerste operaties van iedere deelnemende chirurg gesuperviseerd door een instructeur. Dit proefschrift richt zich op de kwaliteitsborging van de behandeling van het rectumcarcinoom, waarbij met name de chirurgische behandeling wordt bestudeerd.

Hoofdstuk 1 is de inleiding van dit proefschrift. Daarnaast wordt in dit hoofdstuk de inhoud van het proefschrift op hoofdlijnen weergegeven.

Het effect van de introductie van TME chirurgie in Nederland op de algehele overleving is onderwerp van studie in hoofdstuk 2. In deze studie met 3179 patiënten werd gebruik gemaakt van de kankerregistratie van de Integrale Kankercentra West (IKW) en Zuid (IKZ). Er werden drie perioden onderscheiden: voor, tijdens en na de TME studie. De algehele overleving was 56%, 62% en 65%, respectievelijk voor, tijdens en na de TME studie (P < 0,001). De algehele overleving, gecorrigeerd voor geslacht, leeftijd, pathologisch T-stadium, lymfklier status en (neo)adjuvante therapie was significant verbeterd in de periode tijdens de TME studie in vergelijking met voor de TME studie (P < 0,001). Dit suggereert een succesvolle introductie van de TME procedure. Preoperatieve radiotherapie werd in de opeenvolgende perioden steeds meer toegepast. In de periode van de TME studie was de algehele overleving van patiënten behandeld met preoperatieve radiotherapie gelijk aan de algehele overleving van patiënten die zonder (neo)adjuvante therapie werden behandeld (P = 0,315). In de periode na de TME studie had de groep patiënten die preoperatief behandeld werd met radiotherapie een significant betere
algehele overleving dan de groep die zonder (neo)adjuvante therapie werd behandeld ($P = 0,002$). De resultaten geven aan dat de algehele overleving is verbeterd sinds de introductie van TME chirurgie in Nederland. Daarnaast resulteert gestandaardiseerde TME chirurgie in combinatie met preoperatieve radiotherapie in een verbetering van de algehele overleving, terwijl de groep die niet wordt behandeld met preoperatieve radiotherapie een slechtere prognose heeft.

Alhoewel in hoofdstuk 2 is aangetoond dat voor de totale populatie van patiënten met een rectumcarcinoom de algehele overleving verbeterd is sinds de introductie van de TME procedure, werd in hoofdstuk 3 en 4 bestudeerd of de uitkomst ook voor de oudere patiënt is verbeterd. In de meeste studies die de behandeling van het rectumcarcinoom onderzoeken zijn patiënten ouder dan 75 jaar ondervertegenwoordigd door exclusie op basis van leeftijd of co-morbiditeit. Het rectumcarcinoom komt echter hoofdzakelijk voor bij oudere patiënten. Voor de hoofdstukken 3 en 4 werd gebruik gemaakt van de gegevens van zowel de TME studie als de Integrale Kankercentra West en Zuid. In **hoofdstuk 3** werd aangetoond dat de 5-jaars overleving voor patiënten jonger dan 75 jaar 60% was voor de introductie van de TME procedure in Nederland, 67% tijdens de TME studie en 70% na de TME studie ($P < 0,0001$). Voor patiënten van 75 jaar en ouder werd geen verbetering in de 5-jaars overleving gevonden: 41%, 40% en 43%, respectievelijk voor, tijdens en na de TME studie. Bovendien was de mortaliteit in de eerste 6 maanden postoperatief significant hoger voor de oudere patiënten in vergelijking met patiënten jonger dan 75 jaar: 14% voor oudere patiënten versus 3,9% voor jongere patiënten in de TME studie ($P < 0,0001$). In de database van het IKW en IKZ werden soortgelijke resultaten gevonden (16% versus 3.9%; $P < 0,0001$). In **hoofdstuk 4** werd de associatie tussen leeftijd, morbiditeit en 6-maanden mortaliteit aangegeven. Sterfte gerelateerd aan de behandeling is waarschijnlijk een belangrijke competitieve risicofactor, die de positieve effecten van TME chirurgie voor patiënten ouder dan 75 jaar doet vervagen. Voor oudere patiënten die een goede lichamelijke en geestelijke gezondheid hebben, lijkt de huidige therapie een goede behandeling. Echter, voor diegene met een vermindere fysiologische reserve door bijvoorbeeld co-morbiditeit, lijkt een alternatieve behandeling met gebruik van radiotherapie en minder uitgebreide chirurgie een meer geschikte optie.

Een andere groep met een relatief slechte uitkomst is de groep patiënten behandeld met een abdominoperineale resectie. In **hoofdstuk 5** wordt een studie omschreven die onderzocht of de abdominoperineale resectie zelf of de combinatie van patiënt- en tumorgerelateerde factoren die resulteerde in de keuze voor een abdominoperineale resectie resulteert in deze slechte uitkomst. De volgende eindpunten werden bestudeerd: radicaliteit (gedefinieerd als een tumor positief circumferentieel snijvlak), lokaal recidiefpercentage, algehele en kanker-specifieke overleving. Voor deze studie werden
de gegevens van de Swedish Rectal Cancer trial, de TME studie, de CAO/ARO/AIO-94 studie, de EORTC 22921 studie en de Polish Rectal Cancer trial gecombineerd (5187 patiënten). Er werd een "propensity score" berekend: de voorspelde kans om een abdominoperineale resectie te ondergaan gegeven geslacht, leeftijd en afstand van de tumor tot de anus. De abdominoperineale resectie was geassocieerd met een toegenomen risico op een positief circumferentieel snijvlak (odds ratio 2,52; \( P < 0,001 \)), een toegenomen kans op een lokaal recidief (hazard ratio 1,53; \( P = 0,001 \)) en een afname van de kanker-specifieke overleving (hazard ratio 1,31; \( P = 0,002 \)); een associatie tussen de "propensity score" en deze eindpunten werd niet gevonden. De resultaten suggereren dat de abdominoperineale resectie zelf een belangrijke voorspeller is voor een niet-radicaal operatie met een toegenomen risico op een lokaal recidief en sterfte door kanker voor patiënten met een gevorderd rectumcarcinoom.

In hoofdstuk 6 werd de groep patiënten behandeld met een abdominoperineale resectie in de TME studie onderzocht om tumor- en patiëntgerelateerde risicofactoren te vinden voor irradicale resecties, lokaal recidief en algehele overleving. Een positief circumferentieel snijvlak werd gevonden bij 29,6% van alle patiënten: 44% bij een anterieur gelegen tumor, 21% bij een lateraal gelegen tumor, 23% bij een dorsaal gelegen tumor en 17% bij een (semi)circumferentiële tumor (\( P < 0,001 \)). In de multivariate analyse waren T-stadium, N-stadium en tumorlocatie onafhankelijke risicofactoren voor een positief circumferentieel snijvlak. Van de vrouwen die een (partiële) resectie van de vagina-achterwand ondergingen, hadden 47,8% nog steeds een positief snijvlak. T-stadium, N-stadium en status van het circumferentiële snijvlak waren onafhankelijke risicofactoren voor een lokaal recidief. De volgende risicofactoren werden gevonden voor algehele overleving: leeftijd, T-stadium, N-stadium, status van het circumferentiële snijvlak en afstand van de tumor tot de anus. De resultaten geven aan dat de chirurgische behandeling erop gericht moet zijn om een adequate afstand tussen tumor en snijvlak te verkrijgen. Om de uitkomsten van patiënten behandeld met een abdominoperineale resectie te verbeteren, moet een adequate preoperatieve stadiëring worden verricht, inclusief een inschatting van de betrokkenheid van het circumferentiële snijvlak (mesorectale fascie). Voor patiënten bij wie de tumor tot in of vlakbij het circumferentiële TME snijvlak komt, is preoperatief 5 x 5 Gy radiotherapie alleen onvoldoende. De behandeling bestaat dan bij voorkeur uit preoperatieve behandeling met chemoradiotherapie en/of een uitgebreidere resectie.

In de EORTC 22921 studie werd de toevoeging van pre- en/of postoperatieve chemotherapie aan een schema van 6 weken preoperatieve radiotherapie bestudeerd voor patiënten met T3 of resectabele T4 rectumcarcinomen.5 De studie was open voor inclusie van april 1993 tot maart 2003. Vanaf 1999 werd in het studieprotocol geadviseerd een TME procedure te verrichten. De betrokkenheid van het circumferentiële snijvlak,
het lokaal recidiefpercentage, de algehele en ziektevrije overleving voor patiënten met een lang preoperatief schema met (chemo)radiotherapie waren onderwerp van studie in hoofdstuk 7. Het percentage positieve snijvlakken was gerelateerd aan de periode van behandeling: er werden minder positieve snijvlakken gevonden na 1999. Alhoewel preoperatieve chemoradiotherapie in vergelijking met preoperatieve radiotherapie resulteerde in een lager TNM-stadium en kleinere tumoren,7 werd geen significant effect van het type preoperatieve behandeling op het percentage positieve circumferentiële snijvlakken gevonden. Een positief circumferentieel snijvlak gaf een hoger risico op een lokaal recidief en een afgenomen ziektevrije en algehele overleving. Alhoewel het nuttig kan zijn om een gevorderd rectumcarcinoom te “downstagen”, suggereren de resultaten dat het ultieme doel een radicale operatie is.

In hoofdstuk 8 werden de gegevens van de EORTC 22921 studie gebruikt om te bestuderen welke groep patiënten met een gevorderd rectumcarcinoom behendd met een schema van 6 weken preoperatieve (chemo)radiotherapie voordeel kunnen hebben van de toevoeging van postoperatieve chemotherapie. In de totale groep patiënten werd geen significant voordeel gevonden voor postoperatieve therapie op de ziektevrije overleving (P > 0,05).6 Het effect van postoperatieve chemotherapie op ziektevrije overleving verschilde echter significant tussen patiënten met een ypT0-2 stadium (“downstaging”) na preoperatieve therapie en patiënten zonder “downstaging” (ypT3-4): alleen de patiënten met ypT0-2 leken een voordeel te hebben van postoperatieve chemotherapie (P = 0,013). Soortgelijke resultaten werden gevonden voor de algehele overleving. De resultaten tonen aan dat er onder andere rekening gehouden moet worden met de reactie van tumoren op preoperatieve therapie bij het ontwerpen en interpreteren van studies over postoperatieve therapie. Bovendien zou de tumorgevoeligheid voor de preoperatieve behandeling gebruikt kunnen worden om een eventuele postoperatieve behandeling aan te passen. Dit kan het gebruik van ineffectieve behandelingen, met de bijbehorende bijwerkingen, verminderen.

Eén van de gevreesde complicaties na een lage anterieure resectie is naadlekkage. In hoofdstuk 9 werden de databases van de Swedish Rectal Cancer trial, de TME studie, de CAO/ARO/AIO-94 studie, de EORTC 22921 studie en de Polish Rectal Cancer trial gecombineerd om de associatie tussen naadlekkage en de gevolgen op lange termijn te bepalen. In totaal werden 2726 patiënten met een lage anterieure resectie geselecteerd. Naadlekkage trad op bij 9,7% van de patiënten. In de groep patiënten met een ontlastend stoma werd minder naadlekkage gevonden (P = 0,002). Na exclusie van patiënten die binnen 90 dagen na de operatie stierven, was naadlekkage een onafhankelijke risicofactor voor verminderde algehele overleving (hazard ratio 1,29; 95% betrouwbaarheidsinterval 1,02-1,63; P = 0,034), maar niet voor kanker-specifieke overleving (hazard ratio 1,12; 95%
betrouwbaarheidsinterval 0,83-1,52; \( P = 0,466 \)). Patiënten die naadlekkage overleefden, hadden na enkele jaren nog steeds een afgenomen algemene overleving.

In de vroege postoperatieve periode wordt naadlekkage gevreesd door de geassocieerde morbiditeit en mortaliteit. Het onderzoek in hoofdstuk 10 richtte zich op deze periode. Patiëntgegevens uit drie ziekenhuizen werden retrospectief verzameld (1066 patiënten). Van deze groep patiënten werd bij 7,0% een symptomatische naadlekkage gediagnosticeerd. Het sterftecijfer voor patiënten met een naadlekkage was 39%. Vertraging in het stellen van de diagnose naadlekkage zou een bijdrage geleverd kunnen hebben aan dit hoge sterftecijfer: 4 dagen (mediaan) nadat de eerste symptomen aanwezig waren, werd de diagnose gesteld. Dientengevolge werd een protocol gemaakt waarin de postoperatieve zorg gestandaardiseerd werd en waarin gebruik werd gemaakt van gemakkelijk beschikbare klinische parameters, zoals temperatuur, hartfrequentie en lichamelijk onderzoek van het abdomen. Vervolgens werd dit protocol prospectief getest tussen augustus 2004 en augustus 2006 (223 patiënten). Naadlekkage werd bij 9,4% van de patiënten in deze periode gediagnosticeerd. Vergeleken met de historische controles was de vertraging in het stellen van de diagnose naadlekkage na het optreden van de eerste symptomen significant korter in de periode waarin gebruik werd gemaakt van de gestandaardiseerde postoperatieve follow-up: de diagnose werd met een vertraging van 1,5 dag in plaats van 4 dagen (mediaan) gesteld (\( P = 0,01 \)). Bovendien daalde de mortaliteit na het optreden van naadlekkage naar 24%, maar dit verschil was niet significant. Concluderend lijkt gestandaardiseerde follow-up voor naadlekkage te resulteren in een kortere periode tussen de eerste symptomen en het stellen van de diagnose naadlekkage. Op dit moment wordt er in meerdere centra in Nederland een registratieproject uitgevoerd om de scoringslijst en beslisboom verder te verbeteren en te valideren (de “DUtch LeaKage score”).

Zowel in hoofdstuk 9 als in andere studies werden bij ontlastend stoma’s minder naadlekkages gevonden.\(^8\) Een deel van deze tijdelijke stoma’s wordt echter nooit opgeheven. In hoofdstuk 11 werden de gegevens van de TME studie gebruikt om het beleid ten aanzien van stoma’s te bestuderen en om factoren te identificeren die gerelateerd zijn aan het niet opheffen van stoma’s. Tijdens de eerste operatie werd bij 523 van de 924 patiënten met een lage anterieure resectie (57%) een stoma aangelegd. Bij 19% van deze patiënten werd het stoma nooit opgeheven. Risicofactoren voor een permanent stoma waren onder andere postoperatieve complicaties en een stoma aangelegd tijdens een tweede of opeenvolgende operatie (bijvoorbeeld na het optreden van naadlekkage). De resultaten tonen aan dat ieder tijdelijk stoma aangelegd moet worden alsof het een permanent stoma is: een juiste plaatsing is dan vooral van belang.

In hoofdstuk 12 wordt dit proefschrift in een bredere context geplaatst. Het belang van kwaliteitsborgingprojecten wordt geïllustreerd, onder andere met de resultaten van de
TME studie. Om een continue kwaliteitsverbetering van de oncologische behandeling te bewerkstelligen, is monitoring nodig. Niet alleen binnen gerandomiseerde studies, maar ook als onderdeel van de dagelijkse praktijk. In diverse landen is de effectiviteit van een audit aangetoond. Recent is een Europese audit geïnitieerd, ondersteund door de European CanCer Organisation (ECCO). Door terugkoppeling van de resultaten van deze audit kan de zorg voor patiënten met kanker uiteindelijk verder worden verbeterd.
REFERENCES


