Summary
&
General discussion

Summary

For rectal cancer treatment, the use of total mesorectal excision (TME) instead of conventional blunt surgery has led to substantial improvements in morbidity and survival. Preoperative short term radiotherapy in combination with conventional surgery improves local control and survival. To investigate the value of short term radiotherapy in combination with TME, the Dutch Colorectal Cancer Group initiated the TME trial. For a reliable assessment of the value of preoperative radiotherapy, surgical, pathological, and radiotherapeutical techniques were standardised and controlled for quality. Early results showed a decreased risk of local recurrence for irradiated patients at 2 years (2% vs 8%, $p<0.001$) without a difference in overall survival. After a median follow-up of 6 years, the effect of radiotherapy on local recurrence persisted (6% vs 11%, $p<0.001$), as well as the absence of a survival benefit. Because of the serious consequences associated with local recurrence, guidelines in the Netherlands and several other countries recommended preoperative radiotherapy for all rectal cancer patients with the exception of those with T1 tumours. Unfortunately, preoperative radiotherapy can induce serious side-effects such as faecal incontinence, sexual dysfunction, and secondary malignancies. In the absence of a survival benefit, for some patient groups the adverse effects might outweigh the benefits of decreased local recurrence. In **chapter 2**, Long term results of the TME trial are reported after a median follow-up of 12 years. Eighteen hundred sixty-one patients with resectable rectal cancer without evidence of distant disease were randomly assigned to TME preceded by 5×5 Gy radiotherapy or TME alone. The primary endpoint was local recurrence, analysed for all eligible patients who underwent a macroscopically complete local resection. Ten year cumulative incidence of local recurrence was 5% in the group assigned to radiotherapy and surgery and 11% in the surgery-alone group ($p<0.0001$). The effect of radiotherapy became stronger as the distance from the anal verge increased. However, when patients with a positive circumferential resection margin were excluded, the relation between distance from the anal verge and the effect of radiotherapy disappeared. Patients assigned to radiotherapy had a lower overall recurrence and when operated with a negative circumferential resection margin, cancer-specific survival was higher. Overall survival did not differ between groups. For patients with TNM stage III cancer with a negative circumferential resection margin, 10-year survival was 50% in the preoperative radiotherapy group versus 40% in the surgery-alone group ($p=0.032$). For all eligible patients, preoperative short term radiotherapy reduced 10-year local recurrence by more than 50% relative to surgery alone, without an overall survival benefit. For patients with a negative resection margin, the effect of radiotherapy was irrespective of the distance from the anal verge and led to an improved cancer-specific survival, which was nullified by an increase in other causes of death, resulting in an equal overall survival. Nevertheless, preoperative

short term radiotherapy significantly improved 10-year survival in patients with a negative circumferential margin and TNM stage III. Future staging techniques should offer possibilities to select patient groups for which the balance between benefits and side-effects will result in sufficiently large gains.

In contrast to loco regional recurrence rates, distant metastasis rates after rectal cancer treatment did not improve in the last decades. Up to 30% of all patients treated with curative intent for localised rectal cancer will develop distant metastases and distant metastases are still the main cause of death after rectal cancer. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME surgery could eradicate micrometastases. This might reduce distant metastases, resulting in improved outcomes. Currently, there is no conclusive evidence on the benefit of adjuvant chemotherapy in rectal cancer treatment after preoperative (chemo)radiotherapy followed by TME surgery, and the debate on this subject is still ongoing. In **chapter 3**, results of the multicentre, randomised PROCTOR-SCRIPT trial are described. This trial randomly assigned 437 eligible patients with histologically proven stage II or III rectal adenocarcinoma to observation or adjuvant chemotherapy after preoperative (chemo)radiotherapy and total mesorectal excision. Radiotherapy consisted of 5x5 Gy. Chemoradiotherapy consisted of 25x 1.8-2 Gy combined with 5-FU based chemotherapy. Adjuvant chemotherapy consisted of 5-FU/LV (PROCTOR), or eight courses capecitabine (SCRIPT). The primary end point was overall survival. The trial was powered for 840 patients but closed prematurely because of slow patient accrual. Two hundred twenty-one patients were assigned to observation and two hundred sixteen were assigned to adjuvant chemotherapy. After a median follow-up of 5 years, five year overall survival was 79.2% in the observation group and 80.4% in the chemotherapy group (HR 0.93, 95% CI 0.62-1.39; p=0.73). The hazard ratio for disease free survival was 0.80 (95% CI 0.60-1.07; p=0.13). Five year cumulative incidence for locoregional recurrences was 7.8% in both groups. Five year cumulative incidence for distant recurrences was 38.5% and 34.7%, respectively (p=0.39). In conclusion, The PROCTOR-SCRIPT trial could not demonstrate a significant benefit of adjuvant chemotherapy with fluoropyrimidine monotherapy after preoperative (chemo) radiotherapy and total mesorectal excision on overall survival, disease free survival, and recurrence rate. However, the trial did not complete planned accrual.

In many European countries, short term 5x5 Gy radiotherapy has become the standard preoperative treatment for patients with resectable rectal cancer. Individualised risk assessment might allow a better selection of patients who will benefit from postoperative treatment and intensified follow-up. In **chapter 4**, nomograms are presented that were developed from patient data from three European rectal cancer trials (n=2881), reflecting the risk for local recurrence (LR), distant metastases (DM) and overall survival (OS). Evaluated variables were age, gender, tumour distance from the anal verge, the use of radiotherapy, surgical

technique (TME/conventional surgery), surgery type (LAR/APR), time from randomization to surgery, residual disease (R0 vs R1+2), pT-stage, pN-stage and surgical complications. The results show that pathological T- and N-status are of vital importance for an accurate prediction of local recurrence, distant metastases and overall survival. Short-course radiotherapy reduces local recurrence rate. The nomograms are capable of predicting events with a validation c-index of 0.79 (LR), 0.76 (DM) and 0.75 (OS). The proposed stratification in risk groups allowed significant distinction between Kaplan-Meier curves for outcome. In conclusion, the developed nomograms enable accurate individual risk prediction for local recurrence, distant metastases and overall survival for patients operated on rectal cancer. The practicality of the three defined risk groups makes decision support in the consulting room feasible, enabling physicians to select patients for postoperative adjuvant therapy or intensified follow-up.

Transanal endoscopic microsurgery (TEM) has gained wide-spread acceptance as a safe and useful technique for the resection of rectal adenomas and selected T1 malignant lesions. If the lesion appears >T1 rectal cancer after resection with TEM, a completion TME resection is recommended. In **chapter 5**, the results of TME surgery after TEM for rectal cancer are investigated. In four tertiary referral hospitals for TEM, all patients with completion TME surgery after initial TEM were selected. All eligible patients who were treated with 5x5 Gy radiotherapy followed by TME surgery from the Dutch TME trial were selected as reference group. A multivariate logistic regression model was used to calculate odds ratio's (OR) for colostomies and for colo- and ileostomies combined. Local recurrence and survival rates were compared in hazard ratio's (HR) by using the multivariate Cox proportional hazard model. Fifty-nine patients were included in the TEM-COMPLETION group and 881 patients from the TME trial. In the TEM-COMPLETION group, 50.8% of the patients had a colostomy compared with 45.9% in the TME trial, OR 2.51 ($p<0.006$). There is no significant difference when ileo- and colostomies are analyzed together. In the TEM-COMPLETION group, 10.2% developed a local recurrence compared with 5.2% in the TME trial, HR 6.8 ($p<0.0001$). In conclusion, completion TME surgery after TEM for unexpected rectal adenocarcinoma results in more colostomies and higher local recurrence rates compared with one stage TME surgery preceded with preoperative 5x5 Gy radiotherapy. Pre-operative investigations must be optimised to distinguish malignant and benign lesions and to prevent avoidable local recurrence and colostomies.

In the Netherlands, the Total Mesorectal Excision (TME) surgical technique for rectal cancer was introduced in a quality-controlled manner within the framework of the TME trial. In **chapter 6**, the effects of the structural changes in rectal cancer care on survival compared to colon cancer for patients treated before, during and after the TME trial are examined. Overall survival of all patients with curatively resected colon (n=15,266) and rectal cancer (n=5839) in the regions of

Comprehensive Cancer Centres South and West between 1990 and 2005 were compared, adjusted for prognostic variables. In the pre-trial period, rectal cancer had a significantly lower survival compared with colon cancer (HR 1.248, $p<0.01$). However, in the post-trial period, survival after rectal cancer was similar to colon cancer (HR 0.987, n.s.). Although survival improved significantly for both colon and rectal cancer in the last 15 years, the substantially worse results after rectal cancer have been eliminated. This study shows the lasting effects that structural surgical training and quality assurance can have on survival outcome.

There is a growing consensus to concentrate high-risk surgical procedures to high volume surgeons in high volume hospitals. However, there is fierce debate about centralizing more common malignancies such as colorectal cancer. In **chapter 7**, the results of a meta-analysis are presented that explores the volume-outcome relationship for colorectal cancer treatment. A systematic search was performed to identify all relevant articles about the relation between hospital and/or surgeon volume and clinical outcomes for colorectal cancer. By means of strict inclusion criteria, 23 articles were selected concerning colon cancer, rectal cancer or both diseases together as 'colorectal cancer'. Pooled estimated effect sizes were calculated by using the case-mix adjusted outcomes of the highest volume group opposed to the lowest volume group. High volume hospitals have a significantly lower postoperative mortality in half of the pooled results. Non-significant results show a trend in favour of high volume hospitals. All results showed a significantly better long term survival in high volume hospitals. High volume surgeons have a lower postoperative mortality, although evidence is sparse. All analyses showed a significantly better long term survival in favour of high volume surgeons. The results show a clear and consistent relation between high volume providers and improved long term survival. This applies to both high volume hospitals and high volume surgeons. Most results show a relation between high volume providers and a reduced postoperative mortality, but here the evidence is less convincing. In the ideal world, extensive population-based audit registrations with case-mix adjusted feedback should make rigid minimal volume standards obsolete. Until then, using volume criteria for hospitals and surgeons treating colorectal cancer can improve mortality and especially long term survival.

Quality of health care is a hot topic and this is especially true for cancer care. New surgical techniques and effective neoadjuvant treatment regimens have significantly improved colorectal cancer outcome. Nevertheless, there seem to be substantial differences in quality of care between European countries, hospitals and doctors. To reduce hospital variation, most initiatives aim on selective referral, encouraging patients to seek care in high-volume hospitals, where cancer care is concentrated to site-specialist multidisciplinary teams. As an alternative to volume-based referral, hospitals and surgeons can also improve their results by learning from their own outcome statistics and those from colleagues treating a similar

patient group. European national audit registries in surgical oncology have led to improvements with a greater impact on survival than any of the adjuvant therapies currently under study. Moreover, they offer the possibility to perform research on patient groups that are usually excluded from clinical trials. Nevertheless, between European countries there remain differences in outcome and treatment schedules that cannot be easily explained. The European CanCer Organisation (ECCO) and the European Society of Surgical Oncology (ESSO) have recognised their importance and created the 'European Registration of Cancer Care' (EURECCA) framework to develop a European colorectal audit structure. In **chapter 8**, the set-up and participants of the EURECCA structure are described. EURECCA will advance future treatment improvements and circulate these to all European cancer patients. It provides opportunities to treat elderly and patients and those with comorbidity evidence-based while it offers an unique insight in social-economical health care matters such as the consequences of commercialisation, treatment availability and screening initiatives. As such, ECCO and ESSO have established the basis for a strong, multidisciplinary audit structure with the commitment to improve cancer care for every European cancer patient.

The cumulative experience of EURECCA's participants could be used to identify a 'core dataset' that covers all important aspects needed for high quality auditing and at the same time lacking needless data items that only consumes administrative effort. In **chapter 9**, the data items used by the nine registries participating in EURECCA are compared to identify a core dataset and explore options for future research. All colorectal outcome registrations participating in the EURECCA project were asked to supply a list with all the data items they score. Items were rated 'present' if they appeared literally in a registration or in case they could be calculated through other items in the same registration. The definition of a 'shared data item' was that at least eight of the nine participating registries scored the item. The number of registered data items varied between 254 (Belgium) and 83 (Norway). Among the 45 variables were patient data, data about preoperative staging, surgical treatment, pre- or postoperative radio- and/or chemotherapy, and follow-up. Items about tumour recurrence or quality of life were scored too infrequently to become shared data items. In conclusion, a total of 45 items were collected by 8 or more of the participating registries and subsequently met the criteria for a shared data item.

Several studies have shown remarkable differences in colorectal cancer survival across Europe. Most of these studies lacked information about stage and treatment. Furthermore, treatment guidelines differ per country. In **chapter 10** we compared short term survival as well as differences in tumour stage and treatment strategies between five European countries: Norway, Sweden, Denmark, Belgium, and the Netherlands. For this retrospective cohort study all patients aged 18 years or older and operated on adenocarcinoma of the rectum without distant metastases

and diagnosed in 2008 and 2009 were selected in national audit registries from Norway, Sweden, Denmark, Belgium, and the Netherlands. Differences in preoperative treatment between the countries were compared by using univariable and multivariable logistic regression. One year relative survival and one year relative excess risk of death (RER) were compared between the five countries. Large variation in the use of preoperative radiotherapy and chemoradiation was found between the countries. Nevertheless, there was little variation in relative survival between the countries, except Sweden, which had a significantly better one year RER of death among the elderly patients after adjustment. The differences in survival are expected to be caused by differences in perioperative care, selection of patients, and especially management of elderly patients. The effects of preoperative treatment are expected to be seen on long term follow-up.

Future perspectives

Prevention

Although this thesis confirms impressive improvements made in survival and morbidity for the treatment of rectal cancer, it is best not to need treatment at all. In other words: prevention is better than cure. An oncological surgeon calling for a cancer-free world might sound as naïve as a Miss Universe wishing for world peace, yet there is nothing wrong with striving towards utopia.[1] Above all, there is quite a lot to win in colorectal cancer prevention. In the Netherlands, 56% of all colorectal cancer cases can be attributed to adverse lifestyle factors such as smoking (+6.7%), alcohol consumption (+10.8%), consumption of red meat (+9.3%), processed meat consumption (+10.7%), poor calcium intake (+10.1%) and low fibre content of food (+8.8%).[2] In the same article, obesity is held accountable for an increase in colorectal cancer incidence of 14.6% and lack of physical exercise for an increase of 12.1%.

While some of the lifestyle factors might be confounders for others and the statistical margin of error is undoubtedly high with this kind of analysis, a more than 50% reduction of colorectal cancer incidence is possible through improvement in life style of the population. Compared with the often scant benefit of expensive new treatments, prevention should have the highest priority in every ministry of health, the more so because the same adverse lifestyle factors are responsible for much other misery and costs. Forces have to be joined to fight smoking, fight unhealthy diets and stimulate exercise. Instead of countering the epidemic of obesity with a tsunami of gastric bypasses, it should be attacked with prevention. Although some (Dutch) politicians take the view that people should not be patronised with regard to their life style, the urgency is too high and the ploys of (commercial) stakeholders too deceptive to allow things to continue the way they do. Prevention is not only the job for politicians and general practitioners. The role of hospital consultants should not be underrated. Without talking down

to patients but with empathic help and sometimes carefully chosen examples, a consultant can successfully use his or her persuasiveness to help and guide them to a healthier way of life (personal experience).

Screening

Without exception, it is better to treat cancer at an early stage because less extensive treatment (less invasive, more organ-sparing) is needed and outcomes are far better. In an era where our cars, heating boilers and even some espresso machines require annual check-ups, it sounds logical to consider screening programmes with the aim of diagnosing cancer in an early and mostly occult stage. Although commercial 'total body scans' generally cause more concern than they contribute to health, there is a growing number of government-initiated screening programmes in the Netherlands. After a nationwide screening programme for cervical cancer (1988) and breast cancer (1990) the phased implementation of a colorectal cancer screening programme started in January 2014 and will be fully operational in 2019. Biennially, Dutch inhabitants aged between 55-75 will be offered a test for occult faecal blood, via the mail. If the faecal haemoglobin level exceeds 275 ng/ml, an invitation for a colonoscopy will follow. With a mortality of approximately 5.000 in 2011 and an estimated incidence of 14.000 in 2015 is it expected that the CRC screening program will ultimately save 2.400 lives every year.

In spite of these impressive numbers there are considerable downsides to screening an entire population with merely age as selection criterion. Apart from the commotion evoked by false positive tests also a new 'screening-induced' patient category is created, of people who undergo invasive and possibly complicated treatment for something that does not make them feel ill and possibly never will. For instance, screening may detect a tubulovillous adenoma, not suitable for endoscopic resection, in a 75-year old patient with diabetes, emphysema and a history of previous abdominal surgery. Faced with this knowledge surgeons are more or less forced to perform a colonic resection by laparotomy and can only wish that no complications occur (anastomotic leakage, fascial dehiscence, bleeding or embolic complications, and so on). Another example is the patient in whom screening detects a ductal carcinoma in situ in the breast that can only be resected with a mutilating breast amputation but might never become invasive. Nevertheless, even if future cost-benefit analyses will show no advantage for certain screening programmes, they will probably stay because in the meantime public opinion is educated in a culture of 'check-ups' and safety, with a limited tolerance for 'bad luck'.

The benefit of screening can possibly be increased if screening programmes become more personal: not only based on age but on other individual risk factors such as family history, co-morbidity and lifestyle. Probably the 'by-catch' of false positive referrals (and collateral damage in terms of anxiety and complications) will also drop if screening becomes more personal.

Imaging

Staging is of utmost importance to enable an optimal treatment strategy. As the number of different treatment paths expands, accurate staging becomes even more important. In many Dutch hospitals, conventional dissemination staging with chest x-ray and an ultrasound of the abdomen have been substituted by high resolution CT of chest & abdomen and a pelvic MRI. Compared with the staging techniques used in the TME trial (chapter 2) and the pooled database used for the nomograms in chapter 4, the standard use of MRI has markedly changed the staging accuracy of rectal cancer.

In the TME trial, resectability-hence T status-was mostly assessed by digital examination of the rectum alone. Since MRI imaging together with multidisciplinary team meetings have been shown to improve outcome, routine MRI scanning followed by a multidisciplinary team discussion are now the standard of care for rectal cancer. Whereas MRI is very accurate for identification of involvement of the mesorectal fascia, endorectal ultrasound is more accurate in predicting T-stage in small rectal tumours. The results of chapter 5 stress the importance of preventing the unexpected finding of non-superficial carcinoma in presumed adenomas or superficial carcinomas. Therefore, the endorectal ultrasound (ERUS) technique should be incorporated in the standard workup for rectal tumours in which local treatment such as TEM is potentially feasible. The availability and quality of ERUS should therefore be improved in hospitals specialised in treatment of rectal cancer.

Another current diagnostic dilemma of MRI is adequate prediction of N status. The results of the TME trial show that nodal involvement should be an important factor in deciding which patients should be treated with preoperative radiotherapy. Therefore, a reliable technique is needed to detect positive lymph nodes before surgery. Although nodal staging has improved with the use of morphological criteria, accuracy is still inadequate with current MRI techniques. Studies with gadofosveset as contrast agent for MRI have reported good and reproducible sensitivity and specificity for the detection of metastatic lymph nodes in rectal carcinoma, also for restaging after preoperative treatment.[3] The limited availability of gadofosveset should be solved and this technique should be further refined for routine use.

FDG-PET scans are not routinely advised for standard work-up but have an important role when a metastasis is suspected. Though FDG-PET is dynamic, it is not intrinsically specific as it highlights all tissues with high glucose consumption. Future tumour-specific targeted agents will make PET a much 'smarter' tool, with a possible role in preoperative workup.

Accurate restaging after neoadjuvant downstaging treatment is of upmost importance to prevent needless irradical resections on the one hand or unnecessary radical resections on the other hand. Despite the accuracy of MRI alone, combining MRI with PET is probably even more precise for monitoring response after neoadjuvant treatment. Currently, studies are being launched to investigate the

accuracy of recently introduced combined PET-MRI scanners to assess clinical response.

Radiotherapy

The long term results of the TME trial described in chapter 2 showed that after a median follow-up of 12 years, preoperative short term radiotherapy in patients with resectable rectal cancer decreases local recurrence rates by more than 50% in comparison with operation alone, with a decreased overall recurrence rate. Cancer-specific survival was significantly higher when short term radiotherapy was followed by surgery with negative resection margins, but did not translate into improvement of overall survival owing to the toxic effects of radiotherapy. With the refinements gained in the last decade for both surgery and radiotherapy, one might conclude that local control of rectal cancer approaches perfection. Yet, despite indisputable reduction of local recurrence, preoperative radiotherapy has considerable side effects such as impaired wound healing, faecal incontinence and sexual dysfunction. Most importantly, radiotherapy does not result in survival benefit when all cases of rectal cancer are included. Nevertheless, in a subgroup of patients with TNM stage III and negative resection margins preoperative radiotherapy resulted in an overall-survival benefit, whereas for patients with a favourable prognosis on preoperative imaging the consequences of adverse effects induced by radiotherapy outweighed the benefits. Because of further refinements in TME surgery and clinical staging with MRI, a patient group with 'good prognosis' can be selected that has such a small chance of developing local recurrence that the morbidity of preoperative radiotherapy probably outweighs a (further) reduction of local recurrence. In other words, the estimated risk of local recurrence defines the benefit of preoperative radiotherapy. Improved staging techniques and nomograms such as those described in chapter 4 should be used as a tool to identify patients for which preoperative radiotherapy can be safely omitted.

In the trials described in this thesis and in current guidelines, 5x5 Gy short-course radiotherapy is commonly followed by surgery within a week and will have no downstaging effect. If downstaging of the tumour is required, long-course chemo-radiation is the preoperative treatment of first choice, which in around 16% of the cases leads to complete disappearance of tumour and involved nodes: a complete pathological remission.[4]

However, there is growing but preliminary evidence that if a waiting period is incorporated after short-course radiotherapy, a downstaging effect will occur as well.

A trial that examines the possible downsizing effects of short-course 5x5 Gy radiotherapy in combination with delayed surgery is the Swedish 'Stockholm III' trial. Control groups are firstly patients treated by short-course radiotherapy followed by surgery within 1 week and secondly patients treated by long-course radiotherapy 25x2 Gy followed by delayed surgery. Accrual started in 1998; according to an interim analysis published in 2010, it seems that short-course radiotherapy with delayed surgery has a downstaging effect as opposed to short-

course radiotherapy without delayed surgery.[5,6] The final results of this trial are awaited in the near future.

With regard to locally advanced rectal cancer, the current standard is preoperative chemoradiotherapy, and, dependent on institution and country, postoperative adjuvant chemotherapy. Now that shortcourse preoperative radiation with delayed surgery seems to induce tumour downstaging, it might be better to administer short-course radiotherapy with delayed surgery and to use the interval before operation for systemic therapy.

The multicentre 'RAPIDO' trial compares an experimental arm with short-course radiotherapy (5 Gy x5) followed by full-dose chemotherapy (capecitabine and oxaliplatin) in 6 cycles before surgery with the standard treatment of chemoradiation followed by surgery and optional postoperative chemotherapy. The hypothesis is that shortcourse radiotherapy with neo-adjuvant chemotherapy increases disease-free and overall survival without compromising local control.[7] Accrual is very good, with many Dutch hospitals participating.

While preoperative short-course radiotherapy, given as external beam therapy, has a low incidence of acute toxicity, the TME trial showed that it increases the occurrence of surgical complications and might even cost lives. As an alternative to external beam therapy, neoadjuvant high-dose-rate endorectal brachytherapy (HDREBT) can be given to patients with resectable rectal cancer. In a study comparing HDREBT (6.5 Gy, daily for 4 days, followed by operation after 4-8 weeks) with short-course radiotherapy directly followed by surgery, HDREBT was associated with lower rates of reoperation and perioperative bleeding, but the incidence of other postoperative complications was similar to shortcourse.[8] Longterm results should make clear whether HDREBT has a role in future treatment of rectal cancer.

Surgery

At present, surgery is still the cornerstone in the curative treatment of most solid cancers and especially of rectal cancer. What is more, good quality surgery seems the most important factor for reducing local recurrence. As shown in chapter 6, the TME trial significantly contributed to the quality of rectal cancer surgery in the Netherlands. After the trial closed in 2001, many further developments and refinements have been made in surgical technique. For instance, the technique of abdominoperineal resections, in the TME trial associated with a high rate of local recurrence, has evolved to a cylindrical extralevatory approach to prevent 'coning in' of the specimen, resulting in good local control.[9,10]

Furthermore, laparoscopic TME surgery has become the standard approach, with clear perioperative benefits for the patient and with results in terms of local recurrence and survival that are similar to those with open surgery. In the Netherlands, 70% of all colorectal operations in 2013 were performed by means of laparoscopy. Apart from a shorter period in hospital, less pain and better cosmetic results, the Dutch Surgical Colorectal Audit showed that laparoscopic resection is associated with a lower risk of cardiac and respiratory complications than open

surgery. The highest absolute benefit was found for high risk patients (old age, poor physical status, according to the American Society of Anaesthesiologists) and seem to be related to the relatively low surgical stress and inflammatory response after minimal invasive surgery.[11] As experience grows and new generations of 'natural born laparoscopic surgeons' hit the road, previous absolute contra-indications against laparoscopy (such as earlier laparotomy or reoperations) will become less important. Developments in laparoscopic instruments such as automated and articulated staplers, 3D camera systems, better sealing devices and robotics are expected to contribute to a further increase of the laparoscopic share in colorectal cancer surgery.

While it seems that the TME surgery is reaching perfection in terms of local control, it still comes with many downsides. The most feared complication has not changed in the last decades: anastomotic leakage. While intensive postoperative monitoring allows early discovery of anastomotic leakage and saves patients from sepsis or death, the anastomosis will usually be sacrificed, with small chances that re-anastomosis will be performed in the future. At present, despite all developments in surgical techniques and perioperative care, the rate of anastomotic leakage after resection of rectal cancer is considerable: in the Netherlands, the proportion with anastomotic leakage after rectal resection in 2013 was 10% for patients with a primary anastomosis and 7% for patients with a primary anastomosis and a temporary ileostomy.[11] Construction of a temporary ileostomy to prevent clinically relevant anastomotic leakage is a rough remedy with many problems, ranging from dehydration, obstruction and complications around the operation needed to restore bowel continuity to an apparently still considerable risk of a clinically relevant anastomotic leakage. Glimmers of light on the horizon to prevent anastomotic leakage are the recently introduced triple stapling techniques, recent insights in the negative effects of NSAIDs on anastomotic healing and new image-guided surgery techniques to assess the vascularisation of the bowel ends that need to be anastomosed.

Another serious and underreported complication that still regularly occurs after TME surgery is damage to the hypogastric nerve plexus, leading to sexual dysfunction and incontinence. In the near future, higher resolution and 3D camera systems, optionally combined with operation robots, may contribute to better identification and preservation of the hypogastric nerve plexus. Even targeted agents are being developed that may visualise nervous structures during surgery.

Up to now, the only certain remedy to prevent nerve damage is to stay away from it and the only way to prevent anastomotic leakage is to not create one, by either creating a permanent stoma in the first place, performing an organ-sparing local resection such as TEM or not to operate at all.

Probably many surgeons recognise the ambiguous feeling when after major rectal surgery following neoadjuvant treatment, the specimen shows a complete pathological remission. The pathology report will be explained as good news to the patient but at the same time the surgeon faces the question whether the (often

mutilating) radical resection was necessary after all. In case of (near) complete response after neoadjuvant chemoradiation, there might be role for 'organ-sparing' treatment options, especially if an abdominoperineal resection or permanent stoma can be prevented.

There is growing evidence that in case of a clinical complete response (no residual tumour on imaging and endoscopy) omission of surgery with intensified follow-up (a wait and see policy) might be an option for selected patients.[12,13] The problem in selecting the right patients for a wait and see policy is that a complete clinical response does not always correspond with a complete pathological response. Patients with a complete pathological response form the safest group for a wait and see policy. However, pathological response can only be assessed after surgery, which leads to the contradictory situation that a patient must be operated to find out that it was probably safe not to operate. Although the results of chapter 5 show that the role of TEM in the treatment of rectal cancer is not without risks, TEM might be a promising compromise between radical and no surgery for patients with a clinical (near) complete response after neoadjuvant treatment.

The Dutch CARTS trial investigated the role of rectum-saving surgery for distal rectal cancer. Patients with a clinical T1-3 N0 M0 rectal adenocarcinoma below 10 cm from the anal verge will receive neoadjuvant chemoradiation therapy followed by TEM after 8 to 10 weeks, depending on the clinical response.[14] Recently published results of this trial show that 21 of the 51 evaluated patients had complete pathological remission in the TEM specimen and after a median follow-up of 17 months, none of these patients developed recurrence. Of the 9 patients with near complete pathological response (ypT1N0), one patient developed a local recurrence and needed a rectal amputation.[15]

If clinical response evaluation reaches levels of accuracy that allows accurate preoperative identification of complete pathological responders, these patients can be safely offered a wait and see policy, while for the near complete responders, TEM might keep its role as alternative to mutilating radical surgery.

A recent development in minimally invasive surgery that might combine the minimal invasiveness of TEM surgery with the radicality of TME surgery is 'Transanal Minimally Invasive Surgery' TAMIS. This is a technique that can be used for local excisions, up to transanal TME resection. The endowrist instruments of the DaVinci surgical robot seem to have added value with the almost parallel instruments as a consequence of the in the small working space. The Dutch COLOR study group is currently setting up the multicentre COLOR III trial, which will randomise patients with rectal cancer <10cm from the anal verge between laparoscopic and transanal TME. Primary outcome will be radicality and local recurrence, secondary outcomes will be the percentage of sphincter preserving procedures.[16]

To epitomise, for surgery and all other treatment modalities as well, physicians need to find the right balance between the risk of recurrence and the risk of side effects and complications. With regard to surgical treatment, there are new devices as well as approaches that may increase the possible treatment options

and warrant a treatment modality that is tailored to the patient. Organ-sparing options are promising even including a selection of patients for whom surgery can completely omitted. Probably the most daunting task for members of the multidisciplinary treatment team is to identify those patients (cancers) who can be treated with minimal side effects as well as those patients (cancers) that must be treated extensively.

Pathology

Even though the landmark publication of Quirke about the importance of lateral spread in rectal cancer was published as early as in 1986, before the TME trial started in 1996, quality of pathology in the Netherlands was mostly limited, with often only distal and proximal tumour involvement reported.[17]

The quality-controlled design of the TME trial contributed to improved pathology reporting, with standardised investigation of the pathological specimen, according to the protocol of Quirke. A quality manager and a pathology review committee (PRC) were installed to ensure consistent quality of all pathological data and procedures. Special care was given to measurement of the circumferential resection margin (CRM). Furthermore, requirements for nodal staging and macroscopical evaluation of the (surgical) quality of the resected specimen were part of the protocol. Nowadays, these requirements are daily routine and have been incorporated into national guidelines.

The next step in pathology assessment might be standard assessment of biomarkers. Several promising biomarkers have been pinpointed that can help to identify those patients who will benefit most from (neo)adjuvant therapy. For instance, research on tissue samples obtained from the TME trial showed that both the level of caspase-3 activity and the presence of mutations in the PIK3CA gene can be used to identify patients with an increased risk of local recurrence. Other markers such as KRAS, BRAF, PTEN and MSI have been found but none of these biomarkers is used routinely in pathology reporting, although they can possibly contribute towards a more personalised treatment.

An example of personalised risk stratification for colon cancer is the 18-gene signature test Coloprint® that proved to be a reliable instrument for estimating recurrence risk in patients with an intermediate recurrence risk according to traditional pathological methods.[18] This test can save patients adjuvant therapy that is burdensome and has potential complications; at the same time it can prevent recurrences by treating high-risk patients with adjuvant treatments that would otherwise not have been offered to them.

There is a growing awareness that tumour biology is probably the most important prognostic instrument for cancer staging, overruling 'organ-based' theories.

Future developments in the routine use of one or more biomarkers can have great impact in allocating patients with rectal cancer to a treatment spectrum that ranges from local resection only to extensive surgery, radiotherapy and adjuvant chemotherapy and to everything in between.

Systemic therapy

Given that local control is nowadays almost always achieved, nearly all deaths after rectal cancer can be attributed to distant metastases. Many efforts have been made to decrease the incidence of fatal metastases with systemic therapy.

Despite the histological similarities, the anatomical continuity between colon and rectal tumours and the undisputed benefit of chemotherapy for colon cancer, the PROCTOR-SCRIPT trial (chapter 3) could not demonstrate a survival benefit for adjuvant chemotherapy in patients with rectal cancer. In addition, no significant differences were demonstrated in disease-free survival or recurrence rates. However, in the South Korean population of the recently published phase II ADORE trial, there seems to be a benefit of adjuvant FOLFOX over 5-FU/LV for patients with yp-TNM stage II or III rectal cancer.[19] Besides, the results of the CAO/ARO/AIO-04 trial are awaited for the effect of combination chemotherapy on disease-free survival.[20]

Despite the incomplete evidence about the efficacy of adjuvant chemotherapy for patients treated with preoperative radiotherapy and TME surgery, many oncologists believe adjuvant chemotherapy might be beneficial for selected patients with rectal cancer. This is probably the main reason that the PROCTOR-SCRIPT trial had a slow accrual and included only half the number of patients that was originally planned.

The nomograms discussed in chapter 4 can assist in the decision when to consider adjuvant chemotherapy for a rectal cancer patient, on the basis of the individual personalised risk for local recurrence and death.

Meanwhile, in the choice of chemotherapy there is a slow shift from an approach in which the tissue of origin and the histology are the guiding principles towards a genotype-centred approach in which the changes in the cancer genome are used to select patients for treatment with highly selective and targeted drugs. While some spectacular effects have been published after treatment with targeted drugs, at present they have no important role in the current schemes aiming at curation by means of systemic treatment. Many pioneers in this field predict an upheaval in cancer treatment in the near future, such as the claim of a top scientist on national Dutch television that in 20 years' time, 90% of all cancers can be cured or considered as a chronic disease, a broadcast that resulted in numerous patient requests for 'the medication from television'.[21]

Although the genome-centered approach for cancer is eye-catching and might lead to major improvements in the way that cancer is diagnosed and treated, sensational claims about 'cure all' systemic therapy for cancer have been made several times in the past decades. At present, surgery is still the cornerstone for curative treatment of solid (non-haematological) cancers.

Follow-up

Apart from early management of complications, documentation of outcome and maintaining the patient-doctor relationship, the main aim of follow-up after cancer treatment is improvement of survival. While it seems obvious that intensive

follow-up improves patient outcome, there is debate about the optimal intensity of these contacts. Recent research shows that intensive follow-up comes with an increased rate of treatment for recurrences, with curative intent, but without any difference in long term survival.[22] Follow-up strategies should therefore include risk stratification, since it is more useful to screen patients with a high risk of developing local or distant recurrences than patients with a low risk. The nomograms described in chapter 4 can assist in creating an individual follow-up schedule. In the future, EURECCA together with other registries and trials can provide updated and detailed data that can enhance the quality of such nomograms, resulting in even more refined prediction of recurrence risk.
Instead of the relatively inaccurate tumour markers such as CEA that are nowadays available, recent insights and future developments in tumour specific markers may lead to very sensitive tests that require only a drop of blood or even better, saliva.

It's the quality, stupid.

It is my sincere hope that the information reflected in this thesis contributes to speed up the tendency towards the only thing that really counts: quality in (cancer) care. While the problem of defining quality can easily fill another thesis, maintaining it requires continues effort and awareness, collaboration and harmonization.
Maybe the most important merit of the national audits and EURECCA is the transformation of the traditionally closed world of surgical oncologists into a open collaboration characterised by introspection, which inspires confidence, leads to improved quality and discipline and takes the wind out of the sails of-at times - ignorant politicians. The transition towards transparency is not easy and takes courage and epoch makers. Especially North European surgeons contributed heavily to this transformation and it is very promising that transparency and collaboration is spreading across Europe and the world.
Whether ongoing or future breakthroughs in radiotherapy, surgery or systemic therapy will lead to shifts in rectal cancer treatment, in any case treatment will become much more personalised. While 'tailor made medicine' is a popular slogan, at the moment rectal cancer treatment is mainly 'ready-made'. The developments in staging, pathology and molecular understanding of tumours, multidisciplinary treatment paths and population-based outcome predictors will enable a revolution of personalised medicine with QUALITY in capitals.

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