Quality assurance in rectal cancer treatment

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Chapter 1

General introduction and outline of the thesis

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INTRODUCTION

The incidence of cancer is increasing in Europe.[1,2] With an estimated 3.2 million new cases of cancer and 1.7 million deaths due to cancer in 2006 in Europe, it is an important health problem.[1] Colorectal cancer is the cancer with the second highest incidence and accounts for 412,900 (12.9%) new cases a year.[1] Besides, it is the second cause of cancer death with an estimated 207,400 deaths a year in Europe.[1] In the Netherlands, 10,851 patients were diagnosed with colorectal cancer in 2005.[3] In general, rectal cancer accounts for roughly 35% of colorectal cancers; currently over 3,000 patients are diagnosed with rectal cancer a year.

Quality assurance in surgical oncology

For almost all solid organ cancers, randomised trials have been performed to study new treatment protocols. It is recognised that variability in treatment could influence treatment outcome and consequently this confounder should be minimised. In radiotherapy, several actions have been taken to reduce variation, such as dosimetry or a pre-trial dummy run.[4-10] Moreover, also for systemic treatment such as chemotherapy, several criteria were defined which were used to asses treatment variation in oncological trials.[11-13]

In contrast to drugs, which are reproducible entities, a characteristic of operations is the large variability making it difficult to reproduce the results. A major variable responsible for this variability is the skills of the surgeon. 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".[14] The skill level of surgeons will not only vary among surgeons, but will increase as a surgeon gains experience. Besides, surgeons with specific interests will perform better and develop more new techniques.[14,15] These new techniques are often tested and analysed in their own centre. This partly explains why so many non-randomised single centre or personal series are reported in surgery.

It is a prerequisite for a randomised trial that the participating surgeons are equally skilled in both techniques. Differences in performances between individual surgeons are rather the rule than the exception. To solve this problem one group of surgeons could only perform the conventional procedure and another group only the experimental operation: a so-called expertise based randomised trial.[16] Another option is to train all surgeons to perform the procedure in the same way and at a similar level. 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. It is a process in which continuous quality improvement is a central issue. Surgical quality assurance measurements were used in the Dutch D1-D2 gastric cancer trial and later in the Dutch TME trial.[17-21]

Quality control in gastric cancer surgery

From August 1989 to June 1993 the Dutch D1-D2 Gastric cancer trial was performed.[17] This trial randomised patients between a limited D1 and an extended D2 lymph node dissection. In the design of this trial, quality assurance measures for both surgery and pathology were incorporated.[17,18,21] Participating surgeons received videotapes and booklets about the technique and were instructed in the operating room by a gastric-cancer surgeon from Japan.[21] This instructing surgeon was present during the first 4 months of the trial, which served as an instruction period. He was also present regularly thereafter. Eight surgeons, from 8 regions, had been specially trained in D2 dissection. These specially trained consulting surgeons attended all operations involving D2 dissections. The study coordinator attended nearly all D1 dissections. The consulting surgeons and the study coordinator monitored the technique and the extend of the lymph node dissection, and after the operation, they divided the perigastric tissue into the proper lymph node stations. Regular meetings about the technique were held with the consulting surgeons, the study coordinator, and the instructing surgeon.[18]

Quality control was also used for pathological examination in the Dutch D1-D2 trial. The number and location of lymph nodes detected at pathological examination were related to the guidelines of the study protocol.[22] If at pathological examination lymph nodes were detected in stations other than those specified by the protocol, this violation of the protocol was called "contamination". If, however, the pathologist could not detect lymph nodes in stations that should have been dissected, this violation was called "non-compliance". These violations could occur in both D1 and D2 dissections. Contamination in the D1 group and non-compliance in the D2 group could blur the distinction between the 2 types of dissection. To account for biological variation, one missing station was allowed.[18]

At the start of the trial, historical data was used to calculate the expected 5-year survival rates after dissection with curative intent: 20% for patients who had a D1 dissection and 32% for patients who had a D2 dissection.[18,23] Although the trial could not demonstrate a difference in overall survival, the 5-year survival rates were much higher than expected: 45% after a D1 dissection and 47% after a D2 dissection.[24] Part of this improved outcome could be explained by an unexpectedly high proportion of pathological T1 (26%) and T2 (47%) tumours, but it could not account for the complete difference. The process of instructing surgeons by videotapes, booklets and instruction sessions, in combination with supervision of dissections by instructor surgeons to standardise the procedure also paid off.

QUALITY CONTROL IN RECTAL CANCER SURGERY

Background

Before the introduction of TME (total mesorectal excision) surgery, blunt digital resection was used, resulting in local recurrence rates of about 20%.[25] In the Swedish Rectal Cancer trial, for example, which included patients from 1987 until 1990, the 5-year local recurrence rate was 27% for patients treated with surgery alone. If the patient was treated with preoperative 5 x 5 Gy radiotherapy, local recurrence rates dropped to 11%.[25]

In the 1990s, the Dutch Colorectal Cancer Group designed a trial using standardised surgery to reduce local recurrence rates: the Dutch TME trial.[19] The surgical procedure used in this trial was new at that time, involving a complete and sharp excision of the mesorectum under direct vision, with preservation of the hypogastric plexus (TME procedure). The approach was advocated by Heald and Enker and resulted in a 5-year local recurrence rate below 10%.[26,27] These rates were almost similar to the recurrence rate found in the Swedish Rectal Cancer trial for conventional surgery combined with preoperative radiotherapy.[25] After the Swedish Rectal Cancer trial had demonstrated the beneficial effect of radiotherapy, the remaining question was whether radiotherapy was still beneficial in combination with standardised, good, TME surgery.[25,28] To standardise treatment and reduce variation, extensive quality control was included in the TME trial for radiotherapy, surgery and pathology.[19,20]

Quality control

Results from a questionnaire which was mailed to all 21 Dutch radiotherapy departments showed that the use of the 5 x 5 Gy scheme, as used in Sweden,[29] was accepted by most institutes. Treatment details, like volume and fields were described meticulously in the protocol, including a mandatory stimulation procedure. All institutes had to use a 3 or 4 fields portal box technique in order to avoid serious non-surgical morbidity which was observed in the Stockholm trial using less fields.[30]

The TME procedure provides an excellent specimen and therefore the pathologist was able to check whether the procedure had been performed according to the protocol, using the transverse slicing method of Quirke.[31] For the pathologists, this way of analysing the specimen was very different from their daily practice. In addition to the TME study protocol, a special pathology protocol was written and distributed to 43 pathology laboratories. A pathology workshop was organised in December 1995 with the attendance of Dr. Quirke. A step-to-step protocol was produced, usable at the dissection table. In addition, the pathology coordinator had set up a Pathology Review Committee to discuss problems and review the slides, reports, and photographs of the specimen.[32]

In the TME trial, a new surgical technique was used by all participating surgeons. For the TME trial, an expertise based randomised controlled trial design was not possible,

as TME surgery was used in both randomisation arms. Besides, due to such a design the change outside the trial would occur at a slower pace, because only part of the surgeons is able to perform the new procedure. Different modalities were used to train the participating surgeons. First, a videotape on radicality and autonomic nerve preservation was produced, with operations performed by professor Moriya. Dr. Heald from Basingstoke (United Kingdom) performed almost 30 operations throughout the Netherlands and produced two videotapes, which were distributed to all participating hospitals. Besides, he has attended all seven workshops, which were organised all over the country from May 1996 to April 2000. A total of 21 instructor surgeons were selected. Their task was to introduce, teach and control the TME operations in their region. In each hospital, the first 5 TME procedures had to be supervised by an instructor surgeon.

Results

A total of 1861 patients were included in the study between January 1996 and December 1999, of whom 1530 from 84 Dutch hospitals.[33] During the TME trial the pathology data were checked.[32] Pathology data from case record forms were compared with hospital pathology reports. Three independent audits were carried out. Special attention was given to the accuracy of parameters, which are important for prognosis and treatment decisions. These quality checks revealed that only one third of the forms were complete and correct. Missing values were most prominent in the number of lymph nodes examined, whereas most errors were made in relation to the circumferential margin. Incorrect and missing data were corrected during these audits. By performing quality checks on all pathology data, the accuracy and completeness of these data were increased, which improved reliability of future analyses.

In the TME trial, the first 5 procedures in each hospital were supervised by an instructor surgeon. This requirement meant that 66% of the TME operations were attended by instructor surgeons during the first year and 58% during the first 500 TME procedures.[19] The pathologist was able to give feedback on the surgical quality of the resection to the surgeon: macroscopic completeness and microscopic circumferential resection margin (CRM) involvement were shown to be good predictors of local recurrence and overall survival.[33,34]

The 5-year local recurrence rates were 5.6% and 10.9% respectively for the group treated with preoperative radiotherapy and for the group treated with surgery alone ($P < 0.0001$), and overall survival rates were 64.2% and 63.5% respectively ($P = 0.90$; median follow up 6.1 years).[33] Compared with historical data derived from trials in which conventional, blunt, non-standardised surgery was used, local recurrence rates were halved and the 5-year overall survival rate improved from 48% to 64% after surgery alone.[25,34] Also in other reports the improved results with standardised surgery for rectal cancer are shown.[35]

The association between CRM involvement and outcome in terms of local recurrence and overall survival, demonstrates the importance of assessing surgical variation: with CRM involvement the 5-year local recurrence rate was 19.7% for patients preoperatively treated with radiotherapy, compared to 3.4% for patients with a negative CRM.[33] If such a parameter of surgical quality is not assessed and used as adjustment in the interpretation of the trial results, drawn conclusions might be made erroneously. Moreover, CRM involvement should be determined in daily clinical practice, as it is an important parameter of outcome and essential for feedback to the individual surgeon.

QUALITY ASSURANCE IN RECENT YEARS

Nowadays, there is a focus on quality assurance. Newspapers publish ranked lists of hospitals with the best care[36,37] and health care insurance companies advertise that they only contract hospitals that provide a certain standard of care. Quantifiable parameters which could be used to determine the quality of care provided are called performance indicators. The Netherlands Health Care Inspectorate has used such performance indicators to protect and promote health and healthcare. An example of interference of the Health Care Inspectorate can be found for oesophageal resections. In literature, an association between volume and postoperative morbidity and mortality was shown: the more oesophageal resections performed in a hospital per year, the lower the complication rate.[38-40] As a result, the Netherlands Health Care Inspectorate nowadays only allows hospitals to perform an oesophageal resection if, annually, 10 or more of these procedures are done. However, to guarantee a certain (high) level of quality of care, it remains important that medical professionals themselves are actively involved in quality assurance. The European Society of Surgical Oncology (ESSO) has recognised the importance of quality assurance and the author of this thesis has received the first Quality Assurance Fellowship. This thesis focuses on quality assurance of rectal cancer treatment, in particular of the surgical treatment. Both oncological short-term and long-term outcome parameters such as circumferential resection margin involvement, local recurrence, and overall survival are studied, but also other end-points which are important for quality assurance are investigated, such as anastomotic leakage and stoma reversal.

OUTLINE OF THE THESIS

Chapter 2 describes the overall survival for resected rectal cancer in the Netherlands before, during and after the TME trial. TME surgery was nationwide introduced during the TME trial in the Netherlands. In the trial, the effects of preoperative 5 x 5 Gy radiotherapy

were studied. In this chapter both the effects of the nationwide introduction of the TME technique and preoperative radiotherapy are investigated.

Chapter 3 and chapter 4 focus on the elderly patients. These patients are underrepresented in most rectal cancer trials, whereas they form the majority of the rectal cancer patient population. It could be questioned whether it is reasonable to apply the guidelines based on relatively younger patients to the elderly. **Chapter 3** discusses this problem, based on analyses of overall survival for elderly patients with rectal cancer. As overall survival failed to improve in the subset of elderly patients since the introduction of TME surgery, in **chapter 4**, postoperative complications and mortality are explored to get more insight in the problems involved.

Apart from the issue of the elderly patients, several studies showed that the type of surgical procedure does also influence outcome: patients treated with an abdominoperineal resection (APR) have a reduced overall survival compared to patients treated with a low anterior resection (LAR).[41-43] In **chapter 5** is studied whether the factors associated with the decision to perform an APR or the APR procedure itself were related to circumferential resection margin involvement, local control, and overall survival. **Chapter 6** describes an in depth analysis in patients treated with an APR in the TME trial to identify tumour and patient related risk factors that contributed to CRM involvement, local recurrence, and reduced overall survival. In both chapters methods which could improve outcome for patients treated with an APR are discussed.

The importance of a resection without involved resection margins or R0 resection has been shown in several studies.[44,45] EORTC trial 22921 compared adjuvant fluorouracil-based chemotherapy to no adjuvant treatment in a 2 x 2 factorial trial with randomisation for preoperative (chemo)radiotherapy in patients with resectable T3-4 rectal cancer. This trial started in April 1993. In 1999, the recommendation to perform a TME procedure was included. In **chapter 7** CRM involvement is investigated in EORTC trial 22921. Furthermore, the effects of CRM involvement on local recurrence and overall survival rates are shown. In **chapter 8**, the same EORTC trial is used to study which subset of patients benefits significantly from adjuvant treatment.

After a resection of the primary rectal tumour, surgeons often create an anastomosis to restore the continuity of the bowel. **Chapter 9** describes a feared complication: anastomotic leakage. Apart from the focus on short-term morbidity, in this chapter long-term end-points are considered including local recurrence, overall survival, disease-free survival, and cancer-specific survival. In **chapter 10**, a protocol for postoperative surveillance after colorectal resection with continuity restoration is described and tested. This protocol aimed at reducing delay in the diagnosis of anastomotic leakage and subsequently at reducing mortality associated with this complication.

Recently, it was shown that the creation of a stoma reduces the rate of symptomatic anastomotic leakage.[46] However, not all stomas that are created with a temporary

intention are reversed. **Chapter 11** describes stoma reversal in the TME trial. Specific attention is given to determine limiting factors for stoma reversal.

Finally, the results of all studies will be summarised and discussed in **chapter 12**.

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