Variation in diagnosis, treatment and outcome in colon and rectal cancer

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Chapter 1

Introduction

Quality of care

Colorectal cancer is a major health problem. In male, it is the third most common cancer, following prostate cancer and lung cancer, and in female, it is the second most common cancer after breast cancer. Eight percent of all cancer patients died from colorectal cancer, making it the fourth most common cause of death from cancer worldwide.[1] Therefore, it is challenging to increase survival of these patients.

Survival has already increased which was accompanied by several changes in therapy of colorectal cancer, including the introduction of the Total Mesorectal Excision (TME) technique and a shift from postoperative to preoperative radiotherapy for patients with rectal cancer and advances in adjuvant chemotherapy for those with colon cancer.[2;3] However, further improvement in outcome could be achieved by optimising the quality of care once actionable factors are identified. Therefore, adherence to the evidence-based guidelines for diagnosis and treatment of patients with colorectal cancer should be high as guidelines provide recommendations for the best care, based, so far as possible, on evidence from scientific research. Due to these national guidelines, a uniform treatment policy is available in the whole country. Several not yet identified factors may lead to variations between regions, hospitals or medical specialists in the adherence to guidelines.

To investigate differences between regions and hospitals in their adherence to guidelines for colorectal cancer, the variations in diagnosis, treatment and outcome among patients with colorectal cancer in the Netherlands will be described in this thesis. The main goal is that these results provide medical specialists, hospitals and regions insight into the guidelines adherence. Feedback about their own performance by monitoring the adherence to guidelines will help medical specialists and hospitals to improve their quality of care. To support the discussion of understanding the differences between medical specialists, hospitals and regions additional factors are analysed. First, factors associated with adequate lymph node examination will be evaluated. High quality of staging is important for planning the most optimal treatment and for accurate estimation of prognosis. Second, factors, especially hospital characteristics, which relate to receiving treatment according to guidelines will be determined. On the basis of the factors which influence adequate staging and optimal treatment, best practices could be identified. Implementing these best practices in the hospitals will improve the quality of colorectal cancer care and might lead to better outcomes. The current Dutch guidelines for colorectal cancer and the Netherlands Cancer Registry will be used for the analyses of this topic.

Guidelines

In the Netherlands, the process around guidelines for cancer care, including development, implementation and evaluation, is supported by the Comprehensive Cancer Centres (CCCs). CCCs are centres of knowledge and quality improvement in oncology as well as palliative care which, by maintaining an extensive network, fulfil an independent coordinating function within the fields of oncology and palliative care. Other activities of the CCCs, besides developing and implementing guidelines, are facilitating consultancy services, improving the organisation of cancer care, coordinating palliative care and realising and maintaining the Netherlands Cancer Registry (NCR). In the guidelines process, CCCs work together with other organizations, including the Dutch Institute for Healthcare Improvement (CBO) and the Dutch Order of Medical Specialists

Development

From 1974 until 2000 consensus-based guidelines were developed and implemented at the regional level by tumour working groups within the network of the CCCs. Since 2000, national evidence-based guidelines for the diagnosis, treatment and follow-up of cancer patients were developed by national working groups. These national working groups are responsible for the content of the guidelines. All guidelines for oncology care can be consulted at a website (www.oncoline.nl). The national multidisciplinary working groups were set up and supported by the CCCs. The members represent different national scientific medical associations and regional multidisciplinary working groups. In addition, oncology nurses, psychosocial oncologists, general practitioners and members of patient associations are involved.

Implementation

Development of guidelines is followed by implementation. The CCCs facilitate several regional tumour working groups. The members of regional working groups, including medical specialists from the different hospitals, pathology laboratories and radiotherapy departments, play an important role in implementing the guidelines in the CCC-region. Implementation is realised through educational programs (at the individual, regional and national level) and quality improvement programs.

Evaluation

Data from the NCR are used for evaluation of the implementation. CCCs give feedback to medical specialists and oncology committees about, among others, adherence to the guidelines at the hospital level compared to the regional average. Furthermore, in the regional working groups the medical specialists discuss the results of benchmarking between the hospitals by comparing the performance of the hospitals. Most of the dis-

cussions focus on understanding which factors might be responsible for the differences. When adherence to guidelines is low, hospitals could start quality improvement programs. Some national and international examples showed improvement in quality of care due to feedback of the individual results to hospitals or medical specialists.[4-6]

Variations in adherence to guidelines

Differences in adherence to guidelines are multicausal. At the regional level, initiatives for implementing and evaluating guidelines might differ between CCCs, leading to variations in quality of care between CCC-regions. Furthermore, hospital characteristics, such as hospital volume and teaching status, may influence the quality of care at hospital level. Numerous studies showed differences in outcome between teaching and non-teaching hospitals and between high-volume and low-volume hospitals, especially for high-risk procedures such as oesophagectomies.[7-9] There are also organisation-related factors at the hospital level that are associated with the quality of care, such as multidisciplinary team work including a multidisciplinary cancer conference at which the diagnosis and treatment of patients are discussed.[10] Other organisation-related factors that could play a role are the availability of up-to-date technology, the organisation of intensive care units and implemented care pathways which could improve waiting times.[11;12]

Comparison is often done at the hospital level, but differences in outcome might be caused also by variation at the individual level of the medical specialists, e.g. volume, specialization and skills of the medical specialist leading to variations in quality of cancer care.[13;14] Furthermore, apart from the role of the individual medical specialist, the whole multidisciplinary team around the medical specialist influences the quality of care.[15]

In addition, there are also patient-related factors that lead to variation in adherence to the guidelines. These case-mix information should be taken into account when differences in guidelines adherence are evaluated. Patients with a poor performance status, mainly elderly patients, often receive less extensive treatment. Extensive treatment is also frequently avoided for patients with co-morbidities.[16] Furthermore, the wish of the patient has to be taken into account.

Netherlands Cancer Registry

The studies in this thesis are based on data from the nationwide population-based NCR, which was established in 1989. The NCR includes all newly diagnosed malignancies in

the Netherlands. Notification of all newly diagnosed malignancies is obtained from the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnoses, haematology departments and radiotherapy institutions. Information on patient characteristics (e.g. gender, date of birth), tumour characteristics (e.g. date of diagnosis, subsite and stage) and primary treatment (type of treatment, date of start of treatment) are collected routinely in the hospitals from the medical records approximately nine months after diagnosis. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O).[17] The stage of the tumours is classified according to the TNM-classification of the UICC.[18] Due to a thorough training of the registrars, computerised consistency checks and regular quality checks at the national level, the quality of the data is high. Completeness is estimated to be at least 95%.[19;20] Vital status of all patients is obtained actively on a regular basis by linking the cancer registry database to the database of the municipal registry and the database of deceased persons of the Central Bureau for Genealogy.[21] The NCR is used for developing and evaluating guidelines as well as for various other purposes, such as supporting epidemiological and clinical research, evaluating screening programs, planning health services and improving quality of care.

Epidemiology of colorectal cancer

Incidence

Worldwide, of all cancer cases among males 10.0% were colorectal cancers and 9.4% of all cancer cases among women were colorectal cancers. In 2008, the age-standardised incidence rate (World Standardized Population, WSR) was 20.4 per 100,000 person-years among males and 14.6 per 100,000 among females, worldwide. Colorectal cancer is frequently diagnosed in the Western world. The incidence rate differs between developed regions and developing regions from respectively 30.1 to 10.7 per 100,000 person-years.[1]

In the Netherlands, over 12,000 new patients with colorectal cancer were diagnosed in 2008. More than 8,600 of these patients had colon cancer and 3,500 patients had rectal cancer. The incidence of colorectal cancer is increasing in the Netherlands with age-standardised incidence rates (WSR) from 30.7 per 100,000 person-years in 1989 to 38.0 per 100,000 person-years in 2008. The life-time risk to develop a colorectal cancer is 6.6% for males and 5.8% for females meaning that 1 in 15 men and 1 in 17 women will develop a colorectal cancer during their life.[21]

Mortality and survival

In 2008, the age-standardised mortality rate (WSR) was 20.4 per 100,000 person-years for males and 14.6 per 100,000 person-years for females, worldwide.[1] In the Netherlands, 4,038 patients died of colorectal cancer in 2008. Mortality due to colorectal cancer is slowly decreasing from 15.9 per 100,000 person-years (WSR) in 1989 to 13.6 per 100,000 person-years in 2008,[22] suggesting an improvement in survival over time.

Results from EUROCARE-4 showed that the Netherlands belongs to the European countries with a high survival rate for colorectal cancer. In the period 1995-1999, 5-year relative survival rate was 54% for the whole of Europe, with rates ranging from 39% to 60% between countries. Patients diagnosed in the Netherlands in this period had a 5-year relative survival rate of 57%.[23] Stage of disease at diagnosis is an important predictor for prognosis. Five-year relative survival rate was 93% for patients with stage I, decreasing to only 9% for patients with stage IV. Survival of both colon cancer patients and rectal cancer patients has increased over time. Five-year relative survival rate was 54% among colon cancer patients diagnosed in the period 1988-1992, which increased to 59% among colon cancer patients diagnosed in the period 2003-2007. For rectal cancer patients, 5-year relative survival rate increased from 52% to 61% in the same period.[21] This increase in survival is probably due to positive changes in treatment.[24]

Risk factors

Hormone replacement therapy and non-steroidal anti-inflammatory drugs, such as aspirin, reduce the risk of developing colorectal cancer.[25;26] Several lifestyle factors, including physical inactivity, high consumption of red and processed meat, alcohol intake, smoking and obesity, increase the risk of developing colorectal cancer.[27] Persons with inflammatory bowel disease like ulcerative colitis and Crohn's disease are also at high-risk of developing a colorectal cancer.[28] Furthermore, there are some genetic risk factors for colorectal cancer. Around 5% of all colorectal cancers are genetically determined. The main hereditary forms are Lynch syndrome (hereditary non-polyposis colorectal cancer (HNPCC)), familial (non-polyposis) colorectal cancer and adenomatous polyposis (FAP or MAP).[29]

Guidelines for colorectal cancer

In the Netherlands, there have been national evidence-based guidelines cancer care since 2000. In the 1980s and 1990s, consensus-based guidelines already existed on the regional level. A national multidisciplinary working group of medical specialists, including surgeons, radiation oncologists, pathologists, medical oncologists, radiologists and gas-

troenterologists developed the national guidelines for colorectal cancer care. The guidelines, revised in 2008, contain recommendations for diagnosis, treatment and follow-up of patients with colorectal cancer.[30;31]

Diagnosis and staging

The aim of diagnostic tests is to detect the colorectal tumour. Furthermore, the stage of the disease is determined which is used by medical specialists to plan the treatment of the patient. A sigmoidoscopy or colonoscopy is used for patients suspected of having a colorectal cancer. During this endoscopy, biopsies can be taken for pathological examination. When colonoscopy is not possible, computed tomography (CT), sigmoidoscopy combined with colonography or barium enema is indicated for colon cancer patients.[30] For patients with rectal cancer diagnostic tests include MRI, especially for assessment of the circumferential resection margins (CRM), and endorectal ultrasound to differentiate between T1 and T2 rectal tumours.[31]

For both patients with colon cancer and those with rectal cancer, hepatic ultrasound, CT or MRI combined with chest x-ray are used to screen for distant metastases. After surgery the pathologist examines the specimen and the lymph nodes to determine the pathological stage. There is no widely accepted standard for the minimum number of lymph nodes which should be examined. In literature, suggestions about the minimum number of evaluated lymph nodes vary from 6 to 17 to as many as possible.[32-34] The guidelines of the International Union Against Cancer (UICC) recommend examination of at least 12 lymph nodes,[18] whereas according to the Dutch guidelines 10 or more lymph nodes should be examined for accepting pN0 status.[30;31] In the Netherlands, the minimum of 10 was chosen, because evaluation of less than 10 lymph nodes is one of the criteria for defining patients with stage II disease as high risk. Adequate lymph node evaluation is important for accurate staging, optimal treatment and a reliable estimation of prognosis.

Treatment

Colon cancer

For patients with colon cancer surgical removal of the tumour, regional lymph nodes and a part of the colon on both sides of the tumour is the primary treatment. Sometimes a temporary colostomy is indicated. The classical abdominal resection is more often being replaced by laparoscopic surgery. Adjuvant chemotherapy should be considered for patients with lymph node metastasis and for high-risk stage II patients, defined as patients with perforation, T4 tumours, venous invasion, fewer than 10 lymph nodes examined or poorly differentiated or undifferentiated tumours. For a small proportion of patients with distant metastases, surgical resection of the metastasis may still be curative. Palliative chemotherapy could be considered for patients with unresectable distant metastases.[30]

Rectal cancer

For patients with rectal cancer, the type of the resection depends on the localization and size of the tumour. For T1 tumours, Transanal Endoscopic Microsurgery (TEM) is recommended. Patients with tumours located in the lower part of the rectum, near the anal sphincter, should undergo an abdominoperineal resection (including a permanent colostomy). For tumours in the middle or upper part of the rectum a low anterior resection might be performed. After a low anterior resection, which preserves the anal sphincter, a permanent colostomy is not indicated. Nowadays, the total mesorectal (TME) technique is used for these resections. Preoperative radiotherapy is indicated for patients with clinical T2-T4 tumours. Since mid-2005, preoperative chemoradiation is recommended for patients with locally advanced tumours, defined as tumours in which a positive CRM is expected or tumours with 4 or more positive lymph nodes. All other patients should receive a short course of radiotherapy. Adjuvant chemotherapy is not recommended for patients with rectal cancer in the Dutch guidelines. Patients with unresectable distant metastases may be treated with palliative chemotherapy.[31]

Follow-up

After initial treatment follow-up is started. Apart from the standard colorectal cancer follow-up schedule, there are separate follow-up schedules for patients with rectal cancer who underwent a TEM-procedure, for patients with hereditary colorectal cancer and for patients with stage IV disease. For all other patients with colorectal cancer follow-up, up to 5 years after treatment, consists of a colonoscopy 3 months after surgery if preoperative a complete colonoscopy could not be performed, another colonoscopy two or three years after surgery, controls by medical specialists and hepatic ultrasound.[30;31] The most important aim of follow-up is to detect recurrences, metastases and metachronous tumours at an early asymptomatic stage in order to have an opportunity to cure the patient.

Since the introduction of the TME technique around 1996, the 5-year local recurrence rate among patients with rectal cancer decreased considerably; a further decrease in local recurrences has been observed since preoperative radiotherapy became part of the state of art in 2001.[2] Before the introduction of the TME, local recurrence rates from 7% to 50% were reported.[35] In the Dutch TME-trial the 5-year local recurrence rate among patients who received short-term preoperative radiotherapy and TME was 5% compared to 11% among patients who underwent TME alone.[36] Less attention is paid to local recurrences among patients with colon cancer compared to patients with rectal cancer. Five-year local recurrence rates after curative resection of colon cancer varied between 6% and 13%.[37;38]

Outline

The main objective of this thesis is to identify factors which influence the quality of care and outcome using the results of the analyses of the variations in diagnosis, treatment and outcome among patients with colorectal cancer in the Netherlands.

In **chapter 2.1** changes in treatment of patients with rectal cancer and the influence of these changes on survival are described. **Chapter 2.2** gives an overview of trends in the treatment of patients with colon cancer and investigates the effect of these trends on survival. **Chapter 2.3** reveals which variables are associated with the occurrence of locoregional recurrences among patients with colon cancer and identifies risk groups. **Chapter 3.1** and **chapter 3.2** describe the variations between hospitals and between pathology laboratories in lymph node evaluation in rectal and colon cancer, respectively. These chapters also analyse factors that influence adequate lymph node evaluation and examine the relationship between number of evaluated lymph nodes and survival. The variations in staging, treatment and outcome according to region and according to type and volume of individual hospitals for patients with rectal and colon cancer are shown in **chapter 4.1** and **chapter 4.2**, respectively.

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