Variation in Occurrence, Management, and Outcome of Colorectal Cancer in the Netherlands, on the Eve of Mass Screening

Variatie in incidentie, behandeling en uitkomst van colorectaalkanker in Nederland aan de vooravond van screening

Liza van Steenbergen

Printing of this thesis was realised with financial support of:
- Comprehensive Cancer Centre South (Integraal Kankercentrum Zuid)
- Department of Public Health, Erasmus MC Rotterdam
- Dutch Cancer Society
- Roche Nederland B.V., Merck-Serano

ISBN: 978 90 5335 264 9

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Cover design: M.P. Reijnders and Ridderprint, Ridderkerk

Printed by Ridderprint, Ridderkerk

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Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. H.G. Schmidt
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
donderdag 27 mei 2010 om 11.30 uur

door

Liza Nicolien van Steenbergen
geboren te Delft

Promotie commissie

Promotor:	Prof.dr. J.W.W. Coebergh
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CHAPTER 1.

INTRODUCTION

1.

Introduction

1.1. Background

General epidemiology of colorectal cancer

The large bowel can be divided into the colon, the rectosigmoid, and the rectum. The colon starts where the small bowel ends and it is 1.5-1.8 metres long when stretched. The rectum forms the final 10-15 cm of the large bowel, opening to the outside at the anus. The rectosigmoid is the transitional zone between the colon and the rectum.[1]

Incidence

Colorectal cancer (CRC) is the third most frequent cancer (14%) among males, after prostate (22%) and lung cancer (16%), and it is the second most common tumour (13%) among females, after breast cancer (31%) in the Netherlands.[1] In 2007, 11,823 patients were diagnosed with CRC and 4,828 patients died of the disease.[2] The incidence in the Netherlands is relatively high compared to other European countries, and ranks in the top 10.[3] Worldwide, CRC accounted for about 1 million of new cancer diagnoses in 2002, representing nearly 10% of all new cancers.[4] It occurs more frequently in the industrialized world. The disease rarely occurs before age 40, and the risk of CRC becomes highest around age 70.[1] It is expected that the absolute number of patients with CRC increases with three percent per year in the Netherlands, mainly due to the aging population. Based on this estimation, the incidence of CRC in the Netherlands increases to 14,000 patients in 2015.[5] As a percentage of total mortality, the risk of dying from CRC in the Netherlands is highest around age 60 (about 5%), which is important because it can be seen as an important cause of death. Later in life other causes of death proportionally start to occur more often.[6]

Stages of the disease

Colorectal carcinogenesis starts with hyperplasia of the epithelial cells, when the tissue becomes dysplastic. This process results in the earliest identifiable lesion, the aberrant crypt focus.[7] The dysplastic tissue may further develop into so-called polyps, which are benign tumours. Several types of polyps exist. The adenomatous polyp, or adenoma, which consists of glandular epithelial tissue that line the inner layer of the wall of the large bowel, is regarded as the most important type of polyp in colorectal carcinogenesis. Approximately 98% of the colorectal cancers are adenocarcinomas, which originate from these adenomas.[8] It has been estimated that CRC takes at least five years to develop from dysplasia, although most studies estimate that it takes between 10 and 30 years.[9, 10] Most of that time is thought to be needed for adenoma formation. The Dukes staging system and the TNM staging system are most commonly used to classify invasiveness of the disease. The systems consist of four stages and are interchangeable; Dukes A to D and stage I to IV. In stage I CRC, the cancer has

grown through several layers of the large bowel, except its muscular wall. Stage II CRCs have grown through the wall, but have not yet involved the lymph nodes. When the cancer has spread to at least one lymph node in the nearby area, but not to other parts of the body, the cancer is classified as being stage III. Stage IV is the most advanced stage of the disease; the cancer has reached distant organs or tissue, most commonly the liver or the lungs. In the Eindhoven Cancer Registry area, the TNM stage distribution was as follows in the period 2006-2007: stage I 20%, stage II 31%, stage III 26%, and stage IV 23% (excluding patients with unknown stage, which is approximately 7%) (Figure 1).

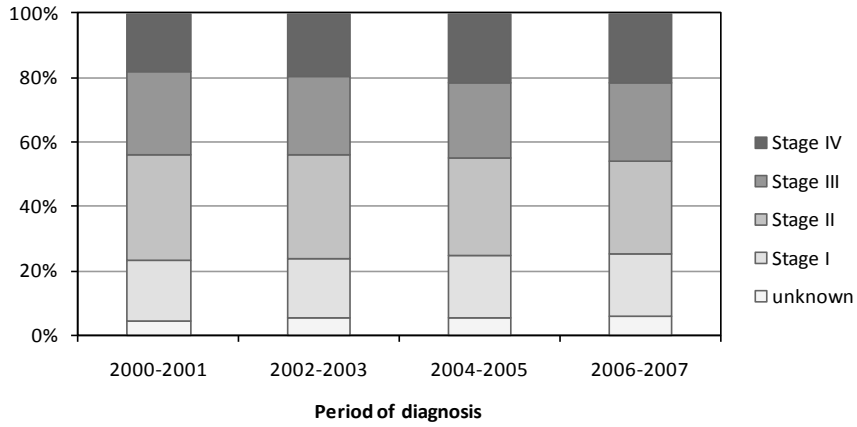

Figure 1: Stage distribution of colorectal cancer in the Eindhoven Cancer Registry region 2000-2007

Survival

The 5-year relative survival rate of patients with CRC in the Netherlands was 59% for patients diagnosed in the period 2002-2006.[1] Survival rates for rectal cancer used to be worse than for colon cancer until recently, but are now at an equal level. Prognosis is better if cancer is detected at an earlier stage. Stage specific survival ranges between 94% for patients with stage I disease at time of diagnosis, to 8% for those with stage IV disease at time of diagnosis.[1] Survival in the Netherlands is above the European average (some of the countries with high survival may be based on a selective, 'better' survival).[11]

Risk factors

Several risk factors, both genetic and environmental influence the formation and development of CRC. Individuals can be at increased risk due to their genetic constitution. The most common hereditary forms of CRC are hereditary non-polyposis CRC (HNPCC), also called Lynch syndrome, which accounts for approximately 3% of cases, and familial adenomatous polyposis (FAP), which

accounts for less than 1% of CRC cases.[12] HNPCC is related to inherited mutations in the APC tumour suppressor gene. Individuals with HNPCC have a lifetime CRC risk up to 80%, and individuals with FAP have a CRC risk of virtually 100%.[13] Other high-risk groups include individuals with adenomas and patients with inflammatory bowel disease like ulcerative colitis and Crohn's disease.[14]

Over the years a number of lifestyle or environmental related risk factors have been identified, although the data are not entirely consistent. These include among others obesity, physical activity, smoking, alcohol consumption, red and processed meat, vitamin D, and folate. Furthermore, aspirin and other non-steroidal anti-inflammatory drugs, oestrogen replacement therapy, statins, cholecystectomy, and prior pelvic radiation are risk factors for CRC (Table 1).[15-28] In most cases, the environment and the genetic background of a person determine the risk of CRC together: the environment affects the activity of the genes and the effect of a certain environmental factor depends on the genes, the so-called environmental interaction.[29-31]

Prognostic determinants for colorectal cancer

Survival of CRC is influenced by determinants which are related to the tumour, the patient or treatment. Apart from tumour stage and differentiation grade, also subsite and lymphocytic reaction are prognostic determinants of CRC.[32, 33] Patient characteristics like age at diagnosis, gender, comorbidity, and socioeconomic status influence survival of patients with CRC.[34, 35] However, patient characteristics often influence the choice of treatment, which resulted in worse survival.[34] Treatment factors including surgery, chemotherapy, and radiotherapy largely influence survival.[36-38] Besides, the number of lymph nodes examined or the ratio between the number of lymph node metastases and assessed lymph nodes also influence survival of CRC patients (Table 2).[39, 40]

Table 1: Risk factors for colorectal cancer

Risk factor	Strength of association (RR)[a]	Strength of evidence	Subsite-dependent effect[b]
Family history	1.8	+++	+++ (colon)
Body height	1.3	++	+ (colon)
Lifestyle			
Obesity	1.5	+++	0
Physical activity	0.8	++	+++ (colon)
Smoking	1.2	++	0, + (rectum)
Alcohol	1.6	++	0, + (colon)
Diet, macronutrients			
Vegetables	0.7-1.0	0, +	0, + (colon)
Fruit	0.8-1.0	0	0
Fibre	0.7-1.0	0	0
Red/processed meat	1.2	+	+ (colon)
Fish consumption	0.9	+	unknown
Saturated fat	1.4	+	unknown
Diet, micronutrients			
Calcium intake	0.6-1.0	0	+ (colon)
Vitamin D intake	0.5	++	unknown
Vitamin B6	0.5	+	+++ (colon)
Folate	0.5	+++	0,+ (colon)
Magnesium	0.5	+	unknown
Selenium	0.6	+	unknown
Medication and treatment			
Statins	0.5	0	+ (colon)
Oestrogen replacement therapy	0.8	++	unknown
Aspirin (long-term regular use)	0.7	+++	unknown
Cholecystectomy	1.2	+	+++ (proximal colon)
Prior pelvic radiation	1.7	+	+++ (rectum)
Chronic diseases			
Diabetes mellitus	1.3	++	++ (colon)
Inflammatory bowel disease	1.5	+++	unknown

RR: relative risk

[a] In absence of a recent meta-analysis, or conflicting results of recent meta-analyses, a range of the reported relative risks in recent studies is given; [b] The subsite having an association with the risk factor is shown between parenthesis

0 inconsistent/inconclusive; + probable; ++ likely; +++ definite

Table 2: Prognostic determinants for colorectal cancer

Determinants	Strength of prognostic impact
Tumour	
Stage	+++
Differentiation grade	++
Subsite	++
Lymphocytic reaction	+
Patient	
Age	+++
Comorbidity	++
Socioeconomic status	++
Gender	+
Treatment	
Surgery	+++
Adjuvant / palliative chemotherapy	+++
Preoperative / postoperative radiotherapy	+++
Lymph node count / lymph node ratio	++

+++ strong; ++ moderate; + weak

Prevention and screening of colorectal cancer

Prevention

Most of the aforementioned risk factors obviously play an important role in primary prevention. For some of them evidence is rather convincing and chemoprevention can be considered. However, aspirin, one of the most promising agents for chemoprevention, has potential adverse effects.[41] Therefore, careful consideration of the risk-benefit ratio is required before general recommendations can be made. Promising in this respect is supplementation with folate, which has a more positive safety profile than for example aspirin.[42]

Screening

Recommendations for CRC screening, as with other mass screening, must take into account the sensitivity, false-positive rate, safety, and convenience of the test.[6] In addition, costs and cost-effectiveness of the screening program need to be considered in the context of what is best for the individual patient, as well as for clinical policy in general. The pathogenesis of CRC allows opportunities to prevent cancer or improve its prognosis by finding and removing polyps to prevent the onset of cancer or removing early cancers to prevent disease progression.[6]

Colorectal tumours can cause blood loss, which can be tested with a faecal occult blood test (FOBT). There are chemical and immunochemical FOBTs. The chemical (guaiac) FOBT (gFOBT) is used for over 40 years and detects blood by a chemical reaction catalyzed with the haem in blood. Therefore, it is not specific for human blood and diet restrictions are necessary before the test can be done reliably.[43] gFOBT, when performed every one to two years in people aged 50 to 80 years, reduces mortality by 15%.[44, 45] The immunochemical FOBT (iFOBT) is an FOBT which can detect occult blood in stool using human antibodies and is therefore specific to human blood. The iFOBT is superior to gFOBT; more CRC is detected using iFOBT, the attendance rate is higher, and better quality assurance in the laboratories is possible.[43, 46, 47] A positive FOBT should be followed by a colonoscopy to examine the colorectum. Screening with sigmoidoscopy can find and remove (pre)cancerous lesions in the rectum and the descending colon directly. It can be an effective screening method, provided that the attendance rate is well over 30%.[43] Colonoscopy is the most sensitive test for detecting (pre)cancerous lesions throughout the entire colon. However, patients who underwent a colonoscopy have a small risk of complications like perforation or bleeding.[48] Besides, the attendance rate for colonoscopy screening is low.[43] It is unknown whether the benefit outweighs the risk of colonoscopy. Colonography (virtual colonoscopy) is a new and promising technique for detecting CRC and advanced adenomas. The sensitivity is similar as with colonoscopy, but it is a non-invasive technique and the burden of people is much smaller than for colonoscopy. Virtual colonoscopy is not yet advised as a screening tool in the Netherlands, since

research has to be conducted first concerning attendance rate and cost-effectiveness.[43] The development of molecular biomarkers is promising, although still in its infancy.[43]

Screening trials in the Netherlands

After a national consensus development meeting for implementation and further development of population screening for CRC based on FOBT in 2005 several projects were started to examine the possibility of CRC screening in the Netherlands.[49, 50] In Maastricht a project was started to examine the detection rate and costs of several screening methods.[51] A second goal is to find a marker on DNA, RNA or protein level (molecular biomarker) in stool usable for CRC screening, which is a part of the DeCoDe (Decrease Colorectal cancer Death) project. In Nijmegen and Amsterdam the FOCUS (Faecal OCcUlt blood Screening)-trial was started in which gFOBT and iFOBT were compared based on pre-randomisation in people aged 50-75 years. Detection rate of (pre)cancerous lesions and acceptability were the main issues examined.[47, 49] In September 2008 the second round of this project was started to examine the attendance at a second screening round two years after the first round using iFOBT. In Rotterdam feasibility studies are being conducted. In the first study screening with sigmoidoscopy, iFOBT and gFOBT were compared in people aged 50-75 years.[46, 52] In the second study, started in 2008, the optimal interval for screening is determined.[52] In the middle of 2009 a randomized trial was started, named COCOS (COlonoscopy or COlonography for Screening) in which virtual colonoscopy is compared with colonoscopy as screening method focussing on attendance rate.[53] Finally, a study conducted by the New Drug Development Organisation Institute for Prevention and Early Diagnostics investigates screening for CRC with colonoscopy based on integrated risk profiling. This is screening on an experimental basis, based on shared risk factors for several diseases including cancer, cardiovascular diseases and mental disorders. For people aged 50-75 years a risk profile for CRC can be made and subsequent colonoscopy can be offered when people seems to be high risk based on risk profiling.[54] Results of most of these Dutch studies are expected in the near future. However, some results have already been published. [46, 47, 55] Based on these results and international literature the Health Council has advised the Dutch government in November 2009 to start with CRC screening using biannual iFOBT for persons aged 55-75 years.[43]

Diagnosis and staging

Patients with CRC may be diagnosed by having one or more of the following symptoms: abdominal pain, changed bowel habit, rectal blood loss, weakness, anaemia, and weight loss.[56] The majority of patients with early disease does however have no clinical symptoms and usually appear with more advanced disease.[57] Diagnostic tests, besides a physical exam, include sigmoidoscopy,

colonoscopy (both comprising the possibility of taking a biopsy), double-contrast barium enema, blood tests (haemoglobin, carcinoembryonic antigen (CEA), CA 19-9), ultrasound (also endorectal and intraoperative), computed tomography (spiral CT, CT-guided needle biopsy, virtual colonoscopy), magnetic resonance imaging (MRI), chest X-ray, positron emission tomography (PET).[58] A number of these tests are also used for pre- and peroperative staging.

After resection, the pathologist examines the specimen. The spread of the disease including the existence of tumour tissue in the lymph nodes present in the specimen is examined. Also histology, degree of differentiation, and radicality of the resection (especially important in case of rectal cancer) are assessed.[59]

Treatment

Surgery

Surgery is the main treatment for CRC. Usually the part of the colon affected by the tumour is removed as well as nearby lymph nodes. The two ends of the colon are reconnected. For colon cancer, a colostomy is usually not needed, although sometimes a temporary colostomy may be constructed. Surgery for colon cancer, and to a lesser extent rectal cancer, can also be performed laparoscopic (also called 'keyhole' surgery) in which it is not necessary to open the abdomen. Laparoscopic surgery for colon cancer works probably as well as the standard approach.[60, 61] For rectal cancer a low anterior resection is used for tumours located in the middle or upper part of the rectum, close to where it connects with the colon. For cancers in the lower part of the rectum, an abdominoperineal resection is done. After this surgery a permanent colostomy is necessary. Surgery that includes total mesorectal excision (TME) often provides the best possible outcomes and survival. For stage IV CRC patients, surgery is often palliative or even omitted because of too widespread disease.[58]

Adjuvant chemotherapy

Stage I patients do not receive any adjuvant therapy (Table 3). A subgroup of patients with stage II colon cancer is considered to receive adjuvant chemotherapy (usually a combination of 5-fluoracil (5-FU), leucovorin, and oxaliplatin). This high-risk stage II group consists of patients with T4 tumours, fewer than ten lymph nodes examined, or a poor tumour differentiation. For stage III colon cancer adjuvant chemotherapy is considered standard practice (same regimen as high risk stage II patients), among rectal cancer patients with a T4 or fixed tumour this may be considered. Selected stage IV patients with CRC may be treated with a combination of the aforementioned agents (or irinotecan instead of oxaliplatin, or capecitabine instead of 5-FU) plus bevacizumab. Treatment with hyperthermic intra peritoneal chemotherapy (HIPEC) can be considered in patients with limited peritoneal metastasis only.[58]

Radiotherapy

Preoperative radiotherapy is considered standard for T2-T4 rectal cancer (Table 3). For patients with proximal or relatively small tumours, it may be omitted. For patients who are expected to have a positive circumferential margin or four or more positive lymph nodes based on clinical staging, radiotherapy may be combined with chemotherapy.[58]

Follow-up

When primary treatment is completed, follow-up is started to detect local recurrences, distant metastases, and metachronous tumours in an early asymptomatic stage resulting in better treatment results.[58, 62] Follow-up usually contains colonoscopy, regular CEA measurements, controls by medical specialist and ultrasounds of the liver for a period of five years.[58]

Table 3: Summary of treatment options for CRC[58]

Stage	Colon	Rectum
I (T1-2N0M0)	- Resection	- Resection with total mesorectal excision (TME) T1: transanal endoscopic microsurgery (TEM) - T2: preoperative radiotherapy (5x5 Gy)
II (T3-3N0M0)	- Resection - High-risk patients: adjuvant chemotherapy (FOLFOX-4)	- Resection with total mesorectal excision (TME) - T3: preoperative radiotherapy (5x5 Gy) - T4/fixed tumours: (chemo)radiation (50 Gy), followed by resection after 6 weeks, possibly intraoperative radiotherapy
III (T_{any}N1-2M0)	- Resection - Adjuvant chemotherapy (FOLFOX-4)	- Resection with total mesorectal excision (TME) - T2-T3: preoperative radiotherapy (5x5 Gy) - T4/fixed tumours: (chemo)radiation (50 Gy), followed by resection after 6 weeks, possibly intraoperative radiotherapy - suspicion of 4 or more positive lymph nodes or positive circumferential margin: chemoradiation is advised
IV ($T_{any}N_{any}$M1)	- Resection can be considered - Palliative chemotherapy	- Resection can be considered - Palliative chemotherapy

1.2. Methods, population and setting

Eindhoven Cancer Registry and the Netherlands Cancer Registry

The Eindhoven Cancer Registry (ECR) was started in 1955 as part of a programme for nation-wide cancer registration in the area of southeastern North Brabant. Data on all new cancer patients were collected directly from pathology reports and patients' medical records. The registry was started in three hospitals in Eindhoven and gradually expanded to include the south eastern part of the province of North Brabant, the northern part of the province of Limburg (since 1970) and the middle and southwestern part of North Brabant since 1986 (except the small most western part) (Figure 2). Other regional registries had discontinued their activities, until a successful nationwide program was re-established since 1984. Since 1989 the whole Dutch population is covered by nine regional cancer registries, which established the National Cancer Registry.

Figure 2: The current area of the Eindhoven Cancer Registry of the Comprehensive Cancer Centre South

The area in the population-based ECR is now served by 10 general hospitals at 16 locations and two large radiotherapy institutes. The area does not contain university or specialized cancer hospitals. There are six pathology laboratories, all participating in the nationwide PALGA network, which also notifies the regional cancer registries. The cancer registry receives lists of newly diagnosed cases on a regular base from the pathology departments. In addition, the medical records departments of the hospitals provide lists of outpatients and hospitalized cancer patients. Following this notification, the medical records of newly diagnosed

patients (and tumours) are collected, and trained registrars from the cancer registry abstract the necessary information. Data are checked for duplicate records. Patients who live in the catchment area of the ECR, but are diagnosed in hospitals elsewhere in the Netherlands, are regularly retrieved from all other Dutch cancer registries since 1989. Before this year it was done directly through retrievals at all the cancer centres.

The region is characterized by good access to medical care without financial obstacles. The distance to a hospital has always been less than 30 kilometres. The population in the area is increasingly aging due to increasing life expectancy and a decreasing amount of births. This results in an increased proportion of elderly women (from less than 5% to more than 10%), and since 1965 a decreasing number of children (Figure 3).

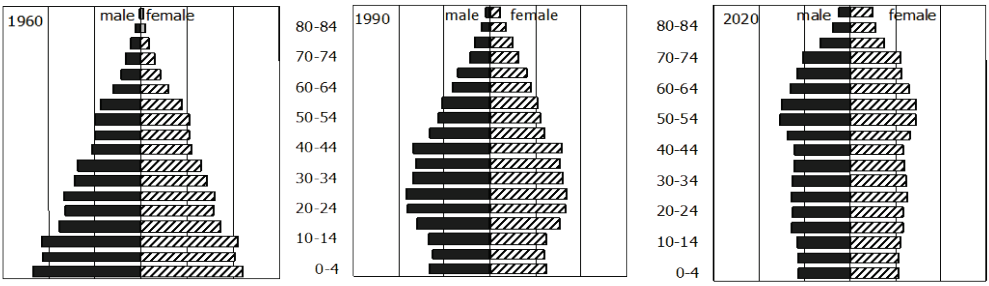

Figure 3: Age-distribution of the population in the area of the Eindhoven Cancer Registry

Staging

Stage of the adenocarcinomas was categorized according to the TNM-classification IUCC for all patients.[63] No major changes in the classification occurred since the mid-1970s which could have led to a shift in stage distribution.

Histological classification

Colorectal tumours were classified based on topography and histology, according to the WHO International Classification of Diseases for Oncology (ICD-O).[64] In the studies presented in this thesis, patients with unclassified malignant neoplasms, sarcomas, lymphomas, carcinoids, and melanomas located in the colorectum were excluded (~5% of total) (Table 4).

Localisation

Topographical codes of colorectal cancer were used to divide the colorectum into subsites (Table 5). Tumours of the anus and the anal canal were excluded throughout the thesis unless stated otherwise.

Table 4: Classification of histology (morphology) according to the WHO ICD-O[64]

Histological group	Morphology code according to ICD-O [a]	Proportional distribution of histology of tumours located within the colorectum [b]
Neoplasm, NOS	8000-8005	1.7%
Epithelial neoplasm, NOS	8010-8046	0.7%
Carcinoid	8240-8249	0.7%
Adenocarcinoma [c]	8140-8231, 8260-8384, 8440, 8470, 8480, 8481, 8490	96.3%
Sarcoma	8800-8990	0.09%
Melanoma	8720-8790	0.02%
Other (squamous cell neoplasm, ductal and lobular neoplasm, acinar cell neoplasm, complex epithelial neoplasm)[a]	8050, 8070, 8500-8576	0.1%
No microscopical confirmation	9990	0.4%

NOS: not otherwise specified
[a] List not exhaustive; non-incident codes (Eindhoven Cancer Registry, 1975-2008) excluded;
[b] Eindhoven Cancer Registry, 1975-2008; [c] Including cystic, mucinous, and serous adenocarcinomas

Table 5: Classification of localisation (topography) according to the WHO-ICD-O[64]

Localisation				ICD-O	Proportional distributional [a]
Colorectum	Colon	Right colon	Coecum	C18.0	12.6%
			Appendix	C18.1	0.6%
			Ascending colon	C18.2	9.9%
			Hepatic flexure	C18.3	4.0%
			Transverse colon	C18.4	4.9%
			Splenic flexure	C18.5	2.7%
		Left colon	Descending colon	C18.6	2.8%
			Sigmoid colon	C18.7	25.1%
			Colon other/NOS	C18.8	1.4%
	Rectum		Rectosigmoid junction	C19.9	7.2%
			Rectum	C20.9	28.7%

[a] Incidence, Eindhoven Cancer Registry, 1998-2008

Comorbidity

Since 1993 the registry also recorded comorbidity according to a slightly adaptation of the list of serious diseases drawn up by Charlson and colleagues.[65] In short, the following important conditions were recorded (Table 6): chronic obstructive pulmonary diseases (COPD), cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell carcinoma of the skin), and diabetes mellitus. Furthermore, hypertension, connective tissue diseases, rheumatoid arthritis, kidney, bowel, and liver diseases, dementia, tuberculosis, and other chronic infections were also recorded.[66]

Table 6: Classification of comorbidity, modified version of the list of Charlson et al.[65]

Chronic obstructive pulmonary disease (COPD)
Cardiovascular disease: myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft (CABG)
Peripheral arterial disease: intermittent claudication, abdominal aneurysm, surgical intervention
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except basal cell carcinoma)
Hypertension
Diabetes mellitus
Other:
Autoimmune diseases: sarcoidosis, Wegener's disease, systemic lupus erythematosis (SLE)
Rheumatoid arthritis
Kidney diseases: glomerulonephritis, pyelonethritis
Gastrointestinal: stomach ulcer and resection, colitis
Liver diseases: cirrhosis, hepatitis
Dementia
Chronic infections

Socioeconomic status

An indicator of socioeconomic status developed by Statistics Netherlands was used.[67] At the six-position level of postal code, data on household income and the economical value of the house are available from fiscal data from the year 2000. Within each postal code there are about 17 households, so this aggregate measure counts for a very small geographic area, which enhances the reliability. Furthermore, the use of routinely collected income tax data (no questionnaires or interviews) gives reliable estimates of household income. Socioeconomic status was categorized according to quintiles ranging from 1 (low) to 5 (high), with a separate class for postal codes with a care providing institution (such as a nursing home). This measure is assumed to be valid ten years before and after the set year (2000). Socioeconomic differences based on neighbourhood data have proven to be a fairly good reflection of socioeconomic differences at an individual level.[68-70]

Data-analysis

Incidence and mortality

Because the age-distribution varies over time, and to enable international comparisons, age-adjustment was performed by direct standardization according to the European Standard Population (European Standardized Rates, ESR). Annual incidence and mortality rates were calculated as 3-year moving averages. Trends in incidence and mortality were estimated by calculating the estimated annual percentage change (EAPC). This was done by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable, i.e., $y=mx + b$ where $y=\ln(\text{rate})$ and $x=$calendar year. Then EAPC = $100*(e^m - 1)$. This calculation assumes that the rates increased or decreased at a constant rate over the entire period.

Joinpoint analyses were performed to discern significant changes in the trend and, if present, when they occurred.[71] Linear line segments are connected on a log scale to identify changes in trend data in terms of the annual rates of change in fixed periods of time,[71] although cross-sectional cancer rates generally do not change abruptly. Age-period-cohort analyses were performed to examine jointly the influence of longitudinal and cross-sectional changes.[72, 73] From the matrix of the age-specific incidence and mortality rates calculated for each 5-year time period and age group, time trends according to age, birth cohort, and period of diagnosis were evaluated using an age-period-cohort model. Drift is a term which was introduced to describe models for which age-period and age-cohort parameters fit the data equally well. The model implies the same linear change in the logarithm of the rates over time in each age group. Such a model thus serves as an estimate of the rate of change of a regular trend.

Survival

Information on the vital status of all patients was obtained initially from the municipal registries and since 1998 from the Central Bureau for Genealogy. These registers provide virtually complete coverage of all deceased citizens. Crude survival analyses were performed. Cox regression models were used to compute multivariable rates. Relative survival (the ratio of the observed to the expected rates) is an estimation of disease-specific survival, which reflects survival of cancer patients adjusted for survival in a background population with the same age structure.[74] Expected survival rates were calculated from life tables for regional populations with the same 5-year age distribution. Generalized linear models with a Poisson structure were used, based on collapsed data and exact survival times.[75]

1.3. Outline

A national consensus development meeting for implementation of population screening for CRC concluded that preceding implementation of a national population FOBT based screening program, feasibility studies should be undertaken with respect to adaptation of the capacity and quality of diagnostic and therapeutic intervention facilities.[50] A grant from the Dutch Cancer Society has made it possible to conduct a number of studies addressing these issues, which are described in the present thesis. ('Impact on mortality of improving quality of colorectal cancer care in the south of the Netherlands, preceding mass screening').

The main objectives of the studies described in this thesis were:

- To investigate the current trends in incidence, stage distribution, survival, and mortality of CRC.
- To determine the extent of recent variation in clinical care of CRC including diagnostic assessment, time from diagnosis to start of treatment, lymph node detection, adjuvant chemotherapy, and follow-up.
- To study the effect of population-based changes in treatment on survival of patients with CRC, with special emphasis on elderly patients.

Long-term trends in incidence, stage distribution, survival, and mortality of colorectal cancer from the Eindhoven Cancer Registry since 1975 are presented in **chapter 2.1**. In **chapter 2.2.** trends in regional incidence and mortality of colorectal cancer are described by period and cohort effects. **Chapter 3.1.** deals with the variation in diagnostic assessment of patients with colorectal cancer and the adherence to diagnostic guidelines in the southeastern region of the Netherlands. The adherence to waiting time guidelines for colorectal cancer patients in 2005 and 2008 in southern Netherlands is shown in **chapter 3.2.** In **chapter 3.3.** the trend in lymph node detection in colon cancer patients is described and methods to increase lymph node detection were explored. National and regional trends in clinical management of patients with colon cancer are described in **chapter 4.1.** and **chapter 4.2.**, with special focus on adjuvant chemotherapy. Additionally, national trends in survival from colon cancer were described. **Chapter 4.3.** describes the trends in treatment and survival of patients with rectal cancer in the Netherlands. In **chapter 4.4.** variation in follow up of patients with colorectal cancer is reported. Outcome of patients with metastatic colon cancer at diagnosis is described in **chapter 4.5.** In **chapter 5.1.** the main results concerning trends in incidence and mortality are discussed. **Chapter 5.2.** discussed the impact of optimalization of CRC disease management on mortality and forthcoming mass screening and future perspectives for research and clinical management are considered.

CHAPTER 2.

TRENDS IN COLORECTAL CANCER INCIDENCE, MORTALITY, AND SURVIVAL

2.1.

Trends in colorectal cancer in the south of the Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival

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Acta Oncologica in press

Abstract

Objective: In the Netherlands over 11,200 patients are yearly diagnosed with colorectal cancer (CRC), of who about 4,700 are expected to die of the disease ultimately. Investigating long term trends is useful for clinicians and policy makers to evaluate the impact of changes in practice and will help predict future developments.

Patients: The 26,826 cases of primary CRC (C18.0-C20.9) diagnosed between 1975 and 2007 in the Dutch population-based Eindhoven Cancer Registry area were included. We analyzed trends in incidence, prevalence, stage distribution, treatment, survival, and mortality.

Results: The age-standardised incidence of colon carcinoma kept increasing, most markedly in males (up to 39 patients per 100,000 inhabitants) and for tumours of the colon ascendens (subsite-specific incidence doubled). The incidence of rectal carcinoma remained stable. The share of patients aged 80 or older rose from 12% to 19% ($p<0.0001$). The proportion of patients diagnosed with distant metastases increased up to 25% for colon carcinoma ($p<0.0001$). Resection rates of the primary tumour remained high except for patients with metastasized disease, showing a decrease since 2000. Recently, the use of adjuvant chemotherapy seemed to level off among patients with stage III colon carcinoma, but the use of neo-adjuvant chemoradiation clearly increased among patients with stage II/III rectal cancer ($p<0.0001$). Five-year relative survival of colon cancer improved from 51% in 1975-1984 to 58% in 2000-2004, for rectal cancer it improved from 44% to 59%. Two-year relative survival of colon cancer in 2005-2006 was 69%, and 77% for rectal cancer.

Conclusions: The changes in management of rectal cancer lead to a superior increase in survival of these patients compared to patients with colon cancer, even surpassing the latter.

Key words: colorectal cancer, survival, treatment, trends, population-based

Introduction

In the Netherlands, yearly over 11,200 patients are diagnosed with CRC, of who about 4,700 are expected to ultimately die of the disease.[76] It constitutes 2-3% of total mortality above the age of 40. During the last 35 years, improvements in endoscopy and imaging, advances in surgery and pathology, better pre- and postoperative care, and more frequent use of adjuvant therapies have led to improvements in survival of patients with CRC.[36, 77-79]

Investigating long term and recent trends will help predict future developments, which is important for planning prospective investments in clinical cancer care. Also, it is useful for clinicians and policy makers to evaluate the impact of all the changes that have taken place in the past. In this study, we focus on the trends in incidence, stage distribution, treatment, survival, and mortality among patients diagnosed with CRC between 1975 and 2007 in the south of the Netherlands.

Patients and methods

The Eindhoven Cancer Registry collected data on all patients with newly diagnosed cancer in a large part of the southern Netherlands. The registry area nowadays comprises about 2.3 million inhabitants. This population-based registry is notified by 6 pathology departments, 10 community hospitals (20 at the beginning of the study period, but many of them have meanwhile merged) at 17 locations, and 2 radiotherapy institutions.

Between 1975 and 2007, 26,828 cases of primary CRC (C18.0-C20.9) were diagnosed in the Eindhoven Cancer Registry area, excluding patients with unknown site of primary tumour within the colorectum (1.5% of total). Information on diagnosis, staging, and treatment is routinely extracted from the medical records by specially trained administrators of the cancer registry. Registration takes place 6 to 18 months after diagnosis. By means of an independent case ascertainment method, the completeness of the registration is estimated to exceed 95%.[80] Vital status of all patients diagnosed until January 1, 2007 was assessed August 1, 2008 through merging with the Municipal Administrative Databases, where all deceased and emigrated persons in the Netherlands are registered. Disease-specific mortality (as stated on death certificate) was made available at an aggregated level by Statistics Netherlands (CBS). Since cause-of-death was not available at individual patient level, survival was calculated using all-cause mortality.

Analyses

Differences in patient/tumour characteristics between different periods were analysed using a two-sided Cochran-Armitage trend test. Incidence/mortality rates are shown as the 3-year moving average of the number of new patients/deaths per 100,000 inhabitants per year. Trends were estimated from the incidence rates

age standardised to the European standard population (ESR).[81] For the period 1975-1984 no data on stage distribution and treatment are presented, because of incompleteness of these data for the earlier years. Trends in detection and stage are shown as the proportional distribution of the Tumour Node Metastasis (TNM) stage in the respective period (1985-1989, 1990-1994, 1995-1999, 2000-2004, and 2005-2007). Stage is postoperative, except for cases where postoperative stage was unknown, in which case preoperative stage was used. Relative survival was used as an estimation of disease specific survival. It reflects survival of cancer patients, adjusted for survival in the general population with the same age structure. Relative survival is calculated as the ratio of the observed rates in cancer patients to the expected rates in the general population with the same structure for age and gender.[74] Multivariable relative survival analyses, using Poisson regression modelling, were performed to estimate the relative risk (RER) of dying for the respective periods of diagnosis (1975-1984, 1985-1994, 1995-1999, 2000-2006) for patients with stage III and stage IV colon carcinoma, and stage II/III and stage IV rectal carcinoma, adjusted for follow-up interval, age, sex, and subsite.[75] Stage IV colon and rectal carcinoma were analysed separately.[82] Treatment variables were added to investigate the effect of therapy on the RER of dying according to period of diagnosis.

Prevalence of patients with CRC up to 10 years at January 1, 1984, 1994, and 2004 was expressed as the age-standardised number of patients alive per 100,000 inhabitants at the respective date.

Results

The age distribution shifted between 1975-1984 and 2005-2007 towards a higher proportion of patients diagnosed at age 80 or older ($p<0.0001$) (Table 1). The male-female ratio of incidence increased from 1.03 to 1.14 (p_{trend} 0.004), and a shift occurred towards a more proximal tumour site (colon vs. rectum) (p_{trend} 0.002).

The age-standardised incidence of colon carcinoma among males gradually increased between 1975 and 2007 from 25 to 39 patients per 100,000 inhabitants (Figure 1). The incidence of colon carcinoma among females increased from 23 to 30. The incidence of rectal carcinoma remained more or less stable among males (about 25 per 100,000 inhabitants) and females (about 15).

The subsite-specific incidence rates showed a marked increase for carcinomas situated in the colon ascendens, among both males and females, and for carcinoma situated in the colon descendens and sigmoid especially among males (Figures 2a and 2b).

The proportional stage distribution of patients with colon carcinoma showed a slightly decreasing proportion of stage II patients, and an increased proportion of patients with stage III ($pT_{any}N1\text{-}2M0$) and stage IV disease ($p<0.0001$) (Figure 3).

Table 1: Age, gender, and tumour site distribution of all patients diagnosed with colorectal cancer in the south of the Netherlands between 1975 and 2007, by period of diagnosis [a]

	Period of diagnosis									
	1975-1984		1985-1994		1995-1999		2000-2004		2005-2007	
Age (yrs)										
19-49	282	(9)	553	(8)	340	(7)	420	(6)	229	(5)
50-64	965	(31)	2,168	(28)	1,466	(28)	1,893	(29)	1,299	(28)
65-79	1,485	(48)	3,488	(48)	2,527	(49)	3,234	(49)	2,244	(49)
≥80	368	(12)	1,130	(15)	876	(15)	1,040	(16)	819	(19)
Gender										
male	1,562	(50)	3,824	(52)	2,746	(53)	3,534	(54)	2,459	(54)
female	1,538	(50)	3,515	(48)	2,463	(47)	3,053	(46)	2,132	(46)
Tumour site										
colon	1,877	(61)	4,589	(63)	3,245	(62)	4,203	(64)	2,955	(64)
rectum	1,223	(39)	2,750	(37)	1,964	(38)	2,384	(36)	1,636	(36)

[a] Data are absolute numbers with percentages between parentheses

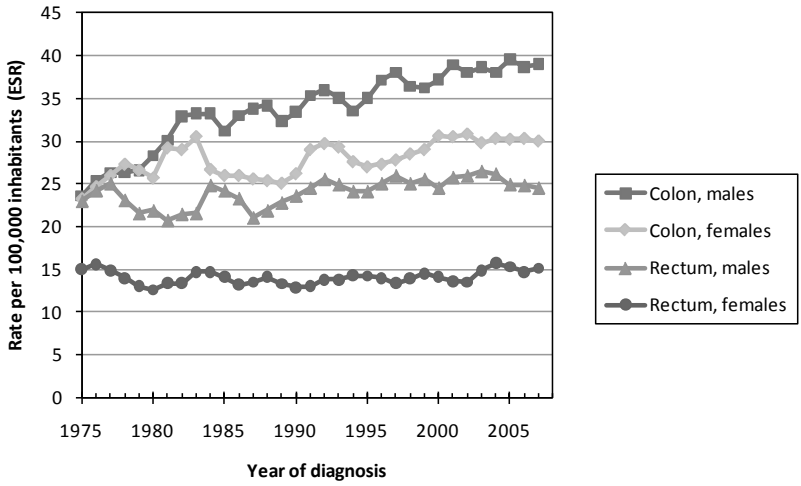


Figure 1: Age-standardized incidence of CRC in the south of the Netherlands, according to gender and tumour site (3-year moving average; ESR: European Standardised Rate)

Comparing proportions of patients diagnosed with stage II and III only, there is a shift towards a higher proportion of patients with stage III disease since 1995-1999 (p=0.01). In the most recent period, an increase in the proportion of stage IV patients could be noted for both colon (up to 25%) and rectum (up to 22%). The proportion of patients with unknown stage remained stable for both colon (2-3%) and rectal cancer (3-5%) (results not shown). Among patients without lymph node metastases (N0), the proportion of patients with T1 tumours decreased from 11% to 5%, the proportion T2 decreased from 28% to 17%, and the proportion T3 increased from 54% to 69% (p<0.0001) (results not shown). The proportion of

patients with a clinically (preoperative) unknown stage decreased between 1985-1994 and 2005-2007: cTx decreased from 89% to 71%, cNx from 89% to 59%, and cMx from 26% to 12% (p<0.0001) (results not shown).

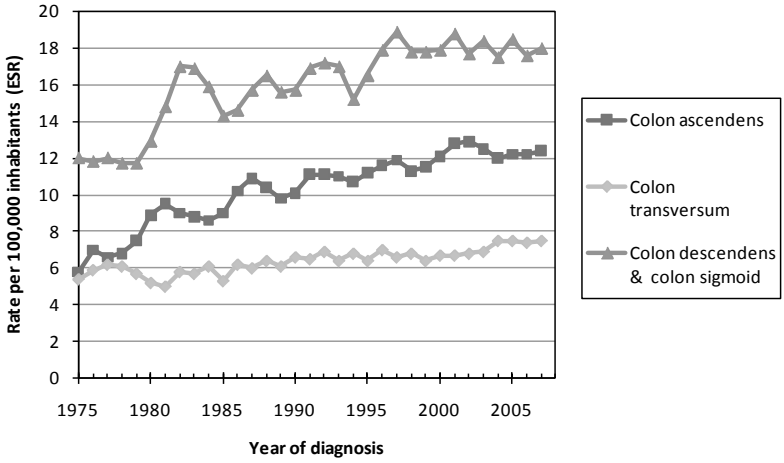


Figure 2a: Age-standardized incidence of colon cancer among males in the south of the Netherlands, according to subsite (3-year moving average; ESR: European Standardised Rate)

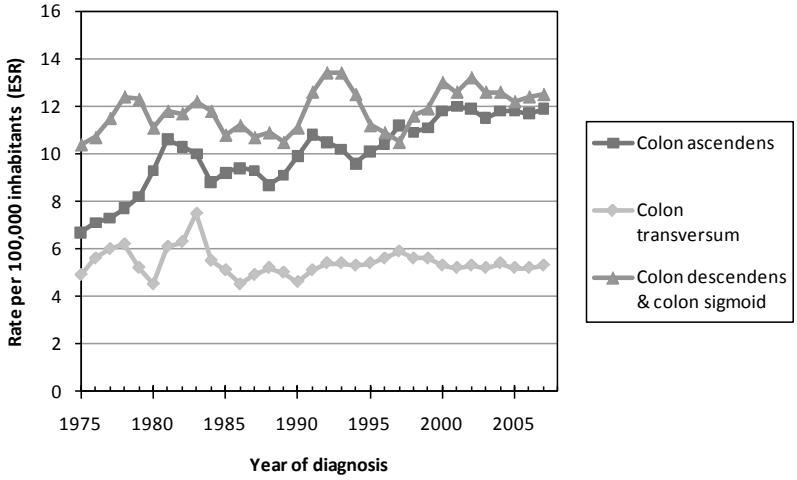


Figure 2b: Age-standardized incidence of colon cancer among females in the south of the Netherlands, according to subsite (3-year moving average; ESR: European Standardised Rate)

Figure 3: Trends in stage distribution of CRC in the south of the Netherlands (excluding unknown stage)

Almost all patients with stage I-III ($pT_{any}N_{any}M0$, if unknown then $cT_{any}N_{any}M0$) colon carcinoma underwent resection, regardless of period of diagnosis and age (ranging from 92% to 100%) (Table 2a). Since the mid 1990s, adjuvant chemotherapy was increasingly administered among all age groups of stage III colon carcinoma patients, but to a lesser extent among the older age groups. Only 5% of patients aged 80 years or older received adjuvant chemotherapy in the most recent period. The use of adjuvant chemotherapy seemed to level off since 2000 among patients younger than 70 years. In 2005-2007, 22% of patients younger than 50 years with stage II disease received adjuvant chemotherapy. Resection rates of the primary tumour initially increased over time among patients younger than 50 years with colon carcinoma stage IV ($T_{any}N_{any}M1$), but decreased again in the most recent period, especially among elderly patients. Metastasectomy was performed in less than 5% percent of patients with stage IV disease. Chemotherapy was increasingly administered to patients with stage IV disease, also for patients over 80 years of age.

Patients with rectal carcinoma increasingly underwent surgery, except for the oldest patients, where surgery rates decreased somewhat since the beginning of the 90's (Table 2b). The use of radiotherapy among stage II/III patients increased between 1985-1989 and 1990-1994 (postoperative radiotherapy), decreased in the subsequent period (transition to preoperative radiotherapy), and increased again in the most recent period (preoperative radiotherapy). With rising age, the use of radiotherapy decreased.

Chemoradiation, especially in the neo-adjuvant setting, was markedly administered more often in the most recent period, especially among patients younger than 70 years old. Stage IV patients less frequently underwent resection, particularly in the most recent period. Opposite to that, the use of chemotherapy among these patients rose clearly, even among the older patients, although less pronounced.

Unadjusted relative survival rates increased for colon and for rectal cancer patients during the 30 year period. For stage I and II colon cancer (Figure 4a), survival improved markedly until 1995-1999, but remained stable afterwards. There was a dramatic improvement in 5-year survival for stage III colon cancer: from 37% to 55% (Figure 4c). Among stage IV patients, there appeared to be an increase in median survival in 1995-1999 (Figure 4d).

Five-year survival of stage I rectal cancer increased drastically between 1985 and 1994, and improved afterwards at a slower rate up to 91% in 2000-2004 (Figure 4e). Stage II also exhibited vast improvements in survival between 1985 and 1994, without further improvement in 2000-2004 (Figure 4f). The developments in survival among stage III rectal cancer patients equalled the improvements seen among stage III colon cancer, with large improvements in 1995-1999 (Figure 4g). There was also a noteworthy improvement in 2-year survival among stage IV rectal cancer patients, especially since the mid 1990s (Figure 4h). The unadjusted cancer survival rate among patients younger than 70 years with colon cancer showed an increasing trend throughout the whole study period, for elderly patients only up to 1995-1999 (Figures 4i and 4j). Among younger patients with rectal cancer, every period exhibited a survival improvement except for 2000-2004, in contrast to the elderly where this improvement in 5-year relative survival was more moderate (Figures 4k and 4l). Five-year survival of all colon cancer patients improved from 51% in 1975-1984 to 58% in 2000-2004; 5-year survival of all rectal cancer patients improved from 44% to 59% in that period (Figures 4m and 4n). Two-year relative survival of colon cancer in 2005-2006 was 69%, and 77% for rectal cancer.

Table 2a: Trends in primary treatment for patients with colon cancer in the south of the Netherlands, according to age [a]

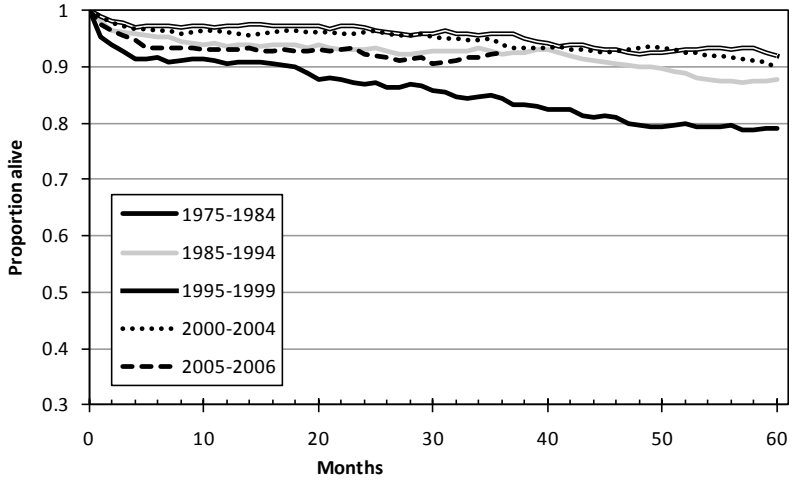
Treatment	Age (yrs)	Period of diagnosis 1985-1989	1990-1994	1995-1999	2000-2004	2005-2007
		%	%	%	%	%
Resection, stage I-III						
	19-49	99	99	92	99	99
	50-59	100	99	95	98	100
	60-69	99	99	98	98	99
	70-79	97	99	97	97	98
	≥80	96	98	97	97	98
Adjuvant chemotherapy, stage II						
	19-49	0	14	2	10	22
	50-59	0	5	5	5	12
	60-69	1	6	2	4	16
	70-79	0	0	1	2	3
	≥80	0	0	0	0	0
Adjuvant chemotherapy, stage III						
	19-49	2	47	72	93	85
	50-59	1	34	60	83	79
	60-69	0	32	52	76	80
	70-79	0	8	25	36	49
	≥80	0	0	1	4	5
Resection of primary tumour, stage IV						
	19-49	76	69	85	83	64
	50-59	80	78	73	70	61
	60-69	82	83	70	70	67
	70-79	78	75	71	68	59
	≥80	78	71	69	64	47
Chemotherapy, stage IV						
	19-49	17	38	60	68	82
	50-59	11	33	44	63	75
	60-69	5	20	28	50	69
	70-79	2	3	12	32	39
	≥80	0	0	1	3	10

[a] Percentages of patients who underwent the respective treatment

Table 2b: Trends in primary treatment for patients with rectal cancer in the south of the Netherlands, according to age [a]

Treatment	Age (yrs)	Period of diagnosis 1985-1989	1990-1994	1995-1999	2000-2004	2005-2007
		%	%	%	%	%
Resection, stage I-III						
	19-49	96	95	94	98	97
	50-59	99	97	97	97	98
	60-69	98	99	97	96	97
	70-79	96	96	94	95	97
	≥80	89	96	93	88	88
Pre/postoperative radiotherapy [b], stage II/III						
	19-49	55	63	58	77	80
	50-59	67	61	54	73	80
	60-69	46	57	47	71	77
	70-79	31	43	37	58	69
	≥80	15	20	19	42	55
(Neo-) adjuvant chemotherapy plus radiotherapy, stage II/III						
	19-49	0	11	14	37	43
	50-59	2	6	11	27	27
	60-69	0	2	4	22	21
	70-79	0	1	1	9	10
	≥80	0	0	0	1	3
Resection of primary tumour, stage IV						
	19-49	53	50	57	66	21
	50-59	72	54	69	56	20
	60-69	75	55	63	60	44
	70-79	63	63	55	42	35
	≥80	78	40	36	31	19
Chemotherapy, stage IV						
	19-49	5	17	54	76	93
	50-59	9	36	49	65	70
	60-69	17	10	35	53	65
	70-79	2	7	17	31	42
	≥80	0	0	0	4	7

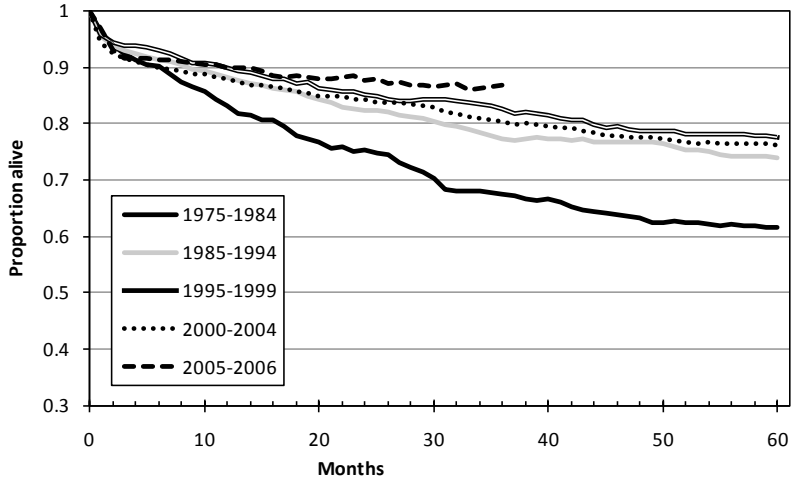
[a] Percentages of patients who underwent the respective treatment; [b] Since mid-1990s, postoperative radiotherapy was replaced by preoperative radiotherapy



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	87 (82-92)	94 (91-97)	96 (93-99)	97 (94-100)	92 (87-97)
5-yr survival (CL)	79 (73-85)	88 (83-93)	92 (87-97)	89 (85-94)	n.a.

CL: confidence limits

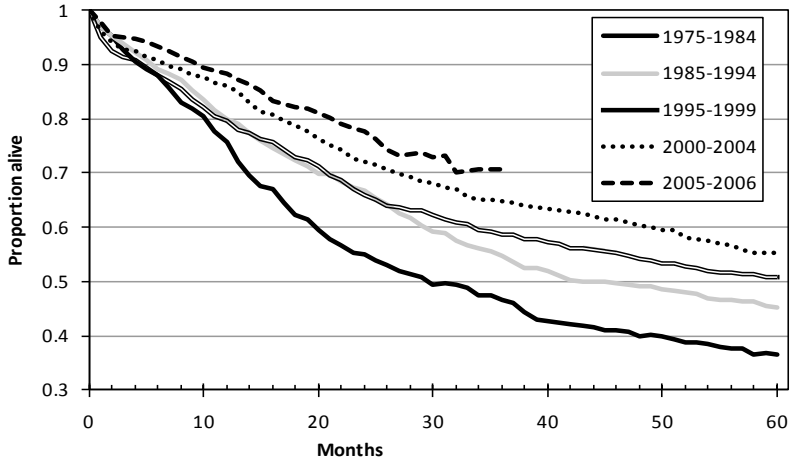
Figure 4a: Relative survival among patients with stage I colon cancer



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	74 (69-79)	82 (79-85)	85 (82-88)	83 (81-85)	88 (85-92)
5-yr survival (CL)	61 (55-67)	74 (70-78)	77 (73-81)	76 (73-79)	n.a.

CL: confidence limits

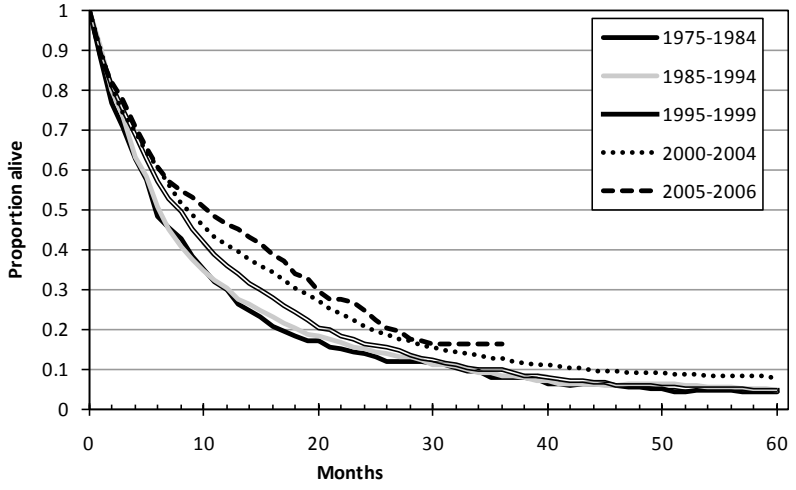
Figure 4b: Relative survival among patients with stage II colon cancer



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	52 (47-58)	64 (60-68)	64 (60-68)	71 (68-74)	75 (70-80)
5-yr survival (CL)	36 (31-41)	45 (45-50)	51 (47-55)	55 (51-59)	n.a.

CL: confidence limits

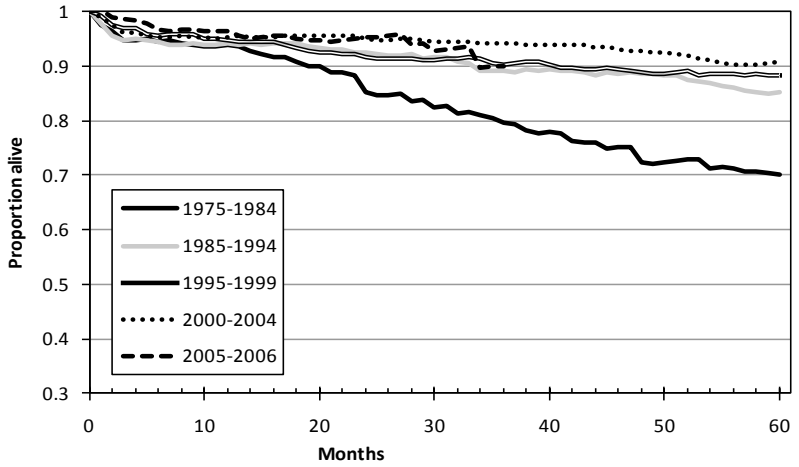
Figure 4c: Relative survival among patients with stage III colon cancer



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	13 (9-17)	14 (11-17)	15 (12-18)	18 (15-21)	20 (16-21)
5-yr survival (CL)	5 (2-8)	4 (2-8)	4 (2-6)	7 (5-9)	n.a.

CL: confidence limits

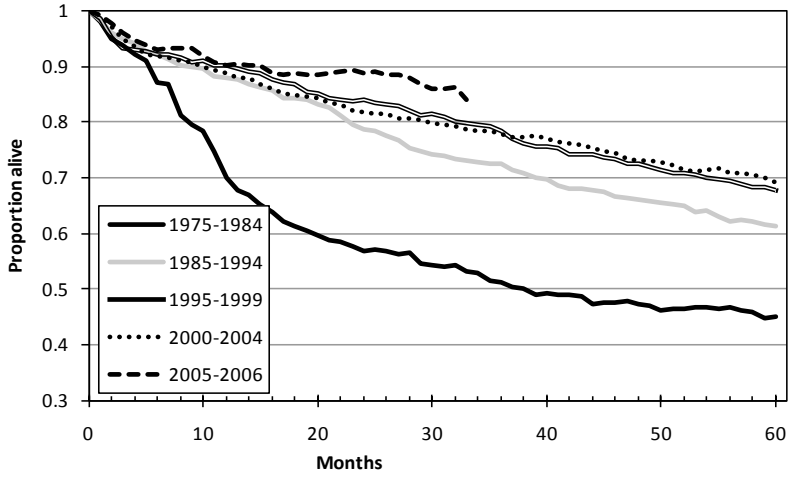
Figure 4d: Relative survival among patients with stage IV colon cancer



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	84 (79-89)	92 (88-96)	91 (88-94)	95 (92-98)	96 (92-100)
5-yr survival (CL)	70 (63-77)	86 (81-91)	88 (83-93)	91 (87-95)	n.a.

CL: confidence limits

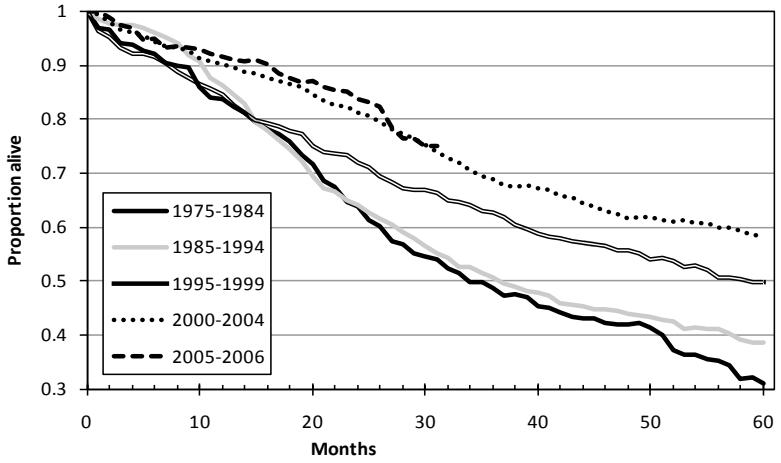
Figure 4e: Relative survival among patients with stage I rectal cancer



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	57 (50-64)	78 (74-82)	83 (79-87)	81 (77-85)	89 (84-94)
5-yr survival (CL)	45 (37-53)	61 (56-66)	63 (62-73)	68 (63-73)	n.a.

CL: confidence limits

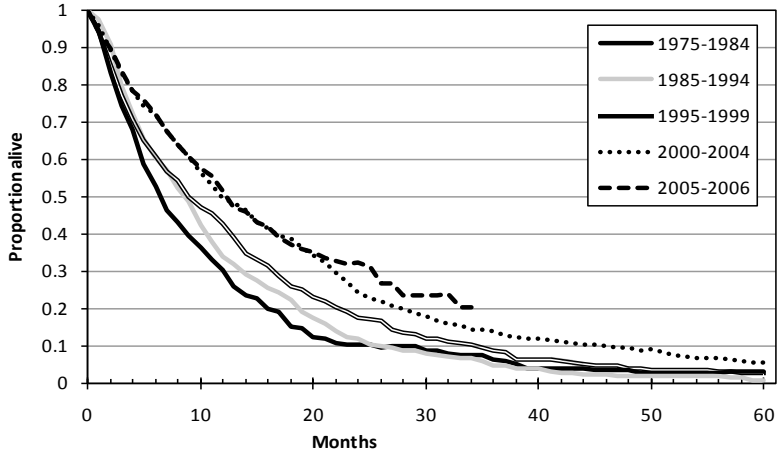
Figure 4f: Relative survival among patients with stage II rectal cancer



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	59 (52-65)	61 (56-66)	70 (65-75)	80 (76-84)	82 (76-88)
5-yr survival (CL)	30 (24-36)	38 (33-43)	50 (44-56)	58 (53-63)	n.a.

CL: confidence limits

Figure 4g: Relative survival among patients with stage III rectal cancer

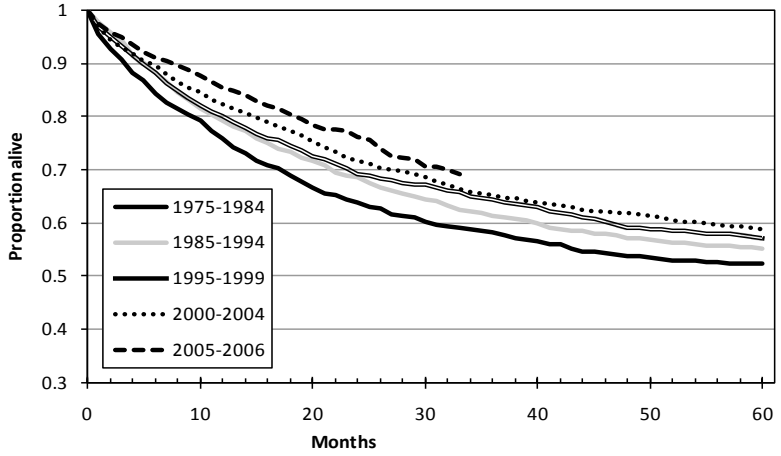


	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	10 (6-14)	9 (6-12)	17 (13-21)	21 (17-25)	30 (23-37)
5-yr survival (CL)	[a]	[a]	[a]	6 (3-9)	n.a.

CL: confidence limits

[a] effective number at risk at 60 months lower than 10

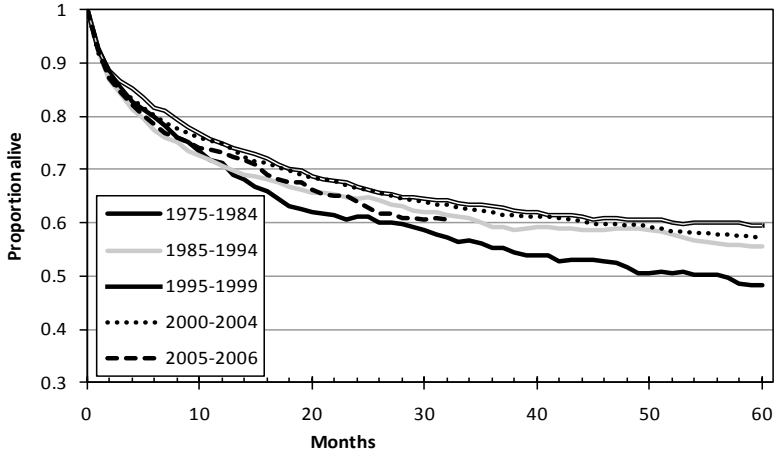
Figure 4h: Relative survival among patients with stage IV rectal cancer



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	63 (60-66)	67 (65-70)	69 (67-71)	71 (69-73)	76 (73-79)
5-yr survival (CL)	52 (49-55)	55 (52-58)	57 (54-60)	59 (57-61)	n.a.

CL: confidence limits

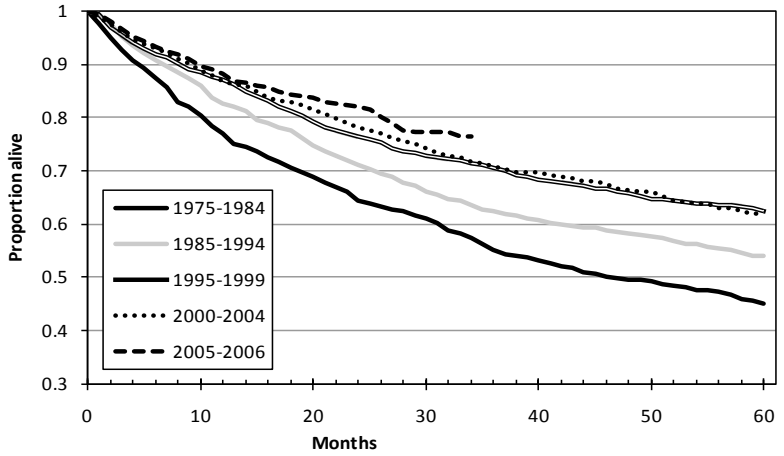
Figure 4i: Relative survival among patients with colon cancer, all stages, younger than 70 years



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	61 (57-65)	65 (62-68)	66 (63-69)	66 (64-68)	63 (59-67)
5-yr survival (CL)	48 (43-53)	56 (52-60)	60 (56-64)	57 (54-60)	n.a.

CL: confidence limits

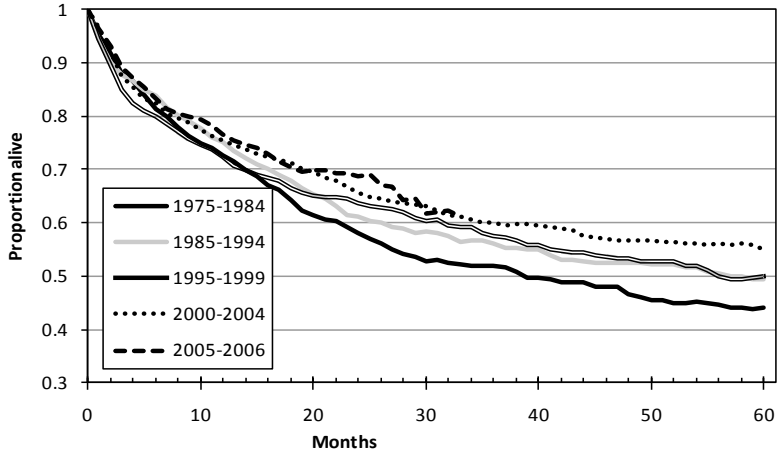
Figure 4j: Relative survival among patients with colon cancer, all stages, 70 years or older



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	64 (60-68)	70 (67-73)	76 (73-79)	77 (75-79)	81 (77-85)
5-yr survival (CL)	45 (41-49)	54 (51-57)	62 (59-65)	62 (59-65)	n.a.

CL: confidence limits

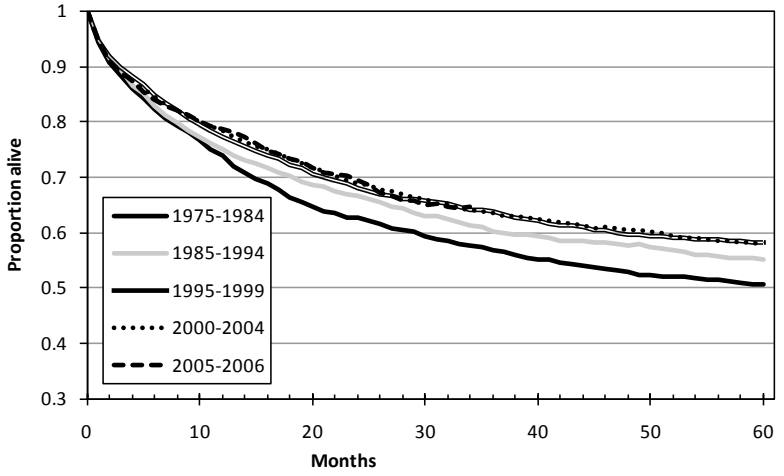
Figure 4k: Relative survival among patients with rectal cancer, all stages, younger than 70 years



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	57 (52-62)	60 (56-64)	63 (59-67)	65 (61-69)	69 (64-47)
5-yr survival (CL)	44 (38-50)	49 (44-54)	50 (56-55)	55 (50-60)	n.a.

CL: confidence limits

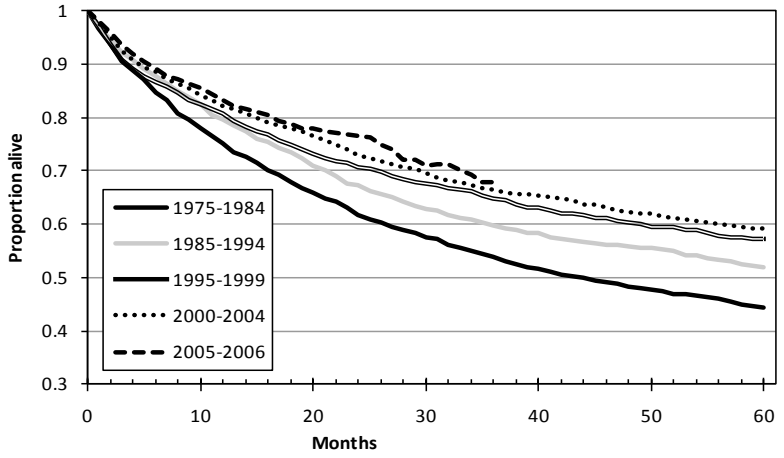
Figure 4l: Relative survival among patients with rectal cancer, all stages, 70 years or older



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	62 (59-66)	66 (64-68)	67 (65-69)	68 (66-70)	68 (65-71)
5-yr survival (CL)	50 (47-53)	55 (53-57)	58 (59-60)	58 (56-60)	n.a.

CL: confidence limits

Figure 4m: Relative survival among patients with colon cancer, all stages and ages



	1975-1984	1985-1994	1995-1999	2000-2004	2005-2006
2-yr survival (CL)	61 (58-64)	66 (63-69)	70 (68-72)	72 (70-74)	76 (73-79)
5-yr survival (CL)	44 (41-47)	52 (49-55)	57 (54-60)	59 (56-62)	n.a.

CL: confidence limits

Figure 4n: Relative survival among patients with rectal cancer, all stages and ages

The multivariable relative survival analyses among stage III colon cancer patients aged younger than 70 showed that without treatment added to the model, there is decreased risk of death over time (Table 3a). However, with the addition of adjuvant treatment to the model, this effect largely disappeared. There was also a significant improvement over time among the older age group, although somewhat more moderate than among younger patients. Among stage II and III rectal cancer patients, there was a marked and significant reduction in death risk over time for both patients younger and older than 70 years, both without and with treatment in the model. Among younger patients with stage IV colon or rectal cancer the risk of death decreased over time (Table 3b). After inclusion of treatment there was still an effect of period of diagnosis, albeit lower than without treatment added to the model. Among older patients with stage IV colon or rectal cancer, no clear effect of period of diagnosis could be noted.

Age-standardised mortality from colon cancer among males fluctuated between 20 to 25 deaths per 100,000 inhabitants during the whole study period (Figure 5). Among females, colon cancer mortality rates showed a steady decrease from 22 deaths per 100,000 inhabitants in 1975, to 16 in 2007. A similar trend could be observed for rectal cancer mortality rates; a decline from 13 deaths per 100,000 inhabitants to 7 among males, and from 8 to 4 among females.

The 10-years prevalence of patients with CRC clearly increased between 1984 and 2004, especially among males (Table 4). Per community hospital in the Eindhoven cancer registry area, this means an increase from 800 colorectal cancer patients per hospital to almost 1,300 patients.

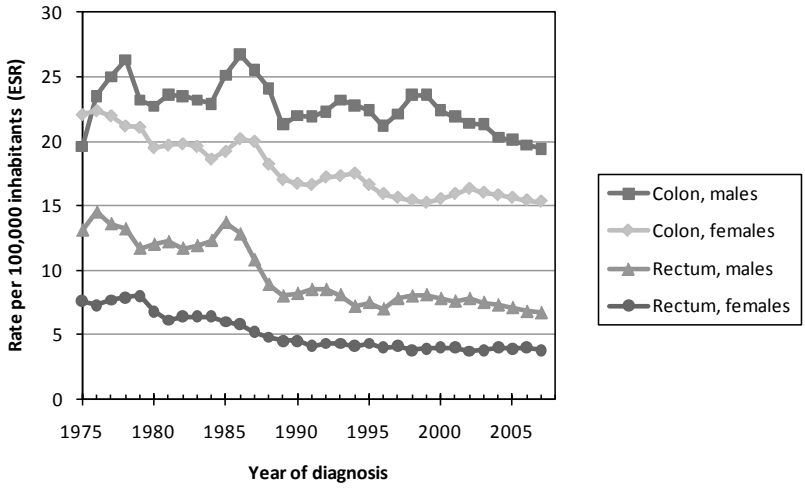


Figure 5: Age-standardized mortality of colorectal cancer in the south of the Netherlands (3-year moving average; ESR: European Standardized Rate), according to gender and tumour site

Table 3a: Multivariable relative survival analysis of patients with stage III colon and stage II/III rectal cancer

		Model without treatment [a]		Model with treatment [a]	
		RER	95% CI	RER	95% CI
Colon, stage III, <70 yrs	Period of diagnosis				
	1975-1984	2.0	1.63-2.52	1.0	0.80-1.35
	1985-1994	1.6	1.32-2.00	0.9	0.71-1.16
	1995-1999	1.3	1.10-1.64	1.1	0.88-1.33
	2000-2006	1.0		1.0	
	Treatment				
	Surgery	-		1.0	
	Surgery + adj. chemotherapy	-		0.4	0.36-0.52
Colon, stage III, ≥70 yrs	Period of diagnosis				
	1975-1984	1.8	1.38-3.00	1.4	1.07-1.80
	1985-1994	1.2	0.96-1.52	1.0	0.77-1.22
	1995-1999	1.2	0.97-1.48	1.1	0.89-1.36
	2000-2006	1.0		1.0	
	Treatment				
	Surgery	-		1.0	
	Surgery + adj. chemotherapy	-		0.4	0.28-0.52
Rectum, stage II/III, <70 yrs	Period of diagnosis				
	1975-1984	2.8	2.24-3.43	3.1	2.42-3.85
	1985-1994	1.9	1.55-2.29	2.1	1.68-2.53
	1995-1999	1.3	1.08-1.63	1.4	1.14-1.78
	2000-2006	1.0		1.0	
	Treatment				
	Surgery	-		1.0	
	Surgery + preop. radiotherapy	-		1.1	0.91-1.26
Rectum, stage II/III, ≥70 yrs	Period of diagnosis				
	1975-1984	2.0	1.51-2.59	2.1	1.51-2.85
	1985-1994	1.4	1.07-1.73	1.4	1.09-1.92
	1995-1999	1.2	0.91-1.50	1.2	0.91-1.63
	2000-2006	1.0		1.0	
	Treatment				
	Surgery	-		1.0	
	Surgery + preop. radiotherapy	-		0.9	0.7-1.09

RER: relative excess risk; CI: confidence intervals

[a] Adjusted for follow-up time, age, gender, subsite, and variables shown

Table 3b: Multivariable relative analysis of patients with stage IV colon or rectal cancer

		Model without treatment [a]		Model with treatment [a]	
		RER	95% CI	RER	95% CI
Colon, stage IV, <70 yrs					
	Period of diagnosis				
	1975-1984	1.7	1.44-1.99	1.4	1.20-1.69
	1985-1994	1.4	1.19-1.59	1.2	1.01-1.37
	1995-1999	1.2	1.09-1.42	1.1	1.00-1.31
	2000-2006	1.0		1.0	
	Treatment				
	No systemic therapy	-		1.0	
	Systemic therapy	-		0.7	0.62-0.79
Colon, stage IV, ≥70 yrs					
	Period of diagnosis				
	1975-1984	0.9	0.75-1.15	0.8	0.60-0.97
	1985-1994	1.2	1.01-1.39	1.0	0.83-1.15
	1995-1999	1.1	0.97-1.33	1.0	0.83-1.15
	2000-2006	1.0		1.0	
	Treatment				
	No systemic therapy	-		1.0	
	Systemic therapy	-		0.5	0.43-0.62
Rectum, stage IV, <70 yrs					
	Period of diagnosis				
	1975-1984	2.3	1.82-2.80	2.0	1.58-2.48
	1985-1994	1.9	1.61-2.36	1.6	1.34-2.02
	1995-1999	1.4	1.14-1.66	1.3	1.06-1.55
	2000-2006	1.0		1.0	
	Treatment				
	No systemic therapy	-		1.0	
	Systemic therapy	-		0.7	0.61-0.84
Rectum, stage IV, ≥70 yrs					
	Period of diagnosis				
	1975-1984	1.0	0.74-1.33	0.8	0.60-1.09
	1985-1994	1.0	0.79-1.29	0.8	0.65-1.09
	1995-1999	1.2	0.96-1.50	1.1	0.88-1.37
	2000-2006	1.0		1.0	
	Treatment				
	No systemic therapy	-		1.0	
	Systemic therapy	-		0.5	0.41-0.68

RER: relative excess risk; CI: confidence intervals

[a] Adjusted for follow-up time, age, gender, site, and variables shown

Table 4: Ten-years prevalence (ESR) of patients with colorectal cancer at January 1, 1984, 1994, and 2004, respectively, in the south of the Netherlands[a]

		Prevalence (ESR)		
		January 1, 1984	January 1, 1994	January 1, 2004
Males	colon	101	138	167
	rectum	70	104	128
Females	colon	96	118	145
	rectum	51	59	75

ESR: European Standardized Rate

[a] Age-standardised number of patients alive, diagnosed with colorectal cancer up to 10 years before the respective date, per 100,000 inhabitants

Discussion

The epidemiology of CRC has changed strikingly in the south of the Netherlands during the period 1975-2007. First of all, there has been a gradual increase in incidence of colon cancer, which was most marked among males and for proximal tumours. Furthermore, survival increased dramatically, especially among patients with rectal cancer. This went together with changes in treatment; particularly since the mid-1990s, a growing proportion of predominantly younger patients underwent adjuvant chemo- or radiotherapy, next to changes in surgical management. The advances in survival led in turn to decreased mortality rates, and consequently to increased prevalence rates. The changes in stage distribution suggested more accurate staging procedures for N and M disease over time, with no evidence that patients diagnosed more recently are diagnosed at an earlier stage of the disease.

The rising age-standardised incidence of CRC in the south of the Netherlands, predominantly among males, is in concordance with patterns of incidence found in many other European countries.[83] Changes in major risk factors such as lifestyle, including physical activity, diet and obesity may account for the rising trend.[83, 84] These trends are however in contrast to patterns found in the US, where overall incidence rates have been steadily declining over the past two decades.[85] One explanation for this reversed trend may be the more extensive implementation of opportunistic screening in the US.[85] The trends in stage distribution as shown by the current study support this hypothesis; no clear shift towards an earlier stage at diagnosis was observed in the south of the Netherlands, which would be expected in case of higher uptake of screening activities. Added to that, one can only speculate about any effect on stage distribution of an increased polypectomy of premalignant adenomas over time.

As in many Western countries, a shift towards a more proximal tumour site was observed.[86-90] This has been related to the use of sigmoidoscopy (and related polypectomy) as a screening tool.[86, 91] However, our data show that the shift towards proximal tumour site is the result of an increase in age-adjusted incidence of proximal tumours, and not merely a decline in distal tumour site. Possibly

changes in diet and lifestyle, and maybe also the use of medications such as aspirin and non-steroidal anti-inflammatory drugs, and hormone replacement therapy in women, are responsible for the rightward shift in CRC incidence through differential effects of these risk factors on the respective subsites.

There was a vast improvement in 5-year relative survival for both colon and rectal cancer, being largest in the latter and among stage III patients. A number of other European population-based studies already earlier reported on these remarkable improvements.[92-95] The low relative excess risks related to adjuvant chemotherapy among patients with stage III colon carcinoma and those related to systemic treatment among patients with stage IV colon or rectal carcinoma are however prone to bias in this retrospective analysis: patients who are fit are more likely to be treated with chemotherapy.[35] The fact that the RER for adjuvant or palliative chemotherapy was alike or even lower among older patients suggests that selection bias influenced our results.

The current study demonstrated that the increase in survival was more pronounced among patients younger than 70. Our observation that survival also improved for older patients with rectal cancer is in contradiction with other Dutch studies using somewhat older data.[77, 96] Indeed, our data did also not show an improvement among these patients during the 1990s. Our finding that recent survival of elderly patients has improved is in line with a SEER registry-based study.[97] For stage III colon cancer patients, the increased use of effective adjuvant chemotherapy regimens for these patients probably largely accounted for the dramatic improvement. Among elderly stage III patients, survival increased more moderately. Adjuvant chemotherapy was administered to only 5% of those aged 80 or older in the period 2005-2007, although several studies have demonstrated the benefit of this therapy at higher ages.[98] Besides age as well as hospital, also comorbidity, gender, and socioeconomic status influenced administration of adjuvant chemotherapy in the south of the Netherlands.[35]

Large changes in treatment have taken place among rectal cancer patients: implementation of Total Mesorectal Excision (TME) and a shift from post- to preoperative radiotherapy together with increased administration of (neo-adjuvant) chemotherapy.[36, 78, 99] The increase in survival for rectal cancer in general was large, and when the survival in the period 1965-1974 (33%) is also taken into account, the relative improvement in survival was the largest of all adult tumours. Also for stage IV CRC patients survival improved; responsible is an increased use of and changes in chemotherapy, and probably a more adequate selection of patients eligible for surgery.[79] Partly, the improved stage-specific survival in these and other patients might be the result of stage migration, as a consequence of more adequate staging procedures.[100] The increased proportion of patients with stage III and IV disease over time underline these developments. Better and more widely applied imaging techniques (MRI, CT-scan) and increasingly adequate pathology (more thorough search for lymph nodes by pathologists) are very likely to have an effect on all stage-specific survival analyses besides stage I. The fact

that after adjustment for treatment, still an effect of period of diagnosis could be noted in the multivariable relative survival analyses, suggests that stage migration has played a role here. However, the improvements seen in non-stage specific survival, especially among patients younger than 70 years, suggests that not only stage migration is responsible for the improvements in stage-specific survival. In most recent years, there has been a regionalisation of the surgical expertise for treating locally advanced rectal carcinoma and liver metastases. As opposed to the use of adjuvant chemotherapy among patients with stage III colon cancer, in our multivariable analyses the survival improvements for stage II/III rectal cancer patients could not be explained by the increased use of preoperative radiotherapy. The majority of studies showed a clear effect of preoperative radiotherapy on local control, but the effect of preoperative radiotherapy on overall survival was less unambiguous.[36, 101] No significant survival improving effects have been reported for preoperative chemoradiation (5-fluoruracil-based) among patients with locally advanced rectal carcinoma, but also here the beneficial effects on local control are well documented.[102, 103] Anyway, changes in surgical management, more accurate staging procedures by surgeon and pathologist, perioperative care, and the establishment of multidisciplinary teams probably all have contributed to the improved survival of rectal carcinoma. Especially the TME trial, in which a large number of hospitals in the Eindhoven Cancer Registry area participated actively, has had a large influence on quality of rectal cancer treatment.[36, 78, 104] However, already before the start of the TME trial, a number of surgeons already performed their resections in a TME-like fashion. The increased survival of patients with rectal carcinoma seen already long before the introduction of TME surgery suggests that other mechanisms and developments play a role, such as more general learning curves in diagnostics and surgery. This is also true for colon cancer, where an increase in survival could be noted already before the widespread introduction of adjuvant chemotherapy. The large effect of for example improved surgical management on long-term survival of both colon and rectal cancer has been reported in a French population-based study; it was calculated that a reduction of 30-day mortality from 18% to 8% had led to a relative improvement of 27.5% in 5-year survival.[105]

Although adherence to clinical guidelines is generally considered a measure of quality of care, deviating from these guidelines in case of an elderly patient is not necessarily indicating inferior quality of care. The large proportion of elderly patients presenting with comorbidity, and the inherent lack of evidence-based guidelines for this group, often call for pragmatic individualised treatment.[34, 106] In view of the growing proportion of elderly CRC patients - partly because of the rising incidence rates but especially because of the aging population - clinicians will more and more often face difficult decisions regarding adjuvant therapy. However, a growing specific knowledge of CRC care of the elderly is probably shifting the approach in elderly patients towards more aggressive treatment and multimodal therapy,[98] as partly confirmed by our data.

The aging of the population and hence the rise in absolute numbers of patients with CRC together with the increased survival rates will also lead to a large number of individuals who were diagnosed with CRC five or more years ago. A report of the Dutch National Cancer Society estimated the prevalence of CRC patients in the Netherlands to increase from 60,000 in 2005 to 100,000 in 2015.[6] These patients have to be followed-up, which will further claim endoscopy capacity, and part of these patients will need extra care, i.e. because of a permanent stoma. Furthermore, patients who have survived several years also have an excess risk of developing a subsequent primary cancer.

The strength of the current study is the availability of long-term, high quality population-based data.[107] Studying long-term trends enables an evaluation of implemented care and eventual screening activities, and an anticipation of developments in the near future. The results of our study showed that the workload of all clinicians involved in the diagnosis, staging, treatment, and follow-up of CRC will keep increasing considerably in the near future. Not only the steady increase in age-adjusted incidence, but especially the demographic changes of the Dutch population and the likely future implementation of CRC mass screening will necessitate investments with relation to education, recruitment, materials, and infra-structure. In many other European countries, the situation is the same.[83] Nevertheless, this study demonstrated large improvements in management and survival of CRC patients between 1975 and 2007. The changes in management of rectal cancer lead to a superior increase in survival of these patients compared to patients with colon cancer, even surpassing the latter.

Acknowledgements

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection.

Funding

This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588).

2.2.

Increasing incidence and decreasing mortality of colorectal cancer due to marked cohort effects in southern Netherlands

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Eur J Cancer Prev 2009;18(2):145-52

Abstract

Background: In preparation for any type of forthcoming colorectal cancer (CRC) mass screening we examined trends in CRC incidence and mortality according to gender, subsite, and age in southern Netherlands.

Methods: Population-based data from the Eindhoven Cancer Registry during the period 1975-2004 were used. Age-period-cohort analyses were performed to investigate possible etiologic, diagnostic, or therapeutic origins of the trends.

Results: Age-adjusted (European Standardized Rates) incidence rates for colon cancer increased since 1975 from 23/100,000 for both genders to about 38/100,000 for males and 30/100,000 for females in 2004. Incidence of rectal cancer remained relatively stable at about 25/100,000 males and 15/100,000 females. The incidence of CRC increased for male patients from birth cohorts between 1900 and 1955 (p=0.010), especially in left-sided colon cancer in the younger birth cohorts (RR_{1900}: 0.8 (95% CI 0.6-1.0), RR_{1960}: 1.6 (95% CI 0.9-2.8), reference: 1910-1919). For females a similar, although weaker increase in CRC incidence was found. Mortality rates for CRC started to decrease since 1975, more pronounced for rectal than for colon cancer. The relative risk for dying in men with CRC decreased from 1.3 (95% CI 1.0- 1.6) in the 1900 birth cohort to 0.1 (95% CI 0.1- 0.4) in the 1960 birth cohort, reference 1910-1919 birth cohort.

Conclusion: The increasing incidence and decreasing mortality in CRC is largely affected by birth cohort effects. Changes in CRC incidence are likely to be attributed to lifestyle factors and decreasing mortality is due to earlier detection and improved treatment, especially among younger patients.

Key words: colorectal cancer, incidence, mortality, age-period-cohort analysis, cancer registry

Introduction

Colorectal cancer (CRC) is the third most frequent cancer in the Netherlands with almost 10,000 new cases annually and a lifetime risk of over 5%.[1, 108] It is the second most frequent cause of cancer death in the Netherlands with over 4,700 deaths in 2006.[2] Age-adjusted incidence has been increasing steadily in the Netherlands[109] and throughout Europe since 1950,[110-112] especially among males, with an increasing proportion of tumours proximal to the sigmoid.[87, 113, 114] Age-adjusted mortality has been decreasing, especially among women.[115]

Age-period-cohort analysis can be used to dissect temporal trends in CRC incidence and mortality, thereby distinguishing between detection and etiological factors with a substantial population-attributable risk. A period of diagnosis effect affects the entire patient population diagnosed at a specific period in time and a cohort effect only affects one or several birth cohorts due e.g. to a change in lifestyle.[72]

Several risk factors for CRC have been implicated in industrialized countries like the Netherlands, with an important role for diet and physical activity.[17, 18, 22, 24, 26, 116] Use of nonsteroidal anti-inflammatory drugs (NSAIDs)[117] and hormone replacement therapy[118] in women had a consistent protective effect. The variation observed in incidence of CRC according to age, gender, and subsite of the tumour[107] is probably due to increased exposure to these risk factors over time. In addition, more endoscopic examinations have been conducted since the 1980s and surveillance has intensified due to the introduction of the flexible endoscope.[91]

Cancers of the right-sided colon, left-sided colon, and rectum are considered to be different disease entities with a distinct pathogenic mechanism.[119, 120] In addition, risk factors for subsites of CRC differ slightly.[121]

A detailed description of trends in CRC incidence and mortality and their possible determinants is needed, since the introduction of potential future mass screening is likely to be affected by these trends. Therefore, the aim was to examine trends in incidence and mortality according to gender and subsite over a 35-year period using population-based data from the south of the Netherlands. This is done in a period in which endoscopy became widely available for diagnostic purposes and familial surveillance. Age, diagnostic period, and birth cohort were investigated as determinants of such trends.

Material and methods

Data collection

Population-based data from the Eindhoven Cancer Registry (ECR), which is maintained by the Comprehensive Cancer Centre South, were used. The ECR records data on all patients newly diagnosed with cancer in the southern part of the Netherlands. During the study period 1975-2004, the population of the ECR

catchment area increased from almost 600,000 to 2,400,000 inhabitants, mainly due to expansion of the registration area in 1988.[107] The ECR is served by ten community hospitals, six pathology departments, and two radiotherapy institutes. Information on patient characteristics such as gender, date of birth, and postal code, and tumour characteristics such as date of diagnosis, tumour type, subsite (International Classification of Diseases for Oncology (ICD-O-3)[64]), histology, stage (Tumour Lymph Node-Metastasis (TNM) clinical classification)[63], grade and treatment, are obtained routinely from the medical records.[107] The quality of the data is high, due to thorough training of the registrars and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[80]

For the present study, all cases with primary colorectal cancer (C18-C20) registered between 1975 and 2004 in the area of the ECR were included (n=23,167). Tumour localization was categorized into three anatomical subsites: right-sided colon, consisting of the coecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0-C18.5); left-sided colon, consisting of the descending colon and sigmoid colon (C18.6-C18.7); and rectum, consisting of the rectosigmoid and the rectum (C19.9, C20.9). Subsite information was unknown for 188 (1%) men and 151 women (1%) (C18.8, C18.9). These cases were excluded in the sub-analyses for incidence of CRC according to anatomical subsite.

For the period 1975 to 1987 age distribution of age groups above 85 years was not available for the general population in the ECR region, which is almost similar to the south-eastern region of Northern Brabant and the northern region of Limburg as defined by Statistics Netherlands. Therefore, the age distribution of persons aged 85 years and older in these regions were used. Comparison of the actual and estimated number of persons in the age groups for more recent years resulted in comparable numbers of persons in each group.

The number of deaths due to CRC as reported to Statistics Netherlands for the provinces of Northern Brabant and the northern region of Limburg in the period 1970 to 2006 were used to analyse the trend in mortality (n=14,047). This area is almost similar to the ECR region, with some small differences at the borders of the region. Tumour subsites were divided as in ICD-O-3.[64] However, the left-sided and right-sided colon were combined (C18) and the rectum (C19, C20) also included the anus and anal canal (C21). Quality of the mortality data is high.[2] The general population used for the mortality analyses consisted of the population of north-eastern Northern Brabant and the northern region of Limburg.

Statistical analysis

Age-adjusted and age-specific trends in incidence and mortality according to gender and subsite were calculated from data from the ECR during the period 1975-2004 for the incidence and 1970-2006 for the mortality. Annual incidence

and mortality rates were calculated per 100,000 inhabitants as three-year moving averages. Age-adjustment was performed by direct standardization according to the European Standard Population (European Standardized Rates, ESR). Trends in incidence and mortality were estimated by annual percentage change (EAPC). This was done by fitting a regression line to the natural logarithm of the rates using calendar year as regressor variable, i.e. y=mx+b, where y=ln (rate) and x=calendar year. The EAPC is then estimated as $100*(e^{m}-1)$. This calculation assumes that the rates increased or decreased at a constant rate over the entire period.

Joinpoint analyses were performed to discern significant changes in the trend and, if present, when they occurred.[71] Linear line segments are connected on a log scale to identify changes in trend data in terms of the annual rates of change in fixed periods of time[71] although cross-sectional cancer rates generally do not change abruptly.

Age-period-cohort analyses were performed to examine jointly the influence of longitudinal and cross-sectional changes.[72, 73] From the matrix of the age-specific incidence and mortality rates calculated for each 5-year time period and age-group, time trends according to age, birth cohort, and period of diagnosis were evaluated using an age-period-cohort model. The number of CRC cases or deaths at a given age and time interval were considered to follow a Poisson distribution for which the logarithm of the average was equal to person-years at risk plus a polynomial function of age, time period and/or birth cohort. For each data set five multiplicative Poisson models were fitted: the age (A), age-drift (AD), age-period (AP), age-cohort (AC), and age-period-cohort (APC) model. Drift is a linear component of the overall rate of change in the incidence or mortality rate with time that describes models for which the age-period and age-cohort parameters fit the data equally well. Such a model thus serves as an estimate of the rate of change of a regular trend.[73] The analyses with Poisson models included cases or deaths diagnosed between 1975 and 2004 for cases aged 20 to 95 years at the time of diagnosis. Cases younger than 20 years were excluded from the analyses, because less than one percent of CRC incidence and mortality occur in this group.[108] Synthetic birth cohorts of ten years were constructed by combining cells along the diagonals in an age-time period table. To test the goodness-of-fit of the models with the observed incidence and mortality rates and to test the models against one another, deviations and differences in deviations with appropriate degrees of freedom were used.[72, 73] Trends in CRC incidence were evaluated according to gender, subsite, and age. Trends in CRC mortality were conducted according to gender, age, and subsite. SAS/STAT® statistical software (SAS system 9.1, SAS Institute, Cary, NC) was used for the analyses. The software for the joinpoint analyses was the Joinpoint Regression Program, version 3.0 of the National Cancer Institute.

Results

Trends in incidence and mortality

The 12,119 male cases and 11,048 female cases newly diagnosed with CRC between 1975 and 2004 had a median age of 68 (interquartile range: 60 - 75) and 70 (interquartile range: 61 - 78) years, respectively. The cases diagnosed between 1975-1990 were slightly younger (median age 67 years for males and 69 years for females) than those diagnosed in 1990-2005 (median age 68 years for males and 71 years for females).

The age distribution of CRC cases was skewed to the left with approximately 7% of the cases under the age of 50 years. Sixty-two percent of male cases and 67% of female cases were aged 65 years or older, and 5% of male cases and 7% of female cases were aged over 85 years. The cases were divided over the subsites as follows: 30% on the right side, 29% on the left side, and 41% at the rectum for males, and 40%, 28%, and 32% for females, respectively.

The incidence rates for colon cancer increased over time for both genders with a larger increase among males than among females. This resulted in an incidence rate for males of 38 and 30 for females per 100,000 inhabitants (ESR) in 2004. For rectal cancer, the incidence remained relatively stable, being much higher among males compared to females (Figure 1a). Mortality rates for CRC have been decreasing among males and females after an increase between 1970 and 1975, especially for colon cancer (Figure 1b). Mortality for rectal cancer has decreased by approximately 50% for both genders since 1975. For colon cancer the decrease was less pronounced, although the mortality rate for colon cancer in females decreased from 23 to 16 per 100,000 inhabitants (ESR) in the 30 years preceding 2004.

Among people over 70 years colon cancer incidence increased, while the incidence was almost stable in both younger males and females (data not shown). Rectal cancer incidence increased in younger males (data not shown). The decrease in mortality was more pronounced in those younger than 70 years, especially for rectal cancer since 1985 (data not shown). The EAPC for male rectal cancer cases under the age of 70 years was -3.02% (95% CI -3.77; -2.25) compared to -2.09% (95% CI -2.57; -1.60) for male rectal cancer cases aged over 70 years. For women similar EAPCs were found.

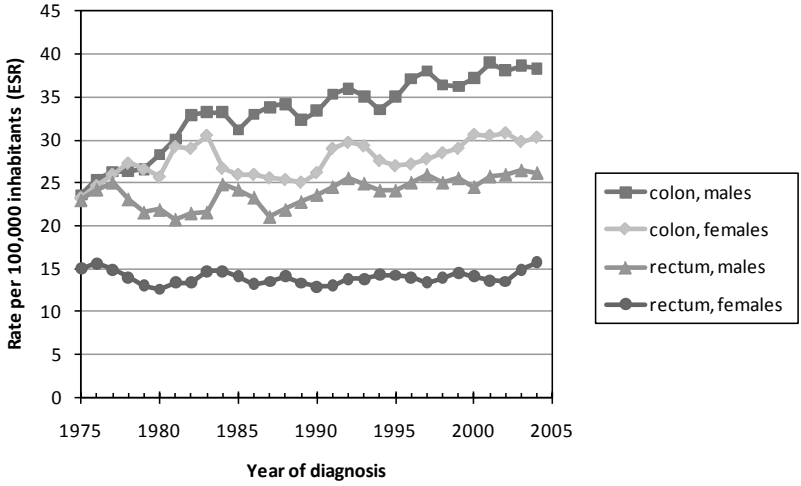

Figure 1a: Trends in colorectal cancer incidence according to gender and subsite in southern Netherlands (3 year moving averages; ESR: European Standardized Rate)

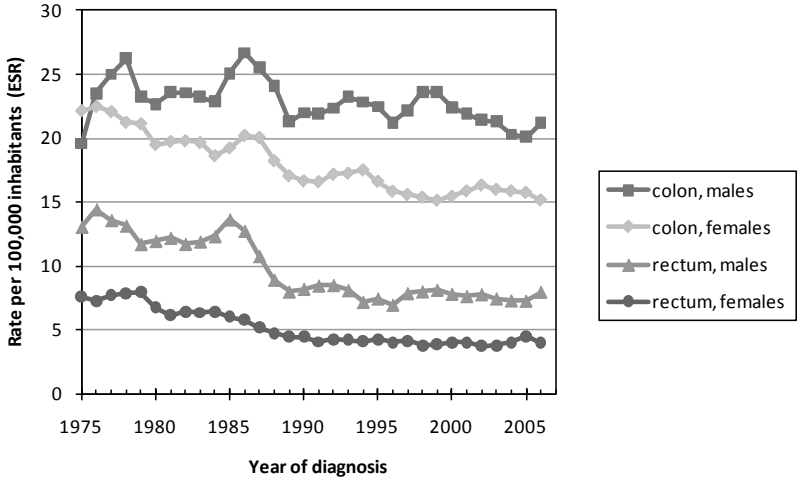

Figure 1b: Trends in colorectal cancer mortality according to gender and subsite in southern Netherlands (3 year moving averages; ESR: European Standardized Rate)

Joinpoint analyses

Changes in the linear trends were detected in joinpoint analyses. A significant change in the linear trend was found in the incidence data for females in which the EAPC changed from -0.07% (95% CI -0.54; 0.40) before 1988 to 0.79% (95% CI 0.46; 1.13) after 1988 (95% CI 1984-1992). For CRC incidence data in males no joinpoint was found, although joinpoint analyses only detect cross-sectional changes (period effects). Two joinpoints were found i.e. a significant change in

linear trend for the mortality in 1986 and 1989 for both genders. Among males the EAPC changed from 0.44% (95%CI -0.49, 1.38) before 1986 to -0.33% (95% CI -0.97; 0.31) after 1989. For females the EAPCs were -2.40% (95% CI -3.24; -1.54) and -0.64% (95% CI -0.97; -0.32), respectively, after a large drop in mortality rate. The observed decreases can be attributed mainly to rectal cancer (results not shown).

Age-period-cohort analysis

Incidence

An increase in CRC incidence can be observed for younger birth cohorts, especially in men. No clear period effect was shown, although the incidence of CRC increased slightly during the period of diagnosis between 1975 and 2004, mainly in women (Figure 2a, 2b). The incidence of tumours in the left-sided colon showed an increase in relative risk from 0.8 (95% CI 0.6-1.0) for male cases born in 1900 to 1.5 (95% CI 0.9-1.5) for the 1955 cohort, using 1910-1919 as the reference birth cohort (Figure 3). The incidence of right-sided colon tumours increased until the birth cohort of 1930 and then stabilized until the 1955 cohort. For rectal tumours the incidence was stable until the birth cohort of 1940 and then increased (Figure 3). No clear trends in CRC by sub localisation were found for women (data not shown).

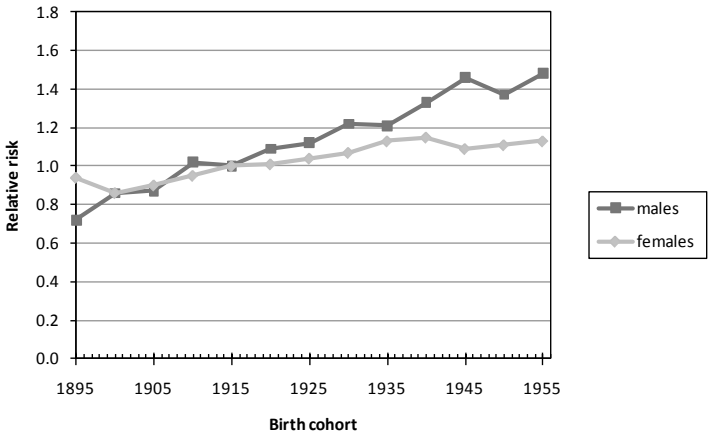

Figure 2a: Relative risk of developing colorectal cancer according to birth cohort and gender in southern Netherlands

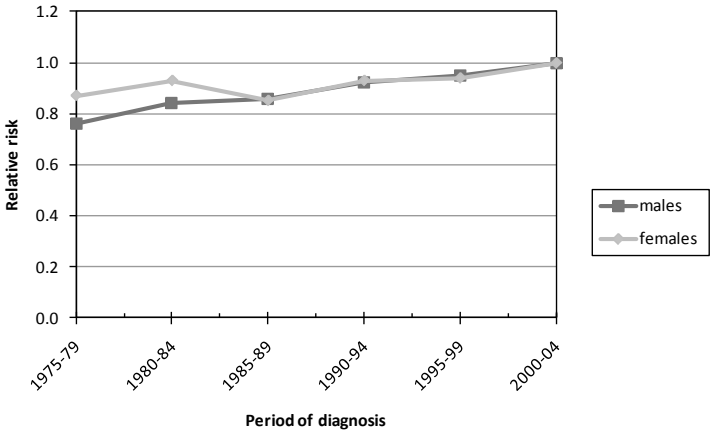

Figure 2b: Relative risk of developing colorectal cancer according to period and gender in southern Netherlands

The age-drift model is a significant improvement of the age model in all subgroups, except for women with rectal cancer (Table 1a, b). The age-period model was the best model to describe the trend among women with CRC, especially with left-sided colon cancer. The age-cohort model fitted the data best for men with CRC, especially with right-sided colon and rectal cancer. The age-period-cohort model was not a significant improvement of either the age-period or the age-cohort model for any of the patient groups.

Mortality

Mortality for rectal cancer decreased in consecutive birth cohorts from 1905 to 1925 and stabilized afterwards until the 1950 birth cohort; then a decrease was seen until the 1960 birth cohort (Figure 4). The relative risk for dying from rectal cancer in men decreased from 1.25 (95% CI 0.96; 1.63) in the 1900 birth cohort to 0.14 (95% CI 0.05; 0.37) in the 1960 birth cohort, using 1910-1919 as reference birth cohort. For colon cancer a similar trend was seen. The age-cohort model was the best fit model for rectal cancer in men and women and colon cancer in women. The age-drift model fitted the data the best for colon cancer in men. The best fit of the age-cohort model indicated that birth cohorts significantly affect mortality.

Figure 3: Relative risk of developing colorectal cancer in men according to birth cohort and subsite in southern Netherlands

Table 1a: Deviations of Age-Period-Cohort modelling for colorectal cancer incidence in southern Netherlands, diagnosed between 1975 and 2004

Model	df	Colon and rectum combined		Right colon		Left colon		Rectum	
		M	F	M	F	M	F	M	F
Age	75	168	106	150	103	130	64	126	83
Age-Drift	74	97	85	104	73	94	59	115	83
Age-Period	70	95	75	102	65	87	47	113	79
Age-Cohort	56	62	70	57	60	79	45	57	71
Age-Period-Cohort	52	61	59	56	51	72	33	55	68

Df: degrees of freedom, M: male, F: female

Table 1b: Difference in deviation of the comparison of models of the Age-Period-Cohort analyses for colorectal cancer incidence southern Netherlands, diagnosed between 1975 and 2004

Models to compare	Δ df	Colon and rectum combined		Right colon		Left colon		Rectum	
		M	F	M	F	M	F	M	F
A vs AD	1	71**	20**	45**	30**	36**	5*	11**	1
AD vs AP	4	2	10*	3	9	8	11*	2	3
AD vs AC	18	35*	16	45**	13	16	14	58**	12
AP vs APC	18	35	17	46**	13	15	14	58**	12
AC vs APC	4	1	11*	1	9	7	12*	2	3

Df: degrees of freedom, M: male, F: female, A: Age, AD: Age-Drift, AP: Age-Period, AC: Age-Cohort, APC: Age-Period-Cohort; ** p-value < 0.001 * p-value < 0.05

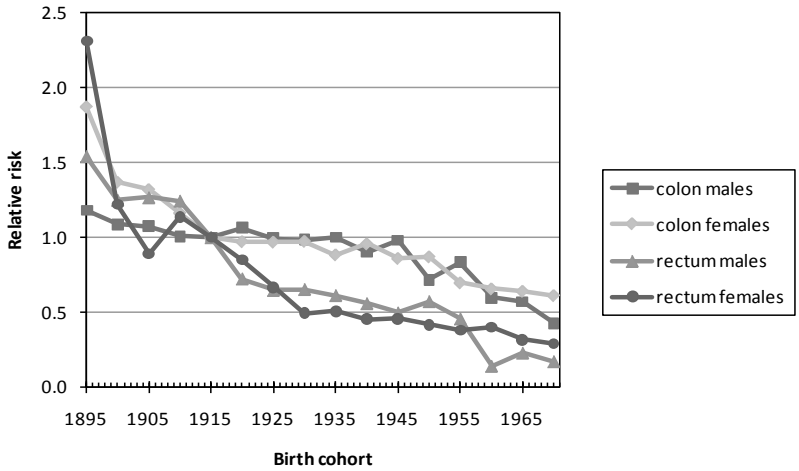

Figure 4: Relative risk of dying from colorectal cancer according to birth cohort, gender, and subsite in southern Netherlands

Discussion

Based on this population-based study which covers a long period, the incidence of colon cancer has increased since 1975 while rectal cancer incidence has remained relatively stable. CRC incidence increased for younger birth cohorts until 1955 in men and 1940 in women. The diverse birth cohort effects on CRC incidence, suggested a different trend and aetiology for subsites of CRC. Mortality rates decreased over time, especially for rectal cancer cases younger than 70 years. Colon and rectal cancer mortality decreased more in younger birth cohorts.

The finding that CRC incidence in the Netherlands has been increasing is as expected.[1] In the Netherlands the incidence of colon cancer increased by 12% in 1989-2003.[122] This is slightly lower than the increase in colon cancer incidence found in our study (19%) using the same period. CRC incidence is increasing similarly across Europe.[110-112, 123, 124] Mortality rates have been decreasing by an estimated annual percentage change of 0.5% in the Netherlands in 1989-2003,[1] which is consistent with our findings. Estimates of CRC mortality in the European Union are also consistent with our results.[3] The disparity between men and women in incidence and mortality is as expected.[4, 125]

The results in literature on age-period-cohort modelling for CRC incidence are diverse. Our finding that trends in incidence were mainly due to cohort effects is consistent with results from a recent French[126] and a Swedish study,[112] although an age-period-cohort model fitted the Swedish data better. Nevertheless, they excluded cases aged 85 years and older, who represent a considerable number of CRC cases.[108] Our finding of a slight period effect in the incidence of CRC, especially among females, was also found in the Côte-d'Or region of France.[123] The

absence of a close-fit model for rectal cancer might be due to the small study population in the French study (n=4,486) and the relatively short period of 19 years of available data. Studies based on Scandinavian cancer registries, which cover periods of 40 years, mainly found an age-period-cohort model as the best-fit model for CRC, with a predominant negative cohort effect related to World War II.[110, 111, 127] In a Spanish[124] as well as an American (Connecticut) study[128] an effect of birth cohort on CRC mortality was found, which is in line with our results. However, the American study also showed an effect of period of diagnosis.[128]

When CRC was divided into three subsites, different cohort effects were found. Our finding that left-sided colon cancer increased in successive birth cohorts is in contrast to the results of a Swedish and New Zealand study. In these studies a decrease in relative risk for cases with left and right-sided colon cancer was found for successive birth cohorts.[112, 129] We do not have an obvious explanation for the discrepancy in cohort effects between those studies and our results for right-sided colon cancer.

The increase in incidence for colon and rectal cancer in both genders is likely to be related to changes in lifestyle factors and better endoscopy techniques for CRC, especially for colon cancer. Many epidemiological studies confirm the importance of lifestyle in CRC,[25] for example physical inactivity,[116] red and processed meat consumption,[22] alcohol intake,[24] obesity,[25] dietary fat intake,[17, 18] and excessive intake of energy.[26] The relative risk of the risk factors for CRC are small, so large effects can only be seen after big changes in exposure. Smoking is strongly associated with CRC with an induction period of three to four decades between exposure and the diagnosis of CRC.[130] Since the proportion of male smokers was high since the 1940s until the 1970s,[131] the increase in CRC incidence after 1975 could be explained partly by smoking. This could have contributed to the cohort effect found in our study, especially for men. The weaker cohort effect found for females could be explained by lower smoking rates for females compared to males.[131] Accumulating evidence suggests that various environmental and genetic factors differ for proximal and distal tumours.[119]

Dietary factors including the intake of fat,[17, 18] red and processed meat,[20, 132] and alcohol[24, 133] generally had a stronger effect in the distal than the proximal colon. The risk factors on CRC changed negatively over time with younger birth cohorts, which could have resulted in a cohort effect in CRC incidence in our study. In addition, since lifestyle habits including diet, alcohol consumption, and physical activity have changed to a less favourable pattern, the increase in left-sided colon cancer is not unexpected. Furthermore, different mechanisms in tumourgenesis are known, and all affect at different parts of the colon.[120] The different cohort effects as well as the possible explanation of these differences indicate differences in the aetiology of CRC.

Our finding that mortality decreased more in younger birth cohorts could be attributed to earlier detection, especially familial surveillance in young and middle age, and advances in treatment with better results among younger cases. Elderly

cases were often treated with less aggressive adjuvant therapy compared to younger cases.[35, 66] Major changes in treatment for CRC were introduced in the period of this investigation. Adjuvant chemotherapy became standard for cases with stage III colon cancer, which increased their survival. Furthermore, treatment for rectal cancer improved by the introduction of total mesorectal excision (TME) surgery and short-term preoperative radiotherapy, which was first administered to the young and middle aged patients and later to the older patients.[77, 134]

Our results can be generalized to all regions in the Netherlands, although the population in the southern part of the country, especially the males, had a higher proportion of smokers and a higher alcohol intake,[135] compared to the more northern parts of the Netherlands.

In conclusion, the increasing trend in CRC incidence is affected by birth cohort effects, especially in the left-sided colon. Decreasing trends in mortality were also affected mainly by birth cohort effects. These results confirm that the changes in CRC incidence could be attributed to changes in lifestyle factors and the decreasing mortality to earlier detection and improved treatment with better results among younger cases.

Acknowledgements

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection.

Funding

This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588).

CHAPTER 3.

DETECTION

3.1.

Improvable quality of diagnostic assessment of colorectal cancer in southern Netherlands

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Eur J Gastroenterol Hepatol 2009;21(5):570-5.

Abstract

Objective: To determine the extent of guideline implementation of the diagnostic approach to patients with colorectal cancer (CRC) in southern Netherlands in 2005, with special focus on colonoscopy.

Methods: Data were gathered from the medical records for a random sample of 257 colon and 251 rectal cancer patients newly diagnosed in 2005 and recorded from the Eindhoven Cancer Registry. Adherence to guidelines was determined for diagnostic assessment. Multivariable logistic regression analysis was conducted to assess determinants of complete colonoscopy.

Results: Diagnostic assessment was carried out mainly by internists (50%) and gastroenterologists (36%). Colonoscopy was performed in 83% of patients with proximal/transverse colon cancer, 55% of those with distal colon cancer, and 65% of those with rectal cancer. A tumour biopsy was taken of 84% of colon and 93% of rectal tumours. Colonoscopy completeness was lower for patients with comorbidity, obstructing tumours, and patients with poor bowel preparation. Abdominal ultrasound was performed for 72% of colon and 52% of rectal cancer patients and a thoracic X-ray of over 80% of CRC patients. Computed tomography (CT) of the abdomen was done in over half of the colon cancer cases and a pelvic CT scan or magnetic resonance imaging (MRI) in 36% of rectal cancer cases.

Conclusion: Improvements in adherence to diagnostic guidelines for CRC appear possible, especially in the performance of imaging procedures. Among patients where complete visualisation of the colon was not feasible with colonoscopy, imaging techniques such as virtual colonoscopy might be of added value in the near future.

Keywords: colorectal cancer, guideline adherence, colonoscopy, diagnostic imaging

Introduction

Colorectal cancer (CRC) is the third most frequent cancer in the Netherlands with over 10,000 new cases annually and a lifetime risk of over 5%.[1, 108] Over a period of more than 20 years, a clear improvement in survival of patients with CRC was attained by earlier detection due to a lower barrier for endoscopy, better staging and surgery, and combined modality treatment.[77, 136] The absolute demand for accurate diagnostic assessment, including endoscopic and imaging procedures, is increasing due to the rising incidence of CRC and the forthcoming introduction of CRC mass screening.

To diagnose CRC accurately, a complete colonoscopy must be performed.[58, 137] Completion rates of over 85% were found in clinical practice data in the US and Canada,[138-140] while for patients with a colon tumour they were 54-70% in the UK and the Netherlands.[141, 142]

The following determinants of incomplete colonoscopy are mentioned in the literature: obstruction due to a distally located tumour, patient discomfort, poor bowel preparation,[48, 139, 142] increasing age,[138, 143] female gender,[138, 143, 144] prior abdominal or pelvic surgery,[138] and low body mass index.[144] Population-based data on these determinants are however scarce. There is also little known about guideline compliance for imaging procedures and blood assessments.

The aim of this study was to determine the extent of guideline implementation in the diagnostic approach to patients with CRC in southern Netherlands in 2005, with special focus on colonoscopy.

Methods

Population-based data from the Eindhoven Cancer Registry (ECR), which is maintained by the Comprehensive Cancer Centre South, were used. The ECR collects data on all patients newly diagnosed with cancer in the southern part of the Netherlands. The ECR covers ten community hospitals, six pathology departments, and two radiotherapy institutes. Information on diagnosis, staging, and treatment is obtained routinely from the medical records.[107] In addition, information on comorbidity was collected based on the Charlson comorbidity index.[66] Socioeconomic status, based on individual fiscal data on the economic value of the home and household income, was provided at aggregated level for each postal code.[67] The quality of the data is high, due to thorough training of the registrars and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[80]

For the present study 257 patients with primary colon cancer and 251 patients with primary rectal cancer were selected at random from the 1471 patients with CRC newly diagnosed in 2005. Patients who underwent an acute resection (n=34) were not included. Colon cancer was defined as C18, rectal cancer as C19-C20 according to ICD-O-3.[64] Tumour localization was categorized into anatomical subsites: proximal colon, consisting of the coecum, appendix, ascending colon, and

hepatic flexure (C18.0-C18.3); transverse colon, consisting of transverse colon and splenic flexure (C18.4-C18.5); distal colon, consisting of descending colon and sigmoid (C18.6-C18.7); colon not otherwise specified (NOS) (C18.8-9), and rectum, consisting of rectosigmoid and rectum (C19.9, C20.9). TNM stage was based on pathological and clinical stage when pathological stage was unknown, since clinical stage alone was unknown for many patients.

National clinical practice guidelines for diagnostic assessment of colon and rectal cancer, version 2001-2005, are described in Table 2. Additional data were extracted from the medical records by the researcher (L.N.S) and a research assistant, under supervision of the treating physicians. This included data on detection of the tumour: reported family history of CRC, comorbidity, physical examination, haemoglobin (Hb), endoscopy (colonoscopy and sigmoidoscopy), contrast enema, carcinoembryonic antigen (CEA), and results of tumour biopsies. For the detection of liver metastases the liver enzymes alkaline phosphatase (AP) and gamma glutamyl transferase (GGT) were assessed. For accurate staging, data were gathered of imaging procedures, including X-ray of the thorax, abdominal ultrasound, abdominal/thoracic/pelvic computed tomography (CT), and magnetic resonance imaging (MRI) of the pelvis. A complete physical examination was defined as palpation of the abdomen, liver, and the supraclavicular and groin glands. When one of those locations was not mentioned in the medical record, the physical examination was considered incomplete. Furthermore, data were collected about the most proximal location reached during colonoscopy, quality of bowel preparation, and reasons for not performing the colonoscopy. A complete colonoscopy comprised reaching the coecum or distal ileum. Furthermore, the specialty of the endoscopist was noted.

Multivariable logistic regression analysis was conducted of determinants of incomplete colonoscopy among patients who underwent a colonoscopy. Adjustments were made for age, gender, comorbidity, socioeconomic status, subsite (proximal colon, transverse colon, distal colon, and rectum), T and M stage, endoscopist, and hospital. (SAS system 9.1, SAS Institute, Cary, NC). P-values below 0.05 were considered statistically significant.

Results

The 257 colon cancer patients had a mean age of 71.2 (range: 36-91) years, versus 68.7 (range: 33-93) years for the 251 rectal cancer patients. In both colon and rectal cancer the majority of patients had a T3 tumour. Twenty-five percent of colon cancer patients and 21% of rectal cancer patients had metastatic disease at diagnosis. However, over 10% of colon and rectal cancer patients were staged as Mx and they were staged according to their T and N stage. The large majority of CRC patients with unknown metastatic disease had a T3 tumour. In colon cancer patients tumour subsite was divided as 25% coecum, 16% ascending colon, 9% hepatic flexure, 9% transverse colon, 6% splenic flexure, 3% descending colon,

30% sigmoid, and 3% colon not otherwise specified. Rectal cancer was divided as 16% rectosigmoid and 84% rectum. The majority of colon and rectal cancer patients suffered from one or more co-morbid conditions, 60% of colon cancer and 50% of rectal cancer patients respectively, mainly in elderly patients. The most common comorbidity was a previous malignancy (mainly previous CRC), which was found in 16% of colon cancer and 9% of rectal cancer patients. Internists and gastroenterologists diagnosed the majority of CRC patients (Table 1).

Table 1: Descriptives of the study population (n=508)

	Colon (n=257)		Rectum (n=251)	
	n	%	n	%
Age (mean (range)) (yrs)	257	71.2 (36-91)	251	68.7 (33-93)
Gender (male)	129	50	136	54
Socioeconomic status				
low	56	22	43	17
intermediate	98	38	105	42
high	86	33	84	33
unknown	17	7	19	8
Comorbidity [a]				
none	88	34	110	44
1	81	31	76	30
≥ 2	73	29	49	20
unknown	15	6	16	6
T stage				
1	11	4	15	6
2	38	15	65	26
3	143	57	103	41
4	30	12	8	3
X	29	12	60	24
M stage				
0	156	60	164	66
1	63	25	54	21
X	38[b]	15	33[c]	13
Stage				
I	33	13	68	27
II	85	33	57	23
III	61	23	56	22
IV	63	25	54	22
unknown	15	6	16	6
Physician				
gastroenterologist	78	30	103	40
internist	141	55	107	43
surgeon	27	10	28	11
other	4	2	6	3
unknown	7	3	7	3

[a] Excluding hypertension; [b] Divided as 4% T1, 10% T2, 55% T3, 28% T4, and 3% Tx; [c] Divided as 4% T0, 20% T1, 32% T2, 36% T3, 4% T4, and 4% Tx

Diagnostic assessment

Detection and verification of tumour

An accurate assessment of a family history of CRC was reported in the medical records for over 80% of CRC patients younger than 60 years. Comorbidity was documented for a large majority of both colon and rectal cancer patients. Physical examination was conducted for 86% of colon and 82% of rectal cancer patients, with 47% recorded completely in the medical records in both groups. Rectal examination was performed in six out of ten colon cancer and seven out of ten rectal cancer cases. Seventy-four percent of colon cancer patients and 65% of rectal cancer patients underwent colonoscopy. Colonoscopy performance rate decreased with a more distal location of the colon tumour, ranging from 83% for patients with a tumour in the proximal and transverse colon to 55% for patients with a tumour in the distal colon. Contrast enema was performed in one out of three colon cancer patients with incomplete colonoscopy. Sigmoidoscopy was carried out in 57% of patients with colon cancer who did not undergo a colonoscopy, versus 94% of rectal cancer patients. Sigmoidoscopy was performed mainly in patients with a tumour in the distal colon (87%) and the transverse colon (71%) (Table 3). A tumour biopsy was obtained from four out of five colon cancer patients and almost all rectal cancer patients (Table 2). The completion rate for colonoscopy was 57% for colon cancer, ranging from 32% for patients with a tumour in the transverse colon to 63% for patients with a tumour in the proximal colon. For rectal cancer the completion rate was 73%.

Staging

Abdominal ultrasound was performed in 72% of colon cancer patients and 52% of rectal cancer patients. Thoracic X-ray was conducted in over 80% of colon and rectal cancer patients. A CT scan of the abdomen to detect abdominal or liver metastases was made for over half of the colon cancer patients and 64% of rectal cancer patients. A pelvic CT scan or MRI was performed for 36% of rectal cancer patients (Table 2). In almost all cases liver examination and slightly less often thoracic examination was performed (Table 3). Endorectal ultrasound was not used in the preoperative staging assessment of rectal cancer in 2005.

A total colon examination by means of a complete colonoscopy or an incomplete colonoscopy or sigmoidoscopy followed by contrast enema was performed in 60% of colon cancer patients and 64% of rectal cancer patients (Table 4). The total colon examination rate ranged from 44% for patients with a tumour in the transverse colon to 66% for patients with a tumour in the distal colon.

Table 2: Adherence to clinical practice guidelines (2004-2005)[58] for diagnostic assessment of colorectal cancer patients in southern Netherlands, 2005 [a]

	Colon (n=257) (%)	Rectum (n=251) (%)
Assessment of family history (age <60 years)	81	80
Documentation of co-morbidity in clinical record	94	94
Physical examination reported [b]	86	82
Rectal examination reported	56	75
Assessment of Hb	97	96
Assessment of alkaline phosphatase level	77	77
Colonoscopy [c]	74	65
proximal and transverse colon	83	
distal colon	55	
Contrast enema in case of incomplete colonoscopy (colon cancer patients only, n=76)	33	-
Abdominal ultrasound	72	52
Thoracic X-ray	85	81
Abdominal CT scan	52	64
Pelvic CT scan or MRI	-	36
Tumour biopsy, unless specific radiological image [d]	84	94

[a] Patients who underwent urgent surgery were excluded; [b] For colon cancer patients 53% incomplete, rectal cancer 54%; [c] Completion rate of colonoscopy was 63% for proximal colon tumours, 32% for transverse colon tumours, 62% for distal colon tumours, and 73% for rectal tumours; [d] At diagnostic endoscopy

Table 3: Diagnostic tests for colorectal cancer patients not mentioned in clinical practice guidelines

	Colon (n=257) (%)	Rectum (n=251) (%)
Sigmoidoscopy (in case of no colonoscopy)	57 (n=68)	94 (n=88)
Assessment of CEA	58	70
Assessment of GGT	75	74
Liver examination [a]	93	94
Thoracic examination [b]	89	88
Liver and thoracic examination	84	85
Abdominal ultrasound and thoracic X-ray	62	45

[a] By means of abdominal ultrasound and/or CT abdomen; [b] By means of thoracic X-ray and/or CT thorax

Large variation in diagnostic assessment was found between hospitals. Colonoscopy performance rate ranged from 59% to 85% (p=0.0082), thoracic examination rate ranged from 77% to 94% (p=0.0042), and liver examination rate ranged from 87% to 98% (p=0.1152). No difference in diagnostic assessment was seen between patients with unknown metastatic stage (Mx) and the total study population (results not shown).

Table 4: Tumour detection method for colorectal cancer patients in southern Netherlands in 2005

Tumour detection method	Colon (n=257) (%)	Rectum (n=251) (%)
Complete colonoscopy	39	43
Incomplete colonoscopy and contrast enema	11	6
Incomplete colonoscopy alone	20	12
Sigmoidoscopy	6	18
Sigmoidoscopy and contrast enema	10	15
Contrast enema alone	4	1
No endoscopy and no contrast enema	7	1
Colonoscopy completeness unknown	4	4

Among patients with stage I-III disease colonoscopy was done more often (79% of colon and 66% of rectal cancer patients) compared to all patients (stage I-IV). Hardly any differences were found in guideline adherence between younger and older CRC patients (<70 years vs. ≥70 years), except for the CT scan of the abdomen which was performed more often among younger colon cancer patients (results not shown). For patients with incomplete imaging, tumour size, stage, and comorbidity were similar to those with complete imaging. However, colon cancer patients with incomplete imaging were somewhat older compared to the total study population (74 vs. 71 years).

Determinants of colonoscopy completeness

Sixty-four percent of the colonoscopies were complete. Significant determinants of incomplete colonoscopy were large tumours, presence of distant metastases, a tumour located in the transverse colon, and having a co-morbid condition (Table 5). Poor bowel preparation also negatively influenced colonoscopy completeness. After adjustment for all variables listed in table 5, large tumours, which are often obstructing tumours, tumours located in the transverse colon, and a co-morbid condition remained significant determinants for colonoscopy incompleteness (Table 5). Poor bowel preparation also remained highly significant ($OR_{poor\ vs\ good,\ adjusted}$: 0.27 (95% CI 0.1-0.7). Patients with cardiovascular or gastrointestinal disease were more likely to have an incomplete colonoscopy. Similar results were found when the analyses were restricted to patients with good bowel preparation (good visualisation of the colon) (n=261), although co-morbidity was then no longer a significant determinant of colonoscopy completeness (data not shown). Differences in completeness rates between younger and older patients (<70 years and ≥70 years) were small. The main reasons for incomplete colonoscopy were obstruction by tumour (equally over the subsites in the colon and rectum) (79%) and poor preparation (8%), although poor preparation may be caused by obstruction by the tumour (Table 6).

Table 5: Logistic regression analysis with all patients with CRC who underwent a colonoscopy (n=324)

	Complete vs. incomplete colonoscopy		
	Number of patients	OR (95% CI)	OR (95% CI)
		Univariable	Multivariable [a]
Age (yrs)			
<70	182	1.00	1.00
≥70	142	1.38 (0.87-2.19)	1.01 (0.58-1.76)
Gender			
male	167	1.00	1.00
female	157	0.86 (0.55-1.36)	0.76 (0.58-1.76)
Comorbidity [b]			
none	112	1.00	1.00
1	102	0.55 (0.32-0.94)*	0.48 (0.26-0.90)*
≥2	89	0.70 (0.40-1.24)	0.68 (0.34-1.35)
Socioeconomic status			
low	68	1.07 (0.58-1.96)	1.15 (0.58-2.29)
intermediate	120	1.08 (0.65-1.80)	1.07 (0.61-1.88)
high	112	1.00	1.00
Subsite			
proximal colon	99	0.64 (0.37-1.10)	0.89 (0.49-1.63)
transverse colon	31	0.18 (0.08-0.42)*	0.23 (0.10-0.57)*
distal colon	42	0.62 (0.30-1.27)	0.74 (0.34-1.63)
rectum	148	1.00	1.00
T stage			
1	21	4.17 (1.19-14.56)*	3.32 (0.88-12.6)
2	62	3.22 (1.59-6.51)*	2.74 (1.29-5.83)*
3	156	1.00	1.00
4	19	0.51 (0.20-1.31)	0.42 (0.14-1.22)
M stage			
0	211	1.00	1.00
1	67	0.18 (0.04-0.90)*	0.71 (0.39-1.31)
X	46	1.02 (0.57-1.84)	1.28 (0.59-2.79)
Endoscopist			
gastroenterologist	265	1.00	1.00
internist	39	1.10 (0.54-2.24)	0.94 (0.42-2.12)
surgeon	7	0.55 (0.11-2.78)	1.03 (0.17-6.33)
Hospital			
reference	68	1.00	1.00
1	60	1.09 (0.53-2.27)	1.48 (0.62-3.53)
2	43	0.83 (0.38-1.84)	1.04 (0.44-2.49)
3	54	1.30 (0.60-2.79)	1.56 (0.66-3.78)
4	57	0.70 (0.34-1.44)	0.89 (0.39-2.02)
5	42	1.09 (0.48-2.46)	1.20 (0.49-2.93)

[a] Adjusted for age, gender, comorbidity, socioeconomic status, subsite (ascending and transverse colon/descending colon and sigmoid/rectum), T stage, M stage, endoscopist, and hospital; [b] Excluding hypertension

* p-value < 0.05

Table 6: Reasons for incomplete colonoscopy

Reason	Number of patients	%
Obstruction by tumour	106	79
Poor preparation	10	8
Discomfort patient	5	4
Looping and reduced mobility	4	3
Other	9	7

Discussion

In this study we demonstrated an improvable adherence to clinical practice guidelines for diagnostic assessment of CRC. Colonoscopy performance is improvable, with tumour obstruction as the main reason for colonoscopy incompleteness. Improvements appear possible; especially in the performance of imaging procedures like contrast enema and thoracic X-ray or CT scans. Just over 60% of the CRC patients had a total colon examination preoperatively. Furthermore, we found that patients with large tumours or a co-morbid condition were at higher risk of incomplete colonoscopy. In general, adherence to clinical practice guidelines increased between 2002 and 2005.

The majority of CRC patients who did not undergo colonoscopy underwent a sigmoidoscopy, especially those with rectal cancer. This is logical, since a colonoscopy cannot be performed when an obstructing tumour is detected by sigmoidoscopy. Additionally, in some cases the tumour was evident based on imaging techniques. Nevertheless, a complete colonoscopy is proclaimed to be the aim for all colon and rectal cancer patients.[137] When visualisation is incomplete, a contrast enema should be performed to detect synchronous polyps and tumours in colon cancer patients.[58] In our study, only 33% of colon cancer patients with incomplete colonoscopy underwent a contrast enema, compared to 27% in 2002.[141] However, the presence of a malignant stricture, the most common reason for incompleteness in our study, is a reason not to perform a contrast enema. Only 60% of the CRC patients had a complete colon examination, which is most likely caused by tumour obstruction. In these patients a postoperative colonoscopy should be performed.

Imaging procedures are preoperatively used to help plan treatment and to predict the circumferential resection margin among patients with rectal cancer.[145-147] Until now, little has been published about the proportion of patients who underwent imaging procedures according to clinical practice guidelines. In a population-based study of CRC patients diagnosed in 2002 in the same region, 73% of colon cancer and 82% of rectal cancer patients underwent an abdominal ultrasound and a thoracic X-ray.[141] In our study of CRC patients diagnosed in 2005 the percentage of patients who underwent both abdominal ultrasound and thoracic X-ray decreased to 62% for colon cancer and 45% for rectal cancer. However, newer imaging techniques like computed tomography (CT) have partly replaced

abdominal ultrasound and/or thoracic X-ray. This resulted in preoperative assessment of the liver and thorax of 94% and 89% respectively for CRC patients. In a British study conducted in 1999-2002, preoperative assessment of the liver occurred in 90% of colon cancer and 88% of rectal cancer patients with abdominal ultrasound, CT scan of the abdomen, or MRI abdomen.[148] These results are in accordance with our results, except for pelvic imaging which was much higher in the British study (91% of rectal cancer patients). A higher performance rate for imaging procedures was expected, since all patients should be screened for distant metastases.

The colonoscopy completion rates of 63% for proximal colon cancer, 32% for transverse colon cancer, 62% for distal colon cancer, and 73% for rectal cancer found in our study were fairly similar to proportions stated in literature. In an English study colonoscopy completion rates were 54% among patients with a tumour and 20% among patients with a malignant stricture before 2003.[142] In a population-based study conducted in the same region, a completion rate of 70% was found for CRC patients.[141] A population-based study in the province of Ontario, Canada showed a completion rate of 89% for patients with right-sided colon cancer,[140] which is comparable to our results for right-sided colon cancer (83%), and also similar to studies of clinical practice in England[149-152] and Ireland.[153] In two large Northern American clinical practice studies completion rates of 82% to 87% were found.[138, 139] The higher rates in studies using clinical practice data are probably caused by the diverse and often less severe indications for colonoscopy, since only about 4% of patients undergoing colonoscopy were diagnosed with cancer.[149] In US CRC screening programmes, completion rates as high as 97% were found,[48, 154, 155] although a lower rate of 91% was found in a recent study using data from a large colonoscopy-based screening program in Poland.[156] The results of these screening programmes are due to the relatively young, asymptomatic study population.

Besides the presence of a large tumour and a tumour in the transverse colon, comorbidity also affected incompleteness of colonoscopy, especially cardiovascular and gastrointestinal disease. An endoscopist is more likely to stop the colonoscopy in the case of fragile patients or patients who suffer during the procedure. Patients with gastrointestinal disease might have an increased sensitivity of the colon. Also, these patients might have already undergone one or more full colonoscopies prior to the endoscopic examination which led to the cancer diagnosis. Poor bowel preparation was also found to be a determinant of colonoscopy incompleteness, which is in agreement with the literature.[48, 139, 142, 149] Besides, poor bowel preparation is often related to the presence of an obstructing tumour. Tumours in the distal colon can often be seen with sigmoidoscopy, thus in case of an obstructing tumour colonoscopy is not performed, resulting in fewer incomplete colonoscopies. A higher patient age and female gender were not found to be significant predictors for incomplete colonoscopy in our study. This is in line with a

large US colonoscopy CRC screening study,[48] but contrary to a recent large population-based study[138] and US clinical practice studies.[143, 144]

In conclusion, improvements in adherence to diagnostic guidelines for CRC appear possible; especially in the performance of imaging procedures like contrast enema and thoracic X-ray or CT scans. Among patients where complete visualisation of the colon was not feasible with colonoscopy, imaging techniques such as virtual colonoscopy might be of added value in the near future.

Acknowledgements

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection.

Funding

This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588).

3.2.

Was there shortening of the interval between diagnosis and treatment of colorectal cancer in southern Netherlands between 2005 and 2008?

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World J Surg 2010 Feb 25 epub

Abstract

Background: The Dutch Cancer Society proposed that the interval between diagnosis and start of treatment should be less than 15 working days. The purpose of this study was to determine whether the interval from diagnosis to treatment for patients with colorectal cancer (CRC) shortened between 2005 and 2008 in hospitals in southern Netherlands.

Methods: Patients with CRC diagnosed in six hospitals in southern Netherlands during January to December in 2005 (n=445) and January to July in 2008 (n=353) were included. The time between diagnosis and start of treatment was assessed, and the proportion of patients treated within the recommended time (<15 working days) was calculated.

Results: The time to treatment for colon cancer patients was 13 working days in 2005 and 17 working days in 2008. For rectal cancer patients, the median time to preoperative radiotherapy was 28 working days in 2005 and 30 working days in 2008, and the median time to surgical treatment for rectal cancer patients was 26 working days in 2005 and 18 working days in 2008. Time to treatment did not shorten between 2005 and 2008 for colon and rectal cancer patients, except for rectal cancer patients who underwent surgery as initial treatment in patients aged >70 years and those with stage I disease. Substantial variation was seen among hospitals.

Conclusion: Time to treatment for patients with CRC in southern Netherlands did not shorten between 2005 and 2008. The time to treatment should be reduced to meet the advice of the Dutch Cancer Society.

Keywords: colorectal cancer, time to treatment, variation

Introduction

Colorectal cancer (CRC) is the third most frequent cancer in the Netherlands with more than 11,000 new cases annually and a lifetime risk of more than 5%.[1] Over a period of more than two decades, a clear improvement in survival of patients with CRC was attained by earlier detection due to a lower barrier for endoscopy, better staging, improved surgery, and combined-modality treatment.[77, 108] Most of these patients still present with symptomatic disease, because population-based screening has not yet been implemented in the Netherlands.

Since 2000, guidelines in Dutch specialized care ('Treeknormen') indicate that the time from diagnosis to start of clinical treatment should be within 35 days for 80% of patients and within 49 days for all patients.[157] For patients with life-threatening disease including cancer, a Dutch Cancer Society working group (consisting of medical specialists, social medicine specialists, and an economist) proposed in 2005 that the interval between diagnosis and treatment of cancer should be less than 15 working days,[158] more or less in agreement with several other countries, including Denmark and the United Kingdom.[159, 160] To decrease the interval between diagnosis and treatment a project called 'Sneller Beter' ('Getting Well Faster') was started in November 2003 in the Netherlands funded by the Ministry of Health.[161]

It is arbitrary to what degree treatment delay contributes to disease stage at presentation.[162] However, a longer time interval from diagnosis to treatment might have a negative effect on the patient's psychological well-being,[163, 164] which may affect the physical condition of the patient. Symptoms or clusters of symptoms might affect the interval between diagnosis and treatment, as symptoms are related to the severity of the disease.[165]

The purpose of this study was to determine whether the time from diagnosis to treatment for patients with CRC shortened between 2005 and 2008 in hospitals in southern Netherlands.

Methods

Data collection

Population-based data from the Eindhoven Cancer Registry (ECR), which is maintained by the Comprehensive Cancer Centre South, were used. The ECR collects data for all patients newly diagnosed with cancer in the southern part of the Netherlands. The ECR serves ten community hospitals, six pathology departments, and two radiotherapy institutes in an area comprising 2.3 million inhabitants. Information on diagnosis, staging, and treatment is obtained routinely from the medical records.[107] In addition, information on comorbidity has been collected since 1993 based on the Charlson comorbidity index.[66] Socioeconomic status, based on individuals' fiscal data on the economic value of the home and

household income, is provided at an aggregated level for each postal code.[67] The quality of the data is high because of thorough training of the registrars and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[80]

Study population

For the present study 445 patients with primary CRC diagnosed in 2005 and 353 patients with primary CRC diagnosed between January 1, 2008 and August 1, 2008 in six hospitals in southern Netherlands were included. All patients underwent resection of their tumour or radiotherapy treatment within 6 months after diagnosis. Patients with previous cancer (n=137) or who underwent acute resection (n=34) were excluded. Colon cancer was defined as C18, rectal cancer as C19-C20 according to the International Classification of Diseases for Oncology 03.[64] Tumour localization was categorized into anatomic subsites: proximal colon, consisting of the coecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0-C18.5); distal colon, consisting of descending colon and sigmoid (C18.6-C18.7); colon not otherwise specified (NOS) (C18.8, C18.9); and rectum, consisting of rectosigmoid and rectum (C19.9, C20.9).

The TNM stage was based on the pathological stage and the clinical stage when the pathological stage was unknown, as clinical stage alone was unknown for many patients. Date of diagnosis was defined as the date of histological verification of the tumour. Time to treatment was defined as the time interval between the histologically confirmed diagnosis and the start of initial treatment, which is surgical resection, except for those undergoing preoperative radiotherapy. Non-elective surgical treatment was defined as surgery and diagnosis on the same day. The starting date of radiotherapy was obtained from both radiotherapy institutes in the ECR region.

Additional data were extracted from the medical records by one of the authors (L.N.S) and a research assistant, under supervision of the treating physicians. This included date of imaging procedures and date of surgery. Imaging procedures included thoracic radiography, abdominal ultrasonography (US), abdominal computed tomography (CT), and magnetic resonance imaging (MRI). For patients diagnosed in 2005, symptoms were registered based on the medical record, with a maximum of four symptoms per patient. An early-stage cluster was created that contained patients who had rectal blood loss, mucus in stool, or no complaints. Data about radiotherapy including starting date of treatment and date of registration at the institute were obtained from the radiotherapy institutes.

Statistical analysis

Time between the diagnosis of CRC and imaging procedures, surgery, and radiotherapy was assessed. Variation in time between diagnosis and treatment was determined per age group (<70 years and ≥70 years), stage, socioeconomic

status, comorbidity, and hospital. The Mann-Whitney test was conducted to test whether the time between diagnosis and treatment differed markedly between predefined groups of patients. Furthermore, the time between diagnosis and treatment was described for symptoms. The proportion of patients who were treated within the time recommended by the Dutch Cancer Society advice were compared between 2005 and 2008.

Survival time was defined as the time from diagnosis to death or January 1, 2009 for the patients who were still alive. A crude 5-year survival rate was calculated, and a log-rank test was carried out to compare survival proportions. A multivariable proportional hazards regression analysis was used to discriminate independent risk factors for death (SAS system 9.1; SAS Institute, Cary, NC, USA). A value of $p<0.05$ was considered statistically significant.

Results

Colon cancer patients diagnosed in 2005 and 2008 were similar in age, socioeconomic status, comorbidity, stage, and timing of surgical treatment. However, those diagnosed in 2008 more often had a tumour located in the distal colon, and the pathologic lymph node status differed. The mean age of patients with colon cancer was 71 years (range 36-91 years), and almost half them suffered from one or more comorbid conditions. Most of the patients had a T3 tumour, and 16% of those diagnosed in 2005 and 11% diagnosed in 2008 had metastatic disease at diagnosis (Table 1).

Most of the rectal cancer patients underwent preoperative radiotherapy. In 2005 the age of rectal cancer patients who did and those who did not undergo preoperative radiotherapy was similar, whereas in 2008 those who underwent preoperative radiotherapy were younger (65 vs. 74 years). In 2008 almost none who underwent radiotherapy had a tumour in the rectosigmoid, whereas 8% did so in 2005. Socioeconomic status, comorbidity, and stage were similar for rectal cancer patients between 2005 and 2008 (Table 2).

For patients with colon cancer the median time to treatment was 13 working days in 2005 and 17 working days in 2008 (Figure 1a). Excluding those who underwent non-elective surgery in 2005 (n=49), the median time to treatment was 20 working days. No differences were found in time to treatment between subgroups of colon cancer patients in 2005, except for hospital of diagnosis and stage of disease. The median time to treatment varied substantially among hospitals, ranging from 5 to 28 working days in 2005. Time to treatment decreased in 2005 with increasing stage, ranging from 21 working days for stage I to 4 working days for stage IV. In 2008 similar results were found, with a significantly longer time to treatment for patients with comorbidity. No differences in time to treatment were found for colon cancer patients between 2005 and 2008, except for one hospital where the time to treatment increased from 5 working days in 2005 to 16 working days in 2008 (Table 3).

Table 1: Descriptives of the study population: colon cancer [a]

	2005 (n=177)		2008 (n=219)	
	n	%	n	%
Age (mean (range)) (yrs)	70 (72-89)		71 (38-94)	
Gender (male)	92	52	110	50
Socioeconomic status				
low	42	24	50	23
intermediate	61	35	84	38
high	64	36	68	31
institutionalized	7	4	8	4
unknown	3	2	9	4
Comorbidity [b]				
none	72	41	106	48
1	51	29	49	22
≥2	42	24	55	25
unknown	12	7	9	4
Tumour site				
proximal colon	122	69	122	56**
distal colon	52	29	96	43
colon other/NOS	3	2	1	1
Pathologic T stage [c]				
1	9	5	17	8
2	24	14	32	15
3	115	65	132	60
4	27	15	29	13
unknown	2	1	9	4
Pathologic N stage				
N0	103	58	113	52*
N+	70	40	90	41
unknown	4	2	16	7
M stage				
0	126	71	172	79
1	29	16	24	11
unknown	22	12	23	11
TNM stage				
I	29	16	39	18
II	66	37	77	35
III	51	29	72	33
IV	29	16	24	11
unknown	2	1	7	3
Timing of surgical treatment				
elective	128	72	157	72
non-elective [d]	49	28	62	28

NOS: Not otherwise specified

[a] No patients with previous cancer; [b] Excluding hypertension, as it is generally a minor comorbidity; [c] If the pathologic stage was unknown, the clinical stage was used; [d] Non-elective was defined as surgery on the same day as the diagnosis

* $p<0.05$ between 2005 and 2008; ** $p<0.0001$ between 2005 and 2008

Table 2: Descriptives of the study population: rectal cancer [a]

	2005 (n=186)				2008 (n=134)			
	No preopRT (n=46)		PreopRT (n=140)		No preopRT (n=27)		PreopRT (n=107)	
	n	%	n	%	n	%	n	%
Age (mean (range)) (yrs)	69 (36-85)		68 (33-90)		74 (58-94)*		65 (31-93)	
Gender (male)	23	50	76	55	21	78*	63	59
Socioeconomic status								
low	8	17	27	19	6	22	22	20
intermediate	12	26	59	42	6	22	49	46
high	20	43	45	32	11	41	34	32
institutionalized	5	11	7	5	2	7	1	1
unknown	1	2	2	1	2	7	1	1
Comorbidity [b]								
none	27	59	65	46	12	44	57	53
1	12	26	40	29	8	30	24	22
≥2	6	13	24	17	7	26	22	21
unknown	1	2	11	8	0	0	4	4
Tumour site								
rectosigmoid	19	41	11	8	6	22**	2	2**
rectum	27	59	129	92	21	78	105	98
Pathologic T stage [c]								
1	5	11	4	3	5	19	5	5
2	14	30	46	33	8	30	32	30
3	25	54	73	52	14	52	50	47
4	2	4	10	7	0	0	8	7
unknown	0	0	7	5	0	0	12	11
Pathologic N stage								
N0	21	46	88	63	12	44	62	58
N+	20	43	45	32	9	33	31	29
unknown	5	11	7	5	6	22	14	13
M stage								
0	33	72	106	76	22	81	84	79
1	7	15	22	16	5	19	11	10
unknown	6	13	12	8	0	0	12	11
TNM stage								
I	15	33	42	30	12	44	27	25
II	10	22	37	26	6	22	32	30
III	14	30	35	25	9	33	28	26
IV	7	15	22	16	0	0	11	10
unknown	0	0	4	3	0	0	9	8
Timing of surgical treatment								
elective	43	93	140	100	18	67*	107	100
non-elective [d]	3	7	0	0	9	33	0	0

PreopRT: preoperative radiotherapy

[a] No patients with previous cancer; [b] Excluding hypertension, as it is generally a minor comorbidity; [c] If pathologic stage was unknown, the clinical stage was used; [d] Non-elective was defined as surgery on the same day as the diagnosis

*p < 0.05 between 2005 and 2005; **p<0.0001 between 2005 and 2008

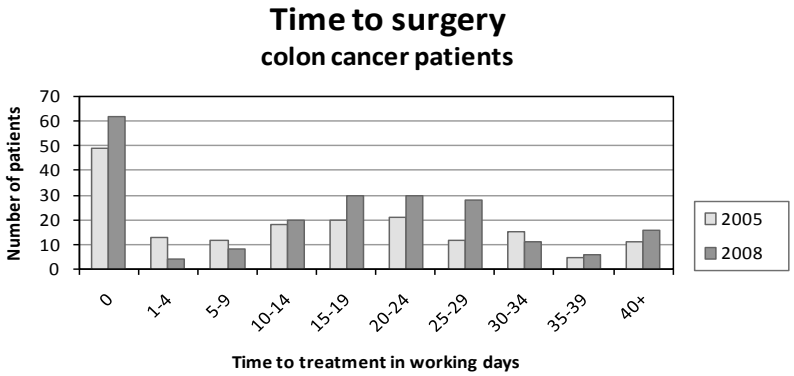

Figure 1a: Time from diagnosis to start of treatment, colon cancer patients

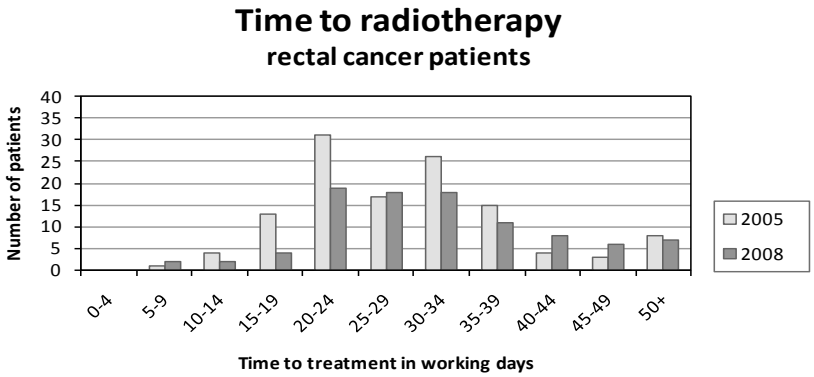

Figure 1b: Time from diagnosis to start of treatment, rectal cancer patients receiving preoperative radiotherapy

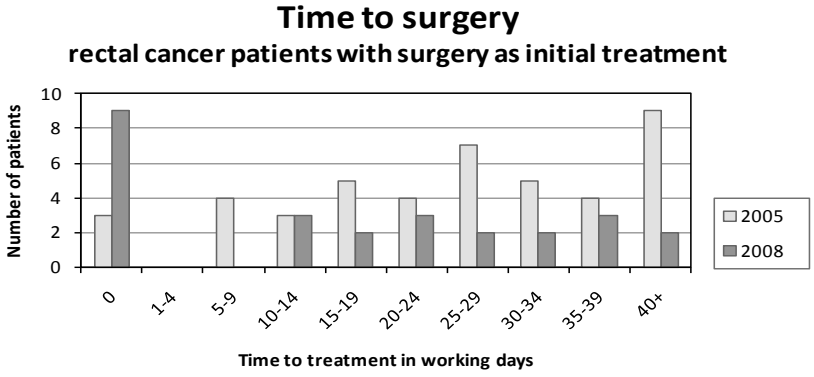

Figure 1c: Time from diagnosis to start of treatment, rectal cancer patients with surgery as initial treatment

Table 3: Time from diagnosis to first treatment (in working days): colon cancer patients

	2005		2008	
	n	Median (5%-95% range) (working days)	n	Median (5%-95% range) (working days)
Overall	171	13 (0-40)	215	17 (0-43)
Age group (yrs)				
<70	71	13 (0-40)	96	15 (0-43)
≥70	100	13 (0-40)	119	18 (0-44)
Stage				
I	26	21 (9-40)	39	21 (0-44)
II	66	16 (0-35)	75	16 (0-36)
III	51	12 (1-37)	72	18 (0-34)
IV	27	4 (0-32)	22	9 (0-30)
unknown	1	n.a.	7	n.a.
Socioeconomic status				
low	42	13 (0-33)	50	17 (0-44)
intermediate	59	12 (0-55)	82	21 (0-43)
high	60	15 (0-37)	66	16 (0-43)
institutionalized	7	14 (0-53)	8	0 (0-28)
unknown	3	n.a.	9	18 (0-49)
Comorbidity				
0	70	14 (0-38)	104	17 (0-43)*
1	51	13 (0-40)	48	17 (0-32)
≥2	39	12 (0-40)	54	19 (0-48)
missing	11	24 (0-76)	9	n.a.
Hospital				
1	26	13 (0-31)*	28	13 (0-42)
2	28	12 (0-28)	46	17 (0-34)
3	27	13 (0-70)	28	18 (0-30)
4	37	28 (0-55)	37	20 (0-66)
5	20	6 (0-41)	15	17 (0-60)
6	33	5 (0-27)	61	16 (0-43)[&]

* $p<0.05$ between hospitals in 2005; [&] $p=0.02$ between 2005 and 2008

For patients with rectal cancer, the median time to preoperative radiotherapy (mainly 5x5 Gy) was similar: 28 working days in 2005 and 30 working days in 2008 (Figure 1b). In 2005 the time to surgery as initial treatment was 26 working days, whereas it in 2008 was 18 working days (Figure 1c). No significant differences were found for subgroups of patients with rectal cancer who underwent preoperative radiotherapy in 2005, but there was a significant difference between hospitals in 2008, ranging from 24 to 38 working days.

Furthermore, a significant increase in time to treatment was found in one hospital. The number of patients with rectal cancer who did not undergo preoperative radiotherapy was small. However, a significant decrease in time to treatment was found between 2005 and 2008 for elderly patients (≥70 years). Similarly, a reduced time to treatment for patients with stage I rectal cancer was

found in 2008 compared to that in 2005. For patients with rectal cancer who underwent preoperative radiotherapy, the median time from diagnosis to registration at the radiotherapy institute was 17 working days (5%-95% range: 5-35 working days) and the median time from registration to start of radiotherapy was 10 working days (5%-95% range: 4-18 working days) in 2005. The median time between start of preoperative radiotherapy and surgery was 7 (5%-95% range: 5-67 working days) in 2005. Similar time intervals were found for 2008. No significant difference was found in time to treatment between the two radiotherapy institutes, although the time to treatment differed by 7 working days between the two radiotherapy institutes in 2008 (Table 4).

In 2005, imaging procedures for diagnostic purposes of CRC largely consisted of thoracic radiography and abdominal US, which were usually conducted 6 to 8 working days after diagnosis. Abdominal and thoracic CT were used more often for CRC patients in 2008 than in 2005. The use of pelvic MRI increased from 39% in 2005 to 66% in 2008 for patients with rectal cancer (Table 5). The time from diagnosis to abdominal and/or thoracic CT was usually 7 working days for CRC patients in 2008, whereas abdominal US and thoracic radiography were usually conducted 4 working days after diagnosis in 2008.

Table 5: Percentages of CT and MRI diagnostic imaging in colon and rectal cancer patients

	2005 (%)	2008 (%)
Colon		
abdominal CT	49	68
thoracic CT	14	26
Rectum		
abdominal CT	61	75
thoracic CT	20	46
pelvic MRI	39	66

CT: computed tomography, MRI: magnetic resonance imaging

In patients with colon cancer, the time to treatment varied by the symptoms at diagnosis, being around 5 working days (5%-95% range: 0-35 working days) for patients with severe symptoms such as diarrhoea, weight loss, and abdominal pain. Patients with symptoms clustered in the early-stage cluster had a time to treatment interval of 21 working days (5%-95% range: 0-38 working days). A less clear pattern was found for rectal cancer (data not shown).

The time to treatment was less than 15 working days in 45% of colon cancer patients in 2008, whereas the corresponding figure was 53% in 2005. Preoperative radiotherapy was given to 4% of rectal cancer patients within 15 working days in both 2005 and 2008. A significantly higher proportion of rectal cancer patients received initial surgery within 15 working days (23% vs. 46%; p=0.04) (Table 6).

Table 4: Time from diagnosis to first treatment (in working days): rectal cancer patients

	2005				2008			
	No preopRT		PreopRT		No preopRT		PreopRT	
	n	Median (5%-95% range) (working days)	n	Median (5%-95% range) (working days)	n	Median (5%-95% range) (working days)	n	Median (5%-95% range) (working days)
Overall	41	26 (0-76)	125	28 (15-53)	26	18 (0-68)	95	30 (13-52)
Age group (yrs)								
<70	20	19 (0-61)	52	30 (16-62)	9	29 (0-37)	60	30 (16-52)
≥70	21	32 (11-79)	73	25 (15-80)	17	10 (0-98)[&]	35	29 (16-59)
Stage								
I	13	33 (0-97)	38	30 (19-60)	11	13 (0-37)[&]	23	32 (19-52)
II	8	27 (0-36)	33	28 (15-95)	6	22 (0-98)	30	29 (20-47)
III	13	24 (0-76)	29	24 (13-43)	9	19 (0-68)	25	28 (16-47)
IV	7	15 (5-26)	21	31 (14-61)	0	n.a.	9	37 (13-113)
unknown	0	n.a.	4	n.a.	0	n.a.	8	29 (8-46)
Socioeconomic status								
low	7	31 (0-97)	28	29 (16-84)	6	n.a.	21	28 (16-59)
intermediate	11	26 (5-47)	46	30 (13-60)	5		41	32 (20-47)
high	17	19 (0-81)	44	26 (18-45)	11		31	28 (19-45)
institutionalized	5	n.a.	5	n.a.	2		1	n.a.
missing	1	n.a.	0	n.a.	2		0	n.a.
Comorbidity								
0	25	25 (0-81)	62	28 (16-47)	12	13 (0-98)	52	30 (16-50)
1	10	33 (0-76)	38	31 (16-62)	7	19 (0-36)	19	30 (7-113)
≥2	5	n.a.	17	27 (14-84)	7	28 (0-68)	20	32 (20-69)
missing	1	n.a.	8	29 (13-220)	0		4	n.a.
Hospital								
1	6	30 (6-76)	24	24 (12-38)	2	n.a.	17	24 (11-44)*
2	6	23 (0-31)	15	36 (17-62)	6		15	30 (7-113)
3	2	n.a.	30	29 (15-60)	5		11	25 (16-59)
4	1	n.a.	24	30 (16-84)	1		14	29 (8-42)
5	14	35 (19-81)	17	31 (20-80)	4		11	28 (20-52)
6	12	20 (0-47)	15	23 (13-130)	8		27	38 (24-79)[&]
Radiotherapy institute								
1	-	-	45	30 (17-53)	-	-	51	32 (20-52)
2	-	-	77	27 (14-60)	-	-	44	25 (13-52)

* $p<0.05$ between hospitals in 2008; [&] $p<0.05$ between 2005 and 2008

Survival analysis showed that a shorter waiting time was not associated with an improved outcome (data not shown). After adjusting for tumour stage, differentiation grade, age, comorbidity, socioeconomic status, and gender in a multivariate proportional hazards regression analysis this result did not change (data not shown).

Table 6: Proportion of patients in whom treatment was started in time according to the 2005 Dutch Cancer Society advice (<15 working days)

	2005 (%)	2008 (%)
Colon cancer	53	45
Rectal cancer without preoperative radiotherapy	23	46*
Rectal cancer with preoperative radiotherapy	4	4

*p<0.05

Discussion

The Dutch Cancer Society working group (consisting of medical specialists, social medicine specialists, and an economist) proposed in 2005 that the interval between diagnosis and treatment of cancer should be less than 15 working days.[158] Based on our results from 2008, we can conclude that this advice seems far from feasible to adhere to in the southern Netherlands; 45% of colon cancer patients, 46% of rectal cancer patients with surgery as their initial treatment, and only 4% of patients with rectal cancer who underwent preoperative radiotherapy were treated within 15 working days in 2008. No shortening of the interval from diagnosis to treatment was seen between 2005 and 2008. Moreover, there was substantial variation in time to treatment among hospitals.

Little is published about time to treatment of CRC patients after diagnosis. However, in Denmark the median time interval from diagnosis to treatment was 9 days for colon cancer patients and 15 days for rectal cancer patients.[160] The Danish fast-track recommendations, introduced in 1998, stated that the time interval between diagnosis and treatment should be less than 14 days. In a large population-based study of CRC patients diagnosed during 2001-2002, these recommendations were poorly met; 79% of the colon cancer patients and 47% of rectal cancer patients started treatment within 14 days after diagnosis.[160] The UK government decided that from July 2000 all patients suspected by their general practitioner to have bowel cancer should be seen by a specialist within 2 weeks of the date of referral.[166] Although cancer patients referred to a 2 week standard clinic were seen more quickly, it did not reduce the overall time to treatment or stage of disease at surgery.[167] It is a good initiative to diagnose patients quickly, but it should be expanded to treatment to reduce the interval from diagnosis to start of treatment.

Although in recent years much attention has been paid to reducing the time to treatment in hospitals in the Netherlands, a shortening in time to treatment between 2005 and 2008 could not be observed. To decrease the interval between

diagnosis and treatment a project called 'Sneller Beter' ('Getting Well Faster') was started in November 2003 in the Netherlands funded by the Ministry of Health.[168] One of the results of this project was a reduction of 30 days (from 69 to 39 days) between first visit to the hospital and start of treatment, usually due to more efficient process reorganization.[169] In October 2004 two hospitals included in our study engaged in this project, which indeed resulted in quicker start of surgical treatment of colon cancer patients in 2005 compared to other hospitals in southern Netherlands. However, the advantage of these two hospitals had diminished in 2008. Another initiative to reduce time to treatment for CRC patients was the advice by the Dutch Cancer Society working group, which proposed in 2005 that all patients with cancer should be treated within 15 working days. Therefore, we expected a decrease in time to treatment between 2005 and 2008. A possible explanation for the lack of improvement is the increased incidence of CRC and the probably more severe and complicated comorbidities of the patients, which need to be managed before treatment can be started.

Imaging procedures for diagnostic assessment changed from largely abdominal US and thoracic radiography in 2005 to abdominal CT and thoracic radiography or thoracic CT in 2008. In addition, pelvic MRI was indicated for patients with rectal cancer in 2008. However, the results of our study indicate that it is unlikely that these changes are responsible for the lack of reduction in time to treatment: moreover the waiting time for a CT scan was similar to the waiting time for abdominal US and thoracic radiography in 2005.

Most patients with CRC diagnosed in 2005 or 2008 in southern Netherlands, especially those with rectal cancer, did not receive treatment within 15 working days. This can be attributed mainly to hospital factors, including logistics and multidisciplinary consultation. There are no quantitative data about the influence of delay on prognosis in the literature. The interpretation of different studies regarding the association between delay and prognosis is hampered by factors such as tumour stage and differentiation as well as patient priority.[162] Therefore, it is controversial to what degree the time to treatment contributes to stage of disease and therefore prognosis.[162]

We did not find a positive association between a short time interval from diagnosis to treatment and survival. Therefore, it can be assumed that other factors not addressed in this analysis – such as priority of a patient for start of treatment - are more important for survival than time to treatment. However, this does not mean that time to treatment is not important for the patients. CRC is a life-threatening disease, and a long time interval from diagnosis to treatment might cause enormous stress for cancer patients. Such stress can result in deterioration of the patient's health, condition, and well-being,[163, 164] which may affect his or her physical condition, in turn resulting in more complications and a longer hospital stay. Therefore, reducing time to treatment can reduce health care costs. Furthermore, patients are generally more satisfied when they are treated soon after being diagnosed, which results in a better working environment for health

care workers and increases the quality of the overall health care system. In addition, based on tumour biology it is important to keep time to treatment as short as possible. It can be assumed that in a large proportion of patients a long time to treatment results in deterioration of the prognosis. Therefore, the time from diagnosis to treatment should be minimized.

It seems far from feasible to follow exactly the current advice of the Dutch Cancer Society in most of our CRC patients. Therefore, we propose new advice based on the general guidelines for time to treatment in Dutch specialized care and the results of this study. Guidelines in Dutch specialized care reveal a time to treatment from diagnosis to start of clinical treatment within 35 days for 80% of patients and within 49 days for all patients.[158] Cancer patients, however, suffer from a life-threatening disease and should definitely be treated within this time. Moreover, they experience a lot of stress and uncertainty during the time to treatment. Therefore, we propose that the time from diagnosis to start of treatment should be an interval of less than 20 working days. According to this rule, 58% of colon cancer patients, 50% of rectal cancer patients with surgery as their initial treatment, and 9% of rectal cancer patients who will undergo preoperative radiotherapy can meet the adviced conditions.

Based on our results, there seems to be no reduction in time to treatment for patients with CRC in southern Netherlands between 2005 and 2008. Attention and effort should be paid to reducing time to treatment, which is especially valuable in view of the increasing proportion of patients with CRC due to the aging population and the introduction of population mass screening for CRC in the near future.

Acknowledgements

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection.

Funding

This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588).

3.3.

Improving lymph node detection in colon cancer in community hospitals and their pathology department in southern Netherlands

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Eur J Surg Oncol 2010; 36: 135-140

Abstract

Objective: The aim was to investigate whether a set of measures directed at increasing lymph node (LN) detection among colon cancer patients led to clinically relevant changes in LN detection rate.

Methods: Data of all patients with curative colon cancer (pT_{any} N_{any} M0) diagnosed in 1999-2007 whose resection specimens were evaluated by the Institute for Pathology and Medical Microbiology in Eindhoven, (n=1,501) were included. Feedback to specialists, increased fixation time, and ex-vivo injection of the specimen with Patent blue V dye were used to increase LN detection rate. Trends in the proportion of patients with insufficient LNs examined were investigated; moreover, the Patent blue stained patients (n=86) were compared with a group of unstained patients (n=84). Based on the decrease in the proportion of high-risk node-negative patients, a calculation of chemotherapy-related costs saved was made.

Results: The proportion of patients with <12 LNs examined decreased from 87% in 1999 to 48% in 2007 (p_{trend}<0.0001). In the stained group this was 37%, versus 56% for the unstained group (p=0.010). In 1999, 79% of stage II patients were high-risk compared to 55% in 2007, which translates to a saving of almost 1,000,000 euro based on 92 stage II patients diagnosed in 2007.

Conclusion: A diverse set of measures increased the number of examined lymph nodes among patients with colon cancer. Large savings can be made due to the reduced proportion of high-risk node-negative patients who would otherwise have received adjuvant chemotherapy.

Keywords: colon cancer, cost-effectiveness, lymph node detection, Patent blue V, trend

Introduction

Colon cancer is one of the most frequent cancers in the Netherlands with over 6,000 new cases annually.[1] In 2007 over 3,800 patients died of colon cancer.[2] Resection of the tumour with adequate margins and the associated mesentery, including draining lymph nodes, is the primary modality of treatment of colon cancer. Generally, only patients with positive lymph nodes benefit from adjuvant chemotherapy.[38] Therefore, lymph node analysis is one of the critical factors for therapeutic decision-making. A minimum number of 12 identified lymph nodes is defined as adequate assessment by the International Union Against Cancer (UICC). Recently, in the Netherlands the minimum number of lymph nodes that should be examined was reduced to 10.[58]

The 5-year survival for patients with pT3-4 N0 M0 (stage II) is approximately 59%, versus only 42% for pT_{any} N+ M0 (stage III) patients.[170] For obvious reasons, high-risk nodenegative patients often receive adjuvant chemotherapy. The Dutch guidelines define high risk as stage II patients with pT4 or poorly differentiated tumours, tumours with angio-invasion, or patients with fewer than 10 lymph nodes evaluated.[58] Recently, the QUASAR trial showed a small survival benefit for these patients compared to high-risk node-negative patients who were not treated with adjuvant chemotherapy.[171] However, a proportion of patients with an insufficient number of lymph nodes examined truly has negative lymph nodes and has received adjuvant chemotherapy unnecessarily. Besides avoiding the potential burden of this treatment for the individual patient, large savings could be made by reducing the proportion of patients eligible for chemotherapy.

The number of lymph nodes examined in colon cancer patients in southern Netherlands is often inadequate, since 70% of the patients had fewer than 12 lymph nodes examined.[172] This was communicated to these departments by means of individual feedback, discussions in multidisciplinary working groups and educational presentations, which increased awareness and resulted in an increased fixation time which has shown to improve lymph node detection.[173] Besides, a subset of colon specimens were injected ex-vivo with Patent blue V dye in the mesocolon next to the tumour. The purpose of this study was to investigate whether this set of measures directed at increasing lymph node detection among colon cancer patients since 1999 led to clinically relevant changes in lymph node detection rate, and to evaluate the costs saved by these interventions.

Materials and methods

Data collection and patients

Population-based data from the Eindhoven Cancer Registry (ECR), which is maintained by the Comprehensive Cancer Centre South, was used to investigate the trend in lymph nodes examined and to select a control group for the comparison with the Patent blue stained group. The ECR collects data on all patients newly diagnosed with cancer in the southern part of the Netherlands. Information about patient characteristics, such as gender and date of birth, and tumour characteristics, such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3)), grade, pathological stage, and number of lymph nodes examined were recorded. Tumour subsite was categorized into two sites; proximal colon, consisting of tumours in the coecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0-C18.5); and distal colon consisting of tumours in the descending colon and sigmoid colon (C18.6-C18.7). This information is obtained routinely from the medical records. The quality of the data is high, due to thorough training of the registration team and computerized consistency checks at regional and national levels. Completeness has been estimated to be at least 95%.[80]

All cases of primary colon cancer stage I to III (pT_{any} N_{any} M0) registered between 1999 and 2007 treated in one of the hospitals served by the regional department of pathology in Eindhoven were included in the lymph node detection trend analysis (n=1,501). For the Patent blue-staining study 86 consecutive patients who underwent elective or nonelective curative surgical resection for colon cancer between May 2007 and February 2008 were included as cases. A subset of 84 patients from the ECR evaluated at the Department of Pathology in Eindhoven and diagnosed in 2007, whose specimen were not stained, was used as the control group for the Patent blue staining study. These were patients who underwent surgery in 2007 before the start of the study and patients who were missed due to logistic reasons. All patients included in the Patent blue staining study, both cases and controls, underwent a standard surgical resection and lymphadenectomy according to the location of the tumour. Patients with rectal cancer were not included, since lymph node detection in rectal cancer is hindered by neoadjuvant treatment.

Immediately after resection, the surgeon injected 0.25-1.0 ml of Patent blue dye V in the mesocolon neighbourhood of the tumour. The injection site was gently massaged for 30 seconds. After 42-48 hours in 4% buffered formalin, the specimen was examined by a pathologist in the routine setting. Afterwards, the colon is cut transversally into slices 0.5 to 1.0 cm thick. All slices of the specimen were examined by the pathologist for lymph nodes, which were routinely processed for histological examination using conventional methods.

Statistical analysis

The median number of lymph nodes examined from 1999 to 2007 was assessed in order to determine the percentage of cases with insufficient lymph nodes examined. A Cochrane-Armitage trend test was used to investigate the trend in the proportion of patients with insufficient lymph nodes examined. Differences between the group who underwent the new lymph node technique and a control group with standard pathology examination were described, focusing mainly on the number of lymph nodes examined and tumour characteristics. Chi-square tests were conducted to test the differences in percentages of patients with insufficient lymph nodes evaluated. A Mann-Whitney test was conducted to test the difference in the number of lymph nodes examined between the Patent blue dye and the control group. SAS/STAT® statistical software (SAS system 9.1, SAS Institute, Cary, NC) was used for the analyses.

Results

The proportion of colon cancer patients with an insufficient (<12) number of lymph nodes examined decreased (p_{trend} <0.0001) (Figure 1). The proportion of patients with less than 10 lymph nodes examined decreased from 79% in 1999 to 35% in 2007. Considering patients with N0 stage only, resulted in a similar proportion of patients with insufficient lymph nodes examined.

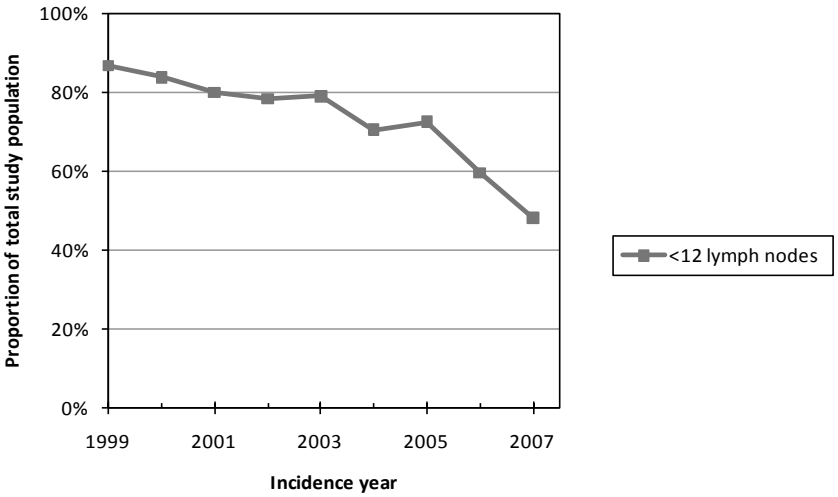

Figure 1: Colon cancer patients with an insufficient number of lymph nodes examined in the region of the Department of Pathology in Eindhoven since 1999 (n=1,501)

Patent blue-staining

The median age of the Patent blue-stained group was 73 years and 72 years for the control group. The control group contained slightly more patients with stage I disease and less stage II. In the Patent blue-stained group less tumours were located in the proximal colon compared to the control group. However, these differences were not found significant (Table 1).

Table 1: General characteristics for patients in the Patent blue stained study group and the control group

	Patent blue V stained group (n=86 (%))	Control group (n=84 (%))	p-value
Mean age (yrs)	71 (SD: 10)	70 (SD: 11)	0.6
Gender			
male	44 (51)	40 (48)	0.7
female	42 (49)	44 (52)	
Depth of penetration			0.1
pT1	4 (5)	9 (11)	
pT2	13 (15)	8 (9)	
pT3	58 (67)	46 (55)	
pT4	11 (13)	20 (24)	
Stage			0.7
I (pT1-2 N0 M0)	13 (15)	16 (19)	
II (pT3-4 N0 M0)	38 (44)	33 (39)	
III (pT_{any} N1-2 M0)	35 (41)	35 (42)	
Tumour site			0.3
proximal colon	44 (53) [a]	51 (61)	
distal colon	39 (47)	33 (39)	

[a] For 3 patients, tumour site was missing

The median number of lymph nodes examined in the Patent blue-stained group was significantly higher compared to the control group (Figure 2). In the Patent blue-stained group 37% of the patients had fewer than 12 lymph nodes examined, while this was significantly higher in the control group (Table 2). After excluding patients with a stage I (T1-2 N0 M0) tumour, the percentage of patients with fewer than 12 lymph nodes examined in the Patent blue-stained group was 37% and in the control group 47% (p=0.40).

With 10 lymph nodes as a cut-off point,[58] 21% of the patients in the Patent blue-stained group and 45% of the control patients had an insufficient number of lymph nodes examined (Table 2). No significant difference was found between the proportion of N+ patients in the Patent blue and the control group. Considering only patients with a pT3 colon tumour, 40% of patients in the Patent blue-stained group versus 34% of patients in the control group had fewer than 12 lymph nodes examined. (p=0.66) A median number of 15 (range 2-45) lymph nodes were examined for patients with a tumour in the proximal colon in the Patent blue-stained group and 13 for patients with a

tumour in the distal colon (results not shown). In the Patent blue-stained group as well as the unstained group, the majority of patients with insufficient lymph nodes examined had stage N0, especially in the categories of 6-8 and 9-11 lymph nodes examined (Figure 3).

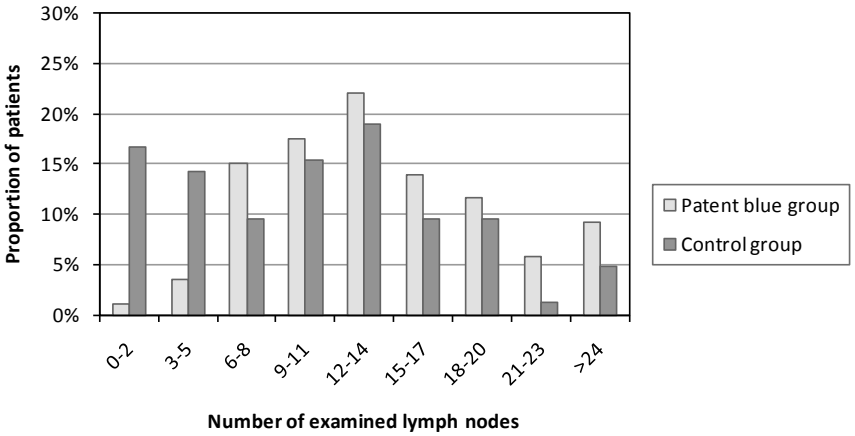

Figure 2: Number of lymph nodes examined in the Patent blue V stained group (n=86) and the control group (n=84)

Table 2: Lymph node involvement in newly diagnosed colon cancer patients in the Patent blue stained study group (n=86) and the control group (n=84)

	Patent blue V stained group (n=86)	Control group (n=84)	p-value
Median number of examined lymph nodes (range)	14 (2-45)	11 (0-39)	<0.0001
N0	51 (59%)	45 (56%)	0.7
N+	35 (41%)	35 [a] (44%)	
<10 lymph nodes examined	18 (21%)	38 (45%)	<0.0001
<12 lymph nodes examined	32 (37%)	47 (56%)	0.014

[a] In the control group 4 patients had Nx stage

Almost 70% of the lymph nodes examined coloured blue, whereas only 9% of the blue lymph nodes being positive in the total study population. In 69% of the N+ patient group non-stained positive lymph nodes were found; however the large majority (78%) of these patients also had blue-stained positive lymph nodes.

In 1999, 79% of the patients with stage II disease were N0 with fewer than 10 lymph nodes examined compared to 55% in 2007. According to the Dutch guidelines these patients are considered high-risk and should receive adjuvant chemotherapy at the cost of approximately €35,000 per person.[174, 175] Extrapolating these results to all patients diagnosed with colon cancer stage II in

the department of pathology in Eindhoven in 2007 (n=92), 22 patients would have been rendered ineligible for adjuvant chemotherapy, because of a sufficient lymph node detection. This would have saved about 22*€35,000 = €770,000 per 92 patients. One third of this saving can be attributed to the Patent blue staining. However, some patients might be upgraded from node negative to node positive and should receive chemotherapy anyway.

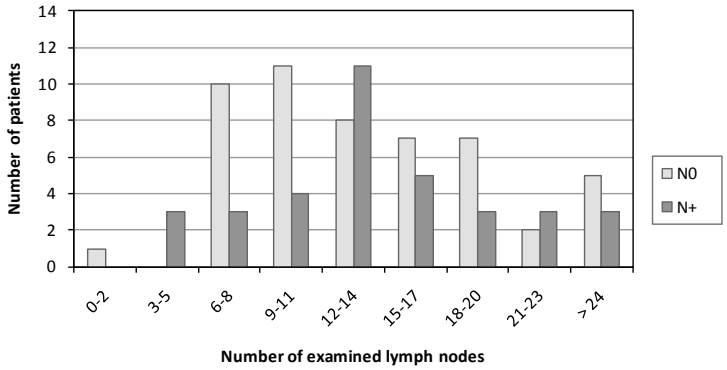

Figure 3: Number of lymph nodes examined in the Patent blue V stained group per N stage (n=86)

Discussion

We demonstrated a significant increase in the number of lymph nodes examined in colon cancer patients by a regional pathology department between 1999 and 2007. Staining the resection specimen ex-vivo with Patent blue V dye clearly increased lymph node detection in colon cancer patients, in addition to the gradual increase observed in the number of lymph nodes examined over time, especially after 2006 when fixation time was increased. In the Patent blue-stained group the median number of lymph nodes examined was higher compared to the control group. The proportion of patients with fewer than 12 lymph nodes decreased from 56% in the unstained control group to 37% in the Patent blue-stained group. Enormous chemotherapy-related savings could be attained by better lymph node detection, and therefore reducing the proportion of high-risk node-negative colon cancer patients. The Patent blue intervention was aimed at increasing the number of lymph nodes examined. The detection of a possible sentinel node was therefore not the aim of this study.

Lymph node detection in a population-based study of colon cancer patients diagnosed in 1999-2002 in southern Netherlands was poor with a median of 6 lymph nodes examined in the ECR region, with the median for the department of pathology in Eindhoven being 8.[172] This result was communicated to the departments of pathology in October 2005 in the region by means of individual feedback and discussions in multidisciplinary working groups. Educational

presentations create awareness among pathologists and surgeons, which result in an improvement in lymph node staging practice. To further increase the number of lymph nodes examined, several steps were taken by various regional pathology departments involved. In 2006 they increased fixation time to 42-48 hours, which has been reported by several studies to lead to an increase in lymph node detection.[173, 176] The closer collaboration between surgeons and pathologists was expressed in 2007 with the start of the Patent blue staining method in the department of pathology in Eindhoven described in this study. Other pathology departments in the ECR region also studied comparable methods to increase lymph node yield.[177] Population-based studies reported a median number of examined lymph nodes of 6 to 12 in the period between 1990 and 2005,[141, 172, 178-182] while single hospital studies reported median numbers up to 18.[183-185]

The experiences of the pathologists with the new staining technique varied and there was some resistance initially. However, this decreased when the technique was well implemented and the surgeons got more experience with the injection of Patent Blue V dye. Some pathologists emphasized the simplified detection of lymph nodes, due to the increased solidness and colouring of the lymph nodes. Whereas other pathologists preferred the traditional method with a more extensive search for lymph nodes to increase the detection rate. To reduce the workload for pathologists and to ensure adequate lymph node detection in the future, technicians will be trained to search for lymph nodes in the specimen.

There are several ways to increase the lymph node detection rate, including fat clearance methods[186] which are rather labour-intensive and hazardous chemicals are needed.[187] Re-fixation of a specimen in a lymph node-revealing solution resulted in a higher detection rate,[188] although it is an extra step for the pathologist. The median number of lymph nodes increased from 5 to 13[189] and from 10 to 17[190] with different modified fixatives. Another research group used a blue marking liquid injected into the rectal artery in 24 patients with rectal cancer with 27 lymph nodes examined in the stained group versus 14 in the controls.[191]

The Patent blue staining method did not change the stage distribution significantly. However, a larger proportion of patients had sufficient lymph nodes examined. Three-year overall survival for stage II patients with sufficient compared to stage II patients with insufficient lymph nodes examined in 1999-2007 in the ECR region was 83% vs. 69%. At hospital level, number of lymph nodes examined was not associated with stage distribution or use of adjuvant chemotherapy.[184, 192] However, at the patient level, higher lymph node count was associated with improved survival, relative to fewer than 12 nodes.[193]

The lymph node detection rate is not only affected by the thoroughness of the surgeon during the lymphadenectomy to remove all potential lymph node metastases, but also to the extent and diligence of the pathologists' examination which is provoked by medical oncologists. The inter-individual differences in biological behaviour of the tumour and/or host also affect the lymph node

detection rate.[179, 194] Furthermore, more lymph nodes were examined during right than left colectomies,[179, 195] which was in line with our results.

Patients with insufficient lymph nodes examined are considered high-risk patients who should receive chemotherapy.[58] Therefore, a large reduction in chemotherapy costs can be achieved by increasing the proportion of patients with a sufficient number of lymph nodes examined. We calculated a saving of almost €1,000,000 per year for one department of pathology comparing the number of node-negative patients with less than 10 lymph nodes examined in 1999 with 2007. One third of this saving can be attributed to the Patent blue staining. However, some patients might be upgraded from node negative to node positive, and should receive chemotherapy anyway, reducing the saving. No previous studies are known in which chemotherapy-related savings are shown like in our study. Thus, the set of measures as described in this study can be considered highly cost-effective.

In conclusion, a diverse set of measures including increased awareness of pathologists and surgeons, improved communication between pathologists and surgeons, increased fixation time, and Patent blue V dye staining increased the number of examined lymph nodes among patients with colon cancer. This would reduce the proportion of node-negative patients who would otherwise have received unnecessary adjuvant chemotherapy. Besides avoiding the potential burden of this treatment for the individual patient, large savings can be made due to the reduced proportion of high-risk node-negative patients.

Acknowledgements

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection. We would like to thank the pathologists of the Institute for Pathology and Medical Microbiology in Eindhoven and the following hospitals for their cooperation: Catharina Hospital Eindhoven, St Anna Zorggroep Geldrop, and Maxima Medical Centre.

Funding

This work was carried out with a grant from the Dutch Cancer Society (IKZ 2006-3588).

CHAPTER 4.

TREATMENT AND OUTCOME

4.1.

Large variation in adjuvant chemotherapy in stage III colon cancer patients by age and hospital and their effect on survival

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Ann Oncol 2009 Oct 30 epub

Abstract

Objective: The purpose was to assess factors associated with the administration of chemotherapy and their relation to survival at a population-based level.

Patients and methods: All patients diagnosed with primary colon cancer stage III from 2001 to 2007 in the area of the Eindhoven Cancer Registry were included (n=1,637). We examined determinants of the administration of adjuvant chemotherapy and their relation to survival.

Results: The proportion of patients receiving adjuvant chemotherapy decreased with increasing age from 85% for patients <65 years to 68% for those 65-74 years and 17% for patients ≥75 years, with large inter-hospital variation. Elderly patients (odds ratio (OR) 0.1 (95% confidence interval (CI) 0.1-0.1)) and those with comorbidity (OR 0.6 (95% CI 0.5-0.8)) received adjuvant chemotherapy less often. Patients with an intermediate (OR 1.4 (95% CI 1.1-1.9)) or high socioeconomic status (OR 1.5 (95% CI 1.1-2.0)) or stage IIIC (OR 1.5 (95% CI 1.1-2.0)) received adjuvant chemotherapy more often. Adjuvant chemotherapy was the most important predictor of survival. In a multivariable analysis, older age was no longer a significant negative predictor of survival, in contrast to comorbidity, higher tumour stage, poor tumour grade, and male gender. The improvement in survival between 2001 and 2006 did not reach statistical significance.

Conclusion: Adherence to guidelines for adjuvant chemotherapy was still suboptimal in 2007, especially for elderly patients, and differed widely between hospitals.

Key words: colon cancer, adjuvant chemotherapy, population-based cancer registries, survival

Introduction

Colon cancer is one of the most frequent cancers in the Netherlands with over 6,000 new cases annually, almost 60% of whom are over 70 years old.[1, 108] In 2007 over 3,800 patients died of colon cancer.[2] Since the mid 1980s, improvement in survival has been achieved, in particular by the use of chemotherapeutic treatment. The role of adjuvant chemotherapy with 5-fluorouracil (5-FU)-based chemotherapy for stage III colon cancer patients is well established.[196] In more recent years in combination with oxaliplatin.[197] However, many elderly patients with stage III colon cancer do not receive adjuvant chemotherapy,[35, 198] despite the fact that they also benefit from 5 FU-based chemotherapy.[98, 199] Comorbidity, hospital volume, as well as socioeconomic status (SES) have all been reported to influence the administration of adjuvant chemotherapy.[200]

Since the mid 1990s, adjuvant chemotherapy has been recommended in Dutch treatment guidelines for stage III colon cancer patients (Table 1).[58] In order to evaluate adherence to these guidelines in southern Netherlands in recent years, we assessed factors associated with the administration of chemotherapy. Variation between hospitals was assessed to differentiate between early and late adaptors for adjuvant chemotherapy administration. In addition, we determined to what extent these factors and the introduction of new chemotherapeutic agents were related to survival at a population-based level.

Table 1: Dutch clinical practice guideline (2001-2008) for adjuvant chemotherapy for stage III colon cancer patients

Adjuvant chemotherapy treatment for 24 weeks with 5-FU/leucovorin and oxaliplatin (FOLFOX 4). In case combination chemotherapy is contraindicated due to high age and/or comorbidity, capecitabine monotherapy can be chosen.

Methods

Population-based data from the Eindhoven Cancer Registry (ECR), which is maintained by the Comprehensive Cancer Centre South, were used. The ECR records data on all newly diagnosed cancer patients in the southern part of the Netherlands with 2.4 million inhabitants. The ECR is served by ten community hospitals, six pathology departments, and two radiotherapy institutes. Information on patient characteristics, such as gender, date of birth, and postal code, and tumour characteristics, such as date of diagnosis, tumour type, subsite (International Classification of Diseases for Oncology (ICD-O-3)[64]), histology, stage (Tumour Lymph Node-Metastasis (TNM) classification),[63] grade, and treatment, are obtained routinely from the medical records.[107] In addition, information on comorbidity based on the Charlson comorbidity index was routinely collected.[65] Socioeconomic status, based on individual fiscal data on the economic value of the home and household income, was provided at an aggregated level for each postal code.[67] The quality of the data is high, due to thorough training of the registration

clerks and a variety of computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[80] For the present study, all cases with primary colon cancer (C18-C18.7) registered between 2001 and 2007 in the area of the ECR were included (n=1,637). Age was divided into three groups: <65, 65-74, and ≥75 years. Follow-up of vital status of all patients was complete up to January 1, 2008. In addition to passive follow-up via the hospitals, the information was actively obtained from civil municipal registries and the Central Bureau for Genealogy.

Proportions of patients who received chemotherapy were described per age group and according to gender, comorbidity, SES, stage, tumour grade, number of examined lymph nodes, period of diagnosis, and hospital. Differences in chemotherapy administration between subgroups were tested by means of a Chi-square test or a Cochran-Armitage trend test. Multivariable logistic regression analysis was conducted for the following determinants of chemotherapy administration: age, gender, comorbidity, SES, stage, tumour grade, period of diagnosis, and hospital. Survival time was defined as the time from diagnosis to death or January 1, 2008 for the patients who were still alive. Crude 5-year survival was calculated and a log-rank test was carried out to compare survival proportions. A multivariable proportional hazards regression analysis was used to discriminate independent risk factors for death. (SAS system 9.1, SAS Institute, Cary, NC). P-values below 0.05 were considered statistically significant.

Results

The proportion of patients with stage III colon cancer (n=1,637) receiving adjuvant chemotherapy decreased with increasing age from 85% among patients younger than 65 years to 68% for those aged 65-74 years and 17% for those ≥75 years (p for trend <0.0001). Patients with comorbidity received chemotherapy less often. A large inter-hospital variation in chemotherapy use was found for all age groups with the proportion of patients younger than 65 years receiving chemotherapy ranging from 82% to 96%. For patients aged 65-74 years chemotherapy use ranged from 59% to 78% and among the elderly from 9% to 25%. The differences in administration of chemotherapy persisted throughout all age groups (Table 2). Increasing age, female gender, comorbidity, and low SES were associated with less frequent administration of chemotherapy. After adjustment elderly patients (≥75 years), those with comorbidity, and patients with a low SES received chemotherapy less often, while patients with a high stage (IIIC, any T, N2) received chemotherapy more often. Furthermore, significant differences in the administration of chemotherapy were found between hospitals (Table 3). Similar results were found after stratifying patients according to comorbidity, although younger (<65 years) patients received chemotherapy significantly more often in the groups with and without comorbidity (data not shown).

Table 2: Stage III colon cancer patients diagnosed between 2001 and 2007 in southern Netherlands; proportion of patients who received adjuvant chemotherapy according to age

	n	Proportion of patients receiving chemotherapy (%)		
		<65 yrs	65-74 yrs	≥75 yrs
Overall	1,637	85	68	17**
Gender				
male	783	85	66	20
female	854	86	71	15
No. of comorbid conditions [a]	601 [b]	89*	80**	19
none	464	82	66	19
1	374	73	55	14
≥2	164	82	72	16
unknown				
Socioeconomic status				
low	443 [b]	83	66	13
intermediate	601	89	69	18
high	467	84	73	24
institutionalized	96	73	33	8
Stage				
IIIA (T1-2, N1)	114	85	58	9*
IIIB (T3-4, N1)	1,068	85	67	15
IIIC (any T, N2)	455	87	74	23
Lymph nodes examined				
<6	483	80	63	15
6-11	551	89	71	18
≥12	603	86	70	18
Tumour grade				
poor	429	83	69	15
moderate/well	1,102	87	68	18
unknown	105	-	-	-
Diagnostic period				
2001-2002	469	86	64	17
2003-2004	416	89	64	14
2005-2006	482	85	75	17
2007	270	81	70	20
Hospital of treatment				
1	85	96	59	16
2	150	89	74	11
3	102	85	67	12
4	134	82	65	17
5	142	93	78	25
6	112	90	83	24
7	117	77	61	21
8	122	86	63	18
9	201	84	68	18
10	222	84	60	9

[a] Excluding hypertension; [b] Does not add up to total due to missing values * p<0.05, **p<0.001

Table 3: The odds of administration of adjuvant chemotherapy in patients with colon cancer stage III diagnosed between 2001 and 2007 (n=1,637)

Covariate	n	Odds ratio (95% CI) crude	Adjusted [a] Odds ratio (95% CI)
Age (yrs)			
<65	514	2.7 (2.0-3.7)*	2.4 (0.2-3.4)
65-74	539	1.0	1.0
≥75	584	0.1 (0.1-0.1)*	0.1 (0.1-0.1)*
Gender			
male	783	1.0	1.0
female	854	0.8 (0.6-0.9)*	0.9 (0.7-1.1)
No. of comorbid conditions			
none	601	1.0	1.0
1	464	0.6 (0.5-0.8)*	0.7 (0.5-0.9)*
≥2	374	0.3 (0.2-0.4)*	0.4 (0.3-0.6)*
Socioeconomic status			
low	443	1.0	1.0
intermediate	601	2.0 (1.6-2.5)*	1.4 (1.1-1.9)*
high	467	2.1 (1.7-2.8)*	1.5 (1.1-2.0)*
Stage group			
IIIA (T1-2, N1)	114	1.0 (0.6-1.4)	0.8 (0.5-1.3)
IIIB (T3-4, N1)	1,068	1.0	1.0
IIIC (any T, N2)	455	1.2 (1.0-1.5)	1.5 (1.1-2.0)*
Tumour grade			
poor	429	1.0	1.0
moderate/high	1,102	1.2 (0.9-1.4)	1.1 (0.9-1.5)
Period of diagnosis			
2001-2002	469	1.0	1.0
2003-2004	416	0.9 (0.7-1.2)	1.0 (0.7-1.4)
2005-2006	482	1.1 (0.8-1.4)	1.3 (0.9-1.8)
2007	270	1.0 (0.7-1.4)	1.1 (0.7-1.6)
Hospital of treatment			
1	85	0.9 (0.6-1.4)	0.9 (0.5-1.6)
2	150	1.0	1.0
3	102	1.0 (0.6-1.5)	1.0 (0.6-1.7)
4	134	0.8 (0.6-1.2)	0.9 (0.5-1.5)
5	142	1.4 (0.94-2.1)	1.9 (1.1-3.2)*
6	112	1.4 (0.9-2.1)	1.8 (1.0-3.1)*
7	117	0.8 (0.5-1.2)	0.8 (0.5-1.3)
8	122	1.1 (0.7-1.6)	1.0 (0.6-1.6)
9	201	1.0 (0.7-1.4)	1.0 (0.7-1.6)
10	222	0.8 (0.6-1.1)	0.7 (0.4-1.0)

[a] Adjusted for all covariables listed

There was no significant increase in chemotherapy use in the period 2001-2007 in any 5-year age group, although the increase was somewhat larger in the higher age groups; patients aged 70-74 years exhibited the largest increase (18%), while those ≥75 years showed a much smaller increase (8% for 75-79 years and 4% for ≥80 years) (Figure 1).

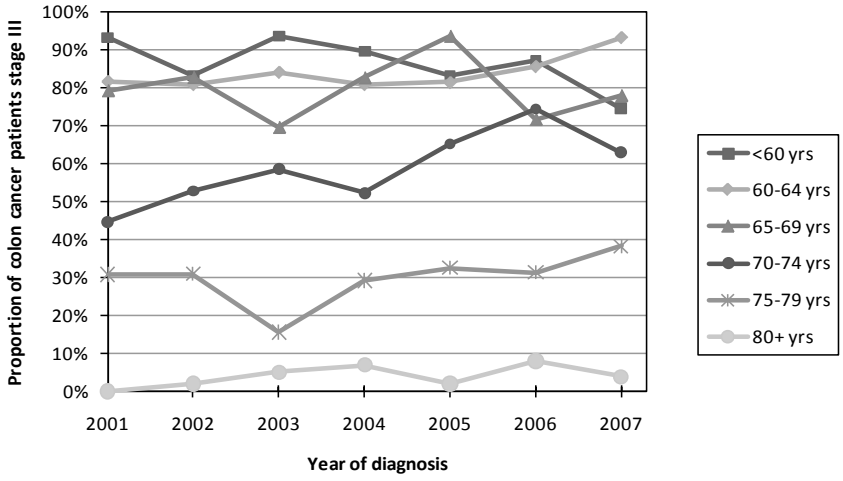

Figure 1: Chemotherapy for colon cancer patients stage III per 5-year age group (n=1,637)

Chemotherapy use changed differently per hospital over time, with large variation between hospitals. Some hospitals exhibited an increase of up to 33% from 2001-2007, while others showed a decrease of up to 33% in the same period. Over time the variation seemed to decrease, although in 2007 the variation still ranged from 38% to 75% between hospitals (data not shown). A significant effect of chemotherapy was found for patients with colon cancer stage III. For patients receiving chemotherapy a significant effect of age on survival was found, while this effect could not be demonstrated for patients not receiving chemotherapy (Figure 2). Crude 5-year survival was 47% for patients with colon cancer stage III. Patients receiving adjuvant chemotherapy had a 5-year survival of 62%, while patients not receiving chemotherapy had a survival of 29% ($p<0.0001$). Increasing age, comorbidity, higher stage, poor tumour grade, and fewer lymph nodes examined were associated with a worse crude 5-year survival. Chemotherapy was the strongest predictor of survival after adjustment for relevant patient and tumour factors (hazard ratio: 0.37 (95% CI: 0.30-0.45)). Colon cancer patients with comorbidity, a high stage tumour, and those with a poor tumour grade had a higher risk of dying of their disease after adjustment for various factors. Female patients had a better survival than male patients (hazard ratio: 0.82 (95% CI: 0.69-0.97)).

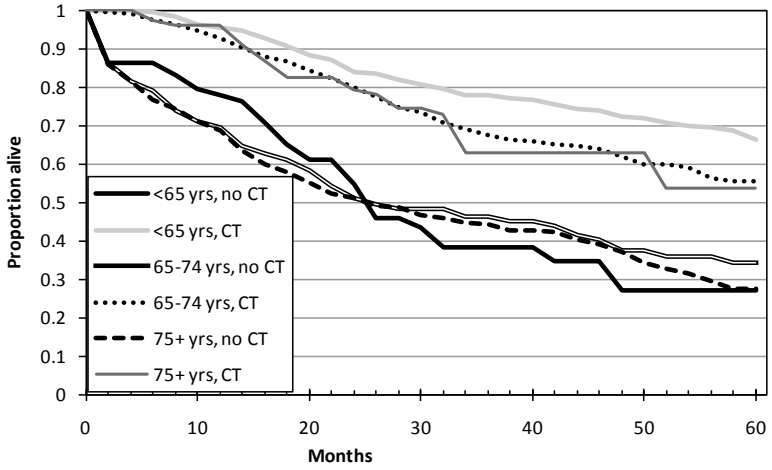

Figure 2: Crude survival according to age and administration of chemotherapy for stage III colon cancer patients (n=1,368)

There was no significant improvement in survival between 2001 and 2006, although survival seemed to increase in the period 2005-2006 (Table 4). No significant differences in survival were found between hospitals (data not shown). No improvement in crude 5-year survival was seen between 2001-2002 and 2003-2004 for either patients receiving or those not receiving chemotherapy (Table 5). Similar overall survival patterns were found after stratification for age, chemotherapy use, or comorbidity (data not shown).

Table 5: Survival of stage III colon cancer patients diagnosed between 2001 and 2006 according to administration of chemotherapy administration by age and period of diagnosis (n=1,368)

	No chemotherapy		Chemotherapy	
	3-yr survival (%)	5-yr survival (%)	3-yr survival (%)	5-yr survival (%)
Age (yrs)				
<65	38	27	78	66
65-74	46	33	69	56
≥75	45	28	63*	54*
Period				
2001-2002	44	30	72	60
2003-2004	42	23	71	62
2005-2006	47	n.a.	78	n.a.

* p<0.05 between the age groups

Table 4: Overall survival (crude and multivariable) for stage III colon cancer patients diagnosed between 2001 and 2006 (n=1,368)

Covariate	n	Crude 5-year survival (%)	Adjusted [a] Hazard ratio (95% CI)
Overall	1,368	47	
Adjuvant chemotherapy			
no	611	29	1.0
yes	757	62*	0.4 (0.3-0.5)*
Age (yrs)			
<65	429	63	0.8 (0.7-1.1)
65-74	453	48	1.0
≥75	486	32*	1.0 (0.8-1.2)
Gender			
male	649	44	1.0
female	719	50	0.8 (0.7-1.0)*
No. of comorbid conditions		57	1.0
none	489 [b]	40	1.2 (1.0-1.5)
1	391	34*	1.3 (1.1-1.6)*
≥2	314		
Socioeconomic status			
low	363 [b]	43	1.0
intermediate	514	49	1.0 (0.8-1.2)
high	382	51	1.0 (0.8-1.2)
Stage			
IIIA (T1-2, N1)	92	67	0.5 (0.3-0.8)**
IIIB (T3-4, N1)	912	49	1.0
IIIC (any T, N2)	364	37*	1.8 (1.5-2.1)*
Tumour grade			
low	360 [b]	34	1.6 (1.4-2.0)*
high	916	52*	1.0
Number of lymph nodes examined			
<6	428	43	1.2 (1.0-1.4)
7-11	460	53	0.9 (0.7-1.1)
≥12	480	46**	1.0
Period of diagnosis			
2001-2002	469	47	1.0
2003-2004	416	43	1.0 (0.8-1.2)
2005-2006	483	n.a.	0.8 (0.7-1.1)

[a] Adjusted for all variables listed; [b] Does not add up to 1,368 due to missing values
* p<0.0001, ** p<0.05

Discussion

In this study we showed that the proportion of stage III colon cancer patients receiving adjuvant chemotherapy decreased with increasing age. Elderly patients (≥75 years), those with comorbidity, and patients with a low SES received chemotherapy less frequently. A large between-hospital variation was found in the

administration of chemotherapy. Receiving chemotherapy was the strongest predictor of survival in this retrospective study, while older age was no longer a significant predictor of survival after adjustment for relevant patient and tumour factors. Five-year life expectancy was not determined by age, but rather by tumour and treatment related factors.

It has been shown in previous studies that a lower proportion of elderly patients receive adjuvant chemotherapy.[35, 200] Several reasons are given in literature to explain why elderly patients are less likely to receive adjuvant chemotherapy, including the presence of concomitant diseases, frailty, the absence of supportive caregivers, and a decrease in the patients' general condition and cognitive ability.[201] Elderly patients seem less willing to accept the negative effects of treatment with adjuvant chemotherapy compared to younger patients,[202, 203] resulting in more patient refusal. In addition, the decision of the medical oncologist which is based on clinical experience plays a role in the choice for adjuvant chemotherapy. However, several studies have shown that elderly patients equally benefit from adjuvant chemotherapy treatment with similar toxicity levels.[98, 199] In addition, the benefit of adjuvant chemotherapy is strongest in the first two years after treatment.[204] In this light it is important to note that the life expectancy of 80-year-old Dutch man is still 7 years and is even more for Dutch woman.[2] Patients presenting with comorbidity received adjuvant chemotherapy less often, which is in agreement with literature.[200]

High stage (IIIC, any T, N2) colon cancer patients more frequently received adjuvant chemotherapy, since they are at high risk of recurrence. In view of the good access to health care facilities and the Dutch health insurance system with a coverage of over 99%,[205] our finding that patients with a low SES are less likely to receive adjuvant chemotherapy is remarkable. However, our results are in line with a previous Dutch study.[35] US population-based studies also reported a negative effect of low SES on adjuvant treatment for colon cancer patients, although it is smaller than in our study.[206, 207] Patients with a higher SES have a more positive self-rated health,[208, 209] which may affect treatment decision-making. In addition, it is possible that patients with a higher SES are more active in terms of seeking more aggressive treatment.

The wide variation in chemotherapy use across hospitals underscores the influence of institutional factors and local practice patterns in determining the use of adjuvant chemotherapy.[210] Physicians generally agree with clinical guidelines recommending adjuvant chemotherapy for stage III colon cancer for relatively young, healthy patients, but differ widely on recommendations for patients who are older and sicker.[211] In addition, fast and slow adaptors in hospitals for the administration of chemotherapy could partly explain variation in chemotherapy use.

Chemotherapy has a marked independent prognostic impact, as reported in several other population-based studies.[212, 213] Due to the population-based nature of our data, we do not know to what extent the positive prognostic impact was

caused by selection of the 'fitter' patients for adjuvant chemotherapy or other factors not included in our analysis. It is likely that frail elderly people, usually having a worse prognosis, receive adjuvant chemotherapy less often, which could have biased our results. This is supported by the smaller survival difference found in randomized clinical trials.[98]

The negative effect of comorbidity on survival is in line with previous Dutch population-based studies[34, 214] and could jeopardize the benefit of chemotherapy treatment. Apart from chemotherapy, tumour stage and to a lesser extent grade are also well-known predictors of survival of stage III colon cancer.[35, 212] No effect of hospital of diagnosis on survival was found, despite the large variation in administration of chemotherapy between hospitals. This is most likely the result of the relatively small numbers of patients per hospital.

The lack of effect of age in the group of patients not receiving chemotherapy reflects the diversity of this group. It contains some young patients who probably could not be treated with adjuvant chemotherapy due to a weak general condition. The equal 5-year survival of the younger and older group of patients not treated by adjuvant chemotherapy is probably also due to the fact that a relatively large proportion of these older patients was relatively fit, with the advanced age itself or a decline of therapy as the main determinants for not receiving chemotherapy. This accentuates the probable undertreatment of relatively healthy elderly patients, although these retrospective data have to be interpreted cautiously.

There seemed to be a trend towards an increased survival over time. This may be partly related to upstaging, since lymph node detection among these patients has improved during the study period.[215] However, survival of patients with colon cancer stage II did not change significantly over time. Furthermore, randomized clinical trials have shown that intensification of chemotherapy by adding oxaliplatin has a positive effect on survival. The addition of oxaliplatin to 5-FU chemotherapy became standard treatment for patients with colon cancer in the Netherlands in 2004. Therefore, a probable positive effect of oxaliplatin on survival cannot be seen yet. Fear for the increased toxicity of these multidrug regimens may have kept oncologists from administering these regimens to elderly patients. Besides, the Dutch clinical guideline indicates that monotherapy capecitabine chemotherapy can be chosen as an alternative treatment in case of aging or comorbidity. Further studies should focus on multidrug less aggressive regimens specifically for the elderly.

In conclusion, adherence to guidelines for adjuvant chemotherapy was still suboptimal in 2007, especially for elderly patients, and differed widely between hospitals. Factors associated with reduced use of chemotherapy are older age, comorbidity, and low SES. Although partly biased by the retrospective nature of our data, chemotherapy was the strongest predictor of survival, while age was no longer significant after correcting for factors affecting survival, indicating undertreatment of elderly patients. To prevent any undertreatment of subgroups of especially elderly patients with colon cancer otherwise fit enough to undergo

chemotherapy, some form of geriatric assessment might be helpful in decision making. Awareness of physicians should reduce hospital variation and prevent undertreatment among lower SES patients.

Acknowledgements

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection.

Funding

This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588).

4.2.

Improved survival of colon cancer due to improved treatment and detection: nationwide population-based study in the Netherlands 1989-2006

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Ann Oncol in press

Abstract

Background: We described changes in treatment of colon cancer over time and the impact on survival in the Netherlands 1989-2006.

Patients and Methods: All 103,744 patients with invasive colon cancer 1989-2006 in the Netherlands were included. Data were extracted from the Netherlands Cancer Registry. Trends in treatment over time were analysed and multivariable relative survival analysis was performed.

Results: The administration of adjuvant chemotherapy in stage III patients <75 years increased from 19% in 1989-1993 to 79% in 2004-2006 and from 1% to 19% in stage III patients ≥75 years. Among stage IV patients resection rates of the primary tumour decreased from 72% to 63%, while chemotherapy administration increased from 23% to 64% in those <75 years. Survival increased from 52% to 58% in males and from 55% to 58% among females. Stage III patients with adjuvant chemotherapy exhibited a relative excess risk (RER) of 0.39 (95% CI: 0.37-0.41) compared to those without. Among stage IV patients, resection of primary tumour, palliative chemotherapy, and metastasectomy were important prognostic factors.

Conclusion: There were substantial improvements in management and survival of colon cancer between 1989 and 2006. Stage III patients with colon cancer experienced the largest improvement in survival, most likely related to the increased administration of adjuvant chemotherapy.

Key words: colon cancer, survival, chemotherapy, population-based

Introduction

Colon cancer is one of the most frequent cancers in the Netherlands with over 7,000 new cases annually of whom about 60% are aged over 70 years.[1] It is the second most frequent cause of cancer death in the Netherlands with over 3,700 deaths in 2008 of whom 68% are aged over 70 years.[2] The incidence of colon cancer has increased over time from 29 in 1989 to 36 per 100,000 person years in 2006, while mortality decreased from 19 to 17 per 100,000 person years in the same period.[1, 2]

According to the evidence-based Dutch clinical practice guidelines, developed by a multidisciplinary working group of medical specialists, patients without distant metastasis should undergo curative resection. Administration of adjuvant chemotherapy for stage III colon cancer patients is recommended in the guidelines since the early 1990s and for high-risk stage II colon cancer patients since 2005.[58] High-risk patients were defined as patients with pT4 or poorly differentiated tumours, tumours with angio-invasion, or patients with less than 10 lymph nodes evaluated.[58]

Since the mid 1980s, improvement in survival has been achieved in randomized clinical trials, in particular due to advances in chemotherapy.[216] The role of adjuvant chemotherapy with 5-fluorouracil (5-FU)-based chemotherapy for stage III colon cancer patients is well established,[196] in more recent years in combination with oxaliplatin.[217] However, many elderly patients with stage III colon cancer do not receive adjuvant chemotherapy,[35, 198] despite the fact that they also benefit from 5 FU-based chemotherapy.[98, 199] The administration of chemotherapy to patients with metastatic colon cancer increased in southern Netherlands from 14% in 1990-1994 to 44% in 2003-2004. Subsequently, survival of unselected patients with metastatic colon cancer increased significantly from 26 (95% CI 22-32) weeks in 1990-1994 to 39 (95% CI 31-48) weeks in 2003-2004.[79] However, the nationwide level of implementation of these treatments and its impact on population-based survival is unknown. Therefore, in this study the changes in treatment of colon cancer over time are described, as well as the influence of these changes on survival in the Netherlands in the period 1989-2006.

Methods

Data collection

Population-based data from the nationwide Netherlands Cancer Registry (NCR), which was started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres, were used.[1] The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnoses, which accounts for up to 8% of new cases, haematology departments

and radiotherapy institutions.[1] Information on patient characteristics, such as gender and date of birth, as well as tumour characteristics such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3)[64]), histology, stage (Tumour Lymph Node Metastasis (TNM) classification),[63] grade, and primary treatment, are collected routinely from the medical records about nine months after diagnosis.[108] The quality of the data is high, due to thorough training of the registrars and computerised consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[80] Vital status of all patients was obtained actively on a regular basis from the integrated database of the municipal registry and the database of deceased persons of the Central Bureau for Genealogy. For the current analyses, the criteria of the International Association of Cancer Registries (IACR) for multiple primaries were applied.[64]

For the present study, all cases of invasive primary colon cancer (C18.0-C18.9) diagnosed in the period 1989-2006 in the Netherlands were included (n=103,744). Patients younger than 15 years and older than 95 years were excluded from the survival analysis, as well as cases diagnosed by autopsy. Age was divided in two groups for the analyses concerning treatment (<75 and ≥75 years) and in four groups for survival analyses (<44, 45-59, 60-74, and ≥75 years). Tumour localization was categorized into anatomical subsites: proximal colon, consisting of the coecum, appendix, ascending colon, hepatic flexure, transverse colon and splenic flexure (C18.0-C18.5); distal colon, consisting of the descending colon and sigmoid colon (C18.6–C18.7); and unknown or overlapping subsites of the colon (C18.8, C18.9). The study period was divided into four categories: 1989-1993, 1994-1998, 1999-2003 and 2004-2006. Stage was based on the pathological TNM classification. For cases where pathological stage was unknown, clinical stage was used. For the period 1989-1994 survival data was only available from four regional cancer registries, which were considered representative of the whole of the Netherlands.

Statistical analyses

Trends in incidence and mortality of colon cancer were described per 100,000 inhabitants, standardized according to the European Standard Population (European Standardized Rate, ESR). Treatment was given as percentages per age group and period. Differences in treatment over time were tested by the Cochran-Armitage trend test. Follow-up was calculated as the time from diagnosis to death or January 1, 2008. Relative survival was used as an estimation of disease-specific survival. It reflects survival of cancer patients, adjusted for survival in the general population with the same structure for age and gender. Relative survival is calculated as the ratio of the observed rates in cancer patients to the expected rates in the general population using the Ederer method.[218] Patients were censored at age 100 years, since follow-up of the very old might be incomplete. For the period 1989-2003 cohort analysis was used. Since follow-up data were only available until January 2008, 5-year follow-up was not feasible for the period 2004-

2006, and period analysis was conducted for this period. Survival trends were quantified as the mean annual percentage change within 1989-2006 estimated by a linear regression model. A positive value of the mean annual change implies an upward trend in survival (i.e. improving) and a negative value implies a negative trend (i.e. deterioration). This calculation assumes that the rates increased or decreased at a constant rate over the entire period. Multivariable relative survival analyses, using Poisson regression modelling,[75] were performed to estimate relative excess risk (RER) of dying adjusted for follow-up interval. For stage III patients, the multivariable relative survival analysis was stratified for adjuvant chemotherapy use, since there was significant interaction between period of diagnosis and adjuvant chemotherapy use. In the multivariable relative survival analysis for stage IV patients, the treatment variables 'chemotherapy', 'resection of primary tumour', and 'metastasectomy' were added to investigate the effect of therapy on the RER of period of diagnosis. (SAS system 9.1, SAS Institute, Cary, NC).

Results

The incidence rate (European Standardized Rate, ESR) of colon cancer increased from 29 in 1989 to 36 per 100,000 inhabitants in 2006 (annual change 1.02 (95% CI 0.84; 1.20)), while the mortality rate (ESR) decreased from 19 in 1989 to 17 per 100,000 inhabitants in 2007 (annual change -0.64 (95% CI -0.83; -0.45)) (Figure 1). The age distribution was stable, with 40% of patients aged 75 years or older. The male to female ratio increased from 0.8 to 1.0 over time. No significant changes were seen in the distribution of tumour subsite, although the proportion of tumours in the proximal colon increased slightly. The proportion of patients with stage III disease increased from 22% in 1989-1993 to 25% in 2004-2006, while the proportion of patients with stage II disease decreased from 37% to 33% in the same periods. The proportion of patients with stage IV disease was constant with 19% in the periods 1989-1993 and 1994-1998 and increased significantly to 22% in 2004-2006 (Table 1).

Treatment

During the whole study period, almost all patients with stage I to III colon cancer underwent resection of their primary tumour. For patients with stage IV colon cancer the resection rate decreased over time; for the younger patients (<75 years) from 72% in 1989-1993 to 63% in 2004-2006 and among elderly patients (≥75 years) from 66% to 56% in 2004-2006. Administration of adjuvant chemotherapy increased over time among patients with stage II colon cancer <75 years from 4% in 1989-1993 to 10% in 2004-2006. Virtually none of the stage II patients ≥75 years received adjuvant chemotherapy.

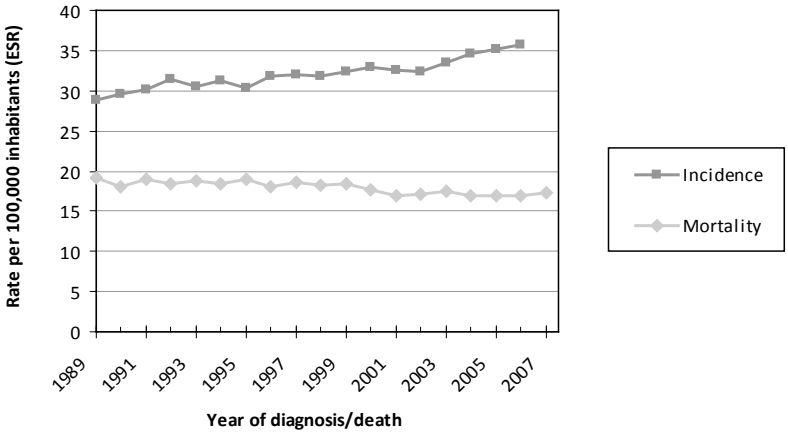

Figure 1: Age-standardized incidence and mortality rates of colon cancer in the Netherlands, 1989-2006 (ESR: European Standardized Rate)

Table 1: Descriptives of all patients diagnosed with colon cancer in the Netherlands between 1989-2006 (n=103,744)

	1989-1993		1994-1998		1999-2003		2004-2006	
	n	%	n	%	n	%	n	%
Gender								
male	11,218	46	13,132	48	14,880	49	10,612	50
female	13,342	54	14,144	52	15,743	51	10,674	50
Age (yrs)								
<75	14,751	60	16,548	61	18,301	60	12,537	59
≥75	9,809	40	10,728	39	12,322	40	8,748	41
Tumour site								
proximal [a]	13,402	55	14,849	54	16,855	55	11,679	55
distal [b]	10,424	42	11,583	43	12,905	42	8,948	42
other/NOS	734	3	844	3	863	3	658	3
Stage								
I	3,593	15	4,022	15	4,261	14	3,072	14
II	9,149	37	9,802	36	10,735	35	6,980	33
III	5,283	22	6,399	23	7,446	24	5,218	25
IV	4,668	19	5,175	19	6,202	20	4,615	22
unknown/n.a.	1,867	8	1,878	7	1,979	6	1,400	7
Total	24,560		27,276		30,623		21,286	

NOS: Not otherwise specified

[a] Including the coecum, appendix, ascending colon, and hepatic flexure; [b] Including the descending colon and sigmoid

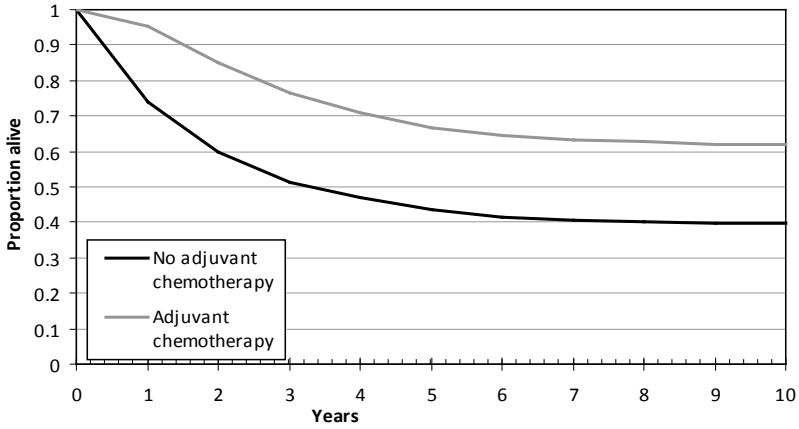

Figure 2: Relative survival of colon cancer stage III patients according to adjuvant chemotherapy administration

There was a steep increase in the administration of adjuvant chemotherapy in stage III patients in both age groups; from 19% in 1989-1993 to 79% in 2004-2006 in those aged <75 years, although it seems to level off in 2004-2006. The proportion of elderly (≥75 years) stage III patients who received adjuvant chemotherapy was much lower, with proportions of 1% in 1989-1993 to 19% in 2004-2006. Chemotherapy administration in patients with stage IV colon cancer increased over time, with a much lower proportion of elderly (≥75 years) patients receiving chemotherapy (Table 2).

Survival

Five-year relative survival from colon cancer in males increased from 52% in 1989-1993 to 58% in 2004-2006 (annual change: +0.38% (95% CI 0.21; 0.56), while in females the 5-year survival increased from 55% to 58% in the same period (annual change +0.18% (95% CI 0.04; 0.32). In 1989-1998, 5-year relative survival was better in females than in males, but this discrepancy disappeared after 1998. Survival decreased with increasing stage of disease, with the 5-year relative survival of around 94% for stage I disease in the entire period 1989-2006, while the 5-year relative survival rates for stage II, III, and IV were respectively around 77%, 53%, and 6% in the entire study period. No significant improvement over time was seen in survival from stage I colon cancer, while survival from stage II colon cancer increased significantly (annual change males: +0.36% (95% CI 0.07; 0.66), females: +0.37% (95% CI 0.13; 0.60)). Survival improved most in patients with stage III colon cancer; an increase from 46% in 1989-1993 to 59% in 2004-2006 (annual change: +0.97 (95% CI 0.59; 1.34)) was seen in male patients and from 48% in 1989-1993 to 60% in 2004-2006 (annual change: +0.88% (95% CI 0.65; 1.12)) in female patients.

Table 2: Trends in primary treatment for patients with colon cancer in the Netherlands by period of diagnosis and age (n=96,620)

Treatment	Age (yrs)	1989-1993		1994-1998		1999-2003		2004-2006		p-trend
		n	%	n	%	n	%	n	%	
Resection, stage I-III										
	<75	10,651	98	12,126	99	13,094	98	8,904	99	0.001
	≥75	7,062	98	7,771	98	8946	98	6,128	98	0.002
Adjuvant chemotherapy, stage II										
	<75	194	4	263	5	426	7	392	10	<0.001
	≥75	5	0	21	1	28	1	22	1	<0.001
Adjuvant chemotherapy, stage III										
	<75	642	19	1,914	47	3,422	74	2,564	79	<0.001
	≥75	21	1	152	6	386	14	367	19	<0.001
Resection, stage IV										
	<75	2,229	72	2,460	71	2,876	68	1,923	63	<0.001
	≥75	1,033	66	1,117	66	1,139	59	857	56	<0.001
Metastasectomy, stage IV										
	<75	41	1	148	4	235	6	253	8	<0.001
	≥75	10	1	26	2	37	2	46	3	<0.001
Chemotherapy, stage IV										
	<75	731	23	1,151	33	2,223	52	1,965	64	<0.001
	≥75	35	2	89	5	210	11	332	40	<0.001

Patients with stage III disease who received adjuvant chemotherapy had a 5-year relative survival of 67%, whereas patients with stage III disease who did not receive adjuvant chemotherapy had a 5-year relative survival of 44% (Figure 2). The 5-year relative survival of patients with stage IV colon cancer increased in males from 5% in 1989-1993 to 7% in 2004-2006 (annual change: +0.15 (95% CI 0.02; 0.28)), while it was stable at around 6% in female patients. Increases in 5-year relative survival seemed more pronounced for younger males (<60 years), while this increase was not seen for younger females. Five-year relative survival in female patients aged ≥75 years was stable at 56%, but rose in men from 52% to 58% (annual change: +0.45 (95% CI 0.13; 0.77)). In males, survival was somewhat better in distally located tumours compared to proximally located tumours (Table 3).

The multivariable relative survival analyses for stage II colon cancer patients showed a decreased risk of death for those with a younger age (<60 years), a tumour in the proximal colon, more recent period of diagnosis, female gender, and administration of adjuvant chemotherapy (Table 4). Omitting adjuvant chemotherapy from the model led to similar results (data not shown).

Table 3: Five-year relative survival (standard error) by period of diagnosis, stage, and age

	Males				
	1989-1993	1994-1998	1999-2003	2004-2006[a]	Annual change (95% CI)
Total	52 (0.9)	54 (0.6)	57 (0.5)	58 (0.7)	+0.38 (0.21; 0.56)*
Stage					
I	92 (2.3)	91 (1.4)	94 (1.2)	94 (1.5)	+0.21 (-0.05; 0.46)
II	74 (1.6)	74 (1.0)	78 (0.9)	78 (1.1)	+0.36 (0.07; 0.66)*
III	46 (1.9)	49 (1.2)	56 (1.1)	59 (1.3)	+0.97 (0.59; 1.34)*
IV	5 (0.7)	5 (0.5)	5 (0.5)	7 (0.7)	+0.15 (0.02; 0.28)*
Age (yrs)					
<44	59 (3.4)	66 (2.5)	70 (2.2)	66 (2.9)	+0.63 (-0.08; 1.34)
45-59	54 (1.8)	55 (1.2)	58 (1.1)	60 (1.3)	+0.42 (0.08; 0.76)*
60-74	52 (1.3)	54 (0.8)	55 (0.7)	57 (0.9)	+0.36 (0.12; 0.60)*
≥75	52 (2.2)	54 (1.4)	57 (1.2)	58 (1.4)	+0.45 (0.13; 0.77)*
Tumour location					
proximal [b]	50 (1.3)	54 (0.8)	55 (0.8)	55 (0.9)	+0.36 (0.13; 0.59)*
distal [c]	56 (1.4)	57 (0.9)	60 (0.8)	61 (0.9)	+0.40 (0.17; 0.62)*
other/NOS [d]	43 (5.5)	31 (2.9)	33 (2.7)	40 (3.7)	n.a.
	Females				
	1989-1993	1994-1998	1999-2003	2004-2006[a]	Annual change (95% CI)
Total	55 (0.8)	56 (0.6)	57 (0.5)	58 (0.6)	+0.18 (0.04; 0.32)*
Stage					
I	96 (1.7)	94 (1.2)	94 (1.1)	92 (1.4)	-0.28 (-0.59; 0.02)
II	75 (1.4)	76 (0.9)	80 (0.8)	80 (1.0)	+0.37 (0.13; 0.60)*
III	48 (1.6)	50 (1.1)	57 (1.0)	60 (1.2)	+0.88 (0.65; 1.12)*
IV	6 (0.8)	5 (0.5)	6 (0.5)	7 (0.7)	+0.14 (-0.05; 0.33)
Age (yrs)					
<44	67 (3.2)	69 (2.3)	64 (2.2)	66 (2.9)	-0.02 (-0.61; -0.58)
45-59	55 (1.8)	58 (1.2)	60 (1.0)	59 (1.3)	+0.27 (-0.07; 0.62)
60-74	55 (1.2)	57 (0.8)	58 (0.7)	61 (0.9)	+0.36 (0.11; 0.62)*
≥75	56 (1.5)	53 (1.0)	56 (0.9)	55 (1.1)	0.00 (-0.21; 0.22)
Tumour location					
proximal [b]	54 (1.1)	56 (0.7)	57 (0.7)	58 (0.8)	+0.21 (-0.04; 0.46)
distal [c]	59 (1.3	58 (0.9)	60 (0.8)	60 (1.0)	+0.14 (-0.08; 0.36)
other/NOS [d]	30 (4.2)	36 (3.0)	36 (3.0)	30 (2.5)	n.a.

NOS: Not otherwise specified

[a] Based on period analysis; [b] Including the coecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure; [c] Including the descending colon and sigmoid

* $p<0.05$

Table 4: Relative excess risk (RER) of dying for patients with colon cancer stage II[a]

	RER	95% CI
Period		
1989-1993	1.0	
1994-1998	1.0	0.9-1.1
1999-2003	0.8*	0.8-0.9
2004-2006	0.8*	0.8-0.9
Gender		
male	1.0	
female	0.9*	0.9-1.0
Age group (yrs)		
<44	0.4*	0.4-0.6
45-59	0.8*	0.8-0.9
60-74	1.0	
≥75	1.4*	1.4-1.5
Subsite		
proximal colon	0.8*	0.8-0.9
distal colon	1.0	
other/NOS	1.7*	1.4-2.0
Adjuvant chemotherapy		
no	1.0	
yes	0.8*	0.7-1.0

RER: Relative excess risk, NOS: Not otherwise specified
[a] Adjusted for follow-up interval, gender, age group, and subsite; * p<0.05

Table 5: Relative excess risk (RER) of dying for patients with colon cancer stage III[a]

	No adjuvant chemotherapy (n=33,138)		Adjuvant chemotherapy (n=32,254)	
	RER	95% CI	RER	95% CI
Period				
1989-1993	1.0		1.0	
1994-1998	1.1*	1.0-1.2	0.8*	0.7-0.9
1999-2003	1.2*	1.1-1.3	0.6*	0.5-0.7
2004-2006	1.2*	1.1-1.3	0.5*	0.4-0.6
Gender				
male	1.0		1.0	
female	0.9*	0.9-1.0	1.0	0.9-1.1
Age group (yrs)				
<44	0.8*	0.6-0.9	0.9	0.7-1.0
45-59	0.9*	0.8-1.0	0.9	0.8-1.0
60-74	1.0		1.0	
≥75	1.0	0.9-1.1	0.8*	0.6-1.0
Subsite				
proximal colon	1.2*	1.1-1.3	1.4*	1.3-1.6
distal colon	1.0		1.0	
other/NOS	1.5*	1.2-1.8	1.8*	1.3-2.4

RER: Relative excess risk, NOS: Not otherwise specified
[a] Adjusted for follow-up interval, gender, age group, and subsite; * p<0.05

Patients with stage III colon cancer who received adjuvant chemotherapy had a significantly lower risk of dying compared to stage III patients who received no chemotherapy (RER 0.39 (95% CI 0.37-0.41). For stage III patients who only received surgery, those diagnosed in the period 1989-1993 had a worse survival compared to patients diagnosed after 1994. Furthermore, patients aged <60 years had a decreased risk of dying, as well as female patients, while a proximal tumour increased the risk of dying. Among stage III patients who received adjuvant chemotherapy survival increased over time, with the RER being 0.49 (95% CI 0.41-0.60) in 2004-2006 compared to 1989-1993. An increased risk of dying for stage III patients with a tumour in the proximal colon was found, while no decreased risk of dying was found among younger (< 60 years) patients (Table 5).

Among patients with stage IV colon cancer the risk of death decreased over time, which only remained significant for the period 2004-2006 after controlling for treatment variables. Resection of the primary tumour, as well as chemotherapy, and liver metastasectomy decreased the risk of death for patients with stage IV colon cancer substantially (Table 6).

Discussion

In this population-based study covering the entire Netherlands over a period of 18 years, we observed substantial changes in treatment of colon cancer in the period 1989-2006. Use of adjuvant chemotherapy in patients with stage III, and to a lesser extent stage II colon cancer increased steeply over time, while resection rates remained stable for curative colon cancer patients. Among metastatic colon cancer patients, the resection rate of primary tumour decreased, while administration of chemotherapy increased. Survival increased over time, particularly in patients with stage III colon cancer.

The changes in treatment and improvements in survival of colon cancer found in this first study using national data covering the entire Netherlands are in line with results from a previous Dutch study covering the southern part of the Netherlands.[157] Our finding that almost all colon cancer patients with stage I-III disease underwent resection of their tumour is similar to the results reported in a French population-based study.[136] The increase in palliative chemotherapy in metastatic colon cancer patients is also in line with a previous regional Dutch study.[79] The large increase in adjuvant chemotherapy among stage III patients, and to a lesser extent among stage II patients is influenced by the results of randomized clinical trials conducted in the 1990s, among which was one Dutch trial, published in 2001.[37, 38, 219-221] During this period there was no consensus about the effect of adjuvant chemotherapy in stage II and III patients in the Netherlands, hindering the introduction of adjuvant chemotherapy.

Table 6: Relative excess risk (RER) of dying for patients with colon cancer stage IV

	Multivariate model 1 [a]		Multivariate model 2 [b]	
	RER	95% CI	RER	95% CI
Period				
1989-1993	1.0		1.0	
1994-1998	1.0	0.9-1.0	1.0	1.0-1.1
1999-2003	0.9*	0.8-0.9	1.0	0.9-1.0
2004-2006	0.7*	0.7-0.8	0.8*	0.8-0.9
Gender				
male	1.0		1.0	
female	1.0	1.0-1.1	1.0*	1.0-1.1
Age group (yrs)				
<44	0.8*	0.7-0.9	0.9*	0.8-1.0
45-59	0.9*	0.8-0.9	0.9*	0.9-1.0
60-74	1.0		1.0	
≥75	1.4*	1.3-1.5	1.1*	1.1-1.2
Subsite				
proximal colon	1.3*	1.2-1.3	1.2*	1.2-1.3
distal colon	1.0		1.0	
other/NOS	1.9*	1.8-2.1	1.4*	1.3-1.5
Chemotherapy				
no			1.0	
yes			0.6*	0.6-0.6
Resection of primary tumour				
no			1.0	
yes			0.4*	0.4-0.4
Metastasectomy				
no			1.0	
yes			0.4*	0.3-0.4

RER: Relative excess risk, NOS: Not otherwise specified
[a] Adjusted for follow-up interval, gender, age group, and subsite; [b] Additionally adjusted for chemotherapy, resection of primary tumour, and metastasectomy
* $p<0.05$

Our findings as well as those in previous studies show that elderly patients receive adjuvant chemotherapy less often than younger patients.[35, 200] Several reasons are given in literature to explain why elderly patients are less likely to receive adjuvant chemotherapy, including the presence of concomitant diseases, frailty, the absence of supportive caregivers, and a decrease in the patients' general condition and cognitive ability.[201] Elderly patients seem less willing to accept the negative effects of treatment with adjuvant chemotherapy compared to younger patients,[202, 203] resulting in more patient refusal. In addition, the decision of the medical oncologist, which is based on clinical experience, plays a role in the choice of adjuvant chemotherapy administration. However, several studies have shown that elderly patients may equally benefit from adjuvant chemotherapy treatment with similar toxicity levels.[98, 199] In addition, the benefit of adjuvant chemotherapy is strongest in the first two years after treatment.[216] In this light it is important to

note that the life expectancy of 80 year old Dutch men is still 7 years and even higher for a Dutch woman.[2]

According to the current Dutch treatment guidelines, adjuvant chemotherapy is not recommended for stage II colon cancer patients.[58] However, those with a T4 tumour, with perforation or obstruction at presentation, with less than 10 lymph nodes examined or with angio invasion are considered high-risk patients, since survival of these patients is similar to stage III patients with colon cancer. These patients should therefore nowadays be considered for treatment with adjuvant chemotherapy.[58] This explains the increase in adjuvant chemotherapy in stage II patients.

Tumours of the proximal colon are usually detected at a late stage.[222] When a proximal tumour lead to symptoms, the tumour can be detected at an earlier stage, resulting in a better survival compared to more distally located tumours as found in our study. The survival of more advanced proximal tumours is worse compared to distal tumours, which is in line with literature.[32]

The considerable improvement in survival of patients with stage III colon cancer is likely to be attributed to the increased administration of adjuvant chemotherapy regimens in these patients. There might be other factors associated with treatment allocation not controlled for in the analysis. Therefore, we do not know the extent to which the prognostic impact observed in this study for treatment factors estimate the real impact on survival due to selection bias. Stage-migration is likely to have occurred since evaluation of lymph nodes has become more adequate in the Netherlands during the study period[39] and imaging techniques have been developing over time detecting smaller metastases, which would have remained undetected otherwise.[100, 223] The lack of effect of age on survival in stage III patients who received adjuvant chemotherapy reflects that elderly patients who receive adjuvant chemotherapy have a similar survival as their younger counterpart.

For metastatic colon cancer, survival improved as well, probably due to an increased use of and changes in chemotherapy, and probably a more adequate selection of patients eligible for surgery.[79] In the most recent years, there has been a regionalisation of the surgical expertise for treating liver metastases. This could have resulted in improved surgery, leading to a better survival in stage IV colon cancer patients in 2004-2006 compared to the previous periods.

Although adherence to clinical guidelines is generally considered a measure of quality of care, deviating from these guidelines in case of an elderly patient does not necessarily indicate an inferior quality of care. The large proportion of elderly patients presenting with comorbidity, and the lack of evidence-based guidelines for this group, often call for pragmatic individualised treatment.[34] In view of the growing proportion of elderly patients with colon cancer, partly because of the rising incidence rates, but especially because of the aging population, clinicians will more and more often face difficult decisions regarding adjuvant chemotherapy.

In conclusion, this study demonstrates substantial improvements in management and survival of colon cancer between 1989 and 2006. Stage III patients with colon cancer experienced the largest improvement in survival, most likely related to the increased administration of adjuvant chemotherapy.

Acknowledgements

The work on this research was performed within the framework of the project 'Progress against cancer in the Netherlands since the 1970s?' (Dutch Cancer Society grant 715401). The authors thank the registration team of the Netherlands Cancer Registry for their dedicated data collection and the working group Output of the Netherlands Cancer Registry for providing data from the cancer registry (J Flobbe, R Damhuis, M van der Heiden, P Krijnen, K Aben, L van de Poll, S Siesling, J Verloop).

Funding

This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588 and 715401).

4.3.

Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy,1989-2006

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Eur J Cancer 2010 Feb 19 epub

Abstract

Background: Since the 1990s, treatment of patients with rectal cancer has changed in the Netherlands. Aim of this study was to describe these changes in treatment over time and evaluate their effects on survival.

Methods: All patients in the Netherlands Cancer Registry with invasive primary rectal cancer diagnosed during the period 1989-2006 were selected. The Cochran-Armitage trend test was used to analyse trends in treatment over time. Multivariable relative survival analyses were performed to estimate relative excess risk (RER) of dying.

Results: In total, 40,888 patients were diagnosed with rectal cancer during the period 1989-2006. The proportion of patients with stages II and III disease receiving preoperative radiotherapy increased from 1% in the period 1989-1992 to 68% in the period 2004-2006 for younger patients (<75 years) and from 1% to 51% for older patients (≥75 years), whereas the use of postoperative radiotherapy decreased. Administration of chemotherapy to patients with stage IV disease increased over time from 21% to 66% for patients younger than 75 years. Both males and females exhibited an increase in 5-year relative survival from 53% to 60%. The highest increase in survival was found for patients with stage III disease. In the multivariable analyses survival improved over time for patients with stages II-IV disease. After adjustment for treatment variables, this improvement remained significant for patients with stages III and IV disease.

Conclusions: The changes in therapy for rectal cancer have led to a markedly increased survival. Patients with stage III disease experienced the greatest improvement in survival.

Keywords: rectal cancer, treatment, guidelines, survival

Background

Each year, over 3,000 new cases of rectal cancer are diagnosed in the Netherlands, with age-standardised incidence rates (European Standard Population, ESR) increasing between 1989 and 2006 from 12.0 to 15.5 per 100,000 inhabitants. Incidence rates were higher for males than for females (ESR 19.6 versus 11.3 per 100,000 inhabitants in 2006).[1]

Previous regional Dutch studies have shown improved survival of patients with rectal cancer since 1980.[77, 78] Especially since the mid 1990s, this improvement in survival was accompanied by changes in treatment for rectal cancer: a shift from postoperative to preoperative radiotherapy, and introduction of the total mesorectal excision (TME) technique, which replaced conventional blunt dissection of the rectum. The TME technique involves radical resection achieved by sharp dissection under direct vision of the rectum with its mesorectum and the visceral pelvic fascia. The introduction of TME resulted in a decreased local recurrence rate.[224] The Dutch Colorectal Cancer Group (DCCG) investigated the effects of preoperative radiotherapy in combination with standardized TME. This and several other studies showed the survival benefits of preoperative radiotherapy, [36, 101, 225] which led to revision of the Dutch national guidelines for treatment of rectal cancer in 2001.[58] Preoperative radiotherapy became standard practice for all patients with clinical stage T2-T4 tumours.

Since 2004, several studies have reported improved local control with preoperative chemoradiotherapy for clinical stage T3-T4 tumours compared to preoperative radiotherapy and postoperative chemoradiotherapy, but no impact on overall survival was found.[102, 103] Based on these results, preoperative chemoradiotherapy became the standard treatment for locally advanced rectal cancer.[58]

The aim of this population-based study is to describe changes in treatment of patients with rectal cancer during the period 1989-2006 in the Netherlands and the influence of these changes on survival.

Methods

Data collection

Population-based data from the nationwide Netherlands Cancer Registry (NCR), which was started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres, were used. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnoses, haematology departments and radiotherapy institutions.[1] Information on patient characteristics such as gender and date of birth, as well as tumour characteristics, such as date of diagnosis, subsite (International Classification of

Diseases for Oncology (ICD-O-3),[64] histology, stage (TNM classification),[226] grade, and primary treatment, are collected routinely from the medical records about nine months after diagnosis. The quality of the data is high, due to thorough training of the registrars and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[80] Vital status of all patients was obtained actively on a regular basis from the integrated database of the municipal registry and the database of deceased persons of the Central Bureau for Genealogy. For the current analyses, the criteria of the International Association of Cancer Registries (IACR) for multiple primaries were applied.[64]

For the present study, all cases of invasive primary rectal cancer (C20.9) diagnosed during the period 1989-2006 in the Netherlands were included. Patients were divided into younger patients (<75 years) and elderly patients (≥75 years) for the analyses of treatment. For the survival analyses we used four age groups (≤44, 45-59, 60-74, and ≥75 years).

The study period was divided into four categories: 1989-1993, 1994-1998, 1999-2003, and 2004-2006. Stage was based on the pathological TNM classification, except when the pathological stage was unknown, in which case the clinical TNM was used. For the period 1989-1994 survival data were only available from four regional cancer registries, which were considered representative of the Netherlands as a whole.

Statistical analyses

Treatment was given as percentages per age group and period. Differences in treatment over time and between the age groups were tested by the Cochran-Armitage trend test.

Follow-up was calculated as the time from diagnosis to death or January 1, 2008. Relative survival was used as an estimation of disease-specific survival. It reflects survival of cancer patients, adjusted for survival of the general population with the same age and gender distributions. Relative survival is calculated as the ratio of the observed rates for cancer patients to the expected rates for the general population using the Ederer method.[218] Patients younger than 15 years and older than 95 years at diagnosis were excluded from analysis, as well as cases diagnosed at autopsy. Patients were censored at the age of 100 years, since follow-up of the very old might be incomplete. For the period 1989-2003 cohort analysis was used. Since follow-up data were only available until January 2008, 5-year follow-up was not feasible for the period 2004-2006, and period analysis was conducted for this period. Overall, 99% of cancers included in the analysis were microscopically verified. The proportion of patients lost to follow-up was less than 1%.

Multivariable relative survival analyses, using Poisson regression modelling, were performed to estimate relative excess risk (RER) of dying for the periods of diagnosis adjusted for follow-up interval and stratified according to stage. Treatment variables were added to investigate the effect of therapy on the RER of dying according to periods of diagnosis. Patients without surgical treatment and

patients who received both pre- and postoperative radiotherapy were excluded from the multivariable analyses of patients with stages II and III disease. All analyses were performed using SAS (SAS system 9.1, SAS Institute, Cary, NC).

Results

During the period 1989-2006, 40,888 patients were diagnosed with rectal cancer. The proportion of patients aged 45-59 years increased over time, while the proportion of patients aged ≥75 years decreased. During this period, the proportion of patients with stage II disease decreased, whereas the proportion of patients with stages III and IV disease increased (Table 1). The age-standardised incidence rate (ESR) increased over time, whereas the age-standardised mortality rate decreased (Figure 1).

Table 1: Characteristics of patients diagnosed with rectal cancer in the Netherlands between 1989-2006 (n=40,888)

	1989-1993		1994-1998		1999-2003		2004-2006	
	n	%	n	%	n	%	n	%
Gender								
male	5,185	56	5,979	57	7,248	58	5,123	58
female	4,010	44	4,509	43	5,174	42	3,660	42
Age at diagnosis (yrs)								
≤44	377	4	418	4	440	4	303	3
45-59	1,676	18	2,070	20	2,795	23	2,031	23
60-74	4,027	44	4,524	43	5,348	43	3,788	43
≥75	3,115	34	3,476	33	3,839	31	2,661	30
Stage								
I	2,526	28	2,876	27	3,408	27	2,348	27
II	2,272	25	2,375	23	2,869	23	1,945	22
III	2,020	22	2,361	23	2,987	24	2,145	24
IV	1,257	14	1,535	15	2,038	16	1,574	18
unknown	1,120	12	1,341	13	1,120	9	771	9
Total	9,195		10,488		12,422		8,783	

Treatment

Surgery

The proportion of patients with stage I rectal cancer who underwent a polypectomy or TEM (Transanal Endoscopic Microsurgery) increased over time with a steeper increase for the elderly patients (≥75 years). The resection rate among younger patients (<75 years) with stages I-III disease remained stable during the study period, but decreased in the elderly from 91% during the period 1989-1993 to 81% during the period 2004-2006. Among patients with stage IV disease, the resection rate for the primary tumour decreased over time, mainly among the

elderly patients. Younger patients underwent a metastasectomy more frequently over time (Table 2).

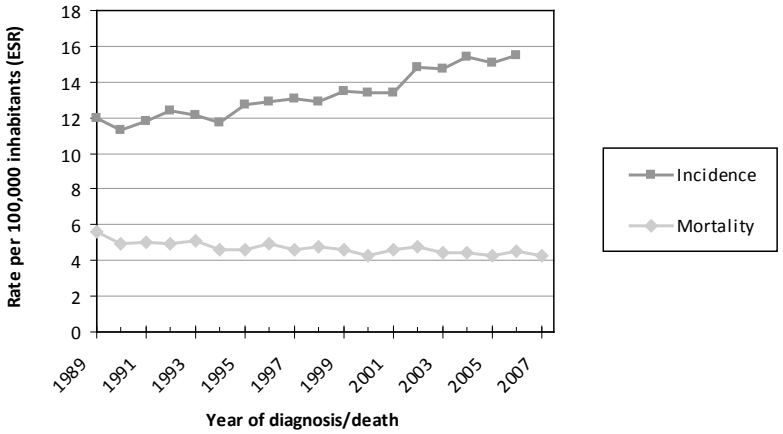

Figure 1: Age-standardized incidence and mortality rates (ESR: European Standardized Rate) of rectal cancer in the Netherlands, 1989-2006

Radiotherapy

The proportion of patients with stages II and III disease receiving preoperative radiotherapy increased sharply from 1% in the period 1989-1993 to 68% in the period 2004-2006 among the younger patients. For elderly patients the proportion increased from 1% to 51%. Postoperative radiotherapy decreased substantially among patients with stages II and III disease, from 46% in 1989-1993 to 4% in 2004-2006 for younger patients and from 23% to 3% for elderly patients.

In the period 1994-1998 neoadjuvant radiotherapy combined with chemotherapy was administered to 1% of the younger patients with stages II and III disease, this proportion increased to 9% in the period 2004-2006. Elderly patients with stages II and III disease received neoadjuvant radiotherapy combined with chemotherapy (3%) less often in 2004-2006 (Table 2).

Chemotherapy

The proportion of patients with stage III disease who received adjuvant chemotherapy increased sharply, particularly among younger patients. The use of chemotherapy for patients with stage IV disease increased over time from 21% in the period 1989-1993 to 66% in the period 2004-2006 for younger patients and from 2% to 25% for elderly patients (Table 2).

Table 2: Treatment of patients with rectal cancer according to period of diagnosis and age at diagnosis

Treatment	Age (yrs)	1989-1993		1994-1998		1999-2003		2004-2006		p[a]
		n	%	n	%	n	%	n	%	
Surgery										
Polypectomy or TEM, stage I										
	<75	65	4	257	13	349	14	279	17	<0.001
	≥75	47	6	134	15	170	18	160	23	<0.001
Resection, stage I-III										
	<75	4,433	94	4,851	93	6,034	92	4,207	93	<0.001
	≥75	1,934	91	2,076	87	2,278	85	1,525	81	<0.001
Resection [b], stage IV										
	<75	473	54	606	56	748	49	507	44	<0.001
	≥75	162	43	181	41	187	36	122	28	<0.001
Metastasectomy, stage IV										
	<75	8	1	45	4	69	5	85	7	<0.001
	≥75	2	1	9	2	8	2	8	2	0.22
Radiotherapy										
Preoperative RT, stage II-III										
	<75	37	1	523	16	2,183	53	1,958	68	<0.001
	≥75	9	1	145	10	683	40	615	51	<0.001
Postoperative RT, stage II-III										
	<75	1,376	46	976	30	375	9	114	4	<0.001
	≥75	310	23	247	17	91	5	36	3	<0.001
Neoadjuvant RT and CT, stage II-III										
	<75	0	0	28	1	165	4	268	9	<0.001
	≥75	0	0	0	0	14	1	40	3	[c]
Chemotherapy										
Adjuvant CT, stage III										
	<75	131	9	374	22	577	26	462	29	<0.001
	≥75	3	1	14	2	20	3	27	5	<0.001
Chemotherapy, stage IV										
	<75	181	21	348	32	779	51	753	66	<0.001
	≥75	7	2	8	2	44	8	108	25	<0.001

TEM: transanal endoscopic microsurgery, RT: radiotherapy, CT: chemotherapy
[a] Cochrane-Armitage trend test; [b] excluding metastasectomy; [c] not analysed

Survival

Five-year relative survival for patients with rectal cancer increased for both sexes between the periods 1989-1993 and 2004-2006, from 53% to 60% for males and from 53% to 59% for females (Table 3). The 5-year survival of patients with stage I rectal cancer was stable over time at around 90% for both sexes. For both males and females with stage II disease, there was a large improvement in 5-year survival, from 63% in 1989-1993 to 72% in 2004-2006 for males and from 59% to 71% for females. The increase in survival was highest for stage III disease. Five-year relative survival for stage III disease for males increased from 44% in 1989-1993 to 56% in 2004-2006, and from 38% to 54% for females. For male patients with stage IV disease, a sharp increase in one-year survival was seen, from 29% in 1989-1993 to 55% in the period 2004-2006. A similar improvement was found for female patients, from 31% to 48%. Similarly, for both males and females, 5-year survival according to depth of invasion (pT) increased, especially for patients with pT2 and pT3 tumours. Five-year relative survival for pT2 tumours in males improved from 79% in 1989-1993 to 85% in 2004-2006, and from 78% to 86% for females. For male patients with a pT3 tumour, 5-year relative survival increased from 51% in 1989-1993 to 57% in 2004-2006. For female patients with a pT3 tumour, 5-year relative survival increased from 47% to 57%. The increase in survival of male patients was the largest in the age group 45-59 years. Five-year relative survival improved from 57% to 67%. For female patients the increase was largest for patients younger than 44 years, from 55% in 1989-1993 to 64% in 2004-2006.

Multivariable relative excess risk of dying

In all multivariable relative survival models for all stages survival decreased with increasing age. The multivariable model for patients with rectal cancer stage I without treatment included in the model, revealed no differences in survival over time. Adding treatment (resection or no resection) to the model had no effect on survival according to period of diagnosis (Table 4). Survival among patients with stage II disease improved over time. This significant increase disappeared after introducing radiotherapy to the model, indicating that the survival probabilities improved due to changes in radiotherapy. Compared to patients who did not receive radiotherapy, patients receiving preoperative or postoperative radiotherapy exhibited a better survival rate (RER 0.51, 95% CI 0.44-0.59 and RER 0.75, 95% CI 0.64-0.89 respectively) (Table 5). In the multivariable model for patients with stage III disease without treatment, survival also improved over time. This remained significant after adding (preoperative and postoperative) radiotherapy and adjuvant chemotherapy to the model. Patients with stage III disease receiving preoperative radiotherapy had a better survival (RER 0.79, 95% CI 0.71-0.88), but there was no survival benefit for patients receiving postoperative radiotherapy

(RER 0.95, 95% CI 0.86-1.06). A better survival was found for patients receiving adjuvant chemotherapy (RER 0.65, 95% CI 0.58-0.73) (Table 6).

Table 3: Five-year relative survival (standard error) according to period of diagnosis, stage and age at diagnosis

	Males			
	1989-1993	1994-1998	1999-2003	2004-2006 [a]
Total	53 (1.3)	54 (0.8)	57 (0.7)	60 (0.9)
Stage				
I	87 (2.5)	88 (1.5)	90 (1.2)	90 (1.5)
II	63 (2.8)	62 (1.8)	67 (1.5)	72 (1.9)
III	44 (2.6)	48 (1.7)	52 (1.4)	56 (1.8)
IV	[b]	4 (0.7)	6 (0.7)	7 (1.1)
Age at diagnosis (yrs)				
≤44	58 (4.7)	63 (3.6)	60 (3.2)	67 (3.9)
45-59	57 (2.5)	58 (1.5)	59 (1.3)	67 (1.6)
60-74	53 (1.8)	56 (1.2)	59 (1.0)	62 (1.2)
≥75	50 (3.2)	48 (2.1)	53 (1.9)	55 (2.3)
	Females			
	1989-1993	1994-1998	1999-2003	2004-2006 [a]
Total	53 (1.4)	57 (0.9)	58 (0.8)	59 (1.0)
Stage				
I	88 (2.3)	90 (1.5)	91 (1.3)	91 (1.6)
II	59 (2.9)	65 (2.0)	68 (1.7)	71 (2.2)
III	38 (2.6)	50 (1.9)	53 (1.6)	54 (2.1)
IV	[a]	4 (0.9)	5 (0.9)	7 (1.2)
Age at diagnosis (yrs)				
≤44	55 (6.1)	70 (3.5)	60 (3.5)	64 4.4)
45-59	58 (2.9)	65 (1.8)	64 (1.5)	66 (1.8)
60-74	56 (2.0)	60 (1.4)	60 (1.2)	64 (1.6)
≥75	48)2.7)	48 (1.8)	50 (1.7)	47 (2.0)

[a] The survival rates of this period were based on period analysis; [b] not analysed, n<10 cases

Similarly, survival of patients with stage IV disease increased over time. After adding the treatment variables adjuvant chemotherapy, primary resection, and metastasectomy to the model, the improvement in survival according to period of diagnosis remained significant for the periods 1999-2003 and 2004-2006 (Table 7).

Discussion

This nationwide population-based study focussed on trends in treatment and survival of patients with rectal cancer in the Netherlands during the period 1989-2006. There were several changes in treatment, which contributed to an improvement in survival, particularly for patients with stage III rectal cancer.

Table 4: Relative excess risk (RER) of dying for patients with rectal cancer stage I

	Multivariable model without treatment variables		Multivariable model with treatment variables	
	RER	95% CI	RER	95% CI
Period of diagnosis				
1989-1993	1.00		1.00	
1994-1998	0.96	0.71-1.29	0.92	0.68-1.25
1999-2003	0.85	0.63-1.14	0.82	0.61-1.10
2004-2006	0.73	0.51-1.07	0.71	0.49-1.03
Age at diagnosis (yrs)				
≤44	0.46*	0.25-0.85	0.45*	0.24-0.83
45-59	0.62*	0.48-0.82	0.62*	0.48-0.81
60-74	1.00		1.00	
≥75	1.76*	1.41-2.21	1.75*	1.40-2.19
Resection				
no			1.00	
yes			0.76	0.58-1.00

RER: Relative excess risk
* $p < 0.05$

Table 5: Relative excess risk (RER) of dying for patients with rectal cancer stage II[a]

	Multivariable model without treatment variables		Multivariable model with treatment variables	
	RER	95% CI	RER	95% CI
Period of diagnosis				
1989-1993	1.00		1.00	
1994-1998	0.91	0.78-1.07	0.95	0.80-1.12
1999-2003	0.77*	0.66-0.90	0.98	0.82-1.16
2004-2006	0.60*	0.49-0.73	0.86	0.69-1.08
Age at diagnosis (yrs)				
≤44	0.68*	0.50-0.94	0.73	0.53-1.01
45-59	0.78*	0.67-0.90	0.81*	0.70-0.94
60-74	1.00		1.00	
≥75	1.64*	1.45-1.86	1.58*	1.40-1.79
Radiotherapy				
no			1.00	
preoperative			0.51*	0.44-0.59
postoperative			0.75*	0.64-0.89

RER: Relative excess risk
[a] Patients without surgical treatment and patients with both pre- and postoperative radiotherapy were excluded
* $p < 0.05$

Table 6: Relative excess risk (RER) of dying for patients with rectal cancer stage III[a]

	Multivariable model without treatment variables		Multivariable model with treatment variables	
	RER	95% CI	RER	95% CI
Period of diagnosis				
1989-1993	1.00		1.00	
1994-1998	0.82*	0.73-0.92	0.87*	0.77-0.98
1999-2003	0.70*	0.62-0.78	0.82*	0.72-0.93
2004-2006	0.50*	0.43-0.58	0.63*	0.53-0.75
Age at diagnosis (yrs)				
≤44	0.71*	0.59-0.86	0.75*	0.62-0.91
45-59	0.82*	0.74-0.90	0.84*	0.77-0.93
60-74	1.00		1.00	
≥75	1.41*	1.28-1.56	1.31*	1.18-1.45
Radiotherapy				
no			1.00	
preoperative			0.79*	0.71-0.88
postoperative			0.95	0.86-1.06
Adjuvant chemotherapy				
no			1.00	
yes			0.65*	0.58-0.73

RER: Relative excess risk

[a] Patients without surgical treatment and patients with both pre- and postoperative radiotherapy were excluded

* $p < 0.05$

The incidence of rectal cancer increased in the Netherlands whereas the mortality decreased, pointing to an increase in survival possibly caused by effective treatment.[227] However, there were other changes in the management of patients with rectal cancer that contributed to improved survival as well, such as better preoperative diagnostic planning, better multidisciplinary decision making, and thorough pathological investigation. Both the concentration of rectal cancer treatment within surgical groups leading to a higher surgical volume and improvements in the treatment of recurrences may have played a role in the improved survival. Unfortunately, we do not have data on these factors and could only evaluate the effect of changes in treatment on survival.

The improvement in survival might be attributed partly to a shift from postoperative to preoperative radiotherapy, in combination with improved (TME) surgery. The TME technique has replaced conventional blunt dissection. In 1979 Heald was the first European surgeon who reported low local recurrence rates due to this technique. With conventional blunt dissection local recurrence rates varied between 7% and 50%,[228] whereas Heald found a local recurrence rate of 6% at five years with the TME technique.[229] A Swedish study demonstrated similar results.[230] In the Netherlands, TME surgery was introduced within the framework

Table 7: Relative excess risk (RER) of dying for patients with rectal cancer stage IV

	Multivariable model without treatment variables		Multivariable model with treatment variables	
	RER	95% CI	RER	95% CI
Period of diagnosis				
1989-1993	1.00		1.00	
1994-1998	0.80*	0.73-0.89	0.93	0.84-1.02
1999-2003	0.71*	0.64-0.78	0.84*	0.76-0.93
2004-2006	0.60*	0.54-0.67	0.76*	0.68-0.84
Age at diagnosis (yrs)				
≤44	0.86*	0.75-0.99	0.96	0.83-1.11
45-59	0.84*	0.78-0.91	0.92*	0.86-0.99
60-74	1.00		1.00	
≥75	1.51*	1.41-1.62	1.18*	1.09-1.26
Chemotherapy				
no			1.00	
yes			0.62*	0.58-0.66
Resection of primary tumour				
no			1.00	
yes			0.42*	0.40-0.45
Metastasectomy				
no			1.00	
yes			0.38*	0.31-0.46

RER: Relative excess risk
* $p < 0.05$

of the TME trial. After this trial, it became standard surgery in the Netherlands. Unfortunately, information about which surgical technique was used (TME or no TME) is not available in the NCR. Therefore, we could only show trends for surgery in general instead of trends for TME surgery.

Thorough examination of the resection specimen by a pathologist is important for adequate staging and adjuvant treatment, but also for feedback to the surgeons about their performance. The results of the TME trial showed the prognostic implication of evaluation of the mesorectum by pathologists. Patients with incomplete resection of the mesorectum developed a recurrence more often. This implies an important role for pathologists in evaluating the TME specimen.[231]

The value of discussing patients preoperatively in multidisciplinary team meetings increased with the development of new treatment strategies. Furthermore, preoperative investigations have become increasingly important for identifying patients with a possibly positive circumferential resection margin (CRM) and selecting these patients for more extensive treatment. A study from the United Kingdom demonstrated a reduced number of patients with a positive circumferential resection margin when the MRI was discussed preoperatively within a multidisciplinary team.[232]

In our results, a change from postoperative to preoperative radiotherapy was found for patients with stages II and III disease in the mid 1990s. After the start of the TME trial in 1996 preoperative radiotherapy was used increasingly in the

Netherlands. It increased in both age groups, although more sharply for patients younger than 75 years. The TME trial showed a reduced risk of local recurrence for patients who received preoperative radiotherapy (5x5 Gy) followed by TME surgery within one week after radiotherapy. However, no improvement in overall survival was seen between TME surgery and TME surgery with preoperative radiotherapy.[36] The results of this population-based study showed, however, an increase in overall survival for stage II rectal cancer and a better survival for patients who received preoperative radiotherapy. In addition, our results showed a significantly better survival for patients with stage II disease, but not for patients with stage III disease who received postoperative radiotherapy compared to patients who did not receive radiotherapy. However, a decreasing risk of dying over time was found for stage III disease, also after adding preoperative radiotherapy, suggesting an effect of TME surgery combined with the preoperative radiotherapy. Because information about the surgical technique (TME or no TME) is missing in the NCR, we were not able to discriminate between the effect of preoperative radiotherapy and that of TME surgery. A Swedish trial also demonstrated the benefits of preoperative radiotherapy with a lower local recurrence rate and an improved 5-year overall survival rate after preoperative radiotherapy.[101] The stage distribution of the current study demonstrated a decrease in stage II and an increase in stage III and IV over time, suggesting a role for stage-migration in the improved stage-specific survival as well. However, survival according to pT stage also increased, suggesting a role for other factors, such as better treatment, as well.

Neoadjuvant chemoradiation was introduced in the Netherlands around 2004, although some patients received this therapy already in the mid 1990s. Before 2004, no benefits were demonstrated for the use of preoperative chemoradiation compared to preoperative radiotherapy alone.[233] In the last decade, however, several studies have shown reduction of the local recurrence rate for patients with T3-T4 or N+ tumours using preoperative chemoradiation, but no improvement in overall survival was observed.[102, 103] Preoperative radiotherapy combined with chemotherapy has only recently been introduced, mainly after our study period. However, our study demonstrated an improvement in overall survival of stages II and III disease in the period 2004-2006, which may be partly due to neoadjuvant chemoradiation.

In many countries, adjuvant chemotherapy is standard therapy for rectal cancer patients with positive lymph nodes. In the Dutch guidelines it is not recommended.[58] Currently, the SCRIPT (Simply Capecitabine in Rectal Cancer After Irradiation Plus TME) study is investigating the effect of adjuvant therapy after preoperative radiotherapy and TME.[234] In our population-based study we found a positive effect of adjuvant chemotherapy on survival for patients with stage III disease.

In metastatic rectal cancer, the increased use of chemotherapy and the improvement in surgery could be explanations for the improved survival of these patients. After adjustment for treatment variables, the improvement in survival

over time remained, suggesting a role for upstaging. New developments in diagnostic imaging techniques may lead to the detection of small metastases which would otherwise have been unidentified.[223]

In Europe, a slower increase in survival of the elderly was found for almost all cancers, leading to a gap in survival between younger and older patients.[235] Our results showed no survival benefits of the improvements in treatment for patients 75 years and older. Two other retrospective Dutch studies did not find improvements in survival for elderly patients either.[96, 134] Comorbidity and treatment-related complications, such as pneumonia and cardiac complications, were possible explanations for the worse prognosis for elderly patients. Furthermore, complications with a comparable occurrence in younger patients as in elderly patients were associated with a higher mortality in elderly patients.[106] However, according to results of the Dutch TME study elderly patients exhibited a good response to preoperative radiotherapy.[96] Furthermore, the EUROCARE study showed a similar prognosis for elderly patients who survived the first year compared to middle-aged patients.[235] Therefore, individualised treatment plans should be used for elderly patients, whereby patients with a good health status could benefit from the same treatment chosen for younger patients and extensive treatment of elderly patients with a poor health status will be avoided.

An increase in survival of patients with rectal cancer has also been seen in other countries. In two French regions, Normandy and Burgundy, 5-year relative survival increased from 35% in the period 1978-1981 to 57% in the period 1985-1989.[236] Five-year survival for women in England and Wales was 39% in the period 1986-1990 and 51% in the period 1996-1999.[237] According to EUROCARE-4, 5-year relative survival for rectal cancer in the period 1995-1999 was 53% for the whole of Europe. However, these estimates varied across Europe, from 39% to 61%.[238] The Netherlands belonged to the countries with the highest survival rates.

A limitation of this study is that we used the pathological stage instead of the clinical stage to describe trends in treatment. However, treatment plans are based on the clinical stage. Furthermore, after a long interval between preoperative radiotherapy and surgery, downstaging might occur.[239] Our choice of the pathological stage was made because the clinical T-stage was often unknown in the NCR, due to an unclear description of the extent of the invasion in the report of the MRI or the MRI was not performed. In addition, our results show a decrease in stage II and an increase in stage III, pointing to a low frequency of downstaging.

In conclusion, this nationwide population-based study of more than 40,000 patients revealed a marked improvement in survival for patients with rectal cancer, especially for patients with stages II and III disease. A shift from postoperative to preoperative radiotherapy, improved (TME) surgery, and for stage III patients, adjuvant chemotherapy have played an important part in the enhanced survival. Further improvement in survival can be expected in future years due to new

therapies such as neoadjuvant chemoradiation for patients with locally advanced rectal carcinoma.

Acknowledgements

The work on this research was performed within the framework of the project 'Progress against cancer in the Netherlands since the 1970s?' (Dutch Cancer Society grant 715401). The authors thank the working group Output (K Aben, R Damhuis, J Flobbe, M van der Heiden, P Krijnen, L van de Poll, S Siesling, J Verloop) of the NCR for providing data from the cancer registry and the registration clerks for their dedicated data collection.

Funding

This work was carried out with a grant from the Dutch Cancer Society (715401).

4.4.

Suboptimal intensity of follow-up for colorectal cancer in southern Netherlands

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Abstract

Aim: To describe follow-up of colorectal cancer (CRC) patients in southern Netherlands and determine the extent of guideline implementation since 2003 for the follow-up of CRC patients.

Methods: Data were extracted from the medical records for 492 randomly selected patients newly diagnosed with CRC in community hospitals in January 2003-July 2005 and recorded in the Eindhoven Cancer Registry. Follow-up intensity schemes were defined as adequate, suboptimal, and insufficient based on national guidelines. Proportions of patients in each scheme were described. Multivariable logistic regression analyses were conducted to assess determinants of follow-up.

Results: Follow-up of CRC patients was usually conducted by a surgeon. Older patients (≥75 years) (OR 0.4 (95% CI 0.2-0.6), those with a rectal tumour (OR 0.5 (95% CI 0.2-0.9), and those with a T1 T2 tumour (OR 0.6 (95% CI 0.4-1.0)) were less likely to receive regular follow-up. Patients <50 years were more likely to receive follow-up (OR 2.1 (95% CI 0.9-5.3)) as well as patients with (neo)adjuvant treatment. Comorbidity did not affect the intensity of follow-up. Thirteen percent of CRC patients aged <75 years received adequate follow-up, while this was insufficient for 26% of these patients in the first year of follow-up. Subsequent follow-up was adequate for 14% of those <75 years, while follow-up was insufficient for 38% of patients <75 years. For over half of the patients aged ≥75 years follow-up was insufficient.

Conclusion: The intensity of follow-up of CRC patients diagnosed in 2003-2005 in southern Netherlands was suboptimal. Clinical guidelines for follow-up were generally not followed.

Key words: colorectal cancer, follow-up, guideline adherence

Introduction

Colorectal cancer (CRC) is the third most frequent cancer in the Netherlands with almost 10,000 new cases annually and a lifetime risk of over 5%.[1] Approximately two-thirds of patients will present with potentially curable disease. Of these, 40% will relapse with metastatic disease.[240] When primary treatment is completed, follow-up is started to detect local recurrences, distant metastases, and metachronous tumours in an early asymptomatic stage resulting in better treatment results.[58]

Intensive follow-up of CRC patients treated with curative intent increased 5-year survival with 7% compared to regular or minimal follow-up.[62, 241-243] CEA measurement and imaging techniques of the liver significantly improve early diagnosis of recurrences or metastases with a favourable effect on survival.[241, 242] Colonoscopy for follow-up of CRC patients is useful to detect synchronous or metachronous neoplasms. The incidence of synchronous tumours is estimated to be 2-7%.[244] Therefore, patients who had no preoperative complete colonoscopy, should undergo one postoperative.[58] In 2007, a Cochrane review concluded that there is an overall survival benefit for follow-up of CRC patients.[62] However, the best combination and frequency of clinic visits, blood tests, endoscopic procedures, and radiological investigations to maximize the outcomes for the patients is unknown.[62] Clinical practice guidelines, developed by a national multidisciplinary working group of medical specialists and published online for easy access, were developed to stimulate uniform diagnostics, treatment, and follow-up of patients according to evidence-based practice. Although there are clinical practice guidelines for the follow-up of CRC patients, different follow-up schemes are used in the Netherlands.[58] However, the general condition of the patients including age and comorbidity plays a major role in the decision for systematic follow-up of CRC patients.[58]

The aim of this study was to describe follow-up of CRC patients in the southern Netherlands diagnosed in 2003-2005 and to determine the extent of guideline implementation for the follow-up of CRC patients.

Methods

Population-based data from the Eindhoven Cancer Registry (ECR), which is maintained by the Comprehensive Cancer Centre South, were used. The ECR collects data of all patients newly diagnosed with cancer in the southern part of the Netherlands. The ECR covers ten community hospitals, six pathology departments, and two radiotherapy institutes. Information on diagnosis, staging, and treatment is obtained routinely from the medical records.[107] In addition, information on comorbidity was collected based on the Charlson index.[66] Socioeconomic status, based on individual fiscal data on the economic value of the home and household income, was provided at aggregated level for each postal code.[67] The quality of the data is high, due to thorough training of the registrars and computerized

consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[80]

For the present study 562 patients with primary CRC were selected at random from the 2730 patients with CRC newly diagnosed in the period January 2003-July 2005. Exclusion criteria were metastatic disease at diagnosis, no resection of the primary tumour, hereditary CRC including HNPCC and FAP, and a survival of less than four months after diagnosis (n= 70). Tumour localization was categorized into anatomical subsites according to ICD-O-3:[64] proximal colon, consisting of the coecum, appendix, ascending colon, and hepatic flexure (C18.0-C18.3); transverse colon, consisting of transverse colon and splenic flexure (C18.4-C18.5); distal colon, consisting of descending colon and sigmoid (C18.6-C18.7); and rectum, consisting of rectosigmoid and rectum (C19.9, C20.9). TNM stage was based on pathological stage. Clinical stage was used when pathological stage was unknown, since clinical stage alone was unknown for many patients.

Additional data were extracted from the medical records by the researcher (L.N.S.) and registration clerks of the cancer registry, under supervision of the treating physicians. This included date of surgery, as well as date of recurrence, metastasis, or death. Preoperative colonoscopy as well as the most proximal location reached during colonoscopy were collected. To describe the timeline and intensity of follow-up of CRC patients the following dates were collected from the end of treatment to the end of the study (January 1, 2008) or date of recurrence, metastasis, or death: endoscopies, CEA measurements, controls by medical specialist, imaging procedures including X-ray of the thorax, abdomen, and colon, abdominal ultrasound, abdominal/thoracic/pelvic computed tomography (CT), and PET scans. Besides, reasons for not receiving (complete) follow-up were collected. Follow-up time was defined as the time between end date of primary treatment and end of the study (January 1, 2008) or diagnosis of recurrence, metastasis, or death.

National clinical practice guidelines for follow-up of colon and rectal cancer, version 2003-2005, are shown in Table 1. Adequate, suboptimal, and insufficient follow-up for the first year after primary treatment were described as well as for the period 12-36 months after primary treatment (Table 2).

Table 1: Dutch clinical guideline for CRC follow-up [a]

Months	3 6 9 12	15 18 21 24	27 30 33 36	39 42 45 48	51 54 57 60
Colonoscopy	•[b] •	•			
Control appointment	• •	• •	•	•	•
Ultrasound liver	• •	•	•	•	•
CEA	• • • •	• • • •	• • • •	• •	• •

[a] Excluding T1N0 rectal cancer patients; [b] When no complete colonoscopy is performed preoperative

Characteristics of patients who had a follow-up time of at least one year as well as those with a follow-up time of at least three years were described per

mode of follow-up and differences were tested using a Chi-square test. The proportions of patients who had a colonoscopy, control(s) by a medical specialist, ultrasound(s) of the liver, CEA measurement(s), and X-ray(s) of the thorax were determined. Multivariable logistic regression analyses were conducted to assess determinants of follow-up among patients who had a follow-up time of at least one year and among those with a follow-up time of at least three years. Follow-up in the first year for the logistic regression analysis was defined as at least two controls by a specialist and two CEA measurements (suboptimal follow-up); in the second and third year follow-up was defined as at least one control and CEA measurement (suboptimal follow-up). Adjustments were made for age, gender, T and N stage, comorbidity, socioeconomic status, year of diagnosis, location (colon and rectum), treatment, specialist doing follow-up, and hospital of follow-up. Finally, the proportion of patients who fulfilled the criteria for the different modes of follow-up in the first and the second and third year after surgery were determined. (SAS system 9.1, SAS Institute, Cary, NC). P-values below 0.05 were considered statistically significant.

Table 2: Modes of follow-up of CRC patients with a minimal follow-up time of 12 and 36 months

Follow-up	0-12 months	12-36 months
Adequate	≥ 1 colonoscopy ≥ 2 controls by specialist ≥ 1 ultrasound liver ≥ 2 CEA measurements	≥ 1 colonoscopy ≥ 1 control by specialist ≥ 1 ultrasound liver ≥ 1 CEA measurement
Suboptimal	≥ 2 controls by specialist ≥ 2 CEA measurements	≥ 1 control by specialist ≥ 1 CEA measurement
Insufficient	< 1 control by specialist < 1 CEA measurement	< 1 control by specialist < 1 CEA measurement

Results

In the majority of patients with CRC, follow-up was conducted by a surgeon, sometimes alternated with an internist in case the patient received chemotherapy. There was a strong age gradient over the different follow-up modes in the first year after primary treatment, with patients who received adequate follow-up having a mean age of 63 years, while patients with suboptimal follow-up had a mean age of 66 years, and those receiving insufficient follow-up 73 years ($p<0.0001$). Patients with comorbidity were less likely to receive intensive follow-up; 41% of those receiving adequate follow-up suffered from a co-morbid condition, while from the patients with insufficient follow-up 64% had at least one co-morbid condition ($p<0.05$). Higher T and N stage were generally associated with more intensive follow-up, as was (neo)adjuvant treatment (Table 3).

Table 3: Descriptives of CRC patients according to adequacy of follow-up in the first year after treatment (n=449) [a]

		Follow-up			
		Adequate (n=46) (%)	Suboptimal (n=250) (%)	Insufficient (n=153) (%)	Total (n=449) (%)
Age, (mean (SD)) (yrs)		63 (10)	66 (11)	73 (10)**	68 (11)
Gender	male	47	54	52	54
	female	53	46	48	46
Socioeconomic status	low	19	26	24	25
	intermediate	43	38	31	36
	high	34	31	37	33
	institutionalized	2	4	7	5
	unknown	2	2	1	2
Comorbidity	none	51	41	33*	40
	1	30	29	31	30
	≥2	9	21	27	22
	unknown	10	9	8	9
Subsite	proximal colon	15	21	14	18
	transverse colon	11	7	6	7
	distal colon	19	19	27	21
	rectum	55	53	53	54
T stage	1	0	1	11*	5
	2	30	26	32	29
	3	66	67	52	62
	4	4	5	5	5
N stage	0	70	61	59*	61
	1	24	29	18	25
	2	6	8	10	8
	unknown	0	2	13	6

Table 3: continued

		Follow-up			
		Adequate (n=46) (%)	Suboptimal (n=250) (%)	Insufficient (n=153) (%)	Total (n=449) (%)
Year of diagnosis	2003	30	24	34	28
	2004	27	34	31	33
	2005	43	41	35	40
Specialist doing follow-up	internist	9	7	13	9
	surgeon	58	68	67	67
	both internist and surgeon	34	25	19	24
	unknown / n.a.	0	0	1	0
Hospital of follow-up	1	11	8	10**	9
	2	9	10	11	10
	3	2	9	8	8
	4	13	5	20	11
	5	7	17	6	12
	6	22	14	5	11
	7	7	14	8	11
	8	6	10	10	16
	9	23	13	22	12

[a] Patients with T1N0 rectal cancer were excluded (n=11), since they have a different follow-up

* $p<0.05$; ** $p<0.0001$

In addition, large differences in follow-up intensity in the first year after surgery were found between hospitals, with the proportion of patients within a hospital receiving insufficient follow-up ranging from 14% to 61% ($p<0.0001$). For the follow-up in the second and third year after treatment a similar effect of age and comorbidity was found, although no effect of stage and hospital was found (data not shown).

Of the patients aged <75 years with a follow-up time of at least 12 months, 41% had a colonoscopy in the first year of follow-up. Almost all patients had at least two control appointments by a medical specialist in the first year of follow-up. To check for liver metastases, at least one abdominal ultrasound was performed in over half of patients aged <75 years and 16% of these patients underwent a second ultrasound in the first year of follow-up. CEA level was assessed at least once in 80% of patients <75 years, while the proportion of patients who received a second, third, and fourth CEA measurement in the first year decreased. Examination of the thorax by X-ray to check for lung metastases was performed once in the first year of follow-up in 44% of patients <75 years (Table 4), although a thoracic X-ray it is not included in the clinical practice guideline for follow-up of CRC. In the second and third year 36% of CRC patients <75 years underwent a colonoscopy. The majority of patients had a control appointment by a medical specialist after the first year of follow-up. An abdominal ultrasound was performed in half of these patients and 33% underwent a thoracic X-ray. In two thirds of patients aged <75 years CEA was assessed. For patients ≥75 years adherence to follow-up activities was lower (Table 4).

Table 4: Follow-up activities of follow-up within 12 months, and 12-36 months after surgery by age

Follow-up activities	0-12 months		12-36 months	
	<75 yrs (n=313) %	≥75 yrs (n=136) %	<75 yrs (n=138) %	≥75 yrs (n=58) %
Colonoscopy	41	24	36	17
First control by specialist	97	100		
Second control by specialist	95	90		
Subsequent control by specialist			80	64
Ultrasound liver 1	55	37		
2	16	6		
subsequent			51	28
CEA measurement 1	80	55		
2	58	32		
3	32	13		
4	16	4		
subsequent			67	41
Thoracic X-ray 1	44	38		
2	19	18		
subsequent			33	22

Only 5% of patients with incomplete preoperative colonoscopy received a colonoscopy within three months after surgery to check for synchronous tumours.

After adjustment for all variables listed in Table 5, a strong age effect remained, with the chance of receiving intensive follow-up decreasing with increasing age. A tumour in the rectum, a low T stage, and diagnosis in 2003 were risk factors for not receiving follow-up in the first year after surgery. Those receiving (neo)adjuvant treatment were more likely to receive follow-up. Large variation among hospitals in follow-up intensity was found (Table 5). Similar results were found for the follow-up in the second and third year, although less clear than in the first year (results not shown).

Thirteen percent of patients with a follow-up time of at least 12 months aged <75 years received adequate follow-up in the first year after treatment. A suboptimal follow-up scheme was given to 61% of these patients, while 26% received insufficient follow-up in the first year after treatment. Adherence to the adequate follow-up scheme in the second and third year after treatment was 14% for those with a follow-up time of at least 12 months <75 years, while 47% received suboptimal follow-up and 39% of these CRC patient did receive insufficient follow-up in the second and third year after treatment. Over half of patients aged ≥75 years received insufficient follow-up (Table 6). Follow-up intensity according to the clinical practice guidelines was conducted in almost none of the CRC patients.

No difference was found in the proportion of patients having a local or distant recurrence between patients receiving adequate or suboptimal follow-up and those receiving insufficient follow-up (data not shown). Besides, time to recurrence did not differ between follow-up intensity schemes (data not shown).

Discussion

Compared to guidelines, follow-up intensity was suboptimal for patients with CRC diagnosed between 2003 and 2005 in southern Netherlands. Older patients (≥75 years), those with a rectal tumour, those with a small T stage, and those diagnosed in 2003 were less likely to receive follow-up comprising of at least two control appointments by a specialist and two CEA measurements. In the second and third year of follow-up, the intensity of follow-up was lower with increasing age.

The large variation in follow-up intensity of patients with CRC found in our study is also reported in literature. A population-based study in 1996-1999 in Norway showed that in 62% of the patients aged <75 years, follow-up was conducted according to the Norwegian guidelines, which is similar to Dutch guidelines.[245] Furthermore, patterns of CRC follow-up were suboptimal compared to the guideline in Canada in 2000.[246] Based on the Surveillance, Epidemiology and End Results (SEER) registry large variation between regions in follow-up procedures was found in the US.[247] A national survey among Dutch surgeons about

Table 5: Logistic regression of chance of suboptimal follow-up in the first year after primary treatment (n=449) [a]

		Multivariate OR (95% CI)
Age (yrs)	<50	2.1 (0.9-5.3)*
	50-75	1.0
	≥75	0.4 (0.2-0.6)*
Gender	male	1.0
	female	1.3 (0.8-2.0)
T stage	1 and 2	0.6 (0.4-1.0)*
	3	1.0
	4	0.8 (0.3-2.2)
N stage	0	1.0
	1	1.2 (0.7-2.1)
	2	0.7 (0.3-1.6)
Comorbidity	none	1.0
	1	1.1 (0.7-1.9)
	≥2	1.1 (0.6-19)
Socioeconomic status	low	1.1 (0.6-1.9)
	intermediate	1.0
	high	0.9 (0.6-1.6)
Year of diagnosis	2003	0.3 (0.2-0.6)*
	2004	0.8 (0.5-1.2)
	2005	1.0
Location	colon	1.0
	rectum	0.5 (0.2-0.9)*
Treatment	surgery only	1.0
	surgery and CT	3.3 (1.3-8.4)*
	surgery and RT	1.4 (0.7-2.8)
	surgery and CT and RT	8.1 (2.3-29)*
Specialist doing follow-up	surgeon	1.0
	internist	0.8 (0.3-1.7)
	both surgeon and internist	0.6 (0.3-1.1)
Hospital of follow-up	1	1.8 (0.7-4.9)
	2	1.0
	3	2.1 (0.8-5.7)
	4	1.2 (0.5-3.1)
	5	4.9 (1.9-13)*
	6	2.8 (1.1-6.9)*
	7	2.5 (1.0-6.1)
	8	1.2 (0.5-2.9)
	9	2.5 (1.0-6.3)

OR: Odds Ratio, CI: Confidence Interval

[a] For patients with a follow-up time of at least 12 months

Table 6: Proportions of follow-up adherence of CRC patients [a]

	First year of follow-up [b]		Second and third year of follow-up [c]	
Follow-up	<75 yrs (n=313) %	≥75 yrs (n=136) %	<75 yrs (n=145) %	≥75 yrs (n=58) %
Adequate	13	4	14	7
Suboptimal	61	44	47	34
Insufficient	26	52	39	56

[a] Excluding patients with T1N0 rectal cancer; [b] For patients with a follow-up time of at least 12 months; [c] For patients with a follow-up time of at least 36 months

CRC follow-up published in 2007 showed a low adherence to Dutch clinical guidelines for the follow-up of CRC. Age and poor physical condition were mentioned in the survey as the main limiting factors.[248]

Although controversy remains about the effectiveness of any surveillance strategies in reducing CRC mortality, some form of surveillance is almost uniformly recommended by experts, specialist organisations and cancer societies.[249] Apart from reducing CRC mortality,[242] follow-up is necessary for patient support and quality assessment by means of checking on treatment outcomes such as complications and cancer recurrence.[240]

Follow-up intensity was suboptimal in southern Netherlands. The question is whether this denies patients the chance for early detection of treatable local or distant recurrences or metastases and potential cure. It is not surprising that elderly patients were less likely to receive intensive follow-up, since follow-up is especially important for patients who are eligible for treatment of local or distant recurrences. Elderly patients might also wish not to receive intensive follow-up due to the absence of supportive care givers, and a decrease in the patients' general and cognitive ability.[201] In addition, we found that patients with small tumours (T1 and T2) tend to be less likely to receive intensive follow-up. However, patients with early-stage disease benefit similarly as late-stage patients from post-recurrence therapy. Therefore intensive follow-up for early stage CRC patients seems appropriate.[250] Large variation among hospitals in follow-up intensity was found, which is possibly due to differences in clinical pathways in the hospitals. Some hospitals have a clear form that has to be filled in by the medical specialist during every follow-up visit. Therefore, in these hospitals it is more likely that patients receive follow-up according to the guidelines. Reasons for lack of adherence to the follow-up guidelines are usually not mentioned in the medical record, but old age, patient preference, and/or comorbidity are mentioned. No effect of follow-up could be shown in our study, which is probably due to the relatively small study population and short follow-up time.

Before 2005 the clinical guideline for CRC contained little information about follow-up and was not very strict in its advice. The medical specialist decided, together with the patient, about the best intensity of follow-up. In 2005 the guideline became more explicit. However, even the revised guideline is rather informal and gives room to conduct follow-up according to the clinical perception

of the medical specialist, who is aware of the controversy about the usefulness of follow-up. However, follow-up programmes with a high (mostly 3 monthly) control frequency did not result in a better survival compared to programmes with less frequent (mostly half yearly) control appointments.[62]

Follow-up became more intensive over time, which is a desirable trend that could be extended. Improved information provision to medical specialists about optimal follow-up and the assistance of nurse practitioners for follow-up activities like three monthly CEA measurements can further improve follow-up intensity. A clinical care pathway accomplished with a clear form and appointment scheme for the follow-up of CRC patients in each hospital will also increase the follow-up intensity.[251] This is especially important since incidence and survival of CRC is increasing.[84] Apart from the increasing proportion of patients who need primary treatment, a growing amount of patients need follow-up, which significantly increases the workload for hospitals. In 2007, the Dutch Health Council advised the government that it is desirable that within five years each cancer patient receives a follow-up plan after primary treatment concerning the physical and psychological consequences of disease, treatment and the intensity of follow-up.[252]

In conclusion, the intensity of follow-up of CRC patients diagnosed in 2003-2005 in southern Netherlands is suboptimal with large variation between patients. Clinical guidelines for follow-up were generally not followed.

Acknowledgement

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection.

Funding

This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588).

4.5.

Significant improvement in survival of patients presenting with metastatic colon cancer in the south of the Netherlands from 1990 to 2004

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Ann Oncol 2008;19(9):1600-4

Abstract

Background: In randomized controlled trials, the median overall survival (OS) for patients with metastatic colon cancer has improved. However, the results of randomized controlled trials should be interpreted with caution and cannot simply be extrapolated to the general practice. We retrospectively analysed population-based survival data of patients who presented with metastatic colon cancer at diagnosis.

Patients and Methods: All patients diagnosed with primary metastatic colon cancer between 1990 and 2004 in the registration area of the Eindhoven Cancer Registry were included. Date of diagnosis was divided into four periods (1990-1994, 1995-1999, 2000-2002 and 2003-2004) according to the availability of chemotherapy for metastatic colon cancer. We assessed OS according to chemotherapy use and period.

Results: Of the 1,769 patients, 30.6 % received chemotherapy. Chemotherapy use over time increased from 24% in 1990-1994 to 55% in 2000-2004 for patients aged under 70 years and from 2% to 22% in patients aged 70 years and older. Median survival for patients diagnosed in 1990-1994 was 26 (95% CI 22-32) weeks, while patients diagnosed in 2003-2004 had a median survival of 39 (95% CI 31-48) weeks. Patients who did not receive chemotherapy had a survival of 22 (95% CI 20-25) weeks, while the survival for patients who did receive chemotherapy was 57 (95% CI 51-65) weeks. OS decreased with increasing age ($p<0.0001$). In the multivariable survival analysis, chemotherapy use, increasing age, having multiple co-morbid conditions, and having more than one tumour site significantly affect survival, with the strongest effect of chemotherapy use.

Conclusion: Palliative chemotherapy significantly improved overall survival in unselected patients with metastatic colon cancer.

Key words: chemotherapy, colon cancer, population-based cancer registries, survival

Introduction

Colon cancer is a common and often lethal disease. In the Netherlands, 9,898 new cases of colorectal cancer were diagnosed and 4,429 patients (45%) died from the disease.[1] Since the mid 1980s improvement in survival has been achieved, in particular by detection of the disease at an earlier stage and advances in chemotherapy, surgery, and radiotherapy. However, the prognosis for patients with metastatic disease remains dismal.

Approximately 20% of patients with colon cancer present with metastatic disease at the time of diagnosis and treatment remains palliative, excluding a small subset of patients with resectable liver and/or lung metastases who are potentially curable.[253-256]

The median overall survival (OS) for patients with metastatic colon cancer who receive supportive care alone is approximately 5-6 months.[255] For decades, 5-fluorouracil (5-FU)-based chemotherapy was the only effective treatment against colorectal cancer. Randomised controlled trials in the mid 1990s showed a better quality of life and a small improvement in OS for patients who received chemotherapy treatment than for those receiving supportive care alone.[257, 258]

Since 2000, with the introduction of the new agents irinotecan and oxaliplatin added to 5-FU-based regimens the median OS increased to 14-16 months.[259-261] More recently, in randomized controlled trials, the OS further prolonged with 4-5 months by combining chemotherapy with targeted therapy (bevacizumab, cetuximab) somewhere in the treatment of this fatal disease.[262-268]

The results of randomized controlled trials should be interpreted with caution and cannot simply be extrapolated to the general practice. Patients entering these studies fulfil the strict selection criteria of these studies. They are often younger, have a better performance status, less comorbidity, and they often have a limited tumour load. Such selection limits the applicability of these results to the general practice.

In addition, another important contributing and confounding factor to prolonged survival might be the early treatment of metastatic disease. Possibly, survival of metastatic colorectal cancer is prolonged more by early diagnosis than a true effect of chemotherapy.

To investigate the effect of chemotherapy in unselected patients, we retrospectively analysed the population-based survival data of patients who presented with metastatic colon cancer at diagnosis in the period from 1990 until 2004 in the south of the Netherlands.

Methods

Population-based data from the Eindhoven Cancer Registry (ECR) was used, which is maintained by the Comprehensive Cancer Centre South. The ECR records data on all patients newly diagnosed with cancer in the southern part of the Netherlands an area with 2.3 million inhabitants. Data of patients diagnosed

between 1990 and 2004 were included. The ECR is served by ten community hospitals, six pathology departments, and two radiotherapy institutes. Data on patient characteristics like gender, date of birth, and postal code, and tumour characteristics like date of diagnosis, tumour type, histology, subsite, stage, and treatment are routinely extracted from the medical records by trained registrars, according to national guidelines.[107] Subsite was classified according to the International Classification of Diseases for Oncology (ICD-O-3).[64] Clinical stage of the disease was defined according to Tumour Lymph Node-Metastasis (TNM) clinical classification.[63] Chemotherapy (yes versus no), also in combination with surgery, was defined as prescription of any chemotherapy at initial diagnosis. Date of diagnosis was divided into four periods according to the availability of chemotherapy for metastatic colon cancer patients: 1990-1994 (period in which almost no chemotherapy was given to metastatic colon cancer patients), 1994-1999 (main treatment was 5FU/LV), 2000-2002 (more agents were available, but not generally used yet), and 2003-2004 (combination therapy more generally used due to the CAIRO study). The quality of the data is content, due to thorough training of the registrars and computerized consistency checks at regional and national level. Completeness is estimated to be at least 95%.[80]

All patients diagnosed with primary metastatic colon cancer (C18.0-C18.9) between 1990 and 2004 aged >40 years in the registration area of Eindhoven were included (n=1,769). Patients diagnosed in the west of the ECR region between 1990 and 1994 for which the follow-up data is not complete and patients with cancer diagnosed at autopsy were excluded.

Follow-up of vital status of all patients was complete up to January 1, 2006. In addition to passive follow-up via the hospitals, this information was actively obtained from the municipal personal records database.

Crude survival rates were computed. Survival time was defined as the time from diagnosis to death or January 1, 2006 for the patients who were still alive. A log-rank test was carried out to evaluate significant differences between survival curves. A multivariable proportional hazards regression analysis was used to discriminate independent risk factors for death. The SAS/STAT® statistical software (SAS system 9.1, SAS Institute, Cary, NC) was used for the analyses.

Results

In the period from 1990 to 2004 1,769 patients were diagnosed with metastatic colon cancer in the ECR region. In only 5% of the patients a (liver) metastasectomy was performed and this percentage remained stable over the entire study period. Additionally, the majority of the study population consists of patients with one tumour site (74%). From the total study population 1,127 (69.4%) patients did not receive chemotherapy compared to 542 (30.6%) who did. Patients who received chemotherapy were logically diagnosed in the more recent periods and they were significantly younger (median age 62 years in chemotherapy

group versus median age 71 years in no chemotherapy group). Chemotherapy use over time increased from 24% in 1990-1994 to 58% in 2000-2004 in patients aged under 70 years. For patients aged 70 years and older an increase in chemotherapy use from 2 to 23% was seen. Patients with one or several comorbid conditions received less chemotherapy compared to patients without comorbidity. Furthermore, patients with a low socioeconomic status received less chemotherapy than patients with a high socioeconomic status. However, this inequality tend to disappear in the most recent period (Table 1).

There was a significant improvement in OS for patients with metastatic colon cancer over time (p=0.01). This was seen in the first two years after diagnosis (Figure 1). Patients diagnosed in the first period (1990-1994) had a median survival of 26 (95% CI 22-32) weeks, while patients diagnosed in the latest period (2003-2004) had a median survival of 39 (95% CI 31-48) weeks. Survival was better in patients who received chemotherapy compared to patients who did not receive chemotherapy (p<0.0001). Patients who did not receive chemotherapy had a survival of 22 (95% CI 20-25) weeks, while the survival for patients who did receive chemotherapy was 57 (95% CI 51-65) weeks. After two years of diagnosis survival of metastatic colon cancer patients is almost similar, independent of chemotherapy use or period of diagnosis.

Table 1: Percentage of patients who received chemotherapy per age group per period (n=1,769)

	1990-1994		1995-1999		2000-2002		2003-2004	
	n	CT (%)	n	CT (%)	n	CT (%)	n	CT (%)
Overall	304	14	643	25	449	40	361	44
Age (yrs)								
<70	173	24	387	36	265	54	217	58
≥70	137	2	256	7	189	20	145	23
Gender								
men	150	16	347	27	206	40	188	45
women	154	13	296	23	243	40	173	42
Comorbidity								
none	-[a]	-	260	30	144	52	111	59
1	-	-	175	23	140	37	121	36
≥2	-	-	119	15	94	31	91	38
Tumour sites								
1	235	14	462	24	297	40	243	41
≥2	67	18	178	26	151	40	117	49
Socioeconomic status								
low	110	11	166	15	109	30	109	47
intermediate	94	16	238	27	155	40	130	39
high	73	22	185	37	150	53	103	50

CT: chemotherapy

[a] No data available about comorbidity for this period

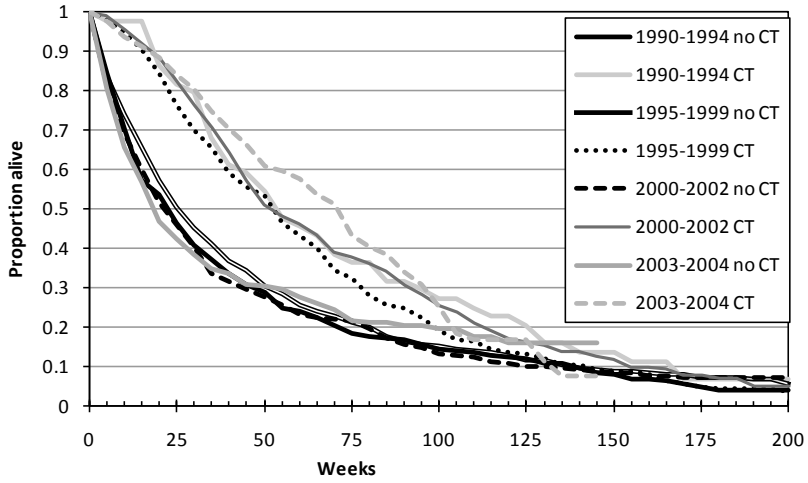

Figure 1: Crude survival for patients with metastatic colon cancer according to period and chemotherapy use

A prolonged survival of patients using chemotherapy was seen compared to patients who received no chemotherapy in all periods. Median survival increased from 54 (95% CI 37-81) in 1990-1994 to 72 (95% CI 58-76) weeks in 2003-2004 for patients who received chemotherapy. Survival of patients who did not receive any chemotherapy treatment remained stable at ~22 weeks for all periods. In addition, OS decreased with increasing age, comorbidity, and number of tumour sites (Table 2). In the unadjusted multivariable survival analysis, a significant effect of period was found. However, this effect disappeared after adjusting for chemotherapy (Table 3). After adjustment for confounders, chemotherapy use, increasing age, having multiple comorbid conditions, and having more than one tumour site significantly affect survival, with the strongest effect of chemotherapy use.

Discussion

In this population based study, we investigated the effect of chemotherapy on survival in patients who presented with metastatic colon cancer at diagnosis. The proportion of colon cancer patients diagnosed with stage IV in the ECR area remained stable at 19% between 1990 and 2004.[1] Thus, a possible positive effect of early diagnosis of metastatic disease with intensive follow up (e.g. carcinoembryonic antigen measurement, computed tomography scans) on survival was probably limited. Furthermore, in our study OS in patients who did not receive chemotherapy in the subsequent periods remained stable at 22 weeks and is equal to the 5-6 months survival in supportive care arms in different randomized controlled trials.[258]

Table 2: Median survival in weeks for metastatic colon cancer patients according to period and age group (n=1,769)

	1990-1994		1995-1999		2000-2002		2003-2004	
	n	Median survival in weeks (95% CI)	n	Median survival in weeks (95% CI)	n	Median survival in weeks (95% CI)	n	Median survival in weeks (95% CI)
Overall	304	26 (22-32)	643	31 (28-36)	449	34 (30-39)	361	39 (31-48)
Chemotherapy								
no	260	23 (16-26)	483	26 (22-29)	274	21 (17-28)	204	17 (15-24)
yes	44	54 (37-81)	160	52 (43-64)	180	51 (45-67)	158	72 (58-76)
Age (yrs)								
<70	173	37 (30-46)	387	38 (32-46)	265	41 (34-48)	217	49 (40-66)
≥70	131	14 (11-23)	256	23 (18-28)	189	24 (20-33)	145	22 (16-32)
Gender								
men	150	26 (22-37)	347	34 (28-40)	206	34 (29-42)	188	43 (31-58)
women	154	26 (17-33)	296	29 (25-35)	243	34 (29-41)	173	38 (28-49)
Comorbidity								
none	-[a]	-	260	33 (28-45)	144	42 (35-52)	111	56 (43-71)
1	-	-	175	32 (27-39)	140	32 (22-42)	121	29 (20-45)
≥2	-	-	119	23 (17-35)	94	30 (24-41)	91	32 (21-62)
Tumour sites								
1	235	30 (24-37)	462	36 (30-41)	297	39 (32-45)	243	54 (39-66)
≥2	67	16 (11-24)	178	23 (19-31)	151	29 (22-34)	117	28 (18-35)
Socioeconomic status								
low	110	22 (15-30)	166	26 (19-32)	109	43 (33-53)	109	43 (31-69)
intermediate	94	37 (24-51)	238	36 (28-42)	155	30 (22-37)	130	48 (31-68)
high	73	31 (16-53)	185	38 (30-47)	150	38 (30-48)	103	30 (21-39)

[a] No data available about comorbidity for this period

Table 3: Multivariable survival analysis for metastatic colon cancer patients (n=1,769)

	Model 1 HR (95% CI)	Model 2 Adjusted HR (95% CI)	Model 3 Adjusted HR (95% CI)	Model 4 Adjusted HR (95% CI)
Period of diagnosis				
1990-1994	1.00	1.00	1.00	1.00
1995-1999	0.92 (0.80-1.06)	0.94 (0.82-1.07)	0.95 (0.83-1.10)	0.89 (0.77-1.03)
2000-2002	0.87 (0.75-1.01)	0.88 (0.76-1.02)	0.97 (0.84-1.13)	0.87 (0.74-1.01)
2003-2004	0.78 (0.66-0.92)*	0.79 (0.67-0.93)*	0.89 (0.75-1.05)	0.79 (0.66-0.94)*
Age		1.02 (1.02-1.02)*		1.01 (1.01-1.02)*
Chemotherapy			0.67 (0.60-0.74)*	0.74 (0.66-0.83)*
Gender				0.94 (0.85-1.04)
Comorbidity				
0				1.00
1				1.11 (0.98-1.25)
≥2				1.17 (1.02-1.35)*
Tumour sites				
1				1.00
≥2				1.46 (1.31-1.63)*
Socioeconomic status				
low				1.00
intermediate				0.98 (0.87-1.10)
high				0.98 (0.86-1.10)

HR: Hazard Ratio; CI: Confidence Interval
Model 1: Unadjusted; Model 2: Adjusted for age; Model 3: Adjusted for chemotherapy use;
Model 4: Adjusted for age, chemotherapy use, gender, comorbidity, number of tumour sites, and socioeconomic status
* p-value < 0.05

Our study showed that of all metastatic colon cancer patients, only 31% received chemotherapy in the period 1990-2004 and that chemotherapy significantly improved OS, 22 weeks in the no-chemotherapy group versus 57 weeks in the chemotherapy group.

Chemotherapy use increased over time from 14% in 1990-1994 to 44% in 2003-2004, resulting in a increased survival from 26 to 39 weeks. For the patients receiving chemotherapy, the survival in the period 1990-1994 was 54 weeks, compared to 52 weeks in 1995-1999, 51 weeks in 2000-2002, and 72 weeks in period 2003-2004. It is not surprising that the median OS with chemotherapy in the period 1990-1994 and 1995-1999 are similar, as in these periods 5-FU-modulated regimens were the only effective regimens producing median OS of ~12 months.[269] With the availability of new effective agents, such as irinotecan and oxaliplatin, a new exciting era in the treatment of colorectal cancer started and resulted in many new combination chemotherapy regimens. With the introduction of capecitabine, an oral fluoropyrimidine that mimics continuous infusion of 5-FU, the convenience for patients improved. Three key trials were conducted in metastatic colorectal cancer and published in 2000.[259-261] On the basis of these trials, using all the three effective drugs preferentially in combination, chemotherapy regimens became the standard of care. Initially, we analysed the periods 2000-2002 and 2003-2004 together. However, the increase in survival was less than expected and therefore the periods were analysed separately. In our study, the period 2000-2004 showed an improvement of OS of ~8 weeks compared to 1995-1999. This in contrast to the reported results that showed 4-5 months improvement of OS since these drugs augmented the therapeutic armamentarium. It was hypothesised that the use of polychemotherapy was delayed to 2003 as in that year the Dutch Colorectal Cancer Group initiated the CAIRO trial,[270, 271] studying sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer and might be the time that regional oncologists became familiar with the use of these drugs. In the period 2003-2004, 21 patients (13% of patients who received chemotherapy) participated in the CAIRO trial and 137 patients were treated outside this trial with (poly)chemotherapy. The OS of all the patients in the period 2003-2004 treated with chemotherapy increased to 72 (95% CI 58-76) weeks. It is remarkable that these survival data outside a trial are similar to the results in the CAIRO study and other randomized trials.[259, 260, 270, 271] In addition, these results support the importance that for metastatic colorectal cancer patients, all active drugs should be considered during the course of the disease to prolong survival. For patients who received chemotherapy, OS in the period 2000-2002 was similar to that in the period 1995-1999, achieved by monotherapy 5-FU, suggesting that in that period polychemotherapy for treatment of metastatic colon cancer was not standard practice. This doctor's delay in accepting and using new active drugs for the treatment of colorectal cancer is now seen again with bevacizumab and cetuximab.

This phenomenon is not uncommon since there is an enormous difference in the use of these new drugs between several European countries.[272]

The percentage of patients receiving chemotherapy increased enormously in both patients <70 years and in patients 70 years and older. These findings subscribe to the ventilated opinion, but not prospectively studied, that all patients profit from chemotherapy, if they are fit enough to tolerate chemotherapy, irrespective of age. In view of the results of the CAIRO study, especially for the aged, sequential chemotherapy is preferential, as toxicity is reduced in this group of often fragile patients. Chemotherapy treatment differed slightly between low and high socioeconomic status patients, which is in line with previous results.[35]

In conclusion, survival of metastatic colon cancer significantly improved in unselected patients. Since 1994, this improvement can be ascribed to the increased use of chemotherapy, especially polychemotherapy. Since our results are comparable to results from randomized controlled trials, the recent introduction of targeted therapy might result in a median survival of >20 months for metastatic colon cancer patients in the general oncology practice.

Acknowledgement

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection.

Funding

This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588).

CHAPTER 5.

DISCUSSION AND CURRENT PERSPECTIVE

5.1.

Trends in incidence of and mortality from colorectal cancer in the Netherlands

One of the main objectives of the studies described in this thesis was to investigate the current trends in incidence, stage distribution, survival, and mortality of colorectal cancer (CRC).

We found that the incidence of colon cancer increased since 1975, while incidence of rectal cancer remained relatively stable (chapter 2.1. and 2.2.). CRC incidence increased mainly for younger birth cohorts until the birth cohort of 1955 in men (men in their fifties in 2010) and the birth cohort of 1940 in females (females in their seventies in 2010) (chapter 2.2.). This is likely to be related to changes in lifestyle factors and the wider application and better techniques of endoscopy since the 1980s, especially in the younger patients. Many epidemiological studies confirm the importance of lifestyle in CRC,[25] for example, physical inactivity,[116] red and processed meat consumption,[20] alcohol intake,[24] obesity,[25] dietary fat intake,[17, 18] and excessive intake of energy.[26] The relative risk of all the aforementioned risk factors for CRC is small, so large effects can only be seen after big changes in exposure and at long term. Based on a micro simulation of the 2000 US population with the MISCAN-Colon model a potential 16% reduction in CRC mortality was estimated by the year 2020 when the prevalence of risk factors could be improved above continued trends.[273] However, this estimated reduction in CRC mortality is optimistic, and will be hard to reach in the Netherlands where the awareness of CRC is low.[274] Besides, the obesity epidemic is important. In the US obesity has risen by 74% in the past decade, with at least one in five adults now classified as obese.[275] Similar trends are seen in most Western countries.[276] The burden of incident cancer attributable to excess BMI based on data from 2002 in the Netherlands was 3% for men and 2% for women, with the largest effect on endometrial, post-menopausal breast and colorectal cancer.[277] Therefore, a reduction of 16% in CRC mortality due to positively changed risk factors seems unlikely.

The doubled incidence of proximal colon tumours (chapter 2.1.) is possibly caused by changes in diet and lifestyle, and maybe also by the use of medications such as aspirin and non-steroidal anti-inflammatory drugs and hormone replacement therapy in women. These risk factors might be responsible for the rightward shift in CRC incidence through differential effects of these risk factors on the respective subsites.

The current male/female difference at old age might be explained by the gender difference in exposure to physical inactivity and smoking. Since the 1950s the proportion of males having a sedentary job increased, resulting in less physical activity (relative risk: 0.8),[21] while women might have been more physically active by doing the household in that period. The relative risk for smoking has been estimated to be 1.2,[15] with an induction period of three to four decades between exposure and the diagnosis of CRC.[15] The proportion of male smokers in the Netherlands was high since the 1940s until the 1970s,[131] resulting in a greater risk of CRC for males. If true, the increase in incidence of CRC after 1975 could be partly explained by smoking and physical inactivity, which could have contributed

to the 1900-1955 birth cohort effects found in our study, especially for men. The weaker cohort effect found for women could be explained by lower smoking rates for women[131] and less physical inactivity compared with men, possibly caused by larger occupational changes to sedentary jobs in men compared with women.

Mortality rates decreased over time, particularly in younger birth cohorts. (chapter 2.2.). This could be attributed to earlier detection, especially familial surveillance in young and middle age, and advances in treatment, albeit with better results among younger patients.[84] Elderly patients were often treated with less aggressive adjuvant therapy compared with younger patients.[34, 66] Major changes in treatment for CRC were introduced in the period of this investigation. Adjuvant treatment became standard for patients with stage III colon cancer, which increased their survival by 7%.[98] Furthermore, treatment for rectal cancer improved by the introduction of total mesorectal excision (TME) surgery and short-term preoperative radiotherapy, which was first administered to the young and middle-aged patients and later to the older patients.[77, 134] Despite a marked increase in endoscopy practices there was no major improvement in stage distribution during the last decades (chapter 2.1.). This probably reflects the relatively low uptake of opportunistic screening activities in the Netherlands. Besides, polypectomy in high-risk patients found during surveillance and the forthcoming screening, can result in an increased detection rate of precursor lesions and a decrease of incidence of CRC, especially affecting stage I disease.

5.2.

The impact of optimalization of colorectal cancer disease management on mortality and forthcoming mass screening

Introduction

Colorectal cancer (CRC) is the third most frequent cancer in the Netherlands with over 10,000 new cases annually.[1] The incidence of CRC is increasing in the Netherlands,[157] which is likely to be attributed to a previous unfavourable pattern in lifestyle[84] and the aging population. The coming years the population is aging further and it is suggested that by 2015 there will be a 22% increase in the proportion of the European population aged over 65 years and a 50% increase in the proportion of people aged over 80 years.[3] Besides, mortality is decreasing in the Netherlands,[157] most likely due to earlier detection and improved treatment,[278, 279] resulting in an even larger proportion of patients with CRC. Therefore, a significant increase in the demand on CRC services is likely in the Netherlands as well as in Europe, especially for elderly. A report of the Dutch Cancer Society estimated the prevalence of CRC patients in the Netherlands to increase from 60,000 in 2005 to 100,000 in 2015.[109] These patients have to be followed-up, which will further claim hospital care and endoscopy capacity. A part of these patients will need extra care, i.e. because of a permanent stoma.

CRC supposedly develops via the adenoma-carcinoma sequence,[280-282] although it can take more than 10 years for malignancy to develop in this way.[283] Consequently, it is a curable disease when detected and treated in time. This provides an opportunity for screening which is already advised in the US[284] and is being implemented in some European countries like the United Kingdom,[285] but only at small scale in the Netherlands. In November 2009 the Dutch Health Council advised the government that mass screening in the Netherlands should be conducted using biannual immunochemical faecal occult blood test (iFOBT) for men and women aged 55-75 years.[43] A working group of the Dutch National Cancer Control Monitor investigated the feasibility of mass CRC screening in the Netherlands with respect to adaptation of the capacity and organisational structure.[286]

For patients with a positive test results based on screening, optimal diagnostics (especially colonoscopy) and treatment are necessary, which has to fit within standard diagnostics and care for CRC patients.

Quality of diagnostic and therapeutic interventions, as well as follow-up can be measured by variation in care and adherence to clinical practice guidelines. Previous studies in southern Netherlands showed considerable variation in diagnostic assessment and adjuvant treatment.[34, 35, 134, 172] Besides, adherence to clinical practice guidelines for CRC in southern Netherlands was suboptimal.[141]

Population-based studies, recording all cases diagnosed in a well-defined population, represent the best way to assess improvements in management or prognosis of CRC. Such studies are rare, because they require accurate and detailed data collection, which is difficult to achieve for many cancer registries. Here we give an overview of studies conducted in southern Netherlands based on cancer registry data and additionally collected data.

We describe variation in clinical care for patients with CRC in southern Netherlands and national changes in treatment on the effectiveness of forthcoming population screening and on the impact of mortality, the second and third objective described in this thesis.

Diagnostic assessment

National clinical practice guidelines stated that for diagnostic assessment of CRC all patients should undergo physical examination, blood analysis including haemoglobin and alkaline phosphatase assessment, colonoscopy, and imaging procedures of the colon, liver, and thorax.[58] Based on data from a population-based study using data from CRC patients diagnosed in 2005 in southern Netherlands guideline adherence percentages for each step to be taken to come to a clear diagnosis are expressed in Table 1.[287]

Table 1: Adherence to clinical practice guidelines (2004-2005)[58] for diagnostic assessment of colorectal cancer patients in southern Netherlands, 2005 [a 287]

	Colon (n=257) (%)	Rectum (n=251) (%)
Assessment of family history (age <60 years)	81	80
Documentation of comorbidity in clinical record	94	94
Physical examination reported [b]	86	82
Rectal examination reported	56	75
Assessment of Hb	97	96
Assessment of alkaline phosphatase level	77	77
Colonoscopy [c]	74	65
tumour in proximal and transverse colon	83	
tumour in distal colon	55	
Contrast enema in case of incomplete colonoscopy	33	-
Imaging procedures		
abdominal ultrasound	72	52
thoracic X-ray	85	81
abdominal CT scan	52	64
pelvic CT scan or MRI	-	36
Tumour biopsy, unless specific radiological image [d]	84	94

[a] Patients who underwent urgent surgery were excluded; [b] For colon cancer patients 53% incomplete, rectal cancer 54%; [c] Completion rate of colonoscopy was 63% for proximal colon tumours, 32% for transverse colon tumours, 62% for distal colon tumours, and 73% for rectal tumours; [d] At diagnostic endoscopy

Improvements in adherence to clinical practice guidelines for diagnostic assessment of CRC appeared possible, especially in the performance of imaging procedures such as contrast enema and thoracic X-ray or CT scans.[287] The majority of CRC patients who did not undergo colonoscopy underwent a sigmoidoscopy, especially those with rectal cancer. This is logical, as a colonoscopy can not be performed when an obstructing tumour is detected by sigmoidoscopy. In addition,

in some cases the tumour was evident based on imaging techniques. Nevertheless, a complete colonoscopy is proclaimed to be the aim for all colon and rectal cancer patients.[137] When visualization is incomplete, a contrast enema should be performed to detect synchronous polyps and tumours in the colon.[58] Only 33% of colon cancer patients with incomplete colonoscopy underwent a contrast enema, compared with 27% in 2002.[141] However, the presence of a malignant stricture, the most common reason for colonoscopy incompleteness, is often a reason not to perform a contrast enema. Therefore, the patients with CRC with an incomplete colon examination should undergo a postoperative colonoscopy. Among patients where complete visualization of the colon was not feasible with colonoscopy, imaging techniques such as virtual colonoscopy are likely to be of added value in the near future.

Diagnostic imaging procedures for liver and thorax examination found in the population-based study in southern Netherlands were in accordance with a British study conducted in 1999-2002 in which preoperative assessment of the liver occurred in 90% of patients with colon cancer and 88% of rectal cancer.[148] A higher performance rate for imaging procedures was expected, as all patients should be screened for distant metastases. This is especially important, since patients with liver metastases can be treated better nowadays.[288]

Time to treatment

On behalf of the Dutch Cancer Society a working group (consisting of medical specialists, social medicine specialists, and an economist) proposed in 2005 that the interval between diagnosis and initial treatment of cancer should be less than 15 working days, which was based more on psychological than on biological grounds.[159] A population-based study conducted in southern Netherlands using data from patients newly diagnosed with CRC showed that for 53% of colon cancer patients and 23% of rectal cancer patients initial surgical treatment started within 15 working days in 2005. For rectal cancer patients diagnosed in 2005 preoperative radiotherapy treatment started in time for only 4% of patients. Similar results were found for patients diagnosed in 2008, although the time to surgery decreased significantly for rectal cancer patients who had surgery as initial treatment (Table 2).[289] The advice from the Dutch Cancer Society seems thus yet far from feasible to adhere to in southern Netherlands[289] and there is little reason to suppose that this will be different elsewhere.

Table 2: Proportion of patients with CRC in whom treatment was started in time according to the 2006 Dutch Cancer Society advice (<15 working days)[289]

	2005 (%)	2008 (%)
Colon cancer	53	45
Rectal cancer without preoperative radiotherapy	23	46*
Rectal cancer with preoperative radiotherapy	4	4

*p<0.05

To decrease the interval between diagnosis and treatment a project called 'Sneller Beter' ('Getting Well Faster') was started in 2004 funded by the Ministry of Health.[168] One of its results was a reduction of 30 days (from 69 to 39 days) between first visit to the hospital and start of treatment, usually caused by reorganising the process.[169] Two hospitals included in our study engaged in this project in October 2004, which indeed resulted in a quicker start of surgical treatment of colon cancer patients in 2005 compared to other hospitals in southern Netherlands. However, the improvement of these two hospitals had again diminished in 2008. A possible explanation for the lack of improvement might be a higher prevalence of more severe and complicated comorbidities of the, often older, patients, which need to be managed before treatment could be started.

Lymph node detection

Lymph node detection in a population-based study of colon cancer patients diagnosed in 1999-2002 in southern Netherlands was poor with a median of 6 lymph nodes examined and the median for the department of pathology in Eindhoven being 8.[172] This result was communicated to the departments of pathology in the region in October 2005 by means of individual feedback and discussions in multidisciplinary working groups. Educational presentations created awareness among pathologists and surgeons, which resulted in an improvement in lymph node staging practice. To further increase the number of lymph nodes examined, several steps were taken by various regional pathology departments. In 2006 the department of pathology in Eindhoven increased fixation time to 42-48 hours, which in several other studies led to an increase in lymph node detection.[186, 187] The closer collaboration between surgeons and pathologists in the Eindhoven region resulted in 2007 in the use of a Patent blue staining method. Another pathology department in the Eindhoven Cancer Registry region also studied comparable methods to increase lymph node yield.[177] This diverse set of measures increased the number of examined lymph nodes among patients with colon cancer in the department of pathology in Eindhoven between 1999 and 2007 and resulted in a reduced proportion of colon cancer patients with insufficient (<12) lymph nodes examined from 87% in 1999 to 48% in 2007 (Figure 1).[215]

Examination of sufficient lymph nodes in each patient will most likely result in a higher proportion of patients with stage III disease who are offered adjuvant chemotherapy which can improve their survival. Since 2007, patients whose lymph nodes are examined insufficiently are considered at high-risk, because their survival is similar to stage III disease patients and they would thus benefit similarly from adjuvant chemotherapy.[290 58] Besides avoiding the potential burden of this treatment for the individual patient, we estimated potential savings up to a million euro for a large hospital when the proportion of high-risk node-negative patients is reduced accordingly.

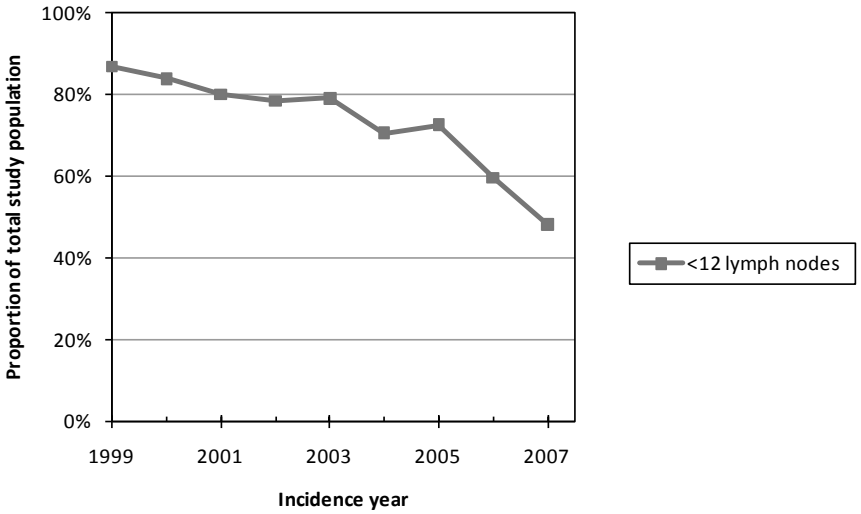

Figure 1: Colon cancer patients with an insufficient number of lymph nodes examined in the region of the department of pathology in Eindhoven since 1999 (n=1501)[215]

Adjuvant chemotherapy

According to the clinical guidelines, patients with stage III colon cancer should receive adjuvant chemotherapy.[58] A recent population-based study using data from all patients with stage III colon cancer diagnosed in 2001-2007 in southern Netherlands showed that elderly patients (≥75 years), those with comorbidity, and patients with a low socioeconomic status (SES) received chemotherapy less frequently. Moreover, there was large variation in adjuvant chemotherapy use between community hospitals (Table 3).[291] Adherence to guidelines for adjuvant chemotherapy appeared still suboptimal in 2007, especially for elderly patients.[291]

It has been shown in several other studies that a lower proportion of elderly patients receive adjuvant chemotherapy.[35, 200] Several reasons are given in the literature to explain why elderly patients are less likely to receive adjuvant chemotherapy, including the presence of concomitant diseases, frailty, the absence of supportive caregivers, and a decrease in the patients' general condition and cognitive ability.[201] Elderly patients seem less willing to accept the negative effects like toxicity of adjuvant chemotherapy compared to younger patients.[202, 203] In addition, the proposal of the medical oncologist, which is based on clinical experience, is important in the choice for adjuvant chemotherapy. However, several studies have shown that elderly patients equally benefit from adjuvant chemotherapy treatment with similar toxicity levels.[98, 199] Therefore, it seems that a larger proportion of elderly patients could receive adjuvant chemotherapy.

Table 3: Stage III colon cancer patients diagnosed between 2001 and 2007 in southern Netherlands; proportion of patients who received adjuvant chemotherapy according to age[291]

	n	Proportion of patients receiving chemotherapy (%)		
		<65 yrs	65-74 yrs	≥75 yrs
Overall	1,637	85	68	17**
Gender				
male	783	85	66	20
female	854	86	71	15
No. of comorbid conditions [a]	601 [b]	89*	80**	19
none	464	82	66	19
1	374	73	55	14
≥2	164	82	72	16
unknown				
Socioeconomic status				
low	443 [b]	83	66	13
intermediate	601	89	69	18
high	467	84	73	24
institutionalized	96	73	33	8
Stage				
IIIA (T1-2, N1)	114	85	58	9*
IIIB (T3-4, N1)	1,068	85	67	15
IIIC (any T, N2)	455	87	74	23
Lymph nodes examined				
<6	483	80	63	15
6-11	551	89	71	18
≥12	603	86	70	18
Tumour grade				
poor	429	83	69	15
moderate/well	1,102	87	68	18
unknown	105	-	-	-
Diagnostic period				
2001-2002	469	86	64	17
2003-2004	416	89	64	14
2005-2006	482	85	75	17
2007	270	81	70	20
Hospital of treatment				
1	85	96	59	16
2	150	89	74	11
3	102	85	67	12
4	134	82	65	17
5	142	93	78	25
6	112	90	83	24
7	117	77	61	21
8	122	86	63	18
9	201	84	68	18
10	222	84	60	9

[a] Excluding hypertension; [b] Does not add up to total due to missings

* p<0.05, **p<0.001

The lack of adherence to clinical practice guidelines for adjuvant chemotherapy for patients with a low SES was also found in a previous population-based study in southern Netherlands.[35] This is remarkable in view of the good access to health care facilities and the Dutch health insurance system with a coverage of over 99%.[205] Patients with a higher SES have a more positive self-rated health,[208, 209] and are more active which may affect treatment decision-making on aggressive treatment.

The wide variation in chemotherapy use across hospitals in southern Netherlands[291] underscores the influence of institutional factors and local practice patterns in determining the use of adjuvant chemotherapy.[210] Physicians generally agree with clinical guidelines recommending adjuvant chemotherapy for stage III colon cancer for healthy and younger patients, but differ widely on recommendations for older and sicker patients.[211] In addition, fast and slow adaptors in hospitals for the administration of chemotherapy could partly explain variation in chemotherapy use. Similarly, large variation between hospitals was also reported in this region for adjuvant systemic treatment for patients with breast cancer.[292]

To prevent any undertreatment or overtreatment of subgroups of especially elderly patients with colon cancer otherwise fit enough to undergo chemotherapy, some form of geriatric assessment might be helpful in decision making. Awareness of physicians should reduce hospital variation and prevent undertreatment among lower SES patients.

Follow-up

Compared to evidence-based guidelines, follow-up intensity was suboptimal for patients with CRC diagnosed in 2003-2005 in southern Netherlands with large variation between hospitals (Table 4).[293] Older patients (≥75 years), those with a rectal tumour, and those diagnosed in 2003 were less likely to receive regular follow-up comprising at least two control appointments by a specialist and two CEA measurements. In the second and third year of follow-up, the intensity of follow-up was higher in younger (<50 years) patients compared to their older counterparts. Similarly, a low intensity of follow-up of CRC patients and a large variation in follow-up intensity between patients were reported in literature.[245-248] Low follow-up intensity might deny patients the chance for early detection of treatable local or distant recurrences or metastases and potential cure. Elderly patients were less likely to receive intensive follow-up, which is not surprising, since follow-up is especially important for those eligible for treatment of local or distant recurrences.

A clinical care pathway accomplished with a clear form and appointment scheme for the follow-up of CRC patients in each hospital will also increase the follow-up intensity and reduce variation in follow-up intensity between hospitals.[251]

Table 4: Adherence to modes of follow-up of CRC patients with a follow-up time of at least 12 months or at least 36 months [a] [293]

Follow-up	<12 months	Adherence percentage (n=449)	12-36 months	Adherence percentage (n=196)
Adequate	≥ 1 colonoscopy ≥ 2 controls ≥ 1 ultrasound liver ≥ 2 CEA measurements	10	≥ 1 colonoscopy ≥ 1 control ≥ 1 ultrasound liver ≥ 1 CEA measurement	12
Suboptimal	≥ 2 controls ≥ 2 CEA measurements	56	≥ 1 control ≥ 1 CEA measurement	43
Insufficient	< 1 control < 1 CEA measurement	34	< 1 control < 1 CEA measurement	45

[a] Excluding patients with T1N0 rectal cancer

Twenty-seven colonoscopies five years after surgery should be performed to detect one patient with curable CRC. Similarly, 27 CT scans of the liver, 32 CT scans of the chest, and 534 CEA measurements are needed to detect one patient with curable CRC.[245] A CEA measurement is much cheaper than a CT scan or a colonoscopy and therefore used in the follow-up of CRC patients to detect patients with a recurrence or metastasis at an early stage.[58]

Before 2005 the clinical guideline for CRC in the Netherlands contained little information about follow-up and was not very strict in its advice. The medical specialist decided with the patient about the best follow-up. In 2005 the guideline became more stringent, but remained rather informal and gave room to conduct follow-up according to the views of the medical specialist. The controversy about the usefulness of follow-up in literature is probably an important reason for the lack of adherence to the guidelines, although a Cochrane review in 2007 concluded that there is an overall survival benefit for follow-up of CRC patients.[62]

Impact on colorectal cancer mortality from optimalization of disease management

The research projects reported in this thesis were intended to give a broad overview of variation of current medical practices for patients with CRC in recent years. It offers a view of potential improvements that could affect quality of life and survival of patients and thus also mortality rates. There is substantial improvement in management and survival of colon and rectal cancer between 1989 and 2006 in the Netherlands. The 5-year relative survival for colon cancer in men increased from 52% in 1989-1993 to 58% in 2004-2006, and from 55% to 58% in women.[278] For rectal cancer the 5-year relative survival increased similarly from 53% in 1989-1993 to 60% in 2004-2006.[279] In the period 1975-2004 in southern Netherlands an increase in 5-year relative survival of colon cancer was

reported from 50% in 1975-1984 to 58% in 2000-2004. The increase in survival for rectal cancer in southern Netherlands increased from 44% to 59%, and when the survival in the period 1965-1974 (33%) is also taken into account, the relative improvement in survival was the largest of all adult tumours.[157]

Stage distribution and the increased use of adjuvant chemotherapy most likely resulted in a substantial improvement in survival, especially in stage III colon cancer patients with an increase in 5-year relative survival from 46% in 1989-1993 to 59% in 2004-2006.[278] For rectal cancer a marked improvement in survival went together with a shift from postoperative to preoperative radiotherapy, improved (TME) surgery, and increased use of adjuvant chemotherapy for stage III patients.[279]

A further increase in survival for patients with colon cancer might be accomplished by administration of adjuvant chemotherapy to some stage III patients, i.e. those who are older and patients with a low SES, since these groups are known to receive adjuvant chemotherapy less frequently for good reasons such as severe comorbidity or patient refusal.[291]

For metastatic colon cancer, median survival improved from 26 (95% CI 22-32) weeks in 1990-1994 to 39 (95% CI 31-48) weeks in 2003-2004,[278] probably due to an increased use of more effective chemotherapy, and probably a more adequate selection of patients eligible for surgery.[79] In the most recent years, there has been a regionalisation of the surgical expertise for treating liver metastases, leading to a better survival in stage IV colon cancer patients in 2004-2006 compared to the previous periods. These results indicate that optimalization of disease management for CRC has also reduced mortality.

The largest effect of optimalization of disease management for CRC in the last decades is due to the introduction and wide use of adjuvant chemotherapy for patients with stage III colon cancer. Based on results from RCTs the absolute effect of adjuvant chemotherapy in patients with stage III colon cancer on 5-year overall survival was 7%.[98] The population of Dutch patients with CRC consisted in 2004-2006 for 59% of patients aged <75 years, 79% of whom received adjuvant chemotherapy. Of the 41% of patients with CRC aged ≥75 years 19% received adjuvant chemotherapy.[278] Therefore, the effect of adjuvant chemotherapy in patients with stage III colon cancer on mortality is estimated to be 7%*0.79=5.5% for patients <75 years and 7%*0.19=1.3% for those ≥75 years. For the total group of stage III patients the effect on mortality is thus estimated to be (5.5%*0.59) + (1.3%*0.41)=3.8%. For all patients with CRC the effect of adjuvant chemotherapy is estimated to be 3.8/4=1%, since a quarter of all patients with CRC have stage III disease.[1] The effect of other improvements in quality of care, like better diagnostic assessment, lymph node detection, and follow-up result in a rather small effect (estimated <1%) on mortality for the total population of patients with CRC.

Based on the MISCAN-Colon micro simulation model using the 2000 US population with respect to CRC risk factor prevalence, screening, and treatment,

the potential reduction of CRC mortality was estimated to be almost 50% by the year 2020 in the US. This was based on a rather optimistic yearly 4% decrease in the prevalence of risk factors, an increase in CRC screening to 70%, and wide-spread use of the best available chemotherapy across all age groups. However, without action to further increase uptake of current effective interventions, the reduction in CRC mortality is likely to be only 17% in the US.[273] Like all projections, uncertainty exists in underlying data and assumptions, especially in the relative risks of the various risk factors. Therefore, the results should be interpreted with some caution. Further micro simulation modelling demonstrated that declines in CRC death rates in the US are largely affected by screening (53% of the mortality reduction) and with a smaller, but demonstrable impact of risk factor reductions (35% of the mortality reduction) and improvements in treatments (12% of the mortality reduction).[294] The effect of better treatment on mortality is thus relatively small, and accounted for an absolute mortality reduction of 3% in the US.[294] A large participation of the general population in mass screening programmes and awareness for symptoms and risk factors of CRC are therefore of vital importance. It is questionable to what extent these results can be extrapolated to the Netherlands, where the awareness for CRC is low[274] and mass screening for CRC is not yet implemented. However, the introduction of mass screening for CRC will probably result in increasing awareness for CRC in the general population and it is estimated, based on randomized population-based CRC-screening trials, that the participation rate for screening will be around 60%.[46, 47] Therefore, it is not unlikely that similar estimates in mortality reduction can be expected in the future in the Netherlands.

Implications of the introduction of colorectal cancer mass screening in the Netherlands

Screening for CRC is widely accepted, but there is no consensus on the preferred strategy. Several screening strategies can be used including guaiac faecal occult blood test (gFOBT), immunochemical faecal occult blood test (iFOBT), flexible sigmoidoscopy, colonoscopy, and colonography (virtual colonoscopy).[43]

Two Dutch randomized population-based CRC-screening trials demonstrated superior participation and detection rates for iFOBT compared to gFOBT and flexible sigmoidoscopy.[46, 47] The participation rate for screening with iFOBT in these Dutch trials was around 60% and the detection rate was 5%.[46, 47] The positive predictive value of iFOBT for advanced adenomas at the initial screening round was 53-55%, whereas this was 10% for CRC.[46, 47] Screening with sigmoidoscopy has a detection rate of 10%, but the participation rate is only 30%.[46] This might be partly caused by the low CRC awareness in the Netherlands.

The iFOBT provides quantitative test results, which allows optimalization of the cut-off value for follow-up colonoscopy.[295, 296] A low cut-off value (50 ng/ml) provided a high detection rate of advanced neoplasia, but also more false positive

test results and thus a higher number of unnecessary colonoscopies. Increasing the cut-off value to 200 ng/ml resulted in a decrease of the detection rate for advanced neoplasia, but a more favourable positive predictive value.[297] In a Dutch randomized population-based CRC-screening trial a cut-off value of 75 ng/ml provided an adequate positivity rate (5.7%) and an acceptable trade-off between detection rate and number needed to scope to find a screened person with an advanced neoplasia.[297] Therefore, this seems to be an acceptable cut-off level.

In November 2009 the Dutch Health Council advised the government that mass screening in the Netherlands should be conducted using biannual iFOBT followed by colonoscopy for those with a positive iFOBT for men and women aged 55-75 years.[43] The target population for mass screening for CRC in the Netherlands will consist of 3.5 million men and women who should be invited for screening biannually. Gradual implementation of the mass screening program is inevitable, and it is expected to take still another five years to increase colonoscopy capacity sufficiently for mass screening.[43] To prevent one death due to CRC 785 persons should perform an iFOBT and 40 persons should undergo a colonoscopy.[43]

Results from population-based studies as described above indicate that quality of care for CRC has improved over time. However, further improvements in especially diagnostic assessment are necessary to optimize care and be prepared for screening. In 2005 in southern Netherlands, just over 60% of patients with CRC had a total colon examination preoperative, with obstruction by a tumour as the most important reason not to perform a colonoscopy to visualise the entire colon.[287] However, patients with incomplete colonoscopy preoperatively, should undergo a complete colonoscopy within three months postoperatively.[58] This is only performed in 5% of patients with preoperative incomplete colonoscopy.[293] Nevertheless, colonoscopy completeness is much higher in persons who should undergo colonoscopy for screening purposes,[48] since in the large majority of these persons no abnormalities are found. At the moment, the colonoscopy capacity in the Netherlands is insufficient, especially when mass screening is introduced. The Dutch Health Council estimated that when mass screening is fully implemented, about 78,000 extra colonoscopies are necessary.[43] In this pre-screening era, the waiting time for a colonoscopy is around 5 weeks, ranging from 1 to 15 weeks depending on geographic region.[298] The Dutch Health Council stated that the waiting time for colonoscopy should be reduced largely for psychological reasons to a maximum of three weeks, even with the introduction of mass screening.[43] To decrease the waiting time for a colonoscopy more gastroenterologists are being trained who already increased fourfold since 1990,[299] with an extra increase of 8% to increase the endoscopy capacity further.[286] Besides, there is a trend that nurse practitioners specially trained in endoscopies can do endoscopies to reduce the workload for the gastroenterologists.[300]

In February 2010 the Minister of Health informed the parliament to postpone the introduction of CRC screening in the Netherlands, since the colonoscopy capacity is insufficient. This is important, since patients who are currently referred

for a colonoscopy should undergo this in time. This group of patients usually has symptoms indicative for CRC or other gastrointestinal diseases or should undergo CRC screening since they are at high risk for CRC caused by hereditary CRC or controls after previous polyps or CRC. If every general practitioner refers about 40 new symptomatic patients per year for a colonoscopy, this would result in about one new patient with CRC per general practitioner. Besides, the incidence of CRC is increasing and the mortality is decreasing,[157] resulting in an increasing amount of patients alive with CRC. This results in an increased necessity of colonoscopy in the coming years, since patients alive with CRC should undergo follow-up colonoscopies regularly. Therefore, a gradual introduction of CRC mass screening seems inevitable to minimize the problems with colonoscopy capacity.[53] To prevent a lack of colonoscopy capacity due to the introduction of mass screening, it could be considered to set the cut-off value for the iFOBT somewhat higher than the optimal cut off value to detect the patients with the highest risk of CRC first when mass screening can not be fully implemented yet. Based on results from a Dutch population-based randomized CRC-screening trial the positivity rate decreased from 5.7% using iFOBT with a cut-off level of 75 ng/ml to 4.8% when the cut-off level was 100 ng/ml.[297]

Increasing colonoscopy use will also result in an increasing workload for pathology departments since biopsies from malignant lesions as well as removed polyps have to be examined. However, after an initial increase in pathological examinations, a decrease is expected, since prevalent malignant lesions and polyps are detected at a first screening round. However, only 52% of colon cancer patients still had sufficient lymph node detection in a regional Dutch pathology department in 2007.[215] National data indicate that insufficient lymph node detection in patients with CRC is still a wider problem.[39, 303] However, if this is rather due to the high workload in pathology departments, then that can be addressed by training assistants.

The costs of treatment of CRC are increasing rapidly, due to new systemic approaches to advanced disease. Lansdorp-Vogelaar et al. conducted a simulation study based on the MISCAN-Colon micro simulation model in the perspective of the health care system for a cohort of 50-year-old American individuals at average risk of CRC and to be screened with 100% adherence from age 50 to 80 years and follow up until death.[302] They concluded that with the projected increase in chemotherapy costs for advanced CRC, screening by annual gFOBT, annual iFOBT, sigmoidoscopy every five years, and the combination of sigmoidoscopy every five years and annual gFOBT have become cost saving.[302] It might technically be concluded that screening is a desirable approach not only to reduce the incidence and mortality of CRC but also to control the costs of treatment for CRC.[302]

In the Netherlands, there are five regional screening organisations for mass screening of breast and cervical cancer. These organisational structures can be used for mass screening for CRC as advised by both the Dutch Health Council and the Dutch National Cancer Control Monitor, since they are experienced in mass

screening programmes.[43, 286] However, adequate linkage between the screening organisation and further (hospital) care and thus also Comprehensive Cancer Centres is important to quickly diagnose a patient and start treatment.

Current perspective

Due to the retrospective nature of population-based studies it was not known to which extent the prognostic impact observed in these studies was caused by a selection of the 'fitter' patients for adjuvant or palliative treatment, or by other factors associated with treatment allocation besides those controlled for in the analysis. Moreover, stage-migration is likely to have occurred, since diagnostic techniques have been improved[146, 147, 303] and lymph node analysis has become more adequate in the Netherlands during the study period.[39, 301]

The clinical practice guidelines in the Netherlands are becoming more and more evidence-based and are developed by a multidisciplinary working group of medical specialists. Adherence to these guidelines indicates the best care for the average patient without severe comorbidity. Therefore, non-adherence to these guidelines indicates - in general - suboptimal care and should be low. However, non-adherence to the guidelines does not necessarily indicate an inferior quality of care, since the 'average' patient does not exist and care deviating from the guideline can be the best care for a specific patient due to i.e. comorbidity, aging, or the wish of the patient. The large proportion of elderly patients presenting with comorbidity, and the lack of evidence-based guidelines for this group, often call for pragmatic individualised treatment.[34] For these patients the reason for deviating from the guidelines should be mentioned in the medical record. In view of the growing proportion of elderly patients with CRC, partly because of the rising incidence rates, but especially because of the aging population, clinicians will more and more often face difficult decisions regarding guideline adherence.

Together with the specialists and hospitals the Dutch government aims to make quality of care visible for everybody in 2011,[304] which means availability and accessibility of information about outcome, quality, and safety of hospital care. Careful registration of variables of care as well as patient characteristics should result in objective and reliable measurements of care. Care professionals should be informed about the care given by means of feedback. Auditing is a tool to reach this goal, therefore the Dutch Surgical Colorectal Audit (DSCA) has been established for CRC.[305] Since January 2009 participation at the DSCA is a performance-indicator for hospitals. By auditing, a large amount of information is collected for each patient, which makes it possible to correct for case mix. In the future, information might be collected directly from the electronic patient file. However, this is not possible yet, which results in a large registration load for the hospital at the moment. The Cancer Registry has a registration system with registration clerks in every Dutch hospital for over twenty year, which collects data at much lower costs. In the southern part of the Netherlands data on comorbidity

is additionally collected for over 15 years. The quality of these data is high, because of thorough training of the registration clerks and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[80] In reply to requests from the various physicians the Cancer Registry has been expanding its data collection for patients with CRC since January 2008 and the following items are additionally collected: the approach of the tumour (endoscopic vs. laparoscopic or conversion); anastomotic leakage including the presence of an abscess; whether the resection was elective or urgent; the circumferential margin; the distance between anal verge and tumour; and whether a stoma was constructed.[1] Thus, there is an overlap between the data collection of the Cancer Registry and the data collection of the DSCA. A difference between both data collections is that the Cancer Registry registers a cancer patient six to nine months after diagnosis[1] while this time window can be much shorter within the framework of the DSCA.

A registration system for gynaecological oncology (Registration system Oncological Gynaecology (ROGY)) was started in 2006 to collect data about every patient with a gynaecological tumour in most hospitals in the Eindhoven Cancer Registry region.[306] Data is collected by the medical specialists themselves, which led in some cases to incompleteness and inconsistencies of the dataset. To solve this problem research nurses were hired in some hospitals to enter the data timely and in a uniform way and make adjustments (in e.g. treatment plan after the oncology meeting) when necessary. Based on this experience, data collection by medical specialists, who usually have other priorities in their work, is far from optimal. Such registration can better be performed by independent registrars, preferably of the Cancer Registry who are trained in working uniformly and checking completeness of the dataset.

Conclusion

Substantial improvements in quality of care have been established in the last decades for patients with colorectal cancer in the Netherlands. Population-based changes in treatment, especially the increased administration of chemotherapy in colon cancer, resulted in an increased survival for patients with colorectal cancer. However, administration of adjuvant chemotherapy, lymph node detection, diagnostic assessment, time to treatment, and follow-up of patients with colorectal cancer are all still suboptimal and require further attention and monitoring. Special emphasis should be paid to elderly patients, since this is a heterogeneous group of patients who often need individualized care.

In the coming years, an increase in incidence is expected due to the aging of the population, the increasing trends towards an unhealthier lifestyle since World War II, and the introduction of mass screening. To adequately handle the large numbers of patients with colorectal cancer, ongoing interventions in infrastructure and monitoring of quality of care are of crucial importance.

CHAPTER 6.

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Summary

Colorectal cancer (CRC) is the third most frequent cancer among males, and the second most frequent cancer among females in the Netherlands. In 2007, almost 12,000 patients were newly diagnosed with CRC and almost 5,000 patients died of the disease. In this thesis, studies on the trends in incidence, mortality, and survival of CRC are presented, as well as studies on different aspects of quality of care for patients with CRC including diagnosis, treatment, and follow-up. The Eindhoven Cancer Registry (ECR) and the Netherlands Cancer Registry were used as the main data sources.

Increasing incidence of colorectal cancer

In this thesis the clinical and epidemiological trends in CRC in the ECR region from 1975 to 2007 are described, including trends in subgroups. Large changes have taken place in this period. First, there has been a gradual increase in incidence, which was most marked for males and proximal tumours. The increasing incidence in de last decades is likely to be attributed to lifestyle factors including smoking, lack of physical activity, obesity, and an increased alcohol consumption. Furthermore, survival increased dramatically, especially among patients younger than 70 years. This was at least partly due to changes in treatment; particularly since the mid-1990s when a growing proportion of patients underwent for example adjuvant chemotherapy. Also, large changes in surgery for rectal cancer took place, such as the introduction of Total Mesorectal Excision (TME). The advances in survival led in turn to decreased mortality rates, and consequently to increased prevalence rates with over 50% since 1984. The decreasing mortality was due to earlier detection and improved treatment. Both the effects on incidence and mortality were strongest in younger patients.

Diagnosis incomplete

Evidence-based guidelines, developed by a multidisciplinary working group of medical specialists, indicate optimal care for an average patient. The level of adherence to these guidelines and interindividual and interinstitutional variation in care may indicate the quality of care. Adherence to diagnostic guidelines for CRC was suboptimal, especially with respect to the performance of imaging procedures. Examination of the liver and lungs to detect metastases was not performed in all patients (85%). All patients should undergo a colonoscopy, but this was done in only two thirds of patients. Besides, the colonoscopy was often incomplete, especially in patients with comorbidity, obstruction by the tumour, or poor bowel preparation. Although there could be a good reason not to perform a complete colonoscopy, a complete bowel examination should be performed preoperatively. When this was impossible it should be done postoperatively to check for second malignancies or polyps. Among patients where complete visualisation of the colon

was not feasible with colonoscopy, imaging techniques such as virtual colonoscopy might be of added value in the near future.

Time to treatment exceeds advice

The time between diagnosis and treatment should be reduced in southern Netherlands to meet the advice of the Dutch Cancer Society in 2005, which stated that the time interval between diagnosis and start of treatment should be less than 15 working days (3 weeks) for all cancer patients. Treatment did not start within 15 working days for half of the patients with CRC receiving surgery as initial treatment. Preoperative radiotherapy for rectal cancer did not start in time for the large majority of patients.

Lymph node detection can be improved

According to clinical practice guidelines, a minimum of 10-12 lymph nodes should be examined in patients with colon cancer. A previous study showed that in the majority of patients insufficient lymph nodes were analyzed in southern Netherlands. A set of measures directed at increasing lymph node detection led to a clinically relevant increase in the number of lymph nodes examined. However, in 2007, there was still a considerable proportion of patients with insufficient lymph nodes examined. Therefore, the resection specimens were stained with blue dye, which further increased the lymph node detection rate. Patients with insufficient lymph nodes examined are considered high-risk and should receive adjuvant chemotherapy. Large savings can be made by increasing the lymph node yield due to the reduced proportion of high-risk node-negative patients who would otherwise have received adjuvant chemotherapy.

Adjuvant chemotherapy administration suboptimal

Regional and national trends in the clinical management of patients with CRC influence survival. The most important change in the treatment of colon cancer was the introduction of adjuvant chemotherapy for patients with stage III in the mid 1990s. Elderly patients received adjuvant chemotherapy less often compared to younger patients in the period 2001-2006, with large interhospital variation. Furthermore, patients with comorbidity and those with a low socioeconomic status received less often adjuvant chemotherapy.

The receipt of adjuvant chemotherapy was the most important predictor of survival. Patients with comorbidity, higher tumour stage, poor tumour grade, and males have a higher risk of dying from colon cancer. There was no clear improvement in survival between 2001 and 2006. After adjustment of the above mentioned factors, age no longer influenced survival. Adherence to guidelines for adjuvant chemotherapy was still suboptimal in recent years, especially for elderly patients.

Increased use preoperative radiotherapy rectal cancer

The introduction of preoperative radiotherapy is the most important change in the treatment of rectal cancer since 1989 in the Netherlands. Similarly as in colon cancer treatment, the large majority of patients with rectal cancer stage I-III underwent a resection, while this proportion is decreasing for patients with metastatic disease. In these patients the use of chemotherapy increased strongly. Survival of patients with rectal cancer increased over time, with the largest improvement found in patients with stage III disease.

Follow-up intensity low

When primary treatment of CRC is completed, follow-up should be started to detect local recurrences, distant metastases, and second tumours in an early asymptomatic stage. The intensity of follow-up for patients with CRC in southern Netherlands is suboptimal with a large variation between patients. Elderly patients, those with a rectal tumour, and those with a small tumour were less likely to receive regular follow-up. Non-adherence to clinical guidelines for follow-up might partly be ascribed to the wish of the (older) patient.

Chemotherapy improved survival in metastatic colon cancer

The proportion of patients diagnosed with metastatic colon cancer was stable over time. The administration of chemotherapy to patients with metastatic colon cancer has increased over time, which was accompanied by an improved survival among these patients. In contrast, survival remained similar over time for patients with metastatic colon cancer who did not receive chemotherapy. Increasing age, comorbidity, and having more than one organ affected by metastatic disease had a negative effect on survival, while chemotherapy use had a strong positive effect on survival. Therefore, the effect of stage migration (an improvement in survival caused by earlier detection of distant metastases) seemed limited. The improvement in survival for patients with metastatic colon cancer could thus be ascribed to an increased administration of increasingly effective chemotherapy regimens.

Quality of care can be further improved

The results presented in this thesis were discussed and a current perspective of the quality of care for patients with CRC was given, with emphasis on diagnosis, treatment, and follow-up. The impact of optimalization of disease management on mortality of colon and rectal cancer and the effect of the forthcoming mass screening for CRC on quality of care were discussed.

The conclusion of this thesis is that substantial improvements in quality of care have been established in the last decades for patients with colorectal cancer in the Netherlands. Population-based changes in treatment, especially the increased administration of chemotherapy in colon cancer, resulted in an increased survival

for patients with colorectal cancer. However, administration of adjuvant chemotherapy, lymph node detection, diagnostic assessment, time to treatment, and follow-up of patients with colorectal cancer are all still suboptimal and require further attention and monitoring. Special emphasis should be paid to elderly patients, since this is a heterogeneous group of patients who often need individualized care.

In the coming years, an increase in incidence is expected due to the aging of the population, the increasing trend towards an unhealthier lifestyle since World War II, and the introduction of mass screening. To adequately handle the large numbers of patients with colorectal cancer, ongoing interventions in infrastructure and monitoring of quality of care are of crucial importance.

Samenvatting

Dikkedarmkanker is een van de meest voorkomende vormen van kanker in Nederland met bijna 12.000 nieuwe gevallen en bijna 5.000 sterfgevallen in 2007. Daarmee komt dikkedarmkanker bij mannen op de derde plaats na prostaat- en longkanker en bij vrouwen komt alleen borstkanker meer voor.

In dit proefschrift worden studies beschreven over de trends in incidentie (het vóórkomen) en overleving van en sterfte door dikkedarmkanker. Ook bevat het studies over verschillende aspecten van kwaliteit van zorg voor patiënten met dikkedarmkanker waaronder diagnostiek, behandeling en follow-up.

Er is gebruik gemaakt van gegevens van de Kankerregistratie van het Integraal Kankercentrum Zuid (IKZ) te Eindhoven en van de Nederlandse Kankerregistratie.

Er zijn verschillende vormen van dikkedarmkanker. Een coloncarcinoom is een kwaadaardige tumor in het colon, het eerste 2/3de deel van de dikke darm. Een kwaadaardige tumor in the laatste 1/3de deel van de dikke darm is een rectumcarcinoom, ook wel endeldarmcarcinoom genoemd. Met een colorectaalcarcinoom wordt een kankergezwel in één van beide delen van de dikke darm (colon of rectum) bedoeld.

Toename van dikkedarmkanker

In dit proefschrift zijn de klinische en epidemiologische trends in Zuid-Nederland (de IKZ-regio) van de afgelopen 33 jaar beschreven (1975-2007) inclusief de trends in subgroepen. Er hebben zich in deze periode grote veranderingen voorgedaan. Zo was er een forse toename van dikkedarmkanker, met name bij mannen. Dikkedarmkanker komt steeds vaker voor in het begin (het opstijgende deel) van de dikke darm. Verder was er een verbetering in overleving, die het grootste was bij het rectumcarcinoom en stadium III coloncarcinoom. Hieraan gingen veranderingen in de behandeling vooraf, zoals adjuvante chemotherapie, de verschuiving van post- naar preoperatieve radiotherapie bij rectumcarcinoom en de introductie van nieuwe chirurgische technieken zoals de Total Mesorectal Excision (TME). De stijging in zowel incidentie als overleving heeft ertoe geleid dat het aantal patiënten in leven dat ooit is gediagnosticeerd met dikkedarmkanker gestaag is toegenomen met meer dan 50% tussen 1984 en 2004. De stijgende incidentie van dikkedarmkanker in de laatste decennia is het gevolg van roken, minder lichaamsbeweging, een ongezond voedingspatroon en toegenomen alcoholconsumptie. Daardoor is vooral bij de jongere patiënten een verhoogde kans op dikkedarmkanker te zien. De dalende sterfte aan dikkedarmkanker komt door vroegere ontdekking en verbeterde behandeling, vooral bij jongere patiënten.

Diagnose onvolledig

Evidence-based richtlijnen, ontwikkeld door een multidisciplinaire werkgroep van medisch specialisten, geven aan hoe de zorg van een patiënt in het algemeen zou moeten zijn. Door te bepalen in welke mate de richtlijnen worden nageleefd en of er variatie is in de zorg, kan de kwaliteit van de zorg bepaald worden.

De naleving van de richtlijn voor het stellen van de diagnose dikkedarmkanker in Zuid-Nederland is suboptimaal, met name de beeldvorming (o.a. röntgen, CT, en MRI scan) werd onvoldoende uitgevoerd. De lever en longen van een patiënt met (verdenking op) dikkedarmkanker moeten worden gecontroleerd op de aanwezigheid van metastasen, maar dit gebeurde niet bij alle patiënten (85%). Hoewel alle patiënten een darmonderzoek (colonoscopie) zouden moeten ondergaan, werd slechts bij 2/3de van de patiënten een dergelijk onderzoek uitgevoerd. Bovendien waren de colonoscopiën vaak onvolledig, vooral bij patiënten met bijkomende ziekten (comorbiditeiten), obstructie van de darm door de tumor en patiënten met een slechte darmvoorbereiding. Hoewel er goede redenen kunnen zijn voor een onvolledige colonoscopie, dient de darm preoperatief of eventueel postoperatief volledig onderzocht te worden op tweede tumoren en poliepen. Als volledige visualisering van de dikke darm niet mogelijk is, zou een virtuele colonoscopie in de toekomst uitkomst kunnen bieden.

Tijd tot behandeling te lang

De tijd tussen de diagnosestelling en de start van de behandeling voor patiënten met dikkedarmkanker in Zuid-Nederland voldoet niet aan het advies van KWF Kankerbestrijding uit 2005. Volgens dit advies zou bij elke kankerpatiënt binnen 15 werkdagen (3 weken) na de diagnose met de behandeling gestart moeten worden. Bij ongeveer de helft van de patiënten met dikkedarmkanker die een chirurgische resectie als initiële behandeling kregen was de behandeling binnen 15 werkdagen begonnen. Bij patiënten met een rectumcarcinoom die preoperatieve radiotherapie hebben ondergaan, was slechts in een beperkt aantal gevallen op tijd gestart met de behandeling.

Meer lymfeklieren onderzoeken

Volgens de klinische richtlijn zouden bij elke patiënt met een coloncarcinoom minimaal 10-12 lymfeklieren moeten worden onderzocht op de aanwezigheid van tumorweefsel. Uit eerder onderzoek blijkt dat er vaak onvoldoende lymfeklieren waren geanalyseerd. Daarom zijn er maatregelen genomen om de lymfeklieropbrengst te verhogen. Dit heeft geleid tot verbetering, want er is een duidelijke afname te zien in het aantal patiënten waarbij onvoldoende lymfeklieren zijn onderzocht. In 2007 was er echter nog steeds een aanzienlijk deel van de patiënten waarbij onvoldoende lymfeklieren op tumorweefsel zijn onderzocht. Dat was de aanleiding voor een studie waarbij er blauwe kleurstof in het resectiepreparaat is ingespoten, zodat de lymfeklieropbrengst is verbeterd.

Patiënten waarvan de lymfeklieren onvoldoende zijn geanalyseerd, worden gezien als patiënten met een hoog risico op terugkeer van de ziekte. Deze patiënten moeten adjuvante chemotherapie (chemotherapie naast een behandeling met in dit geval chirurgie) krijgen. Verkleining van deze groep hoogrisico patiënten door een adequater lymfeklieronderzoek leidt tot een grote kostenbesparing voor het ziekenhuis, omdat minder chemotherapie nodig is.

Adjuvant chemotherapie gebruik suboptimaal

Regionale en nationale trends in klinisch management van dikkedarmkanker hebben invloed op de overleving. De belangrijkste verandering in de behandeling van het coloncarcinoom was het gebruik van adjuvante chemotherapie bij patiënten met stadium III (metastasen in de lymfeklieren). Oudere patiënten kregen minder vaak adjuvante chemotherapie dan jongere patiënten. Dit was ook het geval bij patiënten met comorbiditeit en patiënten met een lage sociaaleconomische status. Bovendien waren er grote verschillen tussen ziekenhuizen.

Het krijgen van adjuvante chemotherapie is de belangrijkste factor voor een betere overleving. Patiënten met comorbiditeit, een hoger tumorstadium (meer uitgebreide ziekte), een slechte tumordifferentiatie en mannen hebben een grotere kans om te sterven aan de ziekte. Er is geen duidelijke verbetering in overleving te zien tussen 2001 en 2006. Leeftijd had na correctie voor bovenstaande factoren geen invloed meer op de overleving. Dit duidt erop dat de naleving van de richtlijn nog steeds suboptimaal is en dat er verbetering mogelijk is, vooral voor oudere patiënten.

Toename preoperatieve radiotherapie rectumcarcinoom

Het sterk toegenomen gebruik van preoperatieve radiotherapie is sinds 1989 de belangrijkste verandering bij de behandeling van het rectumcarcinoom in Nederland. Net als bij het coloncarcinoom ondergaat de overgrote meerderheid van de patiënten met een rectumcarcinoom stadium I-III een chirurgische resectie, terwijl dit deel kleiner wordt bij patiënten met gemetastaseerde ziekte. Bij deze patiënten is het gebruik van chemotherapie sterk toegenomen. De overleving van patiënten met een rectumcarcinoom nam toe door de tijd, waarbij de grootste overlevingswinst bij patiënten met stadium III werd gezien.

Follow-up intensiteit dikkedarmkanker laag

Om tijdig metastasen, een recidief of een nieuwe tumor te ontdekken bij patiënten die dikkedarmkanker hebben gehad, moet een patiënt regelmatig gecontroleerd worden (follow-up). De intensiteit van follow-up in Zuid-Nederland was suboptimaal, waarbij grote verschillen tussen patiënten te zien waren. Meer dan de helft van de patiënten ontvingen onvoldoende follow-up. Met name oudere patiënten, patiënten met een rectumcarcinoom en diegene met een kleine tumor, hadden een kleinere kans om een regelmatige follow-up te krijgen. De richtlijnen

werden in het algemeen slecht gevolgd, wat deels toegeschreven kan worden aan de wens van de (oudere) patiënt.

Chemotherapie verlengt overleving gemetastaseerd coloncarcinoom

Het gebruik van chemotherapie nam toe bij patiënten met een gemetastaseerd coloncarcinoom, waardoor de overleving van deze groep is gestegen. Bij deze patiënten was de overleving slechter als ze ouder zijn ten tijde van de diagnose, als ze bijkomende ziekten hebben, en als ze meer dan één orgaan met uitzaaiingen hebben. De overleving verbeterde sterk door chemotherapie. Voor patiënten zonder chemotherapie bleef de overleving ongeveer gelijk. Een verbetering in overleving doordat er eerder metastasen op afstand werden gevonden, lijkt daardoor beperkt. De winst in overleving in patiënten met een gemetastaseerd coloncarcinoom kan dus worden toegeschreven aan de palliatieve chemotherapie.

Kwaliteit van zorg kan nog beter

De hier beschreven resultaten worden bediscussieerd en de stand van zaken met betrekking tot de kwaliteit van zorg voor dikkedarmkanker is in dit proefschrift samengevat. De nadruk ligt daarbij op diagnostiek, behandeling en follow-up. De gevolgen van optimalisering van de zorg op de sterfte aan dikkedarmkanker en het effect van het aankomende bevolkingsonderzoek naar dikkedarmkanker op de kwaliteit van zorg worden besproken.

We kunnen concluderen dat er de laatste decennia aanzienlijke verbeteringen in de kwaliteit van zorg voor dikkedarmkanker hebben plaatsgevonden in Nederland. Veranderingen in behandeling, voornamelijk het toegenomen gebruik van adjuvante chemotherapie, leidden tot een verbeterde overleving voor patiënten met dikkedarmkanker. Maar het gebruik van adjuvante chemotherapie, lymfeklierdetectie, diagnostische verrichtingen, tijd tot behandeling en de follow-up van patiënten met dikkedarmkanker zijn alle suboptimaal en verdienen aandacht en monitoring. Speciale aandacht is nodig voor de oudere patiënten, omdat dit een heterogene groep patiënten is die vaak individuele zorg nodig hebben. Door de vergrijzing, de ongezonde leefstijl van de bevolking sinds de Tweede Wereldoorlog en de introductie van een bevolkingsonderzoek naar dikkedarmkanker neemt het aantal patiënten met dikkedarmkanker de komende jaren fors toe. Om goede zorg te kunnen bieden, zijn verdere verbeteringen in de infrastructuur en monitoring van de kwaliteit van zorg van cruciaal belang.

Curriculum Vitae

Liza van Steenbergen haalde in 2001 haar VWO diploma aan het Sint Stanislas College in Delft waarna zij begon met haar studie Voeding en Gezondheid aan de Wageningen Universiteit. Tijdens haar afstudeervak epidemiologie en volksgezondheid deed zij onderzoek naar het effect van ontstekingsmarkers in het bloed op het cognitief functioneren (Wageningen Universiteit, afdeling Epidemiologie en Volksgezondheid, prof. P. van 't Veer). Voor haar tweede afstudeervak zette ze een project op over patiënten met het prikkelbare darm syndroom (Wageningen Universiteit, afdeling Humane Voeding, ziekenhuis De Gelderse Vallei, Ede, prof. E. Kampman). In Cambridge (Verenigd Koninkrijk) doorliep ze haar stage bij het Medical Research Council Human Nutrition Research waar ze epidemiologisch onderzoek deed naar de associatie tussen folaatinname en folaatstatus.

In september 2006 studeerde Liza van Steenbergen cum laude af in de Humane Voeding aan de Wageningen Universiteit, richting Epidemiology and Public Health. Als junior-onderzoeker trad ze in dienst van het Integraal Kankercentrum Zuid (IKZ) in Eindhoven. Haar belangrijkste project was het door KWF Kankerbestrijding gesubsidieerde onderzoek naar het effect van verbetering van zorg voor patiënten met dikkedarmkanker op de sterfte. De resultaten hiervan vormen een groot deel van dit proefschrift. Daarnaast analyseerde ze voor het rapport van de Signaleringscommissie Kanker van KWF Kankerbestrijding de gegevens van de kwaliteit van zorg voor patiënten met borstkanker. Ze voerde tevens de analyses uit van het Registratiesysteem Oncologische Gynaecologie (ROGY) voor de jaarverslagen. Ook beantwoordde ze vragen van medisch specialisten uit de regio met behulp van de gegevens uit de Kanker Registratie. Bovendien voerde ze een project uit waarbij het effect van screening op de incidentie en behandeling van het ductaal carcinoma in situ (DCIS) van de borst werd beschreven.

List of publications

Publications in this thesis

1. **van Steenbergen LN**, Lemmens VE, Louwman MJ, Straathof JW, Coebergh JW. Increasing incidence and decreasing mortality of colorectal cancer due to marked cohort effects in southern Netherlands. Eur J Cancer Prev 2009; 18(2):145-52.

2. **van Steenbergen LN**, Lemmens VE, Straathof JW, Nijhuis PH, Geldermand WA, Coebergh JW. Improvable quality of diagnostic assessment of colorectal cancer in southern Netherlands. Eur J Gastroenterol Hepatol 2009; 21(5):570-5.

3. **van Steenbergen LN**, van Lijnschoten G, Rutten HJ, Lemmens VE, Coebergh JW. Improving lymph node detection in colon cancer in community hospitals and their pathology department in southern Netherlands. Eur J Surg Oncol 2010:36; 135-140.

4. **van Steenbergen LN**, Rutten HJ, Creemers GJ, Pruijt JF, Coebergh JW, Lemmens VE. Large age and hospital-dependent variation in administration of adjuvant chemotherapy for stage III colon cancer in southern Netherlands. Ann Oncol 2009 Oct 30 epub ahead of print.

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Dankwoord

Mijn onderzoek is afgerond, mijn proefschrift is klaar. Iedereen die dat mogelijk heeft gemaakt wil ik daarvoor bedanken.

Allereerst mijn promotor, prof. Jan Willem Coebergh, zonder hem was dit proefschrift er niet gekomen. Mijn inzicht in de kankerepidemiologie is verrijkt door jouw enorme kennis en de interessante wijze waarop je over het onderwerp kon vertellen. Het heeft mij de nodige achtergrondinformatie voor mijn onderzoek gegeven. Je vertrouwen en interesse zorgden ervoor dat ik altijd weer enthousiast en vol goede moed verder ging, zodat ik uiteindelijk mijn proefschrift kon schrijven.

Maar ook mijn co-promotoren, dr. Valery Lemmens en dr. Harm Rutten zijn belangrijk geweest voor mijn onderzoek. Valery, bedankt voor de goede en fijne begeleiding. Ik ben blij dat je altijd direct klaar stond voor mijn vragen en dat ik altijd aan kon kloppen voor tips en advies. Ook met mijn grote hoeveelheid artikelen-in-wording wist je goed raad. Elke keer wist je precies de vinger op de moeilijkheid of het probleem te leggen en kwam je met nuttige suggesties om het op te lossen. Harm, zonder jouw deskundigheid over de behandeling van dikkedarmkanker en je kennis over de dagelijkse praktijk in het ziekenhuis was het nooit gelukt. Je enthousiasme werkt aanstekelijk. Ik hoop in de toekomst nog meer met je te mogen samenwerken.

De leden van mijn kleine commissie: prof. Steyerberg, prof. van Krieken, en prof. Kuipers, veel dank voor de bereidheid mijn proefschrift te lezen en te beoordelen. Jullie interesse in mijn proefschrift en de opmerkingen van jullie bij het overhandigen van mijn manuscript zorgden er voor dat ik met een goed gevoel weer naar huis ging. De overige leden van mijn promotiecommissie, bedankt dat u op mijn verdediging aanwezig wilt zijn en uw kritische klinische licht over mijn onderzoek wilt laten schijnen. Ik kijk er naar uit op 27 mei met u in discussie te gaan.

Een proefschrift schrijven over klinische epidemiologie gaat uiteraard niet zonder de nauwe samenwerking met clinici. Veel clinici uit de IKZ-regio en daarbuiten hebben een bijdrage geleverd aan de artikelen die ik heb geschreven en in dit proefschrift staan. Mijn bijzondere dank gaat uit naar dr. van Lijnschoten. Ineke, je hebt mij kennis laten maken met de pathologie, een terrein dat voor mij grotendeels onbekend was. Ik mocht meekijken in het pathologie laboratorium toen je preparaten van de dikkedarm ging onderzoeken. Samen keken we door de microscoop naar de coupes. Je gaf me zo een goed beeld van wat er gebeurt tijdens het pathologisch onderzoek voor een patiënt met dikkedarmkanker. Ook je betrokkenheid en hulp bij het schrijven van het uiteindelijke artikel heb ik als erg plezierig ervaren. Dr. Creemers, Geert-Jan, onze discussies, vaak via de mail, en je

energieke enthousiasme zorgden ervoor dat we in een hoog tempo een aantal mooie artikelen hebben kunnen publiceren. Dr. Martijn, ik was gewaarschuwd voor je rode pennetje, en ja mijn hele artikel kwam vol met rode opmerkingen terug. Maar je telefoontje dat er direct op volgde om alles uit te leggen en de leuke discussies daarna, namen al mijn zorgen weg. Bovendien kan ik nu met een gerust hart zeggen dat de aantallen kloppen. Dr. Gelderman, je nam de tijd om mij wegwijs te maken in de colorectale chirurgie en hebt mij goed geholpen met het verzamelen van allerlei chirurgische gegevens. Dr. de Hingh, je enthousiaste hulp en je vele ideeën voor verder onderzoek zorgden ervoor dat de data die ik in mijn laatste studie heb verzameld optimaal gebruikt zijn én zullen worden! Dr. Straathof en dr. Rijk, ondanks de hoge werkdruk maakten jullie tijd om naar mijn stukken te kijken. Bedankt! Uiteraard wil ik ook de andere clinici waarmee ik samengewerkt heb, hartelijk bedanken: dr. Marijnen, dr. Meulenbeld, dr. Nagtegaal, dr. Nijhuis, dr. Pruijt en dr. Richel. Mevrouw Bieger, hartelijk dank voor het corrigeren van mijn manuscripten.

Ook de (collega) epidemiologen met wie ik samengewerkt heb tijdens het schrijven van artikelen wil ik bedanken voor hun input en waardevolle advies: Maryska Janssen-Heijnen, Henrike Karim-Kos, Pieta Krijnen, Marieke Louwman, Sabine Siesling en Esther de Vries. Marloes Elferink, onze samenwerking vond ik altijd erg plezierig. Succes met het schrijven van je proefschrift. Dr. Janny van den Eijnden, als onderzoekers voelen wij ons goed vertegenwoordigd met u als directrice in deze roerige tijden.

Onderzoek met data van de kankerregistratie is niet mogelijk zonder de nauwkeurige en consequente registratie door de registratiemedewerksters. Bedankt daarvoor, niet alleen voor het leveren van de gegevens, maar ook voor de gezellige dagen die ik samen met jullie in de ziekenhuizen doorbracht voor mijn dossieronderzoek. Het zou een stuk lastiger zijn geweest als jullie mij niet zo goed hadden geholpen.

Natuurlijk wil ik ook mijn collega's bedanken voor de gezellige tijd bij het IKZ. Helemaal alleen in het verre Eindhoven, zo voelde het toen ik begon. Maar gelukkig zorgde een alsmaar groeiende groep collega's ervoor dat ik me al snel thuis voelde in het zuiden. Saskia, we zijn ongeveer gelijk begonnen, en eindigen ook weer bijna gelijk. Ik ben blij dat je vandaag tijdens mijn promotie naast me staat voor de nodige morele steun. In september is het jouw beurt. Corina, Mieke, Simone, Esther, Rob, Lonneke, Melissa, Mijke, Marinka, Anke, Floor, Marrigje, Gitty, Erica, Louis en alle anderen, bedankt voor alles. Eén klein zinnetje in dit dankwoord is eigenlijk niet voldoende om jullie te bedanken voor de gezelligheid. Mijn inburgering in Brabant is door jullie een stuk sneller verlopen.

Mijn familie, Guus en Jelske, jullie hebben me altijd gestimuleerd om door te zetten, te studeren, een leuke baan te vinden, ook al is deze ver van Delft. Een promotieonderzoek past mooi in deze lijn en ik ben er zeker van dat jullie vandaag trots zijn dat ik hier sta. Thomas en Hanna, mijn broer en zus, jullie waren en zijn er voor de morele steun en als hulp bij mijn dossieronderzoek. Vriendinnen, ik noem jullie maar even zo samen, ik ben erg blij dat ik mijn verhalen en frustraties bij jullie kwijt kon. Marlies, we begonnen samen aan onze studie in Wageningen. Wat fijn dat je mij bij wil staan bij de verdediging van mijn proefschrift. Angélique, door onze eindeloze telefoongesprekken heb ik helemaal niet het idee dat we ver uit elkaar wonen. Wat ben ik daar blij om! Tenslotte, Merijn, lieve Merijn, je weet precies hoe je mij kunt 'ontstressen' en hoe je me weer op kunt vrolijken als ik het even niet meer zag zitten. Je bent een schat.

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: Liza van Steenbergen Erasmus MC Department: Public Health / Comprehensive Cancer Centre South (Eindhoven) Research School: a.o. NIHES	PhD period: Sept 2006 - March 2010 Promotor(s): Prof.dr. J.W.W. Coebergh Supervisor: Dr. V.E.P.P. Lemmens

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication	2006-2010	40 hrs (1.4 ECTS)
- Research Integrity	2006-2009	40 hrs (1.4 ECTS)
Research skills		
- Statistics	2006-2009	40 hrs (1.4 ECTS)
- Methodology	2006-2009	40 hrs (1.4 ECTS)
In-depth courses (e.g. Research school, Medical Training)		
- 'Basiscursus oncologie', Nederlandse Vereniging voor Oncologie	2007	40 hrs (1.4 ECTS)
- 'Cancer Epidemiology', Netherlands Institute for Health Sciences	2007	40 hrs (1.4 ECTS)
- 'Diet and Cancer', Voeding, Levensmiddelentechnologie, Agrobiotechnologie en Gezondheid (VLAG) Graduate school	2007	16 hrs (0.6 ECTS)
- 'Career development in academia' and 'Subsidie aanvragen', Nederlandse Organisatie voor Wetenschappelijk Onderzoek	2008	8 hrs (0.3 ECTS)
- 'Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen' Erasmus Medical Centre	2009	8 hrs (0.3 ECTS)
- 'Write it right' and 'Netwerken doe je zo', Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO)	2009	8 hrs (0.3 ECTS)

	Year	Workload (Hours/ECTS)
Presentations		
- Oral presentation ENCR	2007	32 hrs (1.1 ECTS)
- Poster presentation WEON	2007	32 hrs (1.1 ECTS)
- Poster presentation EMCC	2008	32 hrs (1.1 ECTS)
- 2 Poster presentations WCGC	2008	64 hrs (2.2 ECTS)
- Poster presentation WEON	2009	32 hrs (1.1 ECTS)
- Oral presentation DCCG-day	2009	32 hrs (1.1 ECTS)
- 5 Oral presentations at IKZ gastrointestinal cancer seminars	2007-2009	80 hrs (3.0 ECTS)
- Oral presentation at IKZ medical oncology seminar	2008	16 hrs (0.6 ECTS)
- Oral presentation at VIKC seminar	2009	32 hrs (1.1 ECTS)
- Oral presentation at IKW breast cancer seminar	2009	32 hrs (1.1 ECTS)
- Oral presentation at EMCCC Pathology seminar	2010	32 hrs (1.1 ECTS)
- 5 Poster presentations at EMCCC	2010	67 hrs (2.4 ECTS)
International conferences		
- Dutch and United Kingdom Cancer Registries (UKACR & NCR) meeting	2006	24 hrs (0.9 ECTS)
- International Association of Cancer Registries Congress (IARC)	2007	32 hrs (1.1 ECTS)
- European Network of Cancer Registries Congress (ENCR)	2007	8 hrs (0.3 ECTS)
- European Multidisciplinary Colorectal Cancer Congress (EMCCC)	2008	24 hrs (0.9 ECTS)
- World Congress on Gastrointestinal Cancer (WCGC)	2008	32 hrs (1.1 ECTS)
- European Multidisciplinary Colorectal Cancer Congress (EMCCC)	2010	20 hrs (0.7 ECTS)
Dutch conferences		
- Dutch Colorectal Cancer Group-day	2007	8 hrs (0.3 ECTS)
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON)	2007	16 hrs (0.6 ECTS)
- Federatie van medisch wetenschappelijke verenigingen (FEDERA) day	2007	
- Werkgroep Epidemiologisch Onderzoek Nederland (WEON)	2008	8 hrs (0.3 ECTS)
- Federatie van medisch wetenschappelijke verenigingen (FEDERA) day 2008	2008	16 hrs (0.6 ECTS)
- Milestone Congres NVvO en GeriOnNe Ouderen en	2008	8 hrs (0.3 ECTS)

Kanker - Werkgroep Epidemiologisch Onderzoek Nederland (WEON) - Federatie van medisch wetenschappelijke verenigingen (FEDERA) day - Cancer screening: trials and modelling to guide public health policies - Dutch Colorectal Cancer Group (DCCG)-day - GeriOnNe day Elderly and Cancer - Invitational Conference KWF Quality of Cancer Care	 2008 2009 2009 2009 2009 2009	 8 hrs (0.3 ECTS) 16 hrs (0.6 ECTS) 8 hrs (0.3 ECTS) 8 hrs (0.3 ECTS) 8 hrs (0.3 ECTS) 8 hrs (0.3 ECTS)
Other - Data-analyses for the Dutch Cancer Society Working Group Quality of Cancer Care and writing scientific article - Data-analyses and reporting results for annual reports Registration Oncological Gynaecology (ROGY) - Development of report with list of publications Netherlands Cancer Registry - Answering questions and doing analysis for specialists	 2008-2009 2007-2009 2009 2007-2009	 100 hrs (3.6 ECTS) 96 hrs (3.4 ECTS) 100 hrs (3.6 ECTS) 50 hrs (1.8 ECTS)
TOTAL		1369 (49 ECTS)