Clinical Epidemiology of Colorectal Cancer in the Netherlands

Studies of variation and trends with the Eindhoven Cancer Registry

Klinische epidemiologie van het colorectaal carcinoom in Nederland

Studies van variatie en trends gebruikmakend van de kankerregistratie van het Integraal Kankercentrum Zuid

Valery Lemmens

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Chapter 1

Introduction

General epidemiology of colorectal cancer

The large bowel

The large bowel can be divided into the colon, the rectosigmoid, and rectum. The colon starts where the small bowel ends. 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

In the Netherlands, colorectal cancer is the third most common cancer (14%) among males, after prostate (21%) and lung cancer (16%), and it is the second most frequent tumor (13%) among females after breast cancer (33%). In 2003, almost 10.000 patients were diagnosed with the disease; in this year, 4.500 patients died of the disease [1]. The incidence in the Netherlands compared to other European countries, is relatively high, and ranks in the top-10 [2]. Worldwide, colorectal cancer accounted for about 1 million of new cancer diagnoses in 2002, representing nearly 10% of all new cancers among both men and women [2]. It occurs more frequently in the industrialised world. The disease rarely occurs before age 40, the risk of colorectal cancer becomes highest around age 70 [1]. The lifetime risk to develop colorectal cancer is 5.6% in the industrialised world [1, 3]. As a percentage of total mortality, the risk of dying from colorectal cancer in the Netherlands is highest around age 60 (about 5%), later in life other causes of death proportionally start to occur more often [4].

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 [5]. The dysplastic tissue may further develop into so-called polyps, which are benign tumors. Several types of polyps exist. The adenomatous polyp, or adenoma, which consists of glandular epithelial tissue that lines 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 [6]. It has been estimated that colorectal cancer takes at least 5 years to develop from dysplasia , although most studies estimate that it takes between 10 and 30 years [7, 8]. 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. They systems consist of four stages and are interchangeable; Dukes A to D and stage I to IV. In stage I colorectal cancer, the cancer has grown through several layers of the large bowel, except its muscular wall. Stage II colorectal cancers 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 body parts, 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 2000-2002: stage

I 21%, stage II 33%, stage III 27%, stage IV 19% (excluding patients with unknown stage, which is approximately 3%) [1].

Survival

The 5-year relative survival rate of patients with colorectal cancer was 59% for patients diagnosed in the period 2000-2002 in the Eindhoven Cancer Registry area [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 more than 90% for patients with stage I disease at time of diagnosis, to less than 5% for patients with stage IV disease at time of diagnosis. Survival in the Netherlands is high compared to other European countries; only France and Switzerland show better survival rates (although the data for these countries may be based on a selective, 'better' population) [9].

Risk factors

Several risk factors, both genetic and environmental influence the formation and development of colorectal cancer. Individuals can be at increased risk due to their genetic constitution. The most common hereditary forms of colorectal cancer are hereditary non-polyposis colorectal cancer (HNPCC), also called Lynch syndrome, which accounts for approximately 3% of cases, and familial adenomatous polyposis (FAP), which accounts for less than 1% of colorectal cancer cases [10]. HNPCC is related to inherited mutations in one of the mismatch repair genes and FAP is caused by inherited mutations in the APC tumor-suppressor gene. Individuals with HNPCC have a lifetime colorectal cancer risk up to 80%, and individuals with FAP have a colorectal cancer risk of virtually 100% [11].

Other high-risk groups include individuals with adenomas, and patients with inflammatory bowel disease like ulcerative colitis and Crohn's disease [12].

Over the years a number of lifestyle- or environment-related risk factors have been identified, although the data are not entirely consistent. These include: physical activity, obesity, vitamin D and calcium, red and processed meat, dietary fat, fish, fruit and vegetables, fiber, folate, smoking, alcohol consumption, aspirin and other non-steroidal anti-inflammatory drugs, and postmenopausal hormone use (Table 1) [13-23].

In most cases, the environment and the genetic background of a person determine the risk of colorectal cancer together: the environment affects the activity of the genes and the effect of a certain environmental factor depends on the genes, the so-called gene-environment interaction [24-26].

Prevention, diagnosis and staging of colorectal cancer

Primary prevention

Most of the aforementioned risk factors obviously play an important role in primary prevention. For some of them, the effect on preventing colorectal cancer has even been established in randomized controlled trials, such as aspirin use [27].

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)
Obesity	1.5	+++	0
Physical activity	0.6	++	+++ (colon)
Vegetables	0.7 – 1.0	0, +	0
Fruit	0.8 – 1.0	0	Unknown
Fibre	0.7 – 1.0	0	0
Red/ processed meat	1.2	+	++ (colon)
Fish consumption	0.7	++	Unknown
Saturated fat	1.4	+	Unknown
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
Smoking	1.5	+	0, + (rectum)
Alcohol	1.4	++	0, + (colon)
Statins	0.5	0	+ (colon)
Oestrogen replacement therapy	0.8	++	Unknown
Cholecystectomy	1.2	+	+++ (proximal colon)
Prior pelvic irradiation	1.7	+	+++ (rectum)
Aspirin (long-term regular use)	0.7	+++	Unknown
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 parentheses.

0 Inconsistent/inconclusive
+ probable
++ likely
+++ definite

However, agents with chemopreventive properties, such as aspirin and postmenopausal estrogens, have potential adverse effects so a careful consideration of the risk-benefit ratio is required before general recommendations can be made. Promising in this respect is supplementation with vitamin D and/or folate, which have a more positive safety profile than for example aspirin [28]. The recommended daily dose of vitamin D is 400 IE, while adverse events (i.e., hypercalcaemia) occur at daily doses of 50,000 IE or more [29]. Calcium supplementation is already recommended by the American College of Gastroenterology to prevent initial or recurrent colorectal adenomas.

Secondary prevention

Recommendations for colorectal cancer screening, as with other screening, must take into account the effectiveness, sensitivity, false-positive rate, safety, and convenience of the test [4]. In addition, cost 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 colorectal cancer allows opportunities to prevent cancer or improve its prognosis finding and removing polyps to prevent the onset of cancer and finding and removing early cancers to prevent disease progression. Also, the length of the progression from polyp to cancer offers a wide window of opportunity so that sensitive tests (e.g., sigmoidoscopy and colonoscopy) do not need to be repeated yearly, and less sensitive tests (e.g., fecal occult blood, FOBT) performed yearly have a chance of finding lesions missed on earlier screening [4].

Studies have proven that FOBT, when performed every 1 to 2 years in people ages 50 to 80, reduces the number of deaths due to colorectal cancer by as much as 30 percent. Unlike FOBT, sigmoidoscopy can find and remove precancerous or cancerous growths in the rectum and lower colon. Studies suggest that regular screening with sigmoidoscopy after age 50 can reduce the number of deaths from colorectal cancer. Often FOBT and sigmoidoscopy are combined in screening programs. Colonoscopy can find and remove precancerous or cancerous growths throughout the colon, including the upper part of the colon, where they would be missed by sigmoidoscopy. However, it is not known whether this benefit outweighs the risks of colonoscopy, which include bleeding and puncturing of the lining of the colon [4]. More research is being conducted to address these issues and to explore the possibilities of other screening tools such as virtual colonoscopy, also in the Netherlands [4].

Tertiary prevention

Increasing levels of physical activity after diagnosis, and vitamin D status (either by ingestion or through solar irradiation) at and after time of diagnosis have been positively related to prognosis of colon cancer, and may act positively in concert with conventional therapies of colon cancer [30, 31].

Diagnosis and staging

Patients with colorectal cancer may be diagnosed by having one or more of the following symptoms: abdominal pain, change in bowel habit, blood in stools, weakness, anemia without other gastrointestinal symptoms, and weight loss [32, 33]. A large proportion of patients with early disease does however have no clinical symptoms (i.e., screen detected patients), these usually appear with more advanced disease [34]. Diagnostic tests, besides a physical exam and a digital rectal 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 (CT, also virtual colonoscopy, spiral CT, portography, CT-guided needle biopsy), magnetic resonance imaging (MRI), chest X-ray, positron emission tomography (PET), angiography [4, 35, 36]. 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 will be examined. Also histology, degree of differentiation, and radicality of the resection (especially important in case of rectal cancer) are assessed [37].

Short overview of treatment options

Surgery
Surgery is the main treatment for colorectal cancer. Usually the cancer and a length of normal bowel on either side of the cancer (as well as nearby lymph nodes) are removed. The two ends are then sewn back together. For colon cancer, a colostomy is not usually needed, although sometimes a temporary colostomy may be constructed. Sometimes very early colon cancer can be removed through colonoscopy. Surgery for colon cancer can also be performed with a new approach called "laparoscopic" or "keyhole" surgery. Laparoscopic surgery for colon cancer works probably as well as the standard approach [38]. For rectal cancer, other types of surgery are requested. 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. Permanent colostomy is not indicated with this procedure. 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 patient outcomes and survival. For stage IV colorectal cancer patients, surgery is often palliative or even omitted because of too widespread disease [39, 40].

Adjuvant chemotherapy
Stage I patients do not receive any adjuvant therapy (Table 2). A subgroup of stage II patients may be considered to receive adjuvant chemotherapy (nowadays in the Netherlands this is usually a combination of 5-fluoruracil (5-FU), leucovorin, and oxaliplatin). This high-risk stage II group consists of patients with T4 tumours, fewer than 10 lymph nodes examined, or a poor tumour differentiation. For stage III colon cancer adjuvant chemotherapy is considered standard receive (same regimen as high risk stage II patients), among stage III rectal cancer patients this may be considered. Selected stage IV colorectal cancer patients may be treated with a combination of the aforementioned agents (or irinotecan instead of oxaliplatin, or capecitabine instead of 5-FU) plus bevacuzimab [39].

Radiotherapy
Preoperative radiotherapy is considered standard for T2-T4 rectal cancer (Table 2). For patients with high and relatively small tumours, it may be omitted. Patients who are expected to have a positive circumferential margin or 4 or more positive lymph nodes (clinical staging), radiotherapy may be combined with chemotherapy. Radiotherapy also may also be used in a postoperative setting, for T4 colon tumours, and in a palliative setting [39].

Table 2: Summary of treatment options for colorectal cancer

	Colon	Rectum
Stage I	- Resection	- Resection - TME for tumours in middle or lower rectum - T1: transanal endoscopic microsurgery (TEM) - T2: preoperative radiotherapy (5x5 Gy)
Stage II	- Resection - High-risk patients: adjuvant chemotherapy (FOLFOX-4)	- Resection - TME for tumours in middle or lower rectum - T3: preoperative radiotherapy (5x5 Gy) - T4/ fixed tumours: (chemo)radiation (50 Gy), followed by resection (TME) after 6 weeks, possibly intraoperative radiotherapy
Stage III	- Resection - Adjuvant chemotherapy (FOLFOX-4)	- Resection - TME for tumours in middle or lower rectum - T2-T3: preoperative radiotherapy (5x5 Gy) - T4/ fixed tumours: (chemo)radiation (50 Gy), followed by resection (TME) after 6 weeks, possibly intraoperative radiotherapy - suspicion of 4 or more positive lymph nodes: chemoradiation can be considered
Stage IV	- Resection can be considered - Palliative chemotherapy	- Resection can be considered - Palliative chemotherapy

Methods, population and setting

Eindhoven 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 southeastern part of province of North Brabant, the Northern part of the province of Dutch Limburg (since 1970) and the middle and southwestern part of North Brabant since 1986 (except the small most western part) (Figure 1).

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

The area in the population-based Eindhoven Cancer Registry 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 hospitalised 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 Eindhoven cancer Registry, 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 centers.
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, with an increased proportion of elderly women (from less than 5% to more than 10%), and since 1965 a decreasing number of children.

Staging
Stage of the adenocarcinomas was categorized according to the TNM-classification IUCC for all patients. No major changes in the classification occurred since the mid-1970s which could have led to a shift in stage distribution [41].

Histological classification
Colorectal tumours were classified based on topography and histology, according to the WHO International Classification of Diseases for Oncology (ICD-O)[42]. 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 3).

Table 3: Classification of histology (morphology) according to the WHO ICD-O[42]

Histological group	Morphology code according to ICD-O [a]	Proportional distribution of histology of tumours located within the colorectum [b]
Neoplasm, NOS	8000-8005	2%
Epithelial neoplasm, NOS	8010-8046	1%
Carcinoid	8240-8249	0.6%
Adenocarcinoma [c]	8140-8231, 8260-8384, 8440, 8470, 8480, 8481, 8490	95%
Sarcoma	8800-8990	0.12%
Melanoma	8720-8790	0.03%
Lymphoma	9590-9729	0.5%
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	0.5%

NOS = not otherwise specified
[a] List not exhaustive; non-incident codes (Eindhoven Cancer Registry, 1975-2004) excluded
[b] Eindhoven Cancer Registry, 1975-2004
[c] Including cystic, mucinous and serous adenocarcinoma

Topographical codes of colorectal cancer were used to divide the colorectum into subsites (Table 4). Tumours of the anus and the anal canal were excluded throughout the thesis unless stated otherwise.

Table 4: Classification of localisation (topography) according to the WHO ICD-O[42]

Localisation				ICD-O	Proportional distribution [a]
Colorectum	Colon	Right colon	Caecum	C18.0	13%
			Appendix	C18.1	0.5%
			Ascending colon	C18.2	9%
			Hepatic flexure	C18.3	4%
			Transverse colon	C18.4	5%
			Splenic flexure	C18.5	3%
		Left colon	Descending colon	C18.6	3%
			Sigmoid colon	C18.7	25%
			Overlapping lesions	C18.8	1%
			Colon, NOS	C18.9	
	Rectum		Rectosigmoid junction	C19.9	8%
			Rectum	C20.9	28%

[a] Incidence, Eindhoven Cancer Registry, 1990-2004

Comorbidity

Since 1993 the registry also recorded comorbidity according to a slight adaption of the list of serious diseases drawn up by Charlson and colleagues [43]. In short, the following important conditions were recorded: 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 [44]. In chapters 2.1, 2.2, 2.3, and 3.2 of this thesis, a table containing the recorded comorbid conditions can be found.

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 Standardised 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 $EAPC=100x (e^m -1)$. This calculation assumes that the rates increased or decreased a a constant rate over the entire period.

Survival

Information on the vital status of all patients was obtained initially from the municipal registries and since 1998 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 [45]. 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 [46].

Outline

The main objectives of the studies described in this thesis were:
1. To investigate clinical care for the growing proportion of elderly patients with colorectal cancer, with an emphasis on the influence of comorbidity on treatment, treatment-related complications, and survival.
2. To explore adherence to colorectal cancer treatment guidelines within the Eindhoven Cancer Registry area.
3. To study the trends in incidence, treatment, stage distribution, and survival of colorectal cancer in a large population-based setting.

In **chapter 2.1** an overview is given of the prevalence of comorbidity among patients with colorectal cancer, and its influence on treatment and long-term survival. This is the first population-based study in literature to give insight in the impact of specific combinations of comorbid conditions on adjuvant treatment and 5-year survival of colorectal cancer. In **chapter 2.2**, it is investigated whether the previously noticed status quo in survival for elderly rectal cancer patients could be due to a lower effectiveness of new treatment regimens in this group [47]. **Chapter 2.3** deals with the unanswered question whether, and if yes, which comorbid conditions predict complications after surgery for colorectal cancer.
An overall overview of the adherence to treatment guidelines for colorectal cancer in the Eindhoven Cancer Registry area is presented in **chapter 3.1**. In-depth studies concerning adjuvant chemotherapy for stage III colon cancer patients and lymph node examination for colon cancer are described in **chapter 3.2** and **chapter 3.3**.
The trends in incidence, treatment, stage distribution, and survival of colorectal cancer are dealt with in **chapter 4.1**. The consequences of the trends described here, an overview of the international population-based literature on the management and survival of colorectal cancer in the elderly, unsolved issues concerning the role of comorbidity, and the meaning of non-adherence to clinical guidelines is discussed in **chapter 5.1 to 5.5**. In **chapter 5.6**, future perspectives for research and clinical management of colorectal cancer are discussed.

Chapter 2

Clinical care:
Influence of age and comorbidity

Chapter 2.1

Comorbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer

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Summary

BACKGROUND: The aim of this study was to evaluate the effects of comorbidity on the treatment and prognosis of elderly patients with colorectal cancer. METHODS: The independent influence of age and comorbidity on treatment and survival was analysed for 6931 patients with colorectal cancer aged 50 years or more diagnosed between 1995 and 2001 in the southern part of the Netherlands. RESULTS: Comorbidity had no influence on resection rate. The use of adjuvant chemotherapy in patients with stage III colonic cancer was influenced by comorbidity, especially a previous malignancy (odds ratio (OR) 0.2 (95 per cent confidence interval (c.i.) 0.1 to 0.6); P = 0.002) or chronic obstructive pulmonary disease (COPD) (OR 0.3 (95 per cent c.i. 0.1 to 0.9); P = 0.043). Comorbidity also influenced use of adjuvant radiotherapy in patients with rectal cancer, especially the presence of hypertension in combination with diabetes (OR 0.5 (95 per cent c.i. 0.2 to 0.9); P = 0.031). Comorbidity influenced survival (hazard ratio up to 1.6), when adjusted for age, sex, tumour stage and treatment. The greatest influence on survival of patients with colonic cancer was previous malignancy, cardiovascular disease and COPD, and that of patients with rectal cancer was COPD, hypertension, and hypertension in combination with diabetes. CONCLUSION: Elderly patients with comorbidity were treated less aggressively and had a worse survival than those with no concomitant disease.

Introduction

Colorectal cancer is the second most common cause of cancer death in industrialized countries [9, 48]. Seventy-five per cent of incident tumours occur in persons aged 65 years or more. Colorectal tumours affect a large number of people who, because of their age, are likely to have other chronic disabling conditions (comorbidity) [49]. In patients with serious comorbidity, the practitioner might decide to alter standard oncological treatment because of increased risk of side-effects or limited life expectancy. Few data are available for treatment outcome in elderly patients with colorectal cancer who are also suffering from serious comorbid conditions, as these patients are generally ineligible for clinical trials. Surgical, sometimes endoscopic, resection of the tumour is the only primary curative treatment for colorectal cancer. Total mesorectal excision (TME) and preoperative radiotherapy for stage II and III rectal cancer, and adjuvant chemotherapy for stage III colonic cancer, improve both disease control and patient survival [47, 50-53]. These treatments have been recommended in the Netherlands since the mid-1990s. In this population-based study, carried out in medium to large general hospitals and two radiation therapy centres, the effect of comorbidity on choice of treatment and survival of patients with colorectal cancer was investigated in association with other prognostic determinants.

Patients and methods

Analyses were based on data for all 6931 patients aged 50 years or more diagnosed with colorectal cancer from 1995 to 2001 in the registration area of Eindhoven Cancer Registry. This registry serves a large part of the southern Netherlands, with 2·4 million inhabitants; it is notified by six pathology departments, the hospital medical records departments of ten community hospitals, and two radiation therapy institutes. Despite lack of access to death certificates, the organization of Dutch healthcare facilities and notification procedures has enabled cancer registries to attain a completeness of data exceeding 95 per cent [54]. Prognostically relevant concomitant conditions were recorded from the medical records according to a slightly adapted version of the Charlson Index (Table 1) [43]; sources used included correspondence between specialists, medical history and preoperative reports. A patient's medical record is regarded as the most complete source of information on past and current health status [55].
Tumour site, stage and morphology were classified according to the International Classification of Diseases for Oncology. Patients with tumour stages I and II were considered as one group, because differences in treatment and 10-year survival were relatively small [56].
Primary treatment of colonic cancer was classified as surgery, surgery followed by chemotherapy, and other (palliative, radiotherapy alone, chemotherapy alone, radiotherapy plus chemotherapy) or no therapy. Rectal cancer treatment was classified as conventional surgery (without TME), surgery including TME (with or without radiotherapy), conventional surgery with radiotherapy, and other (palliative, radiotherapy alone, chemotherapy alone, radiotherapy plus chemotherapy) or no therapy. No differentiation was made between TME with and TME without radiotherapy

because a large national trial comparing these two treatments was being conducted during the study period, and included a large proportion of patients in the region.

Table 1. Classification of comorbidity according to an adapted version of the Charlson Index [43]

Previous malignancy (except basal skin carcinoma and carcinoma *in situ* of the cervix)
Chronic obstructive pulmonary disease (COPD)
Cardiovascular disease (myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm, peripheral arterial disease)
Cerebrovascular disease (cerebrovascular accident, hemiplegia)
Hypertension
Diabetes mellitus
Digestive tract disease (stomach diseases, Crohn's disease, ulcerative colitis, liver cirrhosis, hepatitis)
Other (connective tissue disease, severe rheumatoid arthritis, kidney disease, dementia, tuberculosis, chronic infection)

It was not possible to differentiate between curative and palliative surgery; in stage IV disease, surgery was expected to be palliative. Chemotherapy given to patients with stage IV disease was classified as chemotherapy, not as palliative treatment.
To avoid bias due to changing guidelines, only recent data on therapy (1997-2001) were used when determining the influence of age and comorbidity on adjuvant chemotherapy in patients with stage III colonic cancer, and adjuvant radiotherapy in patients with rectal cancer.
The prevalence of comorbidity was analysed according to age (50-64, 65-79 and 80 or more years), sex and tumour site (colon or rectum). The independent influence of comorbidity on adjuvant chemotherapy in patients with stage III colonic cancer, and adjuvant radiotherapy in patients with rectal cancer, was examined in a logistic regression analysis, controlling for age, sex and tumour stage (only for rectal cancer). The influence of comorbidity on TME was also examined by logistic regression. The influence of age (50-64, 65-79 and 80 or more years) and number of comorbid diseases on the rate of permanent stoma formation was analysed using the Chi^2 test (excluding patients who had excision of the rectum).
The survival of patients at 1 January 2004 was assessed through civil municipal registries and the Central Bureau for Genealogy, which collects data on all Dutch citizens who die. Patients who left the Netherlands (estimated as 0.2 per cent) were lost to follow-up. A total of 3486 patients (50.3 per cent) died and 3445 (49.7 per cent) were still alive; the latter were censored at 1 January 2004. Crude survival was determined from date of diagnosis to death or end of study. The log rank test was used to compare survival between groups of patients. Multivariable proportional hazards regression methods were used to calculate hazard ratios adjusted for probable

confounders. The likelihood ratio method was used to determine hazard ratios for death. The effects of comorbidity were first evaluated in a model with the number of comorbid conditions, age, tumour stage and sex, without treatment. Treatment was then included in the model, in order to investigate whether the prognostic effects of age and comorbidity could be fully explained by less aggressive treatment. This procedure was repeated for each comorbid condition (or combinations of conditions) in place of the number of comorbidities. Patients who coded positive for a pair of conditions did not code positive for each condition singly. Univariate survival analysis (modelling a single explanatory variable) was stratified according to age at diagnosis. For facilitated application of the results in clinical practice, patients aged 65-79 years were stratified into 5-year age groups (50-64, 65-69, 70-74, 75-79 and 80 or more years).
Multivariable survival analysis was stratified according to tumour site (colon and rectum). All data analysis was performed using SAS/STAT® software, version 8 (SAS Institute, Cary, North Carolina, USA).

Results

The 6931 patients newly diagnosed with colorectal cancer between 1995 and 2001 had a mean age of 70 (maximum 98) years. Characteristics according to tumour site and age are shown in Table 2. Stage was more often unknown for older patients, especially those with rectal cancer. The number of comorbid conditions increased with age. For all age groups the most frequent single concomitant diseases were hypertension (9.4 per cent of patients, decreasing with age), previous malignancy (7.1 per cent of patients, increasing with age) and cardiovascular disease (5.6 per cent of patients, increasing with age). The prevalence of COPD was 4.0 per cent, that of diabetes mellitus 3.4 per cent and digestive tract disease 1.9 per cent. The most frequent combination of comorbid conditions was cardiovascular disease plus hypertension (3.3 per cent of patients). Combinations of hypertension with diabetes (2.1 per cent), previous malignancy with cardiovascular disease (up to 1.8 per cent of patients aged 80 years or more) and cardiovascular disease with COPD (up to 2.4 per cent of patients with rectal cancer aged 80 years or over) were also common. Women suffered more often from hypertension than men, and less often from concomitant cardiovascular disease and COPD. The prevalence of comorbidity was similar in patients with colonic and rectal cancer. However, previous malignancy was more frequent in patients with colonic cancer aged 80 years or more (9.1 per cent *versus* 5.3 per cent of patients with rectal cancer), and COPD was more frequent in patients with rectal cancer aged 80 years or more (5.2 per cent *versus* 3.1 per cent of patients with colonic cancer). Previous malignancy consisted mainly of colorectal, genital and breast tumours (in women). The prevalence of comorbidity was not related to tumour stage.
Most patients with stage I-II colonic cancer received surgical treatment only (Figure 1); less than 2 per cent of patients with stage II disease had adjuvant chemotherapy. For stage III colonic cancer, surgery followed by adjuvant chemotherapy was the most frequently used treatment for patients younger than 65 years (82.8 per cent). Adjuvant chemotherapy was given to 42.4 per cent of patients with stage III disease aged 65-79

years, but to only 1.2 per cent of those aged 80 years or more. For stage IV disease, the proportion receiving chemotherapy decreased from 41.3 per cent of patients aged 50-64 years to 1.8 per cent of those in the oldest age group.

Table 2. General characteristics of patients with colorectal cancer according to tumour site and age (1995-2001).

	Frequency (%)					
	Colonic cancer			**Rectal cancer**		
	50-64 years (*n*=1226)	**65-79 years (*n*=2331)**	**80+ years (*n*=842)**	**50-64 years (*n*=865)**	**65-79 years (*n*=1265)**	**80+ years (*n*=402)**
Sex						
M	54·2	50·9	39·0	62·6	60·0	45·3
F	45·8	49·1	61·0	37·4	40·0	54·7
Stage						
I-II	47·8	55·3	55·2	50·0	56·5	47·2
III	26·5	23·9	22·1	24·0	18·2	17·3
IV	23·4	16·8	13·6	17·1	15·2	11·5
Unknown	2·3	4·0	9·1	8·9	10·1	24·0
No. of comorbid conditions [*]						
0	55·5	33·9	26·2	60·2	35·7	29·7
1	30·0	35·4	33·8	27·0	35·8	34·0
2	9·8	19·1	24·4	9·5	17·4	22·0
3	3·4	7·8	10·0	2·7	8·4	10·4
4+	1·3	3·8	5·6	0·6	2·7	3·9
Unknown	10·8	8·2	9·9	8·5	7·0	9·1
Treatment						
Surgery alone	63·6	79·1	86·5	35·0	42·4	44·5
Surgery including TME ± radiotherapy				22·0	20·8	11·0
Surgery + adjuvant therapy [a]	29·5	12·3	0·2	34·3	23·5	11·1
Other or no therapy [b]	6·9	8·6	13·3	8·8	13·3	33·4

[*] Proportion of patients excluding unknown comorbidity.
[a] Adjuvant chemotherapy for colonic and adjuvant radiation therapy for rectal cancer.
[b] Other treatment comprises therapy not otherwise specified and metastasis-directed therapy such as metastasectomy and metastasis-directed radiotherapy, but not metastasis-directed chemotherapy, which is classified as chemotherapy.

In patients with stage I-II and III rectal cancer, surgery alone or in combination with radiotherapy was the most common treatment (Figure 2). TME was performed in 20.1 per cent of patients with stage I-II disease and in 28·0 per cent of those with stage III. Most patients with stage IV rectal cancer received palliative therapy alone. For all stages of disease, the proportion receiving adjuvant radiotherapy decreased with increasing age.

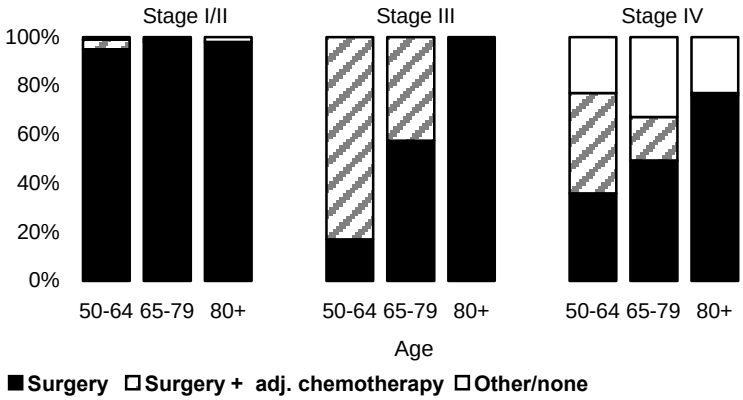

Figure 1. Choice of therapy for patients with colonic cancer according to stage and age (1997-2001)

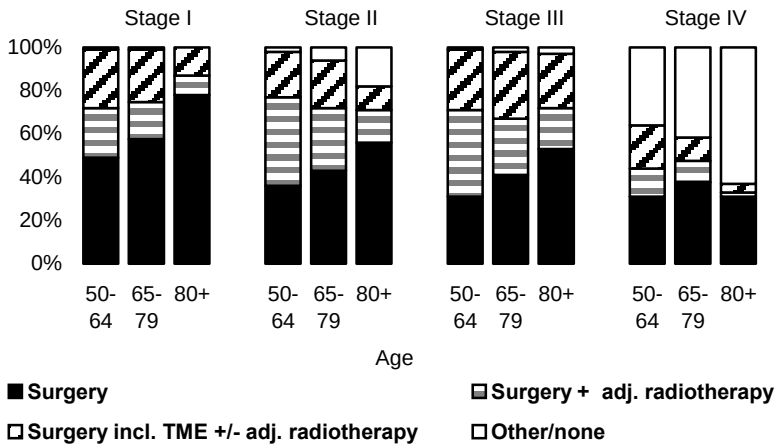

Figure 2. Choice of therapy for patients with rectal cancer according to stage and age (1997-2001)

The proportion of patients with stage II and III rectal cancer who received adjuvant chemoradiotherapy increased from 3.9 per cent in 1995-1999 to 15.9 per cent in 2001 (data not shown). Owing to small numbers in 1995-1999, adjuvant chemoradiotherapy was not taken into account in further analyses.
In logistic regression analysis of patients with stage III colonic cancer, controlling for age and sex, comorbidity was associated with a lower probability of receiving adjuvant chemotherapy (Table 3). Previous malignancy (odds ratio (OR) 0.2 (95 per cent confidence interval (c.i.) 0.1 to 0.6); $P = 0.002$) and COPD (OR 0.3 (95 per cent c.i. 0.1 to 0.9); $P = 0.043$) were mainly responsible for this effect (subanalysis; data not shown). Older age was also clearly related to less frequent administration of adjuvant therapy. Patients with rectal cancer and comorbidity had a lower probability of receiving adjuvant radiotherapy; previous malignancy and the combination of hypertension and diabetes had the greatest effect on treatment (OR 0.5 (95 per cent c.i. 0.2 to 0.9); $P = 0.031$). The use of adjuvant radiotherapy decreased with age. Elderly patients with rectal cancer and patients with comorbidity were less likely to have TME (Table 4). The effect of comorbidity was largely due to previous malignancy. The rate of permanent stoma formation increased with age, from 16.7 per cent of patients aged 50-64 years to 26.7 per cent of those aged 80 years or more ($P = 0.001$), but was not influenced by comorbidity ($P = 0.298$; data not shown).

For colonic cancer, patients aged 50-64 years without recorded concomitant disease had a crude 5-year survival rate of 58.4 per cent. In patients aged 65-79 years without comorbidity the survival rate was 58·4 per cent (age 65-69 years, 56.1 per cent; 70-74 years, 59.9 per cent; 75-79 years, 57.3 per cent), and in those aged 80 years and older 39.2 per cent (Table 5). Survival decreased with the number of comorbid conditions. In a multivariable analysis, comorbidity was a significant predictor of death even when adjusted for age, sex and disease stage. The inclusion of treatment in the model did not affect the significance of comorbidity. Patients with previous malignancy, cardiovascular disease, COPD, the combination of previous malignancy and COPD (hazard ratio (HR) 1.8 (95 per cent c.i. 1.1 to 1.7)), and the combination of hypertension and diabetes (HR 1.6 (95 per cent c.i. 1.2 to 2.0)) had a worse survival.

For rectal cancer, patients without recorded comorbidity aged 50-64 years had a crude 5-year survival rate of 60.0 per cent (Table 6). In patients without comorbidity aged 65-79 years the survival rate was 53.9 per cent (age 65-69 years, 52.8 per cent; 70-74 years, 55.9 per cent; 75-79 years, 52.4 per cent), and in those aged 80 years or more 32.9 per cent. Survival decreased with number of concomitant diseases. In a multivariable analysis, age, stage and comorbidity were prognostic factors in patients with rectal cancer; these factors remained significant after the inclusion of treatment in the model. Patients with COPD, hypertension, and the combination of hypertension and diabetes (HR 1.8 (95 per cent c.i. 1.2 to 2.7)) had a worse survival.

Table 3. Administration of adjuvant therapy for patients with stage III colonic cancer or rectal cancer diagnosed between 1995 and 2001; logistic regression model including all listed variables

	Odds ratio	P^*
Colonic cancer		
Age (years)		
50-64	1·0	
65-79	0·2 (0·1, 0·3)	< 0·0001
80+	0·01 (0·001, 0·02)	< 0·0001
Sex		
M	1·0	
F	0·7 (0·5, 0·9)	0·045
No. of comorbid conditions		
0	1·0	
1	0·8 (0·6, 1·1)	0·057
2+	0·5 (0·3, 0·8)	0·001#
Rectal cancer		
Age (years)		
50-64	1·0	
65-79	0·7 (0·5, 0·9)	0·041
80+	0·4 (0·2, 0·5)	< 0·0001
Sex		
M	1·0	
F	1·0 (0·8, 1·2)	0·970
Stage		
I-II	1·0	
III	1·3 (0·9, 1·6)	0·071
IV	0·5 (0·4, 0·7)	< 0·0001
No. of comorbid conditions		
0	1·0	
1	0·9 (0·7, 1·2)	0·535
2+	0·7 (0·5, 0·9)	0·040#

Values in parentheses are 95 per cent confidence intervals.
* Wald Chi^2 test
# Chi^2 test for trend

Table 4. Total mesorectal excision for patients with rectal cancer diagnosed between 1995 and 2001; logistic regression model including all listed variables

	Odds ratio	*P**
Age (years)		
50-64	1·0	
65-79	1·0 (0·8, 1·3)	0·898
80+	0·6 (0·4, 0·9)	0·038
Sex		
M	1·0	
F	0·9 (0·7, 1·1)	0·762
Stage		
I-II	1·0	
III	1·5 (1·2, 1·9)	0·016
IV	1·1 (0·8, 1·5)	0·294
No. of comorbid conditions		
0	1·0	
1	0·7 (0·5, 0·9)	0·008
2+	0·8 (0·6, 1·1)	0·192#

Values in parentheses are 95 per cent confidence intervals.
* Wald Chi^2 test
# Chi^2 test for trend

Discussion

In this study of the influence of prognostically relevant comorbidity on choice of treatment and long-term survival of unselected patients with colorectal cancer, the proportion of patients with comorbidity varied from almost 40 per cent patients aged 50-64 years to more than 70 per cent in those aged 80 years or older. The most common concomitant diseases were hypertension, cardiovascular diseases and previous malignancy.

The proportion of patients undergoing surgery was not affected by age or comorbidity. This can be explained by the fact that resection is the only primary curative treatment for colorectal cancer, and is often necessary to prevent obstruction. This contrasts with resectable non-small cell lung cancer, for example, in which the proportion of patients undergoing surgery decreases with age [57]. However, the rate of permanent stoma formation in the present study increased with rising age.

Adjuvant chemotherapy is recommended in treatment guidelines for patients with stage III colonic cancer, whereas adjuvant radiotherapy is recommended for patients with stage II and III rectal cancer [51, 58]. However, the use of adjuvant therapy decreased

Table 5. Uni- and multivariable analyses for overall survival of colon cancer patients, according to age(1995-2001).

	50-64 yrs Univariable[1]		65-79 yrs Univariable[1]		80+ yrs Univariable[1]		Multivariable		
	5 yrs % (SE)		5 yrs % (SE)		5 yrs % (SE)		Hazard ratio (CI)		*p*
Age									
50-64 yrs	56	(1)					1.0		
65-79 yrs			46	(1)			1.3 (0.06)	(1.2-1.5)	<.0001
80+ yrs					28	(2)	2.0 (0.07)	(1.8-2.4)	<.0001
Sex									
Male	56	(2)	43	(1)	28	(3)	1.0		
Female	57	(2)	50	(1)	28	(2)	0.9 (0.04)	(0.8-0.9)	.008
Stage									
I/II	80	(2)	63	(1)	39	(3)	1.0		
III	55	(3)	39	(2)	25	(3)	2.1 (0.06)	(1.9-2.3)	<.0001
IV	9	(2)	4	(1)	4	(2)	5.2 (0.06)	(4.7-5.9)	<.0001
Treatment									
Surgery	66	(1)	52	(1)	32	(2)	1.0		
Surgery + chemotherapy	46	(2)	41	(3)	.		0.7 (0.07)	(0.7-0.9)	<.0001
Other/none		.	2	(1)	.		1.5 (0.08)	(1.3-1.8)	<.0001
No. of comorbid conditions									
0	58	(2)	55	(1)	39	(4)	1.0		
1	55	(3)	44	(1)	27	(3)	1.2 (0.05)	(1.1-1.3)	.0003
≥ 2	50	(4)	38	(2)	22	(3)	1.4 (0.05)	(1.2-1.5)	<.0001
Type of comorbid condition(s)[2]									
Previous malignancies	61	(6)	40	(3)	30	(6)	1.3 (0.08)	(1.1-1.5)	.002
Cardiovascular	46	(7)	43	(4)	21	(6)	1.3 (0.09)	(1.1-1.8)	.008
COPD	55	(9)	39	(5)	35	(11)	1.3 (0.12)	(1.1-1.7)	.010
Diabetes	58	(11)	45	(5)	34	(11)	1.1 (0.13)	(0.9-1.4)	.386
Hypertension	59	(5)	56	(3)	29	(7)	1.1 (0.08)	(0.9-1.2)	.074
Cerebrovascular		.	32	(9)	.		1.6 (0.19)	(1.1-2.3)	.018
Digestive tract	59	(10)	45	(5)	31	(8)	0.9 (0.19)	(0.7-1.4)	.849
Other single diseases		.	45	(7)	.		1.5 (0.16)	(1.1-2.1)	.007

SE= standard error; CI=Confidence interval
[1] Crude actuarial 5 year survival rates
[2] Reference category: no comorbidity

Table 6. Uni- and multivariable analyses for overall survival of rectum cancer patients, according to age (1995-2001).

	50-64 yrs Univariable[1]		65-79 yrs Univariable[1]		80+ yrs Univariable[1]		Multivariable		
	5 yrs % (SE)		5 yrs % (SE)		5 yrs % (SE)		Hazard ratio (CI)		*p*
Age									
50-64 yrs	58	(2)					1.0		
65-79 yrs			45	(2)			1.4	(1.2-1.6)	<.0001
80+ yrs					24	(2)	2.1	(21.7-2.5)	<.0001
Sex									
Male	58	(2)	41	(2)	20	(3)	1.0		
Female	58	(3)	50	(2)	27	(3)	0.9	(0.8-1.0)	.057
Stage									
I	87	(2)	71	(3)	37	(6)	1.0		
II	63	(4)	52	(3)	37	(5)	1.7	(1.4-2.1)	<.0001
III	55	(4)	36	(3)	26	(6)	2.5	(2.1-3.0)	<.0001
IV	5	(2)	2	(1)	6	(4)	6.1	(5.0-7.5)	<.0001
Treatment									
Surgery	64	(3)	51	(2)	35	(4)	1.0		
Surgery + radiotherapy	60	(3)	50	(3)	24	(7)	1.0	(0.8-1.2)	.889
Surgery incl. TME +/- radiotherapy	65	(4)	55	(3)	44	(8)	0.8	(0.7-0.9)	.009
Other/none	8	(3)	6	(1)	3	(2)	1.9	(1.5-2.3)	<.0001
No. of comorbid conditions									
0	60	(2)	54	(2)	33	(5)	1.0		
1	61	(4)	44	(2)	20	(4)	1.3	(1.1-1.5)	.001
≥ 2	43	(5)	33	(2)	19	(4)	1.6	(1.4-1.9)	<.0001
Type of comorbid condition(s)[2]									
Previous malignancies	46	(8)	54	(5)	.		1.2	(0.9-1.6)	.125
Cardiovascular	65	(8)	37	(6)	.		1.3	(0.9-1.6)	.082
COPD	59	(11)	41	(7)	17	(10)	1.4	(1.1-1.9)	.021
Diabetes	67	(11)	49	(9)	.		1.1	(0.8-1.6)	.554
Hypertension	63	(7)	40	(5)	35	(11)	1.3	(1.1-1.6)	.014
Cerebrovascular	.		51	(11)	.		1.1	(0.6-1.9)	.763
Digestive tract	60	(10)	35	(6)	.		1.3	(0.8-2.1)	.210
Other single diseases	64	(12)	38	(8)	.		1.3	(0.8-2.3)	.283

SE=standard error; CI=confidence interval
[1] Crude actuarial 5 year survival rates
[2] Reference category: no comorbidity

strongly with increasing age for both colonic and rectal cancer, as has been shown previously [59-64], for several reasons. As well as comorbidity and the decrease in patients' general condition and cognitive ability, data on the efficacy of chemotherapy and radiotherapy in patients older than 70 years are limited. In addition, elderly patients are more likely to decline adjuvant treatment, especially in the absence of supportive caregivers [59, 65, 66].

In agreement with previous studies, patients with comorbidity were less likely to be offered adjuvant therapy [59, 62-64]. A history of previous malignancy contributed particularly to this effect, presumably because of a less favourable risk: benefit balance for patients with a second tumour. Patients with rectal cancer who also had a combination of hypertension and diabetes were less likely to receive adjuvant radiotherapy, which may be explained by the increased likelihood of radiotherapy-related complications in patients with these conditions [67, 68]. The combination of adjuvant chemoradiation in patients with stage II and III rectal cancer increased from 3.9 per cent in 1995-1999 to 15.9 per cent in 2001. These rates contrast with the results of a SEER (Surveiliance, Epidemiology, End Results)-Medicare-based study (1992-1996), in which 37 per cent of patients aged 65 years or more with stage II and III disease received adjuvant chemoradiotherapy [69].

TME-based surgical resection is strongly recommended for all resectable cancers of the mid or lower rectum [58]. TME was performed less often in older patients and those with comorbidity, especially previous malignancy. The effect of comorbidity on TME surgery could be explained partly by the fact that a large national trial on the management of rectal cancer (the Dutch TME trial) was ongoing between 1996 and 1999; previous malignancy was an exclusion criterion for this study [70].

Age and comorbidity were independent prognostic factors after adjustment for stage, sex and mode of treatment. Previous malignancy, cardiovascular diseases, COPD, the combination of previous malignancy and COPD, and the combination of hypertension and diabetes increased the risk of postoperative mortality in patients with colonic cancer. For patients with rectal cancer, increased mortality was associated mainly with COPD, hypertension, and the combination of hypertension and diabetes.

The presence of concomitant disease had an impact on both crude and relative survival rates, an effect not mediated purely by changes in treatment [71]. However, information was not available on possible dose reductions for adjuvant therapy in patients with comorbidity. A negative effect of comorbidity on survival of patients with colorectal cancer was demonstrated in an earlier population-based study in which 2-year survival was affected by high-impact cardiac-related comorbid conditions, COPD, renal failure and liver disease [72].

The present population-based study has the advantage of avoiding selection bias, but detailed information on performance status of the patient (as measured by means of the Karnofsky scale [73]), dosages of chemotherapy and radiotherapy, and treatment-related complications was not available. Although performance status and comorbidity are both predictive factors for survival in patients with cancer, they are independent of one another [74, 75]. These and other factors, such as socioeconomic status, cognitive disorders and frailty, also play a role in the selection of patients in terms of the administration of effective and safe treatment [76].

The recording of comorbidity in patients with colorectal cancer diagnosed between 1995 and 1999 and registered in the Eindhoven Cancer Registry was validated in a subset of 507 patients [77]. Agreement of almost 70 per cent was found between the registry data and the findings of a medical doctor plus an epidemiologist; differences related mostly to minor comorbidity and to a lesser extent vascular diseases, which tended to be underscored in the registry. This may have led to an underestimation of the prognostic effects of comorbidity in the present study.
Comorbidity did not affect the resection rate of patients with colorectal cancer, but led to less frequent use of adjuvant chemotherapy in patients with colonic cancer and of adjuvant radiotherapy in patients with rectal cancer, especially in those with previous malignancy. Comorbidity was also an independent negative prognostic factor, with previous malignancy and COPD having the greatest negative effect. Future studies on the treatment and outcome of elderly patients with colorectal cancer suffering from comorbidity should also take account of treatment dosages and complications, as well as broader geriatric assessment.

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Chapter 2.2

Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study

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Summary

It is likely that the shift from post- to preoperative radiotherapy and the introduction of total mesorectal excision (TME) surgery have contributed to the observed improved survival of rectal cancer in the south of the Netherlands. However, no improvement was seen for patients aged 70 or older. To investigate possible causes of this lack of improvement, we examined the risk of treatment-related complications and overall survival. Therefore, a random sample of 455 patients with rectal cancer aged 60 years or older, diagnosed between 1995 and 2001 was extracted from in the Eindhoven Cancer Registry database. Fifty-one percent of patients aged 60-69 years old had any complication within one year of diagnosis compared to 65% of patients aged 70 or older (p=0.007). Older patients were at higher risk of developing treatment-related complications (odds ratio (OR) 1.8; p=0.01), as were patients with comorbidity (OR 1.7; p=0.07), and those who received preoperative radiotherapy (OR 1.8; p=0.02). In a multivariable analysis, age older than 70 (hazard ratio (HR) 2.2; p<0.0001), comorbidity (HR 1.7; p=0.03), and having two or more complications (HR=2.2; p=0.0002) had a negative effect on survival. The lack of improvement in the prognosis of elderly patients with rectal cancer might partially be explained by a higher risk of treatment-related complications and the high prevalence of comorbidity among these patients.

Introduction

The treatment of rectal cancer has changed during the last two decades. In the south-east Netherlands, the shift from postoperative towards preoperative radiotherapy (5x5 Gy) and the introduction of total mesorectal excision (TME) surgery have been the most important changes. It is very likely that these developments have contributed to the improved survival of patients with rectal cancer that was observed in this region. [47] The decline in the relative risk of death in the period 1995–2000 versus 1980–1989 of patients with rectal cancer appeared to be related to age. Comparing both periods, the relative risk of death was 0.45 for patients under 60 years of age and 0.62 for those 60-74 years old. However, no improvement in risk of death was found for patients over 74 years of age. [47]
Current treatment guidelines for patients with rectal cancer include preoperative radiotherapy (5x5 Gy) for cT1-3 tumors, and prolonged chemoradiotherapy followed by resection and intraoperative radiotherapy (IORT) for cT4 tumors. Elderly patients are more likely to suffer from other chronic illnesses (comorbidity) which may contra-indicate the standard treatment because of the fear of an increased risk of complications and death. [78-80] The results of a systematic review examining the outcome of surgery for colorectal cancer in elderly patients showed a progressive increase of postoperative morbidity and mortality with advancing age. [81] The contribution of age to this increased morbidity and mortality in elderly patients is not clear. The increased proportion of patients undergoing emergency surgery, together with more frequent comorbidity could contribute significantly to the increased risk of an adverse outcome in the elderly. [81-83] In this study, we investigated the influence of age and comorbidity on treatment related complications and survival of elderly patients with rectal cancer in the south-east of the Netherlands.

Patients and methods

Eindhoven Cancer Registry
The Eindhoven Cancer Registry has been collecting data on patients with newly diagnosed cancer in a large part of southern Netherlands with a population of 2.3 million inhabitants. The registry is notified by six pathology departments, 10 community hospitals and two radiotherapy institutes. Despite the lack of access to death certificates, the infrastructure of and good access to Dutch health care facilities in combination with the notification procedures used have made it possible to establish a completeness of the registry exceeding 95%. [54]
Information on diagnosis, staging, comorbidity at time of diagnosis, and treatment is routinely extracted from the medical records by the registrars usually 6 to 18 months after diagnosis. Prognostically relevant concomitant conditions are recorded from the medical records according to a slightly adapted version of the Charlson Index (Table 1).[43] In the original version used by Charlson and colleagues, not only the number but also the seriousness of the comorbid condition was taken into account. Within the framework of the cancer registry it was not feasible to register severity of comorbidity, but we only recorded serious comorbid conditions with possible prognostic impact. We

also included hypertension, which has been shown to be a prognostic factor in some previous studies. In the analyses we classified comorbidity as no comorbidity, one comorbid condition, or two or more comorbid conditions.

Table 1. Classification of comorbidity, according to an adapted version of Charlson *et al.* (1987)

Previous malignancies (except basal skin carcinoma and carcinoma in situ of the cervix)
Chronic Obstructive Pulmonary Diseases (COPD)
Cardiovascular diseases (myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm, peripheral arterial disease)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Hypertension
Diabetes mellitus
Digestive tract diseases (stomach diseases, Crohn's disease, ulcerative colitis, liver cirrhosis, hepatitis)
Other (connective tissue diseases, severe rheumatoid arthritis, kidney diseases, dementia, tuberculosis, chronic infections)

Patient population

The total number of patients with rectal adenocarcinoma aged 60 years or older diagnosed between 1995 and 2001 in the Eindhoven Cancer Registry area amounted to 2094. Patients presenting with distant metastases (N=322) were excluded. Of the remaining patients, we randomly selected 455 patients, since the total patient population was too extensive to gather the additional information from the medical files (see below). The random selection procedure was carried out using SAS statistical software (SAS Institute Inc., Cary, North Carolina, USA, 1999). From the sample of 455 rectal cancer patients, 29 clinical records could not be found in the hospitals due to migration, death or an unexplained reason. These 29 patients were excluded from the study. Fourteen of these patients (48%) died during the follow-up period completed on January 1st, 2005.

Preoperative findings / social status

Additional information on performance status, urgency of surgery, preoperative radiotherapy, and hemoglobin level, was recorded by two researchers (an epidemiologist and an experienced surgeon), with the approval and under supervision of the treating physicians. Performance status of patients was extracted from the medical record using the Karnofsky scale. For patients who underwent surgery we also recorded the American Society of Anesthesiologists (ASA) score. However, since 45% of the ASA score and 49% of the Karnofsky score were not mentioned in the medical

files, we did not include these variables in our analyses. Patients with hemoglobin levels below 6.5 mmol per liter (before treatment or any transfusion) were assigned to the low hemoglobin group.
Socio-economic status (SES) of the patient was defined at neighbourhood level (based on postal code of residence area, 17 households on average) combining mean household income (in 1998) and mean value of the house/apartment (in 2000), derived from individual fiscal data made available at an aggregated level. Postal codes were assigned to 3 SES categories: low (1st –3rd decile), intermediate (4th-7th decile), and high (8th-10th decile). Postal codes of institutions, such as nursing homes, were assigned to a separate category and were excluded from the logistic regression and survival analysis (19 patients, all aged 70 or older).

Postoperative findings
Serious complications occurring within one year of diagnosis were recorded. These were defined as minor infections (e.g. wound infections, urinary tract infections), major infections (e.g. abscess, peritonitis, anastomotic leakage), pulmonary complications (e.g. pneumonia), hemorrhage (requiring blood transfusion or surgery), thrombo-embolic events, cardiac complications (e.g. cardiac failure, ischaemic heart disease), hematological complications, complications typically due to radiotherapy (e.g. radiation enteritis), stoma problems, death due to complications (stated in the medical file), and other complications (e.g. kidney failure, lymphoedema, fatigue, cerebral problems, ileus, incontinence, urine retention).
Also the date of a local tumour recurrence was recorded.

Follow-up
Information on vital status of the patients was obtained from the hospital records, the civil municipal registries and the death register of the Central Bureau for Genealogy. The latter is an institution that registers all deceased Dutch citizens via the municipal civil registers. In this way, information on patients who had moved outside the registry area was also obtained. In total 201 (47%) colorectal cancer patients died during follow-up, which was completed on January 1st, 2005. The median follow-up in months was 48.5 (range 0-119).

Statistical analyses
The prevalence of complications was analysed according to age (dichotomised into <70 and ≥70 years); significance was tested by means of a Chi square test. The independent influence of age, gender, stage, comorbidity, socioeconomic status, haemoglobin level and treatment on development of complications was analysed in a logistic regression analysis. Crude survival was computed with date of diagnosis as the starting point and death or end of study as endpoint. The log-rank test was used to compare univariable survival rates between groups of patients. Univariable survival analyses were stratified according to age at diagnosis (<70 and ≥70 years). Multivariable proportional hazards regression methods were used to discriminate independent risk factors for death. The likelihood ratio method was used to determine

hazard ratios. The SAS computer package (version 8.2) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1999).

Results

The general characteristics are shown in table 2; 182 patients were between 60 and 69 years old and 244 were aged 70 years or older. The male-female ratio was 1.8 among patients aged 60-69 and 1.0 among the elderly (p=0.004). Patients aged 70 years or older were more likely to have rectal cancer in an unknown stage than patients aged 60-69 (12% vs. 7%, respectively), although there was no trend for older patients to be diagnosed in a more advanced stage of disease (p=0.3). Eighty-one percent of the patients aged 70 or older had one or more concomitant diseases compared to 64% of patients aged 60-69 (p<0.0001). Fourteen percent of patients aged 70 or older had low hemoglobin levels, in contrast to 7% of patients aged 60-69 (p=0.02). Of patients aged 70 or older, 36% underwent preoperative radiotherapy, compared to 49% of younger patients (p=0.004); the proportion receiving other or no treatment was higher among the elderly. Four percent of patients underwent emergency surgery (2% of patients aged 60-69 vs. 5% of patients 70 or older, p=0.2; data not shown).

Table 2. General characteristics of patients with rectal cancer diagnosed in 1995-2001 in the southern Netherlands, by age

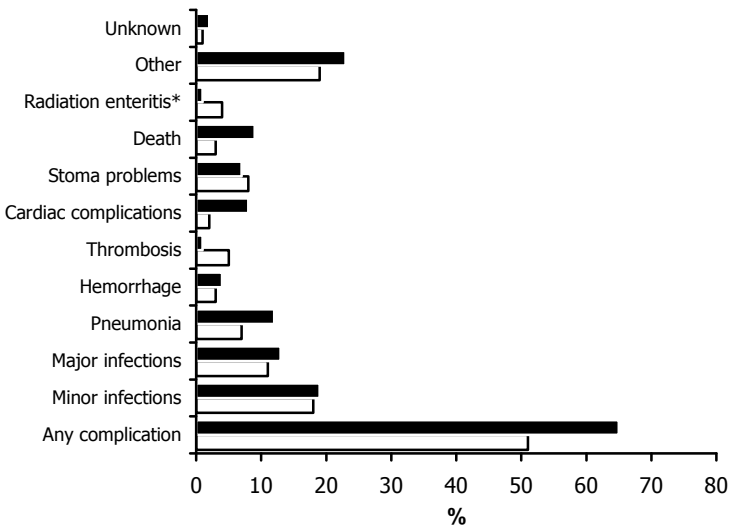
	60-69 years (N=182)		**70+ years (N=244)**		
	N(%)		**N(%)**		p-value*
Gender					
Male	116	(64)	121	(50)	0.004
Female	66	(36)	123	(50)	
Stage (TNM)					
I	56	(31)	69	(28)	0.3
II	58	(32)	81	(33)	
III	55	(30)	64	(26)	
Unknown	13	(7)	30	(12)	
Comorbidity					
No comorbidity	61	(34)	41	(17)	<0.0001
1 comorbid condition	55	(30)	64	(26)	
2 or more comorbid conditions	62	(34)	134	(55)	
Unknown comorbidity	4	(2)	5	(2)	
Socio-economic status					
High	63	(35)	81	(33)	0.0006
Intermediate	61	(34)	88	(36)	
Low	58	(32)	56	(23)	
Institutionalized	0	(0)	19	(8)	
Haemoglobin level					
Normal (>6.5 mmol/l)	161	(89)	197	(81)	0.02
Low (≤6.5 mmol/l)	13	(7)	34	(14)	
Unknown	8	(4)	13	(5)	
Treatment					
Surgery alone	78	(43)	115	(47)	0.004
Preoperative radiotherapy	89	(49)	87	(36)	
Other/none	15	(8)	42	(17)	

* Chi-square test for equal proportions, the null hypothesis specifies equal proportions of the total sample size for each class.

Fifty-one percent of patients aged 60-69 years old had any complication within one year of diagnosis compared to 65% of patients aged 70 or older (p=0.007) (figure 1). The most frequent complications within one year of diagnosis were minor infections, major infections, and pneumonia. Elderly patients suffered more from cardiac complications (8% vs. 2%, p= 0.01) and pneumonia (12% vs. 7%, p= 0.13) than younger patients, and there were also more deaths due to treatment complications (especially cardiac) among these patients (9% vs. 3%, p= 0.01).

According to the results of the logistic regression analysis, the risk of developing complications was almost twice as high for patients aged 70 or older compared to younger patients (p=0.01, Table 3). Females appeared to have a lower risk of developing complications than males, whereas patients with stage III disease had a higher risk than those with stage I or II. The risk of developing complications was higher for patients with comorbidity compared to those without comorbidity, although not significantly (OR=1.7 for one concomitant disease; OR=1.5 for two or more concomitant diseases). This effect was more pronounced among patients aged 70 or older (OR=2.3, p=0.04 for one concomitant disease; OR=2.3, p=0.03 for two or more concomitant diseases; data not shown). Patients who underwent surgery plus radiotherapy had a significantly higher risk of developing complications (OR=1.8, p=0.02) compared to those who underwent surgery alone.

Figure 1. Age-specific prevalence of complications during the first year after diagnosis among rectal cancer patients diagnosed between 1995 and 2001



*Percentage of patients receiving radiotherapy

70+ years (N=244)
60-69 years (N=182)

Table 3. Risk of developing complications within one year after diagnosis for patients who underwent elective surgery for rectal cancer diagnosed between 1995 and 2001 in the southern Netherlands; multivariable logistic regression model including all variables listed*

	Odds ratio	p-value
Age		
60-69 years†	1.0	
70+years	1.8	0.01
Gender		
Male†	1.0	
Female	0.7	0.08
Stage (TNM)		
I†	1.0	
II	1.1	0.7
III	1.8	0.04
Comorbidity		
No comorbidity†	1.0	
1 comorbid condition	1.7	0.07
2 or more comorbid conditions	1.5	0.2
Socio-economic status		
High†	1.0	
Intermediate	0.8	0.4
Low	1.0	0.9
Hemoglobin level		
Normal (>6.5mmol/l) †	1.0	
Low (≤6.5mmol/l)	1.1	0.3
Treatment		
Surgery alone†	1.0	
Surgery + radiotherapy	1.8	0.02

*Cases with missing values for any of the covariates were left out of the analyses
† Reference category

The rate of local recurrence was similar for patients who underwent surgery plus preoperative radiotherapy and for those who underwent surgery alone (6% vs. 8%, p=0.4; no difference by age).

The crude 5-year survival rate was 70% for patients aged 60-69 years old and 44% for patients aged 70 or older (p<0.0001, table 4). These rates increased to 79% for patients aged 60-69 years without comorbidity and 60% for patients aged 70 or older without comorbidity. For both age groups the crude survival decreased with an increasing number of comorbid conditions, higher stage and number of complications. For patients aged 70 or older crude survival was also worse for those with a low hemoglobin level and for those receiving adjuvant radiotherapy or other/none treatment. In a multivariable analysis, higher age (hazard ratio (HR) =2.2), comorbidity (HR=1.7) and the development of 2 or more complications had a negative effect on survival. The receipt of preoperative radiotherapy had a borderline significant negative influence on survival (HR=1.4, p=0.10).

Table 4. Uni- and multivariable analyses for overall survival of patients with rectal cancer diagnosed between 1995 and 2001 in the southern Netherlands.*

	Univariable				Multivariable	
	60-69 years		70+ years		All ages	
	5 yrs%	P-value	5 yrs%	p-value	Hazard ratio	p-value
Age						
60-69 years†	70				1.0	
70+ years			44	<0.0001	2.2	<0.0001
Gender						
Male†	67		46		1.0	
Female	76	0.2	42	0.2	1.0	0.8
Stage (TNM)						
I†	82		63		1.0	
II	68		45		1.3	0.3
III	59	0.03	30	0.001	2.0	0.002
Comorbidity						
No comorbidity†	79		60		1.0	
1 comorbid condition	71		47		1.7	0.05
2 or more comorbid conditions	63	0.03	38	0.09	1.7	0.03
Socio- economic status						
High†	79		42		1.0	
Intermediate	65		52		0.7	0.10
Low	66	0.3	42	0.6	0.9	0.6
Hemoglobin level						
Normal (>6.5mmol/l)†	71		46		1.0	
Low (≤6.5mmol/l)	58	0.7	34	0.01	1.1	0.2
Treatment						
Surgery alone†	70		56		1.0	
Surgery + radiotherapy	71		42		1.4	0.10
Other/none	‡		18	0.002	‡	
Complications						
No complication†	81		58		1.0	
1 complication	69		50		1.1	0.8
2 or more complications	54	0.007	29	0.0003	2.2	0.0002

*Cases with missing values for any of the covariates were left out of the analyses
[1] Reference category
‡ Analyses could not be completed due to small numbers

Discussion

Patients aged 70 years or older underwent surgery in combination with preoperative radiotherapy (36%) less often than patients aged 60-69 years (49%). Elderly patients and those who underwent surgery plus radiotherapy had a significantly higher risk of developing complications, especially pneumonia, cardiac complications and death due to complications. Independent prognostic factors were higher age, comorbidity, higher stage, and having two or more complications.

Previous population-based studies already described the influence of age on the receipt of adjuvant radiotherapy for rectal cancer patients. [59, 79] The physician might decide not to refer elderly patients for radiotherapy because of advanced age or serious comorbidity, but other factors might also play a role, such as a decreased general

mental and physical condition, refusal of the patient, the absence of caregivers in the family situation, and distance to the radiotherapy institute. [59, 79] It is likely that the influence of these factors is more important in the longer-term postoperative setting than in the relatively short (5x5 Gy) preoperative setting. Since 1995, postoperative radiotherapy has been largely replaced by preoperative radiotherapy in the south of the Netherlands; the rate of postoperative radiotherapy has dropped to 4%.[47]

The current study showed that elderly patients developed more treatment related complications, especially pneumonia and cardiac complications, and were at a higher risk of dying due to a complication. The effect of age on postoperative morbidity and mortality has already been described in a number of other studies. [84-87] A recent prospective multicenter study in France found age older than 70 years and neurologic and cardiorespiratory comorbidity to be independent risk factors of morbidity after colorectal surgery, and age older than 70 years and neurological comorbidity were preoperative risk factors of mortality. [88] In a review of 28 studies on colorectal cancer surgery in the elderly, an increased frequency of postoperative morbidity and mortality with advancing age was reported. [81] Pooled data suggested an age-related increase for pneumonia/respiratory failure, cardiovascular complications, cerebrovascular accident, and thromboembolism. There was no increased frequency of anastomotic leaks in the elderly. Overall 5-year survival decreased by age, although there was only little difference in cancer-specific survival. Unfortunately, in this retrospective population-based study we did not have data on cause of death at our disposal.

Preoperative radiotherapy reduces the risk of a local recurrence; it tends however to increase the risk of developing complications, including impaired wound healing and bowel dysfunction. [50, 84, 89-92] Some authors considered preoperative radiotherapy as a risk factor for anastomotic leakage. [93, 94] Also in our study, patients who underwent surgery plus preoperative radiotherapy developed more complications than patients undergoing surgery alone. Minor infections such as delay of wound healing were the most frequent complications after adjuvant radiotherapy (18%). Prognosis was negatively affected by age and comorbidity, in line with previous studies. [72, 81, 95-97] The Stockholm II Trial reported that both the increase in postoperative mortality and the higher incidence of intercurrent death after radiotherapy were mainly caused by cardiovascular disease. [98] The cause of the increased cardiovascular mortality is not known. One explanation is that, in addition to a local effect on the vascular bed, there is also a systemic effect that may result in thromboembolic and cardiovascular complications developing with time. [99, 100] In the current study the risk of local recurrence for the group as a whole was low and was similar for patients receiving preoperative radiotherapy and for those undergoing surgery alone. However, regardless of having recurrence or survival as an endpoint, comparison of treatment outcome in a retrospective population-based study may be biased due to selection of patients by the treating physician.

Unfortunately, ASA and performance score were not mentioned in the majority of the medical files, so that these important variables could not be included in our study. Performance score is found to have a prognostic impact, independent of comorbidity. [74] On the other hand, performance score is often amenable to the malignant disease and its treatment, in contrast to comorbidity. ASA score was found to be a predictor of

mortality following surgery for colorectal cancer in some studies [101, 102]; however, others did not find an independent effect of ASA on perioperative mortality or morbidity. [83, 88] This may be due to the considerable interobserver inconsistency of classification of ASA score. [103, 104]

In a previous study it was shown that survival of rectal cancer patients aged 75 or older did not improve in the south of the Netherlands between 1980 and 2000, whereas there was a clear improvement for the younger patients. [47] This observation seems to be partly explained by the results of the current study: elderly patients were at higher risk of developing treatment-related complications. Also the high prevalence of comorbidity is likely to contribute to the lack of improvement for the elderly patients. In order to optimize the risk/benefit ratio of elderly patients, individualization of treatment by means of a comprehensive geriatric assessment will be of critical importance.

Chapter 2.3

Which comorbid conditions predict complications after surgery for colorectal cancer?

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Summary

Background: Accurate presurgical assessment is important to anticipate postoperative complications, especially in the growing proportion of elderly cancer patients. We defined which comorbid conditions at time of diagnosis predict complications after surgery for colorectal cancer.
Patients: A random sample of 431 patients recorded in the population-based Eindhoven Cancer Registry who underwent resection for stage I-III colorectal cancer, newly diagnosed between 1995 and 1999.
Methods: The influence of specific comorbid conditions on the incidence and type of complications after surgery for colorectal cancer was analysed.
Results: Overall, patients with comorbidity did not develop more surgical complications. However, patients with a tumour located in the colon who suffered from concomitant chronic obstructive pulmonary disease (COPD) more often developed pneumonia (18% vs. 2%; p=0.0002) and haemorrhage (9% vs. 1%; p=0.02). Patients with colon cancer who suffered from deep vein thrombosis (DVT) at the time of cancer diagnosis more often had surgical complications (67% vs. 30%; p=0.04), especially more minor (44% vs. 11%; p=0.002) and major infections (56% vs. 10%; p<0.0001), pneumonia (22% vs. 2%; p=0.01), and thromboembolic complications (11% vs. 3%; p=0.02). Patients with a tumour located in the rectum who suffered from COPD more frequently had any surgical complication (73% vs. 46%; p=0.04), and presence of DVT at time of cancer diagnosis was predictive of thromboembolic complications (17% vs. 4%; p=0.045).
Conclusions: Among patients undergoing surgery for colorectal cancer, development of complications was especially predicted by presence of COPD and DVT. In the latter, regulation of the pre- and postsurgical haemostatic balance needs full attention.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death in industrialized countries [105]. Seventy-five percent of incident tumours occur in persons aged 65 years or older. Because of their age, these patients are likely to suffer from other chronic illnesses in addition to the colorectal malignancy (comorbidity). In the Netherlands, 60% of patients with CRC over the age of 70 suffer from comorbidity [80]. Resection rates however remain at a high level among these patients, explained by the fact that resection is the only primary curative treatment for CRC, and often necessary to prevent obstruction. In the last decades, the safety of surgery for CRC has improved by advances in surgical technique, anaesthesia, intensive care therapy, antibiotic treatments, thromboprophylaxis, and other supportive measures [106, 107]. Especially in patients suffering from comorbidity, an accurate presurgical assessment is important in planning surgery and supportive treatment. In order to stratify patients into groups with varying risks of complications based on their comorbidity, we evaluated the influence of specific comorbid conditions on incidence and type of complications after surgery for CRC, using data from the population-based Eindhoven Cancer Registry in the Netherlands.

Patients and methods

The Eindhoven Cancer Registry (ECR) collects data on all patients with newly diagnosed cancer in a large part of the southern Netherlands with a population of 2.4 million. The registry is notified by 6 pathology departments, 10 community hospitals and 2 radiotherapy institutes. There are no university hospitals in the region. Registration takes place 6 to 18 months after diagnosis. Despite the lack of access to death certificates, the infrastructure of and good access to Dutch health care facilities in combination with the notification procedures used have made it possible to establish a completeness of the registry of more than 95% [54].
Between 1995 and 1999, 5352 patients were diagnosed with primary CRC in the ECR area. Since it was not feasible to review the medical records of all patients in order to collect additional data, a random sample of 545 patients aged 40 years and older with colorectal adenocarcinoma diagnosed between 1995 and 1999 was extracted. The randomisation procedure was run by a computer program (SAS statistical software, SAS Institute Inc., Cary, North Carolina, USA, 1999). Colon tumours were defined as C18.0-C18.7 and rectal tumours as C19.9-C20.9, according to ICD-O-3. For the random sample of 545 colorectal cancer patients, 31 clinical records could not be found in the hospitals (i.e. patients moved to another area or country) and 8 clinical records were incomplete. These 39 patients were excluded from the study. They did not differ from the study population according to age or stage (the latter known for 29 out of 39 excluded patients) at diagnosis. Next, we excluded patients who presented with distant metastasis (n=27), patients with unknown stage of disease (n=40), and patients who did not undergo a resection (n=21).
Information on diagnosis, staging, comorbidity at time of diagnosis, and treatment is routinely extracted from the medical records by the registrars. Comorbidity was

recorded according to a slightly adapted version of the Charlson Index (table 1). In the original version used by Charlson and colleagues, not only the number but also the severity of the comorbid condition was taken into account. Within the framework of the cancer registry it was not feasible to register severity of comorbidity; the comorbid conditions as listed in table 1 were recorded if they were present at the time of cancer diagnosis. We also included hypertension, which has been shown to be a prognostic factor in some previous studies. Additional information was recorded by two researchers (an epidemiologist and an experienced surgeon, always working together), with the approval and under supervision of the treating physicians. Performance status of patients was extracted from the medical record using the Karnofsky scale [108]. Also the American Society of Anaesthesiologists (ASA) physical score was recorded [109]. However, due to incomplete documentation of performance status (87% missing) and ASA scores (65% of the scores for resected patients missing), these variables could not be included in our analyses.

Table 1. Classification of comorbidity, according to an adapted version of Charlson *et al.* (1987)[43]

Previous malignancies (except basal skin carcinoma and carcinoma in situ of the cervix)
Chronic Obstructive Pulmonary Diseases (COPD)
Cardiovascular diseases (myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm, peripheral arterial disease)
Deep vein thrombosis (DVT)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Hypertension
Diabetes mellitus
Other (digestive tract disease, connective tissue diseases, severe rheumatoid arthritis, kidney diseases, dementia, tuberculosis, chronic infections)

Blood haemoglobin level (before any transfusion) was extracted from the medical record; patients with haemoglobin levels below 6.5 mmol per litre were assigned to the low haemoglobin group [110].
Preoperative radiotherapy was recorded as yes vs. no. Timing (elective vs. emergency) and type of surgery was also recorded.
Serious surgical complications as described in the medical records, occurring within 60 days of diagnosis were recorded. Complications registered were minor infection (e.g. wound infections, wound dehiscence, urinary tract infections), major infection (e.g. abscess, peritonitis, anastomotic leakage), pulmonary complications (e.g. pneumonia), haemorrhage (requiring blood transfusion or reoperation), thrombo-embolic events, cardiac failure (e.g. cardiac insufficiency), kidney failure, stoma problems (e.g. stomal necrosis), and other complications. Also death due to complications was recorded,

judged from the information in the medical record whether the patient's death could be directly linked to a preceding complication.
The association between comorbidity and complications was analysed using a chi-square test. Then, the association between comorbidity and complications was evaluated in a logistic regression model; first, a model including age, gender, stage, tumour site, haemoglobin level, timing of surgery, preoperative radiotherapy, and presence of comorbidity (yes vs. no) was built. No interaction term reached statistical significance. Thereafter, the model was run again with presence of comorbidity replaced by presence of the respective comorbid condition (having no comorbidity as a reference). All variables were included in the model without the use of a forward or backward procedure, in order to conclude about the effects of the all included variables on the development of complications. The SAS computer package (version 8.2) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, USA, 1999).

Results

The general characteristics of the 418 patients are depicted in table 2. The use of preoperative radiotherapy for patients with rectal cancer increased during the study period, from 24% in 1995 to 53% in 1999.
The most frequent comorbid conditions at the time of the colorectal cancer diagnosis were cardiovascular disease, hypertension, and a previous malignancy, for both colon and rectal cancer (table 3).

In table 4 the frequency of surgical complications are depicted. Minor and major infections were the most frequent complications for both colon and rectal cancer patients.
Thirty percent of patients with colon cancer who did not suffer from comorbidity developed surgical complications (table 5). Patients with thrombosis present at the time of cancer diagnosis were at higher risk of developing any surgical complication ($p=0.04$). Especially minor infections ($p=0.002$), major infections ($p<0.0001$), pneumonia ($p=0.01$), and thrombo-embolic complications ($p=0.02$) more frequently developed among these patients. Among patients who suffered from COPD at time of cancer diagnosis, pneumonia ($p=0.0002$) and haemorrhage ($p=0.02$) were more frequent than among patients without comorbidity. Patients with COPD also seemed to develop more major infections, although this relation did not reach statistical significance ($p=0.07$).

Forty-six percent of patients with rectal cancer not suffering from comorbidity developed a surgical complication (table 6). Patients presenting with COPD more frequently developed any surgical complication ($p=0.04$), and patients with thrombosis at time of cancer diagnosis developed more often thrombo-embolic events postoperatively ($p=0.045$).
Eight percent ($n=22$) of patients with colon cancer and 7% ($n=9$) of patients with rectal cancer died within 60 days of diagnosis, following a surgical complication (mainly after cardiac complications and deep infections). Thirty-six percent ($n=11$) of the

deceased patients underwent an emergency operation. The presence of comorbidity increased the risk of dying following a complication (3% of patients without comorbidity vs. 10% of patients with comorbidity, p=0.04)

Table 2. Patient characteristics and treatment of 418 patients who underwent resection for colorectal cancer between 1995 and 1999 in the southern Netherlands.

	Colon (n=279)		**Rectum** (n=139)	
Mean age (range in yrs.)	70	(41-92)	67	(42-86)
	n	**(%)**	**n**	**(%)**
Gender				
Male	133	(48)	84	(60)
Female	146	(52)	55	(40)
Stage				
I	51	(18)	46	(33)
II	134	(48)	50	(36)
III	94	(34)	43	(31)
Site of tumour				
Colon ascendens	109	(39)		
Colon transversum	62	(22)		
Colon descendens	108	(39)		
Rectosigmoid			31	(22)
Rectum			108	(78)
Number of comorbid conditions				
0	77	(28)	53	(38)
1	87	(31)	38	(28)
2+	103	(37)	45	(32)
Unknown	12	(4)	3	(2)
Type of surgery				
Surgery, not specified	13	(5)	6	(4)
Total procto-colectomy	1	(0.4)	2	(1)
Subtotal colectomy	12	(4)		
Hemicolectomy, right / ileocoecal resection	135	(48)		
Hemicolectomy, left	33	(12)		
Sigmoid resection with primary anastomosis	85	(31)		
Rectosigmoid resection with Hartmann-procedure			10	(7)
Low anterior resection with primary anastomosis			78	(57)
Abdominoperineal resection			43	(31)
Timing of surgery				
Elective operation	227	(81)	125	(90)
Emergency operation	37	(13)	5	(4)
Unknown	15	(5)	9	(6)
Pre-operative radiotherapy			55	(40)[a]

[a] Ranging from 24% in 1995 to 53% in 1999.

After adjustment for age, gender, stage, tumour site, haemoglobin level, timing of surgery, and preoperative radiotherapy, patients with comorbidity in general did not have a higher risk of developing any surgical complication (odds ratio (OR) 1.1, p=0.2) (table 7). However, presence of DVT at time of cancer diagnosis increased the risk of developing a complication compared to patients without comorbidity (OR 9.0; p=0.04). The risk of developing a complication also seemed to be increased for patients with

COPD (OR 1.8, p=0.2), and decreased for patients with diabetes (OR 0.6, p=0.2), although both effects did not reach statistical significance. Furthermore, age older than 70 years, a tumour located in the rectum, and emergency surgery all independently increased the risk of developing a surgical complication.

Table 3. Prevalence of comorbidity at time of diagnosis according to tumour site, among patients who underwent resection for colorectal cancer diagnosed between 1995 and 1999 in the southern Netherlands.[a,b]

	Colon (n=267) n (%)		**Rectum** (n=136) n (%)	
No comorbidity	77	(29)	53	(39)
Previous malignancy	54	(20)	18	(13)
Cardiovascular disease	90	(34)	38	(28)
COPD	36	(13)	12	(9)
Diabetes mellitus	26	(10)	13	(10)
Hypertension	68	(25)	37	(27)
DVT	9	(3)	6	(4)
Other[c]	51	(19)	20	(15)

[a] Excluding patients with unknown comorbidity (n=15)
[b] More than one condition per patient possible
[c] Including digestive tract diseases, connective tissue diseases, severe rheumatoid arthritis, kidney diseases, dementia, tuberculosis, and chronic infections

Table 4. Postoperative complications within 60 days of diagnosis according to tumour site, among patients with colorectal cancer diagnosed between 1995 and 1999 in the southern Netherlands.[a,b]

	Colon (n=270) n (%)		**Rectum** (n=136) n (%)	
Any complications	96	(36)	63	(46)
Minor infections[c]	33	(12)	18	(13)
Major infections[d]	27	(10)	17	(13)
Pneumonia	13	(5)	8	(6)
Haemorrhage	7	(3)	8	(6)
Thrombosis	5	(2)	4	(3)
Cardiac failure	24	(9)	8	(6)
Kidney failure	6	(2)	5	(4)
Stoma problems	4	(1)	7	(4)
Death due to complication	20	(7)	9	(7)
Other[e]	5	(2)	5	(4)

[a] Excluding patients with unknown complications (n=12).
[b] More than 1 complication per patient possible.
[c] Including wound infections, wound dehiscence, urinary tract infections.
[d] Including abscess, peritonitis, anastomotic leakage.

Discussion

Unsurprisingly, a large proportion of the colorectal cancer (CRC) patients in our study presented with one or more comorbid conditions at the time of cancer diagnosis.[80] Overall, comorbidity was not associated with postoperative morbidity after surgery for CRC, but several specific comorbid conditions were related to a more frequent

development of complications. Especially patients suffering from deep vein thrombosis (DVT) or chronic obstructive pulmonary disease (COPD) at time of diagnosis were at higher risk.

Operative morbidity clearly depends on patient selection and underlying pathology. Many studies have therefore attempted to link presurgical risk factors to morbidity and mortality.[81, 83, 88, 93, 106, 111-115] Most of these were single-hospital studies; only few population-based studies have been able to stratify patients into groups with varying risks of complications based on their comorbid conditions.[88, 93, 106, 114] One of the advantages of using population-based data is the avoidance of several potential sources of bias, such as referral bias and exclusion of emergency cases. Also, inclusion of non-academic hospitals of different size, subspecialties, and levels of surgical experience may provide a more realistic image of every-day practice, including postoperative morbidity.[106] The complication rate of 39% in the current study is higher than that found in most other studies, which could partly be explained by the more accurate reflection of postoperative morbidity than in other, mostly single-hospital studies.[81, 83, 88, 93, 106, 111-115] However, the higher rate of complications in our study was probably also caused by the fact that we scored all surgical complications within 60 days of diagnosis (due to the lack of the date of operation) instead of the commonly used period of 30 days within operation. Unfortunately, performance status and ASA score were in many instances not adequately documented in the medical records, so this information could not be used in our analysis.

We found that patients with colon cancer and presence of deep vein thrombosis (DVT) at time of cancer diagnosis were at higher risk of developing complications. These patients especially had more infections, pneumonia, and postoperative thrombo-embolic events. The complex relation between cancer and DVT has been well-established.[116, 117] Besides the fact that cancer patients are at high risk of DVT, surgery for malignant disease increases the risk development of DVT, further enhanced by the presence of central venous catheters and prolonged bed rest.[107, 117] There is evidence that a hypercoagulable state may contribute to the development of anastomotic leakage by facilitating formation of microthromboses in the perianastomotic region.[118] It seems plausible that in patients with clinically evident DVT at time of cancer diagnosis, major abdominal surgery will further stress the haemostatic balance. This consequently leads to impaired wound healing and a higher risk of developing surgical complications.[116] To our knowledge, only one population-based study has described the relation between preoperative haemostatic balance and postoperative morbidity after surgery for colorectal cancer.[106] Using data from the National Veterans Affairs Surgical Quality Improvement Program, the authors found preoperative prothrombin times of less than 12 seconds to be predictive of three of the most frequently occurring complications after colectomy. The management of DVT in the presence of malignancy is complex, due both to the effects of the cancer itself and its treatment. Recent research indicates that the use of low molecular weight dalteparin, instead of vitamin K antagonists such as warfarin, offers an effective alternative in the management of DVT, free from the practical problems associated with the use of vitamin K antagonists, and without increasing the risk of bleeding.[116, 117, 119, 120]

Table 5. Development of postoperative complications within 60 days of diagnosis according to comorbid condition, among patients with colon cancer diagnosed between 1995 and 1999 in the southern Netherlands.

		Surgical complication								
Comorbid condition	n	Any surgical Complication (n=96)	Minor Infections (n=33)	Major Infections (n=27)	Pneumonia (n=13)	Haemorrhage (n=7)	Thrombosis (n=5)	Cardiac failure (n=24)	Kidney failure (n=6)	Stoma problems (n=4)
No comorbidity	77	30%	11%	10%	2%	1%	3%	6%	3%	1%
Previous malignancy	54	47%*	16%	10%	10%*	6%	0%	10%	2%	2%
Cardiovascular disease	90	39%	11%	11%	7%	5%	1%	13%	1%	1%
COPD	36	42%	15%	18%*	18% **	9%**	0%	15%	0%	3%
Diabetes	26	21%*	8%	0%*	4%	4%	0%	0%*	4%	0%
Hypertension	68	33%	10%	11%	3%	2%	0%	8%	2%	0%
DVT	9	67% **	44%**	56%**	22%**	11%	11%**	22%	0%	0%

Percentages depict the proportion of patients which developed the respective complication in presence of the respective comorbid condition.
** $p < 0.05$ (chance of developing a complication in presence of the respective comorbid condition vs. chance of developing a complication in absence of comorbidity).
* $p < 0.10$ (chance of developing a complication in presence of the respective comorbid condition vs. chance of developing a complication in absence of comorbidity).

Table 6. Development of postoperative complications within 60 days of diagnosis according to comorbid condition, among patients with rectal cancer diagnosed between 1995 and 1999 in the southern Netherlands.

		Surgical complication								
Comorbid condition	**n**	Any surgical Complication (n=63)	Minor Infections (n=18)	Major Infections (n=17)	Pneumonia (n=8)	Haemorrhage (n=8)	Thrombosis (n=4)	Cardiac failure (n=8)	Kidney failure (n=5)	Stoma problems (n=7)
No comorbidity	53	46%	13%	10%	8%	10%	4%	4%	2%	6%
Previous malignancy	18	50%	22%	17%	6%	11%	0%	6%	11%	0%
Cardiovascular disease	38	53%	15%	9%	3%	6%	0%	6%	6%	3%
COPD	12	73%**	9%	18%	9%	0%	0%	18%*	0%	18%*
Diabetes	13	62%	15%	15%	0%	0%	8%	0%	8%	8%
Hypertension	37	53%	14%	19%	6%	6%	0%	8%	6%	11%*
DVT	6	67%	33%*	17%	0%	0%	17%**	17%	0%	0%

Percentages depict the proportion of patients which developed the respective complication in presence of the respective comorbid condition.
** $p < 0.05$ (chance of developing a complication in presence of the respective comorbid condition vs. chance of developing a complication in absence of comorbidity).
* $p < 0.10$ (chance of developing a complication in presence of the respective comorbid condition vs. chance of developing a complication in absence of comorbidity)

Table 7. Risk of developing a surgical complication among patients with colorectal cancer diagnosed between 1995 and 1999 in the southern Netherlands, calculated by means of a logistic regression analysis. [a]

	Odds ratio	p-value
Age		
<70 years [b]	**1.0**	
70+ years	1.8	0.02
Gender		
Male [b]	1.0	
Female	1.1	0.8
Stage		
I [b]	1.0	
II	1.0	0.9
III	1.2	0.6
Tumoursite		
Colon [b]	1.0	
Rectum	1.9	0.03
Haemoglobin level		
Normal (>6.5 mmol/l) [b]	1.0	
Low (≤ 6.5 mmol/l)	1.2	0.6
Timing of surgery		
Elective surgery [b]	1.0	
Emergency surgery	3.2	0.005
Preoperative radiotherapy		
No [b]	1.0	
Yes	1.5	0.18
Comorbidity		
No comorbidity [b]	1.0	
Any comorbidity	1.1	0.2
-Previous malignancy	1.2	0.5
-Cardiovascular disease	0.9	0.6
-COPD	1.8	0.2
-Diabetes	0.6	0.16
-Hypertension	0.7	0.4
-DVT	9.0	0.04

[a] Adjusted for all listed variables
[b] Reference category

The presence of COPD was predictive of development of pneumonia and haemorrhage among patients with colon cancer in our study. Cardiopulmonary comorbidity was also associated with a higher risk of postoperative morbidity after colorectal surgery in a French prospective multicenter study,[88] while a history of COPD was an independent predictor of postoperative 30-day morbidity in patients after colectomy for colon cancer in a large US population-based study.[106] Surprisingly, COPD was not predictive of pneumonia in that study, opposite to being a current cigarette smoker. COPD was found to be related to the development of major infections in two studies;[106, 114] among the colon cancer patients in our study, this effect did not reach statistical significance. Among rectal cancer patients, COPD was predictive for development of any surgical complication. The effect of COPD might be distorted by smoking status; smoking may have an independent negative effect on the development of complications.[121] Smoking is associated with microvascular disease, which in turn predisposes to anastomotic breakdown. This effect may in part be due to vasospasm in the diseased vessels, which are hypersensitive to serotonin, a vasoactive amine known to be present in increased

quantities in the serum of smokers. Treatment with serotonin antagonists in the perioperative period may therefore be beneficial to anastomotic healing, helping to maintain microvascular flow.[121] In the logistic regression analysis, COPD did not have a significant effect on the development of complications, probably due to the relatively small sample size used in our study and the resulting lack of power.
To conclude, we found that among patients undergoing surgery for colorectal cancer, development of complications was especially predicted by presence of COPD and DVT. The effect of DVT on postoperative complications will have to be addressed in larger, prospective studies. Meanwhile, regulation of the pre- and postsurgical haemostatic balance in these patients needs full attention.

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Chapter 3.1

Mixed adherence to clinical practice guidelines for colorectal cancer in the Southern Netherlands

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Summary

Aims: Population-based cancer registries can provide excellent data for insight in disease management practice. This study examines the extent to which the consensus-based national clinical guidelines (version 2000-2001) for colorectal cancer (CRC) had been implemented in the diagnostic and treatment approach in the southern Netherlands in 2002.
Methods: Data were gathered from the medical records for a random sample from the Eindhoven Cancer Registry of 308 patients with colorectal cancer. Adherence to clinical guidelines was determined for diagnostic assessment, pathology, and treatment during the first year after diagnosis.
Results: Surgical procedures and referral for preoperative radiotherapy were carried out largely conform the recommendations. The number of performed colonoscopies among colon cancer patients amounted to 60%; contrast enemas after incomplete colonoscopy were performed in only 27% of patients. The median number of examined lymph nodes was only 6 for patients with colon and 5 for patients with rectal cancer; the administration of adjuvant chemotherapy for patients with stage III colon cancer decreased from 95% of patients younger than 70 years to 48% of patients over 70.
Conclusions: Adherence to clinical guidelines was not optimal. Feedback to surgeons and pathologists should improve adherence, especially with respect to nodal retrieval and assessment.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer in industrialized countries [105]. In the year 2001, over 9200 patients were diagnosed with CRC in the Netherlands; almost 4300 patients died of their disease [122]. Over a period of more than 20 years, a clear improvement in survival of patients with CRC was attained by earlier detection (e.g. by low barrier endoscopy), better staging, improved surgery and combined modality treatment [47, 123, 124]. Promoted by concerns regarding practice variations, the standard of care for CRC in the Netherlands is formulated in clinical practice guidelines since the mid 1990s. Clinical practice guidelines are defined as "systemically developed statements to assist both practitioner and patient decisions about appropriate health care for specific clinical circumstances"[125]. Explicit guidelines improve clinical care including patient survival [126, 127]. However, recommendations made in guidelines are not always followed; important variations in clinical practice are well documented in the Netherlands and elsewhere [128, 129]. Reasons for non-compliance may be high complexity of recommended procedures, high age of the patient, disagreement with guidelines, new developments described in recent literature, and a lack of manpower, money, space or equipment [130, 131].
Population-based cancer registries can provide excellent data for drawing an accurate picture of disease management practice. The objective of this study was to determine the extent to which the guidelines for CRC had been implemented in the diagnostic and treatment approach of general hospitals in the Eindhoven Cancer Registry area in the southern Netherlands, in 2002.

Patients and methods

The Comprehensive Cancer Centre South is one of nine regional cancer centers in the Netherlands with a policy of improving the quality of oncological care in a broad sense, thereby using the data of the Eindhoven Cancer Registry for studies on the effectiveness of care. The Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, comprising an area of 2.3 million inhabitants. The registry is notified by six pathology departments, hospital medical records offices in 10 community hospitals, and two radiotherapy institutes. There are no university hospitals in the region. Information on diagnosis, staging, comorbidity and treatment is routinely recorded from the medical records by trained registrars. The medical records contain letters from and to other specialists, the medical history, pathology reports, information on previous admissions, current medication, and preoperative screening. For this study additional data were gathered for a random sample of 170 patients newly diagnosed with colon cancer in 2002, and for a random sample of 138 patients who underwent surgery for a primary rectal tumor in 2002. Colon cancer was defined as C18, rectal cancer as C19-C20 according to ICD-O-3. Patients with cancer diagnosed at autopsy were not selected. The additional data were retrospectively extracted from the medical records by an experienced medical doctor (C.D.G.W.V.), on request and under supervision of the treating physicians. Additional data concerned diagnostic assessment, treatment, and pathology, covering all

Table 1. Summary of the consensus-based national clinical guidelines (2000-2001) for colon and rectal cancer.

Colon	Rectum
Diagnostics	
Assessment of family history	Assessment of family history
Documentation of comorbidity	Documentation of comorbidity
Physical examination	Physical examination
Assessment of Hb and alkaline phosphatase	Assessment of Hb and alkaline phosphatase
Colonoscopy; if not complete: contrast enema	Colonoscopy. Suspicion of extended or fixed tumor: pelvic CT or MRI
Liver ultrasound and thoracic X-ray	Liver ultrasound and thoracic X-ray
Tumor biopsy, unless specific radiological image	Tumor biopsy
Treatment	
Resectable tumors: resection with lymphadenectomy; if necessary "en bloc"	*Mobile tumors:* if well differentiated tumor (T1), then local excision (transanal endoscopic microsurgery); else resection (TME for tumors in middle or lower rectum). Preoperative radiation (5 x 5 Gy), followed by resection within 1 week
Irresectable tumors: palliative resection can be considered. Induction chemotherapy followed by evaluation of tumor response, with option for resection with or without radiotherapy. Palliative chemotherapy. In case of obstruction: formation of stoma.	*Fixed tumors:* (chemo)radiation (50 Gy), followed by resection (TME) after 4-6 weeks, possibly IORT. In case of obstruction or incontinence: formation of stoma with use of biologic spacer.
Irresectable metastases: palliative resection unless extensive metastases or severe comorbidity. Palliative chemotherapy.	*Irresectable metastases:* palliative resection can be considered for vital patients. Palliative chemotherapy. In case of hemorrhage or pain: radiotherapy.
(Adjuvant) treatment after initial treatment: stage III: 6 months 5-FU/Leucovorin. Stage IV: palliative chemotherapy 5-FU-Leucovorin, if necessary followed by second-line chemotherapy.	*(Adjuvant) treatment after initial treatment:* stage III: adjuvant chemotherapy is not considered standard treatment. In case of resection margin less than 1 mm, and no preoperative radiotherapy: postoperative radiotherapy (50 Gy). Stage IV: palliative chemotherapy 5-FU-Leucovorin, if necessary followed by second-line chemotherapy.
Pathology	
The pathologist has to report at least: histology, differentiation grade, resection margin expressed in mm, a conclusion regarding radicality, the number of examined (minimum 12) and positive lymph nodes, localization of lymph nodes.	The pathologist has to report at least: histology, differentiation grade, resection margin expressed in mm, a conclusion regarding radicality, the number of examined (minimum 12) and positive lymph nodes, localization of lymph nodes.

recommendations from the clinical guidelines for colon and rectal cancer, version 2000-2001 (table 1). Data on diagnostic assessment included a reported family history (for patients < 60 years), a physical examination, a colonoscopy or sigmoidoscopy, X-ray of the abdomen/thorax, abdominal computed tomography (CT), magnetic resonance imaging (MRI), ultrasound examination, biopsy, and laboratory tests (hemoglobin (HB), alkaline phosphatases (AP), carcinoembryonic antigen (CEA)).

Additional treatment data (performed vs. not performed) included intent of treatment (curative resection with no microscopic evidence of positive margins, palliative resection, palliative radio- or chemotherapy, or adjuvant chemotherapy), type of rectal cancer surgery (low anterior resection (LAR), abdominal perineal resection (APR), Hartmann procedure, total mesorectal excision (TME)), and radiotherapy (intra-operative radiotherapy, preoperative radiotherapy). Emergency of surgery was recorded for colon cancer. Pathological data consisted of tumor differentiation grade, the number of lymph nodes examined, the number of positive lymph nodes, indication of histological type, indication of lymph node localization, and indication of radicality. Diagnostic and treatment data for colon cancer patients who underwent urgent surgery (N=35) were assessed separately. The association between age (<70 years vs. 70+ years), stage and diagnostic and treatment items was analysed using a chi-square test (SAS system 8.2, SAS Institute, Cary, NC). P-values below 0.05 were considered statistically significant.

Results

The mean age at diagnosis of the 308 patients was 70 years for patients with colon cancer, and 64 years for patients with rectal cancer (ranging from 41 years to 91 years, and from 33 years to 86 years, respectively).

Diagnostic assessment

Colon cancer

An accurate family-anamnesis was reported in the medical record for 88% of colon cancer patients younger than 60 years (100% of patients younger than 50 years) (table 2). 60% of the patients underwent colonoscopy (ranging from 81% of patients with stage I disease to 42% of patients with stage III disease, p=0.03; no difference by age). 30% of the performed colonoscopies were documented to be incomplete (ranging from 8% of patients with stage I disease to 54% of patients with stage II disease, p=0.05). Of the patients who did not have a complete preoperative colonoscopy, an obvious reason for not performing this procedure postoperatively was present for half of the patients (e.g. all colon proximal of tumour removed, death of the patient, palliative treatment only). Eighteen percent of the remaining patients underwent complete postoperative colonoscopy.

Rectal cancer

A family-anamnesis was documented for 75% of rectal cancer patients younger than 60 years (83% of patients <50 years). The proportion of patients who received colonoscopy decreased with increasing stage of disease: from 39% of patients with stage I to 21% of patients with stage IV disease (p=0.07).

Table 2. Diagnostic assessment of patients with colorectal cancer in the southern Netherlands, 2002 (excluding patients with urgent surgery).

	Management according to guidelines					
	Colon			Rectum		
	Yes	No	Unknown	Yes	No	Unknown
Assessment of family history (age <60 yrs)	88%	6%	6%	75%	18%	7%
Documentation of comorbidity	96%	4%	0%	92%	7%	1%
Assessment of Hb level	95%	1%	4%	93%	1%	6%
Assessment of alkaline phosphatase level	88%	6%	6%	78%	13%	9%
Assessment of CEA level	24%	62%	14%	23%	67%	10%
Colonoscopy	60%[a]	40%	0%	31%	67%	2%
Contrast enema in case of incomplete colonoscopy	27%	70%	3%	n.a.		
Abdominal ultrasound + thoracic X-ray	73%	11%	16%	82%	8%	10%
Tumor biopsy[b]	80%	1%	19%	97%	0%	3%

[a] Of which 70% complete.
[b] Recommended for patients with colon cancer unless radiological image is specific.

Treatment

Colon cancer

95% of the colon cancer patients received radical surgical treatment. In the remaining patients, surgery was not performed for reasons of comorbidity, old age, and advanced cancer extension (not shown). Of patients with resectable tumors, 89% underwent a curative resection (no difference by age) (table 3). The use of adjuvant chemotherapy for patients with stage III disease decreased by age: 95% to patients younger than 70 vs. 48% of patients over 70; p=0.0004.

Of the 35 patients who underwent urgent surgery, 23 underwent a resection with curative intent. Fourteen of these patients appeared to have positive lymph nodes; 11 of them received adjuvant chemotherapy. Seven patients undergoing urgent surgery had distant metastasis; 4 of them received palliative chemotherapy.

Rectal cancer

76% of the rectal tumors was considered to be mobile (table 4). The proportion of patients undergoing a total mesorectal excision (TME) did not differ by age. 58% of patients underwent a low-abdominal resection, 37% an abdominoperineal resection, and 5% underwent a Hartmann procedure (not shown). The proportion of patients receiving preoperative radiotherapy did also not differ by age.

Pathology report

Colon cancer

The histological tumor type and the differentiation grade were reported for nearly all patients (table 5). The median number of lymph nodes examined was 6.0 (table 6). 78% of the patients had less than 12 lymph nodes examined. In 10% of the pathology reports the number of lymph nodes examined could not be found.

Table 3. Primary treatment of 128 patients with colon cancer in the southern Netherlands, diagnosed 2002 (elective surgery only).

	Management according to guidelines		
	Yes	**No**	**Unknown**
Resectable tumors			
-resection with curative intent	89%	11%	0%
Irresectable tumors			
- chemotherapy	19%	81%	0%
Irresectable metastases			
-palliative chemotherapy	37%	62%	1%
Adjuvant chemotherapy stage III disease	71%	37%	2%
Chemotherapy stage IV disease	65%	35%	0%

Table 4. Treatment of 138 patients who underwent surgery for rectal cancer in the southern Netherlands, 2002.

	Management according to guidelines		
	Yes	**No**	**Unknown**
Mobile tumors			
-TME [a]	90%	4%	6%
-preoperative radiotherapy	78%	20%	2%
Fixed tumors			
-TME [a]	45%	21%	34%
-preoperative radiotherapy	97%	3%	0%
-preoperative chemo	93%	7%	0%
Irresectable metastases			
-palliative chemotherapy	22%	78%	0%

[a] Percentage of patients with a tumour of the middle or lower part of the rectum.

Rectal cancer

The median number of examined lymph nodes was 5.0 (table 6). 91% of rectal cancer patients had less than 12 lymph nodes examined.

Discussion

This study demonstrates a diverse overall concordance of practice with the clinical guidelines for CRC. The relatively low rate of performed and completed colonoscopies among patients with colon cancer in the current study may partly be explained by the absence of the intention to achieve pancolonoscopy. This is indicated by the relatively large proportion of colon cancer patients undergoing a sigmoidoscopic procedure. Furthermore, completion rates are reported to be lower among patients with colonic symptoms than among relatively young asymptomatic individuals or as part of colon cancer screening programmes [132]. A study conducted in an asymptomatic American population reported rates of total colonoscopy of over 95%, with minimal sedation, little patient discomfort, and low complication rates [133].

Table 5. Documentation of items in the pathology report of resected patients with colorectal cancer in the southern Netherlands, 2002.

	Documented according to guidelines			
	Colon		Rectum	
	Yes	No	Yes	No
Histological tumor type	98%	2%	99%	1%
Differentiation grade	97%	3%	99%	1%
Localization of examined lymph nodes	25%	75%	17%	83%
Circumferential margin	73%	27%	69%	31%
Conclusion of radicality	10%	90%	48%	52%

Table 6. Number of examined and positive lymph nodes of resected patients with colorectal cancer in the southern Netherlands, 2002.

	Colon		Rectum	
	Median	Range	Median	Range
Number of lymph nodes examined	6.0	0-27	5.0	0-28
Number of positive lymph nodes	1.2	0-10	1.0	0-15

In an English study complete colonoscopy rates were 77% among patients undergoing the procedure for surveillance and various diagnostic and therapeutic reasons [35], but this proportion dropped to only 54% among patients with a tumour, and to 20% among patients with a malignant stricture. In line with this, the rate of complete colonoscopy among patients with colon cancer in the present study was highest among patients with stage I disease (T1 and T2 tumours), and lowest among patients with stage II disease (T3 and T4 tumours). Nevertheless, pancolonoscopy is proclaimed to be the aim in all patients [132] and when visualization is incomplete, a contrast enema should be performed to detect all polyps and tumours. This happened in only one quarter of the patients in the current study. However, the presence of a malignant stricture may also be good reason not to perform a contrast enema.

The high resection rate of colon cancer patients in our study was in agreement with other European studies, remaining at a high level until old age [80, 134, 135]. Selecting only rectal cancer patients who underwent tumour resection kept the resection rate for this group of patients unknown. However, from the cancer registry we can derive it to be 85%. The proportion of 90% of patients receiving TME surgery is in concordance with TME rates reported in literature [136, 137].

A large age-related decrease in administration of adjuvant chemotherapy for stage III colon cancer patients was observed in this study. Elderly patients are less likely to undergo adjuvant treatment due to the presence of comorbidity and a decrease in the patients' general condition and cognitive abilities [138, 139]. Also more patient refusal among the elderly and a shortage of supportive caregivers self-evidently results in a lower use of adjuvant treatment [59]. Moreover, limited data on chemotherapy efficacy exist among patients older than 70 years [66, 140]. Most of the available studies however present evidence of tolerance and efficacy of chemotherapy among both selected and

unselected elderly colon cancer patients, thus counteracting the persisting "ageism" in colon cancer care [141, 142].

There was a large discrepancy between everyday practice and clinical guideline with respect to the number of lymph nodes examined. This is of importance since previous research reported a more than 20% increase in overall, cause-specific, and disease-free survival of colorectal cancer patients upon examination of an increased number of lymph nodes [143-146]. It is unknown to what degree adequate staging and subsequent therapy, or the therapeutic effect of a complete lymphadenectomy itself may explain the positive effect on prognosis [147]. Yet, a less adequate lymph node evaluation may have several causes. It is depending on anatomic subsite, since a specimen of right-sided resections often contains a larger amount of mesentery; there can also be variations in the extent of the dissection by the surgeon, and in the applied thoroughness by the pathologist [146-149]. The biologic behaviour of the tumour and the immune response of the patient can also explain a lower number of evaluated lymph nodes [146]. Nonetheless, the median number of lymph nodes evaluated in the current study is low compared to most other studies [143, 146, 147, 149]. An educational intervention targeted at surgeons and pathologists seems undoubtedly warranted. The effectiveness of such an intervention was shown in a Canadian single institution study, where the median number of evaluated lymph nodes increased from 8 to 18 within 30 months of the intervention [150].

Sometimes the reason for not complying with clinical guidelines may be clear and legitimate, such as not performing a complete colonoscopy in case of a malignant structure, or refraining from chemotherapy for frail elderly patients. Often, the situation is more complex. For example, the threshold of 12 lymph nodes required for optimal staging is not accepted universally. The Royal College of Pathologists in the United Kingdom recommends that all lymph nodes identified in the resection specimen should be examined histologically but does not specify an arbitrary minimum number[151]. On might argue whether lymph node examination is not optimal, or that the guidelines are not realistic. However, as stated earlier, comparison with the results of other studies indicates that there is room for improvement of the quality of nodal retrieval and assessment.

This study demonstrated a mixed adherence to the clinical practice guidelines for CRC in 2002. Currently, the present consensus-based guidelines are being exchanged for evidence-based guidelines. Feedback to and discussions with surgeons and pathologists should improve adherence to these guidelines, with special attention to nodal retrieval and assessment.

Chapter 3.2

Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity

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Summary

Background: Adjuvant 5-fluoruracil-based chemotherapy significantly decreases mortality among patients with stage III colon cancer, but is less prescribed with rising age. We were interested in the pattern of adjuvant treatment and possible effects on survival among elderly patients.
Patients & Methods: All resected patients aged 65-79 with stage III colon carcinoma, diagnosed between 1995 and 2001 in the Comprehensive Cancer Centre South registry area in the Netherlands were included (n=577). We examined determinants of receipt of adjuvant chemotherapy, and their relation to survival.
Results: The proportion of elderly patients receiving adjuvant chemotherapy increased from 19% in 1995 to 50% in 2001, but a large inter-hospital variation remained. In a multivariable analysis, females (odds ratio (OR) 0.5, p=0.006), patients with comorbidity (OR 0.5, p=0.005), and patients with a low socio-economic status (OR 0.5 p=0.02) received less adjuvant therapy. Between 1995 and 2001 survival of elderly patients improved (hazard ratio 0.8, p=0.04).
Conclusion: Although an increasing proportion of elderly patients with colon cancer is treated with adjuvant chemotherapy, many elderly patients still do not receive this treatment. As expected, receipt of adjuvant treatment decreased in presence of comorbidity, but the clinical rationale for undertreatment of women and patients with low socio-economic status is not clear.

Introduction

The prognosis for elderly patients who have undergone resection of a stage III colon carcinoma remains relatively poor; the relative 5-year survival proportion of patients aged 65 years or older diagnosed between 1995 and 1999 in the south of the Netherlands was 30% [56]. Several trials have established 5-fluorouracil (5-FU)-based chemotherapy as the standard adjuvant treatment for patients with stage III disease [51, 53, 142, 152]. However, retrospective analyses showed such adjuvant chemotherapy to be administered less with increasing age. Also presence of comorbidity, higher refusal rates among elderly patients, hospital volume, and socioeconomic factors are reported to influence administration of adjuvant chemotherapy [59, 61, 63, 141].
Since the mid 1990s, administration of adjuvant chemotherapy is recommended in Dutch treatment guidelines [153]. In order to evaluate adherence to these guidelines for elderly patients with stage III colon cancer in the south of the Netherlands, we determined the proportion of patients receiving adjuvant chemotherapy. We assessed factors associated with receipt of chemotherapy, and to what extent these factors were related to survival.

Patients and methods

Data collection
The Comprehensive Cancer Centre South (Eindhoven Cancer Registry) covers a large part of the south Netherlands with approximately 2.4 million inhabitants. This population-based registry is notified by six pathology departments, the hospital medical records offices in -at time of the study- 15 community hospitals and two radiotherapy institutes. There are no university hospitals in the registry area. Registration takes place between 6 and 18 months after diagnosis. Despite the lack of access to death certificates, the infrastructure of and good access to Dutch health care facilities, together with the notification procedures used, have made it possible to establish cancer registries with a completeness exceeding 95% [54].
Colon tumours were defined as C18.0-C18.7 according to ICD-O-3. All patients aged 65 years or older diagnosed in the period 1995-2001 who had been operated on for stage III colon adenocarcinoma were selected from the database of the Eindhoven Cancer Registry (n=772). Only one patient older than 80 years received adjuvant chemotherapy. Therefore, we restricted our analyses to patients aged 65-79 (N=577).
Trained registrars recorded the following patient characteristics: age at time of diagnosis, gender, and serious comorbidity, the latter according to a slightly modified version of the Charlson classification (table 1) [43]. Socio-economic status (SES) of the patient was defined at neighbourhood level (based on postal code of residence area, 17 households on average) combining mean household income (in 1998) and mean value of the house/apartment (in 2000), derived from individual fiscal data made available at an aggregated level. Postal codes were assigned to 3 SES categories: low (1st –3rd decile), intermediate (4th-7th decile), and high (8th-

10th decile). Postal codes of institutions, such as nursing homes, were assigned to a separate category and were excluded from the logistic regression and survival analysis (33 patients). These excluded patients had a median age of 76,5 years, compared to a median age of 72 years of the total study population.
The following tumour characteristics were recorded: tumour grade (low grade (well or moderately differentiated) vs. high grade (poorly or undifferentiated tumours)), postoperative extent of disease (T1/T2, T3, T4), and lymph node involvement (N1, N2). The stage III patients were classified into three subgroups (IIIA: T1-2/N1, IIIB: T3-4/N1, IIIC: any T/N2) according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours (6^{th} edition) [154]. The N3 designation, as used by prior editions of the UICC TNM classification of Malignant Tumours, was incorporated into the N1 or N2 categories, according to the number of tumour positive lymph nodes.
Also adjuvant chemotherapy (yes vs. no; information on type and dose was not available), year of diagnosis (periods 1995-1998 and 1999-2001), and hospital of surgery were recorded.
Vital status of all patients on 1st of January 2004 was assessed through the Central Bureau for Genealogy, the institution where all deceased persons in The Netherlands are registered. Patients who had moved abroad (estimation: 0.2%) were possibly wrongly considered as being alive. At the end of follow-up (January 2004) 219 patients (38%) were still alive.

Table 1. Classification of comorbidity, according to an adapted version of Charlson et al. (1987).

Previous malignancies (except basal skin carcinoma and carcinoma in situ of the cervix)
Chronic Obstructive Pulmonary Diseases
Cardiovascular diseases (myocardial infarction, heart failure, angina pectoris, intermittent claudication, abdominal aneurysm, peripheral arterial disease)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Hypertension
Diabetes mellitus
Digestive tract diseases (stomach diseases, Crohn's disease, ulcerative colitis, liver cirrhosis, hepatitis)
Other (connective tissue diseases, severe rheumatoid arthritis, kidney diseases, dementia, tuberculosis, chronic infections)

Analyses

Differences in adjuvant treatment between subgroups were tested by means of a chi^2 test (gender and tumour grade) or a Cochran-Armitage trend test (number of comorbid conditions, SES, stage group, and year of diagnosis).
The independent influence of the patient and tumour characteristics on administration of adjuvant chemotherapy was evaluated by means of a logistic regression analysis (LOGISTIC procedure). A log rank test was used to compare 5-year survival proportions (LIFETEST procedure). Multivariable proportional hazards regression analysis (PHREG procedure) was used to discriminate independent risk factors for death. Since the numbers of patients treated with adjuvant chemotherapy were very low in some hospitals, we did not incorporate hospital of treatment in the logistic regression or survival analysis.
For all analyses the SAS/STAT® statistical software (SAS system 8.2, SAS Institute, Cary, NC) was used.

Results

Among the 577 patients with stage III colon cancer aged 65-79, administration of adjuvant chemotherapy decreased with rising age (in 2001: 80% of patients aged 65-69 vs. 28% of patients aged 75-79, $p_{trend}<0.0001$) (table 2). Overall, the proportion of elderly patients receiving adjuvant chemotherapy increased from 19% in 1995 to 50% in 2001 ($p_{trend}<0.0001$). In all age groups, adjuvant chemotherapy was administered more often to males (p=0.03) and patients with high grade tumours (p=0.04). Chemotherapy was administered less often to patients with comorbidity (from 50% of patients without comorbidity to 33% of patients with 2 or more comorbid conditions, $p_{trend}=0.0006$) and to those with a lower SES (from 29% of patients with a low SES to 49% of patients with a high SES, $p_{trend}<0.0001$). The proportion of patients who received adjuvant chemotherapy clearly increased between 1995 and 2001 (from 46% to 80% of patients aged 65-69, $p_{trend}<0.0001$; from 16% to 48% of patients aged 70-74, $p_{trend}=0.02$; and from 5% to 28% of patients aged 75-79, $p_{trend}=0.02$). A large hospital variation in the administration of adjuvant therapy could be observed. This variation was not related to the size of the hospital. Twenty-three percent of the excluded institutionalised patients with a median age of 76,5 years received adjuvant chemotherapy. Among the excluded patients, also females (21% vs. 27% of male patients) and patients with comorbidity (16% vs. 36% of patients without comorbidity) were less likely to receive adjuvant chemotherapy (results not shown).
In a multivariable logistic regression analysis, age independently influenced the odds of receiving adjuvant chemotherapy, as did comorbidity (table 3). Previous malignancies (mostly colorectal tumours) (odds ratio=0.2; p=0.001) and COPD (odds ratio 0.3; p=0.03) in particular contributed to this effect. Females were significantly less likely to receive chemotherapy than males, while patients with a high SES were twice as likely to receive adjuvant treatment compared to patients with a low SES. Patients with a high grade tumour and patients with substage IIIB disease received chemotherapy more often. Patients diagnosed between 1999 and

2001 were 2.4 times more likely to receive chemotherapy compared to patients diagnosed between 1995 and 1998.
In a proportional hazards regression analysis adjusting for age, gender, number of comorbid conditions, SES, substage, tumour grade, and period of diagnosis, adjuvant chemotherapy was associated with a 50% lower mortality risk (hazard) than patients who did not receive adjuvant treatment. Patients aged 70 years or older exhibited a lower mortality risk than patients aged 65 to 69 years. Survival was worse for patients with comorbidity (hazard ratio 1.4) and patients diagnosed with a more advanced substage (hazard ratio 1.8). Patients diagnosed more recently had a more favorable

Table 2. Stage III colon cancer patients diagnosed between 1995 and 2001 in the southern Netherlands; proportion of patients who received adjuvant chemotherapy according to age.

		Proportion of patients treated with chemotherapy		
		65-69 years (n=181)	**70-74 years (n=196)**	**75-79 years (n=200)**
	n	**%**	**%**	**%**
Gender				
Male	284	62	41	23
Female	293	56	37	17
No. of comorbid conditions				
0	184	72	44	28
1	194	58	34	16
2+	159	49	41	15
Unknown	40	33	30	27
SES				
High	148	67	45	28
Intermediate	205	43	41	19
Low	191	19	34	16
Stage group [a]				
IIIA (T1-2 N1)	28	88	22	18
IIIB (T3-4 N1)	438	62	42	20
IIIC (any T N2)	107	44	32	19
Tumour grade				
Low	386	54	39	18
High	148	73	44	27
Unknown	33	62	13	8
Year of diagnosis				
1995	52	46	16	5
1996	77	41	35	8
1997	75	41	40	35
1998	75	61	40	19
1999	86	57	48	17
2000	103	73	35	22
2001	109	80	48	28
Hospital of treatment [b]				
#1	74	79	44	20

#2	51	65	40	0 [c]
#3	51	77	42	32
#4	54	70	40	45
#5	41	57	25	0 [d]
#6	44	63	73	2
#7	37	50	31	31
#8	53	32	11	13

a Four patients with Tx were not assigned to a substage; none of them received adjuvant chemotherapy.
b Only the 8 largest (according to treated number of stage III patients) out of 15 hospitals are shown here.
c Out of 14 patients.
d Out of 18 patients.

prognosis (hazard ratio 0.8). There was no significant difference in adjusted survival between males and females, SES categories, and tumour grade.

Discussion

In our study of 577 patients with stage III colon cancer aged 65 to 79 years we found that adjuvant chemotherapy was administered less often with increasing age. Also females, patients with comorbidity, and patients with a low social-economic status received adjuvant therapy less often. There was a clear rise in administration of chemotherapy between 1995-1998 and 1999-2001, but a large inter-hospital variation remained.

Table 3. Stage III colon cancer patients diagnosed between 1995 and 2001 in the southern Netherlands; odds of administration of adjuvant chemotherapy, as calculated from a logistic regression model which included all listed variables.[a]

Covariate	Odds ratio[c]	p-value
Age		
65-69[b]	1.0	
70-74	0.4	.001
75-79	0.1	<.0001
Gender		
Male[b]	1.0	
Female	0.5	.006
No. of comorbid conditions		
0[b]	1.0	
1	0.5	.005
2+	0.4	.004
SES		
High[b]	1.0	
Intermediate	0.7	.2
Low	0.5	.02
Stage group		
IIIA (T1-2 N1)	0.5	.3
IIIB (T3-4 N1)[b]	1.0	
IIIC (any T N2)	0.5	.02
Tumour grade		
Low[b]	1.0	
High	1.6	.07
Period of diagnosis		
1995-1998[b]	1.0	
1999-2001	2.4	.0003

[a] Cases with missing values for any of the covariates were left out of the analyses.
[b] Reference category.
[c] Adjusted for all variables listed.

Table 4. All stage III colon cancer patients diagnosed between 1995 and 2001 (follow-up until January 2004) in the southern Netherlands; crude and multivariable analysis for overall survival, model including all listed variables.[a]

Covariate	Crude 5 year survival (%)	Hazard ratio[c]	p-value
Adjuvant chemotherapy			
No[b]	32	1.0	
Yes	51	0.5	<.0001
Age			
65-69[b]	31	1.0	
70-74	48	0.6	.0008
75-79	37	0.6	.007
Gender			
Male[b]	41	1.0	
Female	37	0.9	.7
No. of comorbid conditions			
0[b]	49	1.0	
1	32	1.4	.02
2+	33	1.4	.04

SES			
High[b]	44	1.0	
Intermediate	39	1.1	.8
Low	38	1.0	.9
Stage group			
IIIA (T1-2 N1)	62	0.7	.3
IIIB (T3-4 N1)[b]	41	1.0	
IIIC (any T N2)	27	1.8	.0001
Tumour grade			
Low[b]	40	1.0	
High	33	1.3	.06
Period of diagnosis			
1995-1998[b]	38	1.0	
1999-2001	39	0.8	.04

[a] Cases with missing values for any of the covariates were left out of the analyses.
[b] Reference category.
[c] Adjusted for all variables listed.

Survival was better for patients receiving adjuvant chemotherapy, for patients aged 70 to 79 years compared to 65-69 years, and for patients diagnosed more recently, and worse for patients with comorbidity or a more advanced substage.

The lower probability of receiving adjuvant treatment for elderly patients with colon cancer had already been shown previously [60-64, 141, 155]. The reason why these patients are less likely to receive adjuvant treatment is multifactorial. In addition to the presence of concomitant diseases, more patient refusal among the elderly, the absence of supportive caregivers, a decrease in the patients' general condition and cognitive abilities, and especially frailty could result in lower chemotherapy rates [59, 65, 138, 156]. Most of the available studies present evidence of tolerance and efficacy of chemotherapy among both selected and unselected elderly colon cancer patients [59, 61, 141, 157], thus counteracting the persisting "ageism" in colon cancer care. However, there are probably still uncertainties about the risk-benefit ratio of aggressive treatment, as is suggested by the observed inter-hospital variation.

The reported higher intolerance among females for 5-fluoruracil-based (5-FU) chemotherapy due to a lower level of dihydropyrimidine dehydrogenase, together with a higher refusal rate among elderly women, may partly be responsible for the finding that they were less likely to receive adjuvant treatment than men [63, 158, 159]. However, higher intolerance among females may have been overcome in most cases by alternative 5-FU doses or schedules, and the magnitude of the observed effect in our study seems too large to be explained by a higher refusal rate among elderly women. In view of the good access to health care facilities and the Dutch health insurance system with a coverage of approximately 99% [160], our finding that patients with a low SES are two times less likely to be treated with adjuvant chemotherapy than patients with a high SES is remarkable. Socio-economic status has previously been reported to influence adjuvant treatment of colorectal cancer patients [59, 63], although the impact was much smaller than that observed in the present study. A possible explanation of the effect of SES on adjuvant treatment may be that patients with a higher SES have a more active behavior, in terms of

seeking more aggressive treatment or making and keeping appointments with specialists. SES could be associated with education as well, which might influence acceptance rates. Patients with a higher SES also have a more positive self-rated health [161, 162], which in turn may affect treatment decision-making [69]. The institutionalised patients who were excluded from the analyses received adjuvant chemotherapy as often as the included patients with the same age and gender. As we do not expect that the average socio-economic status of nursing home residents differs significantly from the average socio-economic status of other patients, we consider the possible impact of excluding the 33 institutionalised patients to be relatively small.

Patients presenting with comorbidity received adjuvant chemotherapy less often, in agreement with previous retrospective studies [59, 62-64]. Few prospective studies have reported the effect of comorbidity on the safety and efficacy of chemotherapy, and, as a result, few guidelines exist for patients with specific comorbid conditions.

We do not have a clear explanation for our finding that patients with stage IIIB disease (T3-4, N1) received adjuvant chemotherapy more often than patients with stage IIIC disease (any T, N2); perhaps these elderly patients with stage IIIC disease were considered to have a less favorable risk-benefit ratio regarding adjuvant treatment.

As reported in several other population-based studies, adjuvant chemotherapy had a marked independent prognostic impact [62, 157]. Due to the population-based nature of our data, we do not know the extent to which this positive prognostic impact was caused by selection of the 'fitter' patients for adjuvant chemotherapy, or by other factors associated with treatment allocation besides those controlled for in our analysis (e.g. performance status). Very likely, frail elderly less often receive adjuvant chemotherapy. The worse prognosis of these frail patients has probably biased the prognostic impact of adjuvant chemotherapy in the current study. This is supported by the fact that the survival difference between treated and non-treated patients was larger than found in randomized clinical trials [141].

A possible explanation for the improved survival between 1995-1998 and 1999-2001 may be more accurate staging due to a more thorough search for positive lymph nodes by the pathologist, promoted by the presence of effective adjuvant treatment for lymph node-positive cancers [143]. Moreover, staging may also have been improved by a better identification of distant metastases.

Our finding that patients aged 70 or older had a better prognosis than patients aged 65-69 years is odd, but in line with the results of a large single-hospital study where patients with stage III colon cancer aged 65 years or older had an overall 5-year survival of 74%, compared to 54% for patients younger than 65 years. [163]. A possible explanation for this finding might be a selection of the more robust individuals living long enough to develop colon cancer, or a potential decrease in aggressiveness of the tumour with rising age.

Data extraction from the patient's medical record is regarded as the most complete source of information on the patient's past and current health status [55]. Yet, performance status could not be included in our study, since this is not mentioned in the medical records routinely. Performance score and comorbidity are both

predictive factors of treatment and survival for cancer patients, independent of each other [74, 75]. However, performance status is often amenable to the malignant disease and its treatment, in contrast to comorbidity.

Although the proportion of elderly patients with colon cancer receiving adjuvant chemotherapy is increasing, many elderly patients still do not receive or accept this treatment. Development of age-based guidelines and increased awareness among both physicians and patients through education is important to prevent undertreatment of (subgroups of) elderly patients who are eligible for chemotherapy. With decision making becoming more individualized with the rise of age, the use of a comprehensive geriatric assessment may be helpful in choosing the most adequate treatment for these patients.

Acknowledgement

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Chapter 3.3

Pathology practice patterns affect lymph node evaluation and outcome of colon cancer: a population-based study

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Summary

Purpose: There is a positive association between the number of lymph nodes examined and prognosis for patients with colon cancer. However, there is a large variation in the number of nodes examined between patients, departments of pathology, hospitals, and regions. We studied the extent to which this variation could be attributed to patient and tumour characteristics versus local patterns in surgical and pathology practice.
Patients and methods: All patients who underwent resection for stage I-III ($pT_{any}N_{any}M0$) colon carcinoma diagnosed between 1999 and 2002 (N=2168) in the Eindhoven Cancer Registry area were included. Determinants of lymph node evaluation and their relationship to survival were assessed, including variation between the 6 departments of pathology.
Results: A median number of 6 lymph nodes per specimen had been examined. The median number for each department of pathology ranged from 3 to 8 ($p<0.0001$). After correction for age, gender, socio-economic status, comorbidity, tumour site, depth of invasion, lymph node involvement, and tumour grade, the large variation between the departments of pathology remained. This resulted in differences in the proportion of N+ tumours between departments from 29% to 41% ($p<0.0001$). The number of nodes examined was positively associated with survival, among both node-negative and node-positive patients. Survival for node negative patients differed between the departments of pathology (up to hazard ratio (HR) 1.5; $p=0.02$).
Conclusion: There was a large variation in lymph node evaluation between the departments of pathology, leading to differences in stage distribution and survival. Intervention strategies should be directed at nodal assessment.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer in industrialized countries.[164, 165] Yearly, over 9200 patients are diagnosed with CRC in the Netherlands, 1300 of whom live in the area covered by the Eindhoven Cancer Registry.[122] Resection of the tumour with adequate margins and associated mesentery, including draining lymph nodes, remains the primary modality of treatment for CRC. Patients with positive lymph nodes may also benefit from adjuvant chemotherapy.[51, 53, 142, 152, 166] Therefore, lymph node analysis is one of the critical factors for therapeutic decision-making. Several studies have not only described a positive association between the number of lymph nodes evaluated and prognosis for CRC patients but also a large variation in the number of lymph nodes examined between patients, departments of pathology, hospitals, regions, and countries.[134, 143, 146, 147, 167, 168] This variation, which influences staging and subsequent therapy, may be explained by several mechanisms: firstly, the thoroughness of the surgical lymphadenectomy in order to remove all potential lymph node metastases; secondly, the extent and diligence of the pathologist's examination; and thirdly, inter-individual differences in the biological behavior of the tumour and/or host, such as immune response, which may affect the number of traceable lymph nodes.[146, 147] In the current study of patients who had a colectomy for stage I-III ($T_{any}N_{any}M0$) colon carcinoma, we determined the variation in lymph node examination and its relationship to stage distribution and survival in the southern Netherlands, and the extent to which this variation could be attributed to local patterns in surgical and pathology practice or patient and tumour characteristics.

Patients and methods

Data collection

The Comprehensive Cancer Centre South (Eindhoven Cancer Registry) covers a large part of the southern Netherlands with approximately 2.4 million inhabitants. This population-based registry is served by ten hospitals, six departments of pathology, and two radiotherapy institutes. There are no university hospitals in the registry area. Between 6 to 18 months after diagnosis the patients are registered by the trained administrators. The completeness of registration is estimated to be >95%.[54]

All patients who had a colectomy for stage I-III (pTanyNanyM0) colon carcinoma in the 4-year period 1999 – 2002 were selected from the database of the Eindhoven Cancer Registry (N=2168). The patients' age at diagnosis, gender and comorbidity according to a slightly modified version of the Charlson classification were recorded. Also, tumour site (right sided: colon ascendens (C18.0-C18.2) and colon transversum (C18.3-C18.5); left sided: colon descendens and sigmoid (C18.6-C18.9)), grade of tumour differentiation (low grade (well or moderately differentiated) vs. high grade (poorly or undifferentiated tumours)), depth of invasion, and nodal involvement were recorded. Furthermore, the number of lymph nodes examined, adjuvant chemotherapy (yes vs. no), hospital of surgery, and the department of pathology were registered. Socio-economic status (SES) of the patient was defined at neighbourhood level (based on postal code of residence area, 17 households on average) combining mean household

income (in 1998) and mean value of the house/apartment (in 2000). The latter was derived from individual fiscal data made available at an aggregated level. Postal codes were assigned to one of 3 SES categories: low (1st –3rd decile), intermediate (4th-7th decile), and high (8th-10th decile).
Vital status of all patients on 1st January 2005 was assessed through the Central Bureau for Genealogy, where all deceased persons in the Netherlands are registered. Patients who had moved abroad (estimation: <0.3%) were possibly incorrectly considered as being alive.
Analyses
Differences between the departments of pathology according to the number of lymph nodes evaluated and the postoperative nodal status were tested by means of a chi2 test. The independent influence of pathology practice or patient and tumour characteristics on the number of lymph nodes evaluated was analysed by means of logistic regression analysis (LOGISTIC procedure). A Cochran-Armitage trend test was used to investigate whether there has been an increase or decrease in the number of nodes evaluated during the study period. To examine the hypothesis that the number of lymph nodes examined is related to survival, a multivariable proportional hazards regression analysis (PHREG procedure) was used to discriminate independent risk factors for death, stratified by nodal involvement. A model was built with and without the number of lymph nodes evaluated to investigate the hypothesis that the prognostic differences between the pathology departments can be fully explained by the number of lymph nodes evaluated (after adjustment for age, gender, SES, the number of comorbid conditions, tumour site, tumour size, and adjuvant chemotherapy). Cases with missing values for any of the covariates were left out of the logistic and regression analyses. All statistical tests were two-sided. For all analyses the SAS/STAT® statistical software (SAS system 8.2, SAS Institute, Cary, NC) was used.

Results

At the end of follow-up (1st of January 2005), 1381 patients (64%) were alive.
The coverage of the six departments of pathology for the colon cancer resection specimens is depicted in table 1. Three departments serve one hospital, while two departments cover 3 hospitals. All hospitals are community hospitals.

Table 1. Coverage of the departments of pathology for colon carcinoma resection specimens.

Path. laboratory	Patients (N)	Hospitals (N) [a]
#1	154	1
#2	460	2
#3	270	1
#4	421	3
#5	608	3
#6	255	1

[a] One hospital is covered by 2 pathology departments: department #3 and #4.

The general characteristics of all 2168 patients are shown in table 2. For 24% of patients 0 to 3 lymph nodes had been examined; for another 24% 4 to 6 nodes were

examined, versus 7 to 9 nodes for 16%, 10 or 11 lymph nodes for 6%, and 12 or more nodes for 13%.
In figure 1a and 1b, the numbers of lymph nodes evaluated among node-negative and node-positive patients are depicted. For all patients, the median number of lymph nodes examined was 6 (table 3); for patients with pN0 and pN1/2 colon carcinoma it was 5 and 6, respectively. The median number of lymph nodes examined in each department of pathology ranged from 3 to 8 ($p<0.0001$).
In table 4 the odds of having 6 or more nodes examined, as calculated by means of a multivariable logistic regression analysis, are listed. The number of lymph nodes examined clearly decreased with increasing age. Also patients with comorbidity were less likely to have had 6 or more lymph nodes examined. The chance was also lower for patients with left-sided tumours, as well as patients with pT1 tumours, male patients, and patients with nodal negative disease. There was a large variation between the departments of pathology; patients whose lymph nodes were evaluated in department nr. 1 were 1.6 times more likely to have a minimum of 6 nodes examined, compared to the reference department. Especially in departments nr. 2 and nr. 6, patients had a lower chance of having 6 or more nodes evaluated.
Overall, there was no significant change in the number of lymph nodes evaluated between 1999 and 2002.
There was no difference in the number of lymph nodes examined between the hospitals which were covered by one and the same department of pathology.
The postoperative stage distribution (pTNM) according to department of pathology is depicted in figure 2. In department nr. 1, there was a relatively large proportion of T4 tumours (32%). The proportion of T2/T3N0 tumours varied from 43% in department nr. 1 to 62% in department nr. 2.
The proportion of patients with lymph node metastases (pN1 or pN2; stage III) ranged from 29% in department nr. 6 and 32% in department nr. 2 to 41% in departments nr. 1 and 5 ($p<0.0001$) (figure 3).
After adjustment for relevant patient and tumour characteristics, the risk of death (hazard ratio (HR)) among node-negative patients differed between the departments of pathology, by up to HR 1.47 (table 5). Inclusion of cases with a missing value for the covariate 'number of nodes evaluated' did not alter the variation between the departments. After adding the number of lymph nodes examined to the model, the differences between the reference department and the other departments became insignificant. The risk of death decreased clearly with increasing number of lymph nodes examined, for both patients with negative lymph nodes and patients with positive lymph nodes (to HR 0.56 and HR 0.68, respectively).

Table 2. General characteristics of all 2168 patients who underwent resection for stage I-III colon carcinoma, diagnosed between 1999 and 2002 in the southern Netherlands.

Age (years)		
Median (range)	70.5 (23-100)	
	N (%)	
Gender		
Male	1064	(49)
Female	1104	(51)
Socio-economic status		
Low	634	(29)
Intermediate	772	(36)
High	617	(28)
Unknown	145	(7)
Comorbidity		
No comorbidity	698	(32)
One comorbid condition	640	(30)
Two or more comorbid conditions	612	(28)
Unknown	218	(10)
Tumour site		
Left-sided	978	(45)
Right-sided	1179	(54)
Unknown	11	(0.5)
Stage		
pT1-2N0	280	(13)
pT3-4N0	1081	(50)
pT1-4N+	798	(37)
Unknown	9	(0.4)
Tumour grade		
Moderately/well differentiated	1635	(75)
Poorly differentiated	405	(19)
Unknown	128	(6)
Adjuvant chemotherapy		
Yes	480	(22)
No	1688	(78)
No. of lymph nodes evaluated		
0-3	513	(24)
4-6	513	(24)
7-9	342	(16)
10-11	130	(6)
≥ 12	291	(13)
Unknown	379	(17)

Table 3. Median number of lymph nodes evaluated, according to department of pathology.

Dep. of pathology	Median number of nodes evaluated	Range
1	7	0-24
2	3	0-26
3	6	0-40
4	8	0-33
5	7	0-29
6	4	0-19
Total	6	0-40

Figure 1a. Number of lymph nodes evaluated among all resected patients with node negative (stage I-II) colon cancer diagnosed between 1999 and 2002 in the Eindhoven Cancer Registry area.

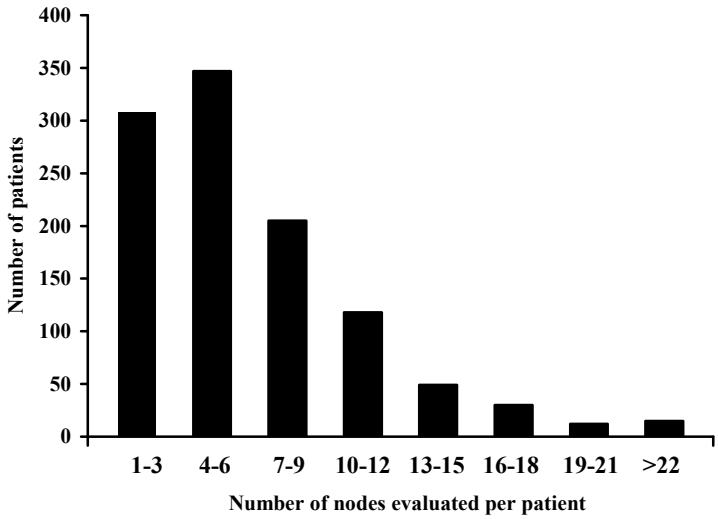
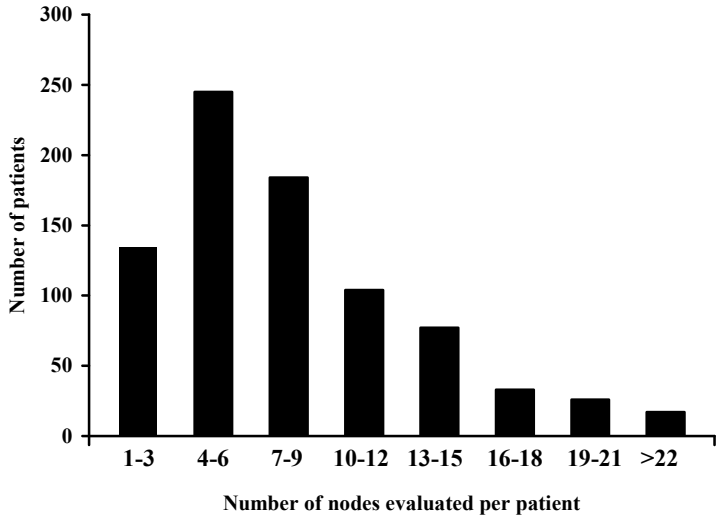
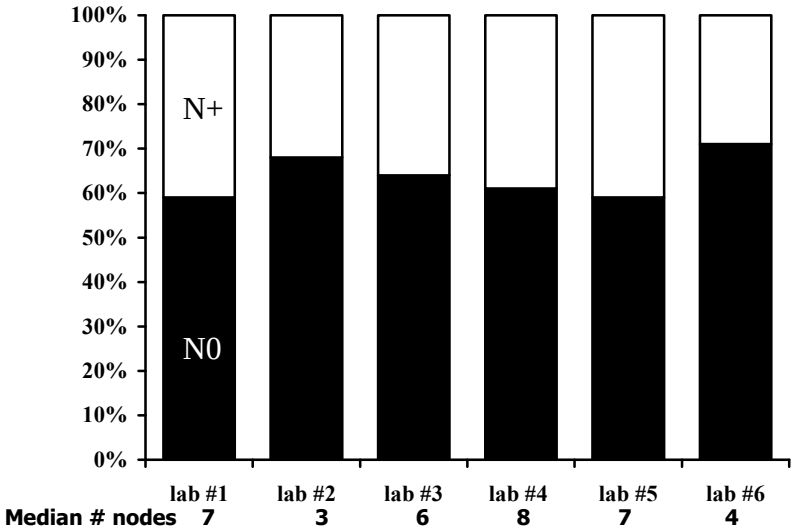


Figure 1b. Number of lymph nodes evaluated among all resected patients with node positive (stage III) colon cancer diagnosed between 1999 and 2002 in the Eindhoven Cancer Registry area.



(for figure 2, see two pages ahead)

Figure 3. Postoperative nodal status of patients with colon carcinoma, according to department of pathology [a].



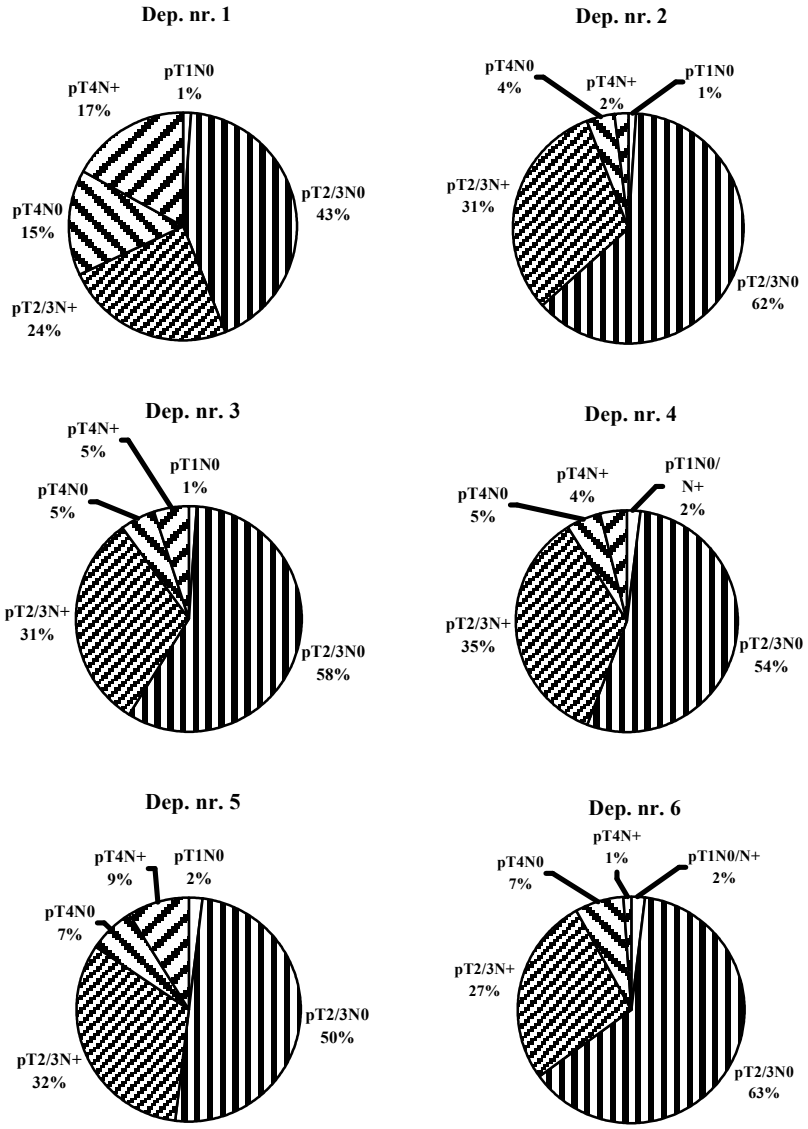
[a] Difference of postoperative nodal status between departments of pathology: chi-square 48.58, p<0.0001.

Table 4. Odds of having 6 or more lymph nodes evaluated by the pathologist; calculated by means of a multivariable logistic regression analysis (model including all listed variables). [a]

	Odds ratio	***p-value***
Age		
19-49 years [b]	1.00	
50-69 years	0.72	*0.047*
70+ years	0.64	*0.004*
Gender		
Male [b]	1.00	
Female	1.29	*0.02*
Socio-economic status		
High [b]	1.00	
Intermediate	1.00	*0.74*
Low	0.85	*0.34*
No. of comorbid conditions		
0 [b]	1.00	
1	0.73	*0.021*
2+	0.61	*0.0005*
Tumour site		
Left-sided tumours [b]	1.00	
Right-sided tumours	2.07	*<0.0001*
Depth of invasion		
pT1	0.10	*0.003*
pT2 [b]	1.00	
pT3	1.31	*0.10*
pT4	0.91	*0.66*
Lymph node involvement		
pN0 [b]	1.00	
pN+	1.51	*0.0004*
Tumour grade		
Well/moderately differentiated [b]	1.00	
Poorly differentiated	1.09	*0.55*
Dep. of pathology		
1	1.62	*0.034*
2	0.12	*<0.0001*
3	0.49	*<0.0001*
4	1.02	*0.89*
5 [b]	1.00	
6	0.20	*<0.0001*

[a] Cases with missing values for any of the covariates were left out of the analyses.
[b] Reference category.

Figure 2. Stage distribution according to department of pathology.



Discussion

The availability of increasingly effective postoperative chemotherapeutic agents for patients with nodal metastasis stresses the importance of lymph node analysis in colon carcinoma. In this population-based study in the southern Netherlands, the median number of lymph nodes examined among patients who underwent resection for stage I-III (pTanyNanyM0) colon carcinoma was 6. Other population-based studies reported median numbers of lymph nodes examined of 7 to 9,[147, 167, 169] while single-hospital studies reported median numbers up to 17.[149, 170] A low number of lymph nodes evaluated in the Netherlands has already been reported by a Eurocare study among patients diagnosed in 1990, covering 11 European cancer registries.[134] The Dutch registries had the smallest proportion of patients with 12 or more lymph nodes examined: 5% in the Dutch Eindhoven Cancer Registry and 2% in the Dutch Rotterdam Cancer Registry. In a large US population-based study, geographic location was an important predictor of adequate lymph node evaluation, indicating that surgical and pathological practice probably play an important role.[147] This was recently confirmed by a Swedish population-based study, where the median number of lymph nodes examined varied from 6 to 12 between the 7 departments of pathology.[167]
Also in the current study there was a large variation between the departments of pathology. The absence of a difference in the number of lymph nodes evaluated between the hospitals covered by one and the same department of pathology indicated that pathology practice patterns probably played a more important role than surgical practice patterns. The significance of the variation in pathology practice is emphasized by the differences in nodal status and survival between the departments of pathology. In addition to different degrees of diligence, the technique used by the pathologist can influence lymph node assessment. Techniques such as xylene or alcohol fat clearance, cytokeratin immunohistochemistry, and multilevel step sectioning can increase the number of nodes identified.[171-173] These techniques are considered too expensive and time-consuming for standard use or are as yet of unproven clinical significance. However, a single-hospital study reported a mean number of over 20 lymph nodes evaluated with standard manual dissection methods of pathology evaluation, without clearing solutions or ancillary techniques.[170] An example of a straightforward way of improving adequacy of nodal harvest is a longer duration of specimen fixation. This may significantly upstage colon carcinoma from node-negative to node-positive after an additional 24 hour fixation in formaldehyde prior to specimen dissection.[174, 175] In a Canadian study, reinforcing strategies aimed at surgeons and pathologists, including the use of a pathology reporting template, increased the median number of lymph nodes evaluated from 8 to 18, in a 30-month period.[150]
The Dutch colorectal cancer treatment guidelines, in agreement with the American Joint Committee on Cancer (AJCC) and the Tumour, Node, Metastasis Committee of the International Union Against Cancer, require a minimum of 12 nodes to be examined for adequate staging.[153] However, this threshold of at least 12 nodes is not universally accepted. The recommendation of the Royal College of Pathologists in the UK is that all lymph nodes identified in the resection specimen should be examined histologically but

does not specify an arbitrary minimum number since it is recognised that the number of lymph nodes identifiable in a specimen varies according to several factors, as indicated also by the results of this and other studies.[151, 175-178]
The number of lymph nodes evaluated may also be related to the immune response of the patient; size and morphology of lymph nodes are modified by immune responses against neoplastic cell products.[146, 178, 179] Older patients probably have a diminished immune response, which would explain the effect of age on the number of lymph nodes examined in this and other studies.[146-148] Table 5. Multivariable proportional hazards regression analyses of survival of patients who underwent resection for colon cancer, diagnosed between 1999-2002 in the southern Netherlands (follow-up until January 1st 2005), according to nodal involvement. [a]
However, since the immune response is expected to be evenly distributed geographically among patients with colon cancer (especially after adjustment for age and other possible relevant factors), this does not explain the variation between the departments of pathology. In agreement with previous studies we also found an effect of gender on the adequacy of node evaluation.[146, 147] The observation that a larger number of lymph nodes was examined with more advanced stage of disease can partly be explained by the fact that retrieval of a higher number of nodes logically increases the possibility that existing positive lymph nodes will be detected. Furthermore, positive lymph nodes are generally slightly larger than negative lymph nodes, thus being more likely to be detected.[149, 180] The presence of an inflammation in the surrounding lymph nodes in patients with T3 or T4 tumours, with subsequent enlargement of these nodes, explains the increased likelihood of an adequate lymph node evaluation among patients with stage II (pT3/4) disease compared to stage I (pT1/2).[147] Another explanation may be a more thorough search by the surgeon or pathologist when a larger, penetrating tumour is present. Our finding that patients with right-sided colon cancer had more lymph nodes evaluated is consistent with other studies and not unexpected, since larger amounts of mesentery are often found in right-sided resections and subtotal colectomy.[146, 148, 181] However, the absence of a difference in the number of lymph nodes examined between the hospitals which were covered by the same department of pathology indicates that pathology rather than surgical practice patterns are responsible for the observed variation in lymph node evaluation.

Table 5. Multivariable proportional hazards regression analyses of survival of patients who underwent resection for colon cancer, diagnosed between 1999-2002 in the southern Netherlands (follow-up until January 1st 2005), according to nodal involvement. [a]

	Model *not* including number of lymph nodes evaluated [b]		Model including number of lymph nodes evaluated [b]	
	Hazard Ratio	p-value	Hazard Ratio	p-value
N0				
Dep. of pathology				
1	1.18	0.49	1.23	0.40
2	1.47	0.024	1.26	0.20
3	1.34	0.14	1.28	0.21
4	1.13	0.49	1.18	0.38
5 [c]	1.00		1.00	
6	1.34	0.12	1.19	0.38
No. of nodes evaluated				
1-4 [c]			1.00	
5-7			0.74	0.047
8-11			0.59	0.009
≥12			0.56	0.016
N1/2				
Dep. of pathology				
1	0.81	0.39	0.86	0.53
2	1.35	0.083	1.22	0.28
3	1.11	0.62	1.07	0.75
4	1.36	0.063	1.39	0.049
5 [c]	1.00		1.00	
6	1.00	0.98	0.90	0.64
No. of nodes evaluated				
1-4 [c]			1.00	
5-7			0.97	0.85
8-11			0.83	0.29
≥12			0.68	0.048

[a] Cases with missing values for any of the covariates were left out of the analyses.
[b] Including the following variables: age, gender, socio-economic status, number of comorbid conditions, tumour site, depth of invasion, tumour differentiation grade, and adjuvant chemotherapy (yes vs. no).
[c] Reference category.

The current study also revealed differences in depth of tumour invasion between the departments of pathology, with one department showing a significant higher proportion of T4 tumours. An explanation for this might be the significantly larger proportion of patients with a low socio-economic status presenting in that hospital; possibly these individuals postpone seeking medical help after being confronted with unexplained symptoms.

Our results confirmed the strong prognostic influence of an adequate lymph node examination, which may partly be related to the intensity of the patient's immune response.[134, 143, 146, 147, 167, 168, 182, 183] After adjustment for relevant factors such as stage and adjuvant therapy - but not the number of lymph nodes examined - there was a variation in patient survival between the departments of pathology. Among node-negative patients, the departments of pathology with the lowest median number of examined nodes yielded the worst patient survival, reflecting that this group of node negative patients contained N1 patients wrongly staged as N0. Inclusion of the number of lymph nodes examined decreased the differences between the departments. This means that a reduction in mortality among these node-negative patients could be achieved by increasing the number of lymph nodes examined in the departments with the lowest numbers. The difference in survival among node-positive patients after adjustment for the number of nodes examined indicated that other relevant clinical features differ between institutions, in addition to the determinants we assessed in our analyses. For example, the surgical technique, the completeness of the resection, and the experience of the surgeon all may have a prognostic influence.[184, 185]

In conclusion, we demonstrated a low number of lymph nodes examined among patients with colon cancer in the south of the Netherlands, with a large variation between the departments of pathology leading to differences in stage distribution and prognosis. This finding becomes more relevant with more frequent use of new, increasingly effective chemotherapeutic agents. In the future, lymphatic mapping might lead to inclusion of all tumour-draining lymph nodes and molecular tumour markers may provide diagnostic information that would preclude assessment of regional lymph nodes.[171, 186-188] Until then, therapeutic decisions will be based on lymph node analysis, and intervention strategies should be directed at nodal assessment.

Acknowledgement

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

Chapter 4.1

Trends in incidence, treatment, survival and mortality of colorectal cancer in the south of the Netherlands

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Summary

Introduction: In the Netherlands, yearly 10,000 patients are diagnosed with colorectal cancer (CRC), of who about 4500 are expected to ultimately die of the disease. Investigating long term and recent trends will help predict future developments, which is important for planning prospective investments in clinical cancer care.
Methods: The 19,099 cases of primary CRC (C18.0-C20.9) diagnosed between 1975 and 2004 in the Eindhoven Cancer Registry area were included. We analysed trends in incidence, prevalence, stage distribution, treatment, survival, and mortality.
Results: The epidemiology of CRC has changed strikingly in the south of the Netherlands during the period 1975 to 2004. First of all, there has been a gradual increase in incidence, which was most marked among males and for proximal tumours. Furthermore, survival increased dramatically, especially among rectal cancer patients and patients younger than 70 years. This went together with changes in treatment; particularly since the mid-1990's, a growing proportion of predominantly younger patients underwent adjuvant chemo- or radiotherapy. The advances in survival led in turn to decreased mortality rates, and consequently to increased prevalence rates. The changes toward an increased proportion of stage III tumours suggested improved staging procedures over time, without evidence that patients diagnosed more recently are diagnosed at an earlier stage of the disease.
Conclusions: The results of our study showed that the workload of all clinicians involved in CRC care will keep increasing considerably in the near future. The steady increase in age-adjusted incidence, 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 presumably the same. Nevertheless, this study demonstrated large improvements in management and survival of CRC patients between 1975 and 2004. The increase in survival of rectal cancer was the largest seen among all adult tumours in the Netherlands. Progress can however still be made, principally regarding management of older patients and early detection of CRC.

Introduction

Based on data from registries assembled in the European Network of Cancer Registries, colorectal cancer (CRC) was estimated to be the most frequent cancer in the European Union in 2004 [189]. In the Netherlands, yearly 10,000 patients are diagnosed with CRC, of who about 4500 are expected to ultimately die of the disease [1]. It constitutes 2-3% of total mortality above the age of 40. During the last 35 years, earlier detection, 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 [47, 50, 53, 152, 190, 191]. However, besides implementing all those changes, the clinicians of today face new challenges: one of them is the rising age of the Western population will lead to an increase in cancer patients, with a higher mean age at presentation.
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 trends in incidence, stage distribution, treatment, survival and mortality among patients diagnosed with CRC between 1975 and 2004 in the south of the Netherlands, and we discuss the likely effects of the most important trends on clinical practice in the near future.

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 grew from an area covering 850.000 to about 2.3 million inhabitants. This population-based registry was notified by 6 pathology departments, 10 community hospitals (20 at the beginning of the study period but many of them have merged) at 17 locations, and 2 radiotherapy institutions.
Between 1975 and 2004, 19,099 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 took 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% [54]. Vital status of all patients diagnosed until 1st of January 2004 was assessed on 1st of January 2006 through merging with the Municipal Administrative Databases, where all deceased and emigrated persons in the Netherlands are registered.

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. The trends are age standardised, using the European

Standardised Rate (ESR). 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 and 2000-2004). Stage is postoperative, except for cases where postoperative stage was unknown, then 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 [192]. Expected survival rates were calculated from life tables for regional male and female populations with the same 5 year age distribution. In order to examine any changes in survival between the periods of diagnosis, a multivariable proportional hazards regression analysis stratified by tumour site (colon vs. rectum) was used to discriminate independent risk factors for death. This model was first built without the variable 'therapy', which was added later in order to investigate to what degree any prognostic effects of period of diagnosis could be explained by changes in treatment. Prevalence of patients with CRC up to 10 years before 1984, 1994, and 2004 was expressed as the age-standardised number of patients alive per 100,000 inhabitants at the respective date.

Results

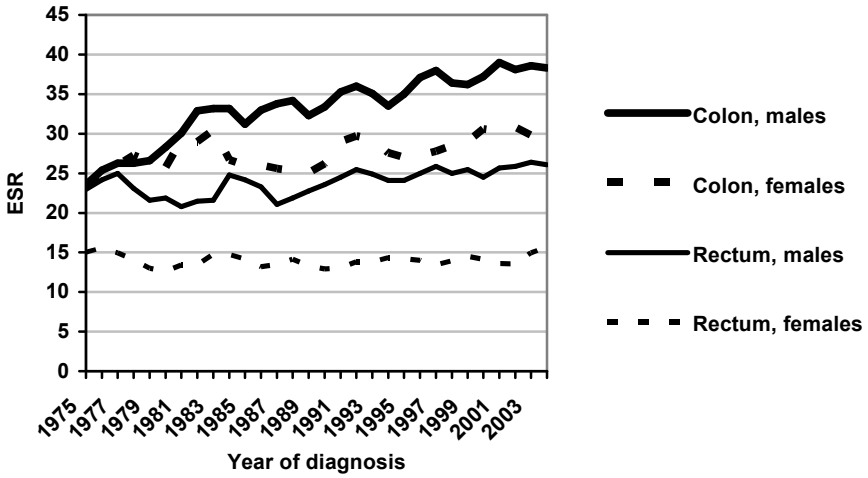
The age distribution shifted between 1975-1984 and 2000-2004 towards a higher proportion of patients diagnosed between age 65 and 79 years ($p_{trend}<0.0001$) (table 1). The male-female ratio of incidence increased from 1.04 to 1.17 (p_{trend} 0.05), and a shift occurred towards a more proximal tumour site (colon vs. rectum) (p_{trend} <0.0001). The age-standardised incidence of colon carcinoma among males gradually increased between 1975 and 2004 from 24 to 38 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).

Table 1. Age, gender, and tumour site distribution of the 19.099 patients diagnosed with colorectal cancer in the south of the Netherlands between 1975 and 2004, by period of diagnosis.[1]

	Period of diagnosis							
	1975-1984		**1985-1994**		**1995-1999**		**2000-2004**	
Age (years)								
19-49	278	(9)	377	(8)	352	(7)	414	(6)
50-64	952	(32)	1329	(31)	1495	(28)	1877	(29)
65-79	1447	(48)	2048	(47)	2585	(49)	3240	(50)
80+	336	(11)	623	(14)	835	(15)	951	(15)
Gender								
Male	1523	(51)	2281	(53)	2802	(53)	3485	(54)
Female	1490	(49)	2056	(47)	2465	(47)	2997	(46)
Tumour site								
Colon	1819	(60)	2672	(62)	3265	(62)	4152	(64)
Rectum	1194	(40)	1665	(38)	2002	(38)	2330	(36)

[1] 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).



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 colon sigmoideum (figures 2a and 2b).

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).

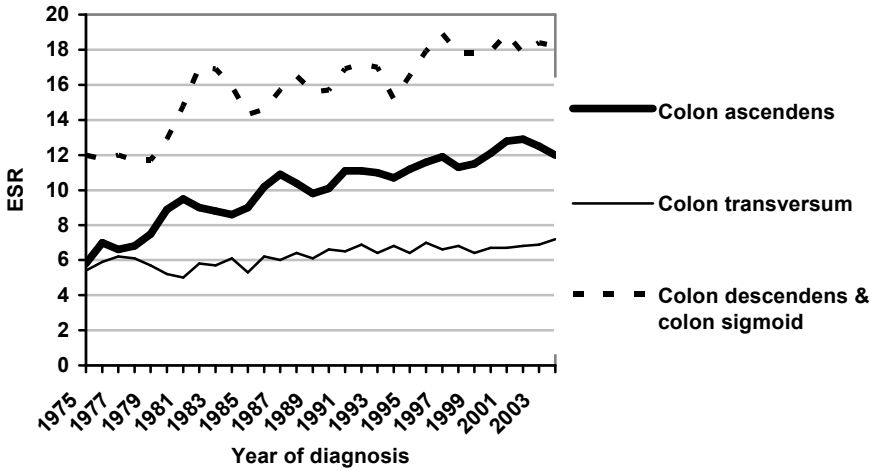
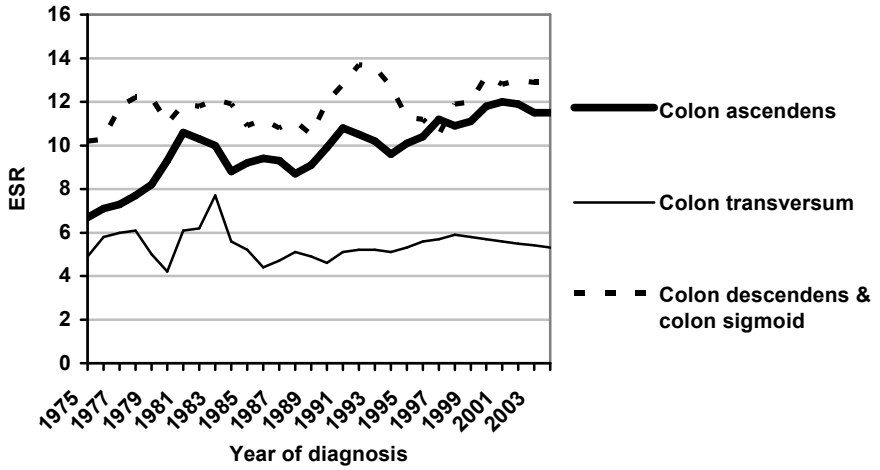


Figure 2b. Age-standardized incidence of colon cancer among females in the south of the Netherlands, according to subsite (3-year moving average; ESR= European Standardised Rate).

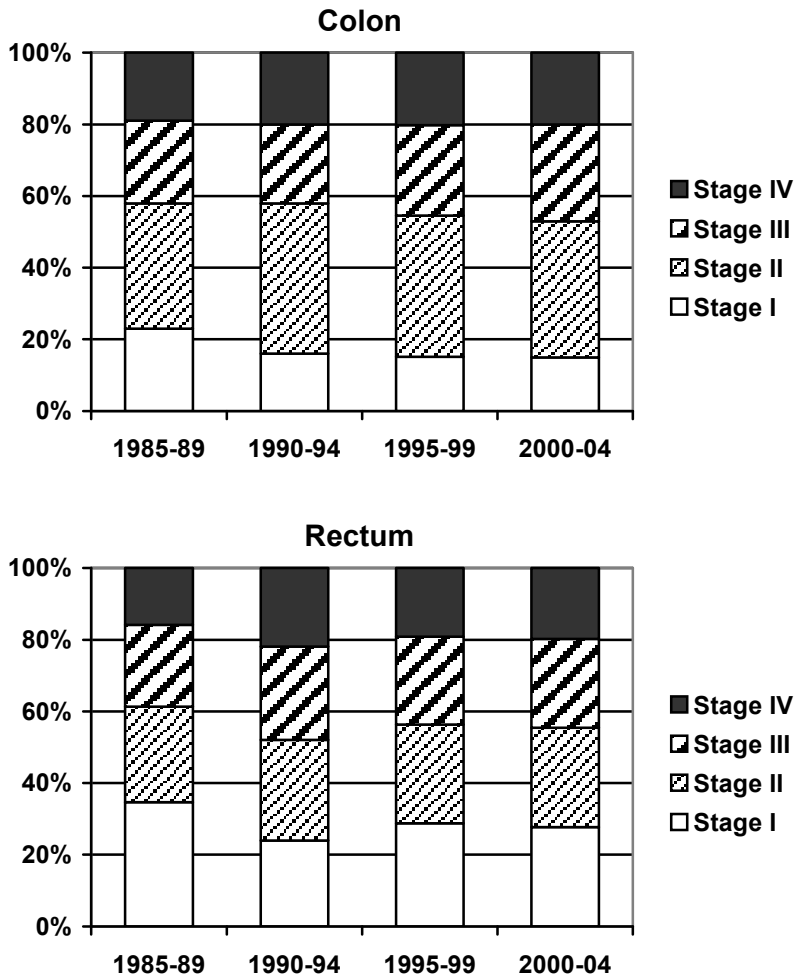


The proportional stage distribution of patients with colonic carcinoma showed a slightly decreasing proportion of stage I patients, and an increased proportion of stage III (T_{any}N1-2M0) patients since 1984-1989 ($p<0.0001$) (figure 3). The proportion of patients with unknown stage remained stable for both colon (2.4%) and rectal cancer (3.5%) between 1985-89 and 2000-2004 (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% 69% ($p<0.0001$).

Almost all patients with stage I-III ($T_{any}N_{any}$M0) colon carcinoma underwent resection, regardless of period of diagnosis and age (ranging from 92% to 100%) (table 2a). Since mid 1990's, adjuvant chemotherapy was increasingly administered among all age groups of stage III colon carcinoma patients, but the increase in the older age groups was much less marked. Only 4% of patients aged 80 years or older received adjuvant chemotherapy in the most recent period. In that period among stage II (T3-4N0M0) patients, 10% of patients younger than 50 years received adjuvant chemotherapy. While resection rates increased over time among patients younger than 50 years with colon carcinoma stage IV ($T_{any}N_{any}$M1), these rates decreased among the older age groups. Chemotherapy was increasingly administered to stage IV patients, except for patients over 80 years of age.

Patients with rectal carcinoma increasingly underwent surgery, except for the most recent period, where surgery rates remained stable or even seemed to decrease somewhat among the oldest patients (table 2b). The use of radiotherapy among stage II/III patients increased between 1980-1989 and 1990-1994 (postoperative radiotherapy), decreased in the subsequent period (transition to preoperative radiotherapy), and increased again in the most recent period (preoperative

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



radiotherapy). With rising age, the use of radiotherapy decreased. The combination of chemo- and radiotherapy was administered mostly to patients younger than 70 years old in the most recent period. The youngest stage IV patients increasingly underwent resection, contrasting the older patients. The use of chemotherapy among stage IV patients rose clearly, but less pronounced among the older patients.
Unadjusted relative survival rates increased markedly for colon and for rectal cancer patients during the 30 year period (figures 4a-4n), especially among patients with stage III colon cancer and stage III rectal cancer. Among stage I and II colon cancer

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

		Period of diagnosis			
Treatment	**age**	1980-89	1990-94	1995-99	2000-04
		%	%	%	%
Resection, stage I-III					
	19-49	99	99	92	99
	50-59	100	99	95	98
	60-69	99	99	98	98
	70-79	97	99	97	97
	80+	96	98	97	97
Adjuvant chemotherapy, stage II					
	19-49	0	14	2	10
	50-59	0	5	5	5
	60-69	1	6	2	4
	70-79	0	0	1	2
	80+	0	0	0	0
Adjuvant chemotherapy, stage III					
	19-49	2	47	72	93
	50-59	1	34	60	83
	60-69	0	32	52	76
	70-79	0	8	25	36
	80+	0	0	1	4
Resection (any), stage IV					
	19-49	76	69	85	83
	50-59	80	78	73	70
	60-69	82	83	70	70
	70-79	78	75	71	68
	80+	78	71	69	64
Chemotherapy, stage IV					
	19-49	17	38	60	68
	50-59	11	33	44	63
	60-69	5	20	28	50
	70-79	2	3	12	32
	80+	0	0	1	3

[a] Percentages of patients who underwent the respective treatment.

patients, survival improved markedly since 1974-1985, but remained stable afterwards. Among stage II patients, survival kept improving throughout the whole period. An improvement in survival can be noted since 111995-99 among stage IV patients, but only for survival up to 2 years. Survival of stage I and II rectal cancer patients improved drastically during the 1970's and '80's, but remained stable afterwards, although in the most recent period an improvement among stage I rectal cancer patients can be noted up to 4-year survival. The improvements among stage III rectal cancer patients are comparable to the improvements seen among stage III colon cancer patients, with large improvements in the 2 most recent periods. There was also a noteworthy improvement among stage IV rectal cancer patients, especially in the period 2000-2004. The unadjusted cancer survival rates for both colon and rectal cancer and for both patients younger and older than 70 years of age did not show a clear improvement since the period 1985-1994. An exception was the unadjusted survival rate among rectal cancer patients younger than 70 years, which improved up

to the period 1995-1999. Five-year survival of all colon cancer patients improved from 45% in 1975-1984 to 56% in 2000-2004; 5-year survival of all rectal cancer patients improved from 39% to 57% in that period.

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

		Period of diagnosis			
Treatment	**age**	1980-89	1990-94	1995-99	2000-04
		%	%	%	%
Resection, stage I-III					
	19-49	96	95	94	98
	50-59	99	97	97	97
	60-69	98	99	97	96
	70-79	96	96	94	95
	80+	89	96	93	88
Pre/postoperative radiotherapy [b], stage II/III					
	19-49	55	63	58	77
	50-59	67	61	54	73
	60-69	46	57	47	71
	70-79	31	43	37	58
	80+	15	20	19	42
(Neo-) adjuvant chemotherapy plus radiotherapy, stage II/III					
	19-49	0	11	14	37
	50-59	2	6	11	27
	60-69	0	2	4	22
	70-79	0	1	1	9
	80+	0	0	0	1
Resection (any), stage IV					
	19-49	53	50	57	66
	50-59	72	54	69	56
	60-69	75	55	63	60
	70-79	63	63	55	42
	80+	78	40	36	31
Chemotherapy, stage IV					
	19-49	5	17	54	76
	50-59	9	36	49	65
	60-69	17	10	35	53
	70-79	2	7	17	31
	80+	0	0	0	4

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

The multivariable 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 disappeared. There was no significant improvement over time for the older age group. Among stage II and III rectal cancer patients, there was a significant reduction in death risk over time for both patients younger and older than 70 years, both without and with treatment in the model. Also among patients with stage IV

colorectal cancer the risk of death decreased, only among younger patients, independent of treatment (table 3b).

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

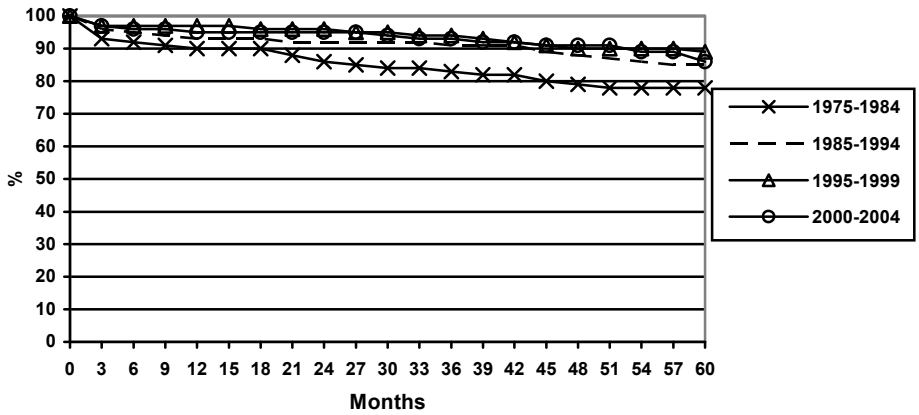


Figure 4b. Relative survival among patients with stage II colon cancer.

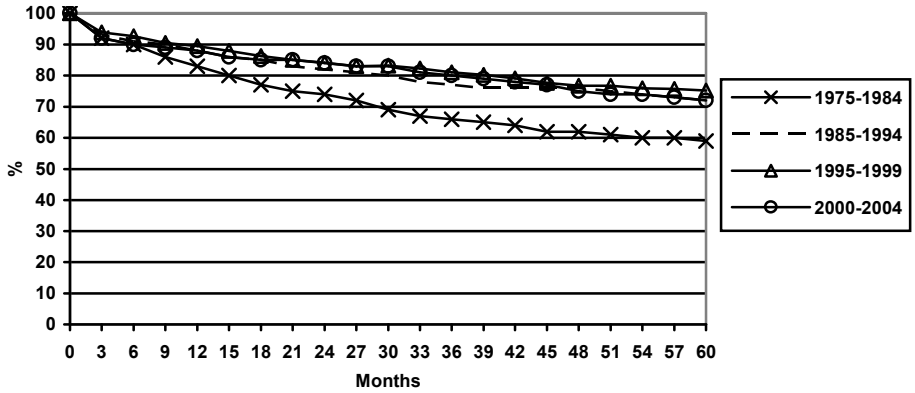


Figure 4c. Relative survival among patients with stage III colon cancer.

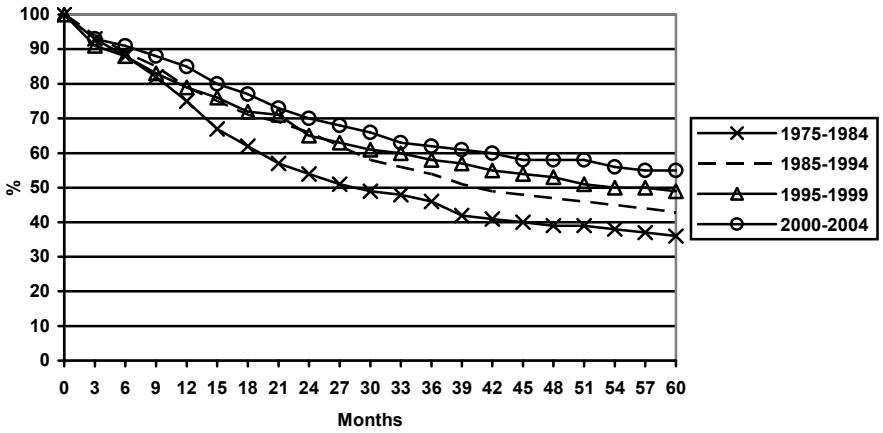


Figure 4d. Relative survival among patients with stage IV colon cancer.

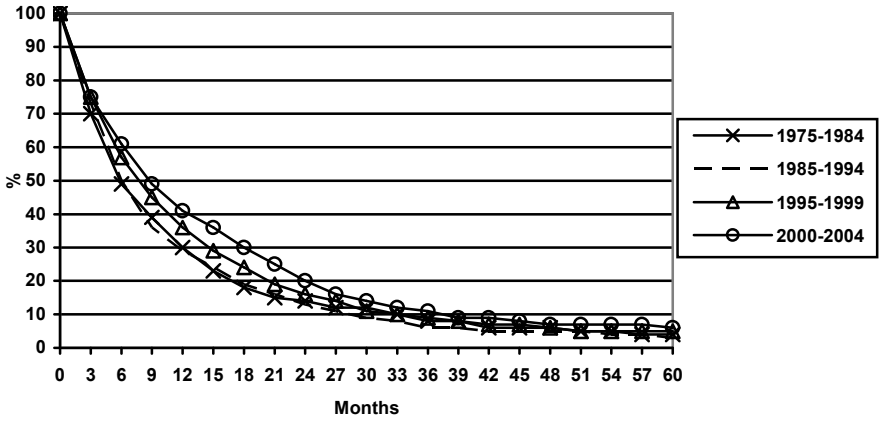


Figure 4e. Relative survival among patients with stage I rectal cancer.

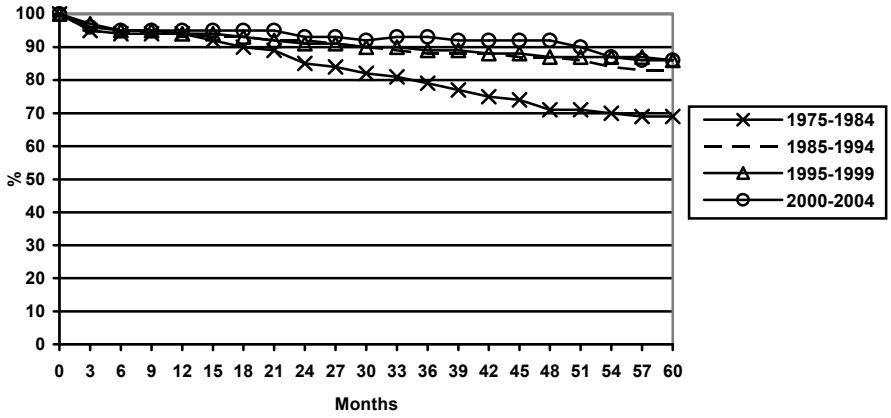


Figure 4f. Relative survival among patients with stage II rectal cancer.

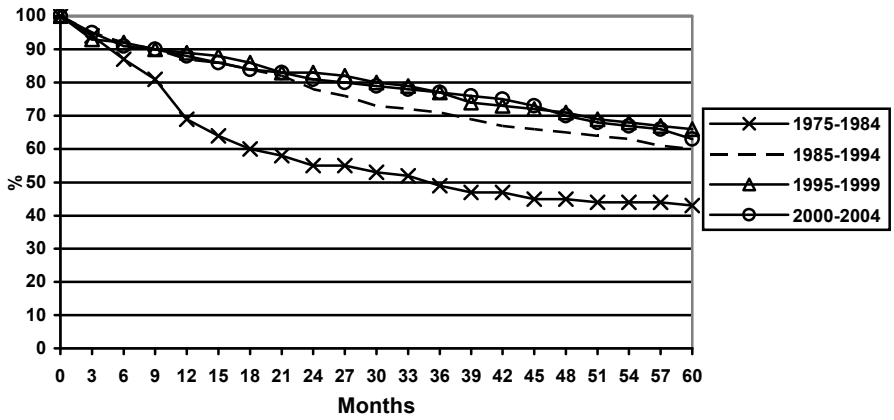


Figure 4g. Relative survival among patients with stage III rectal cancer.

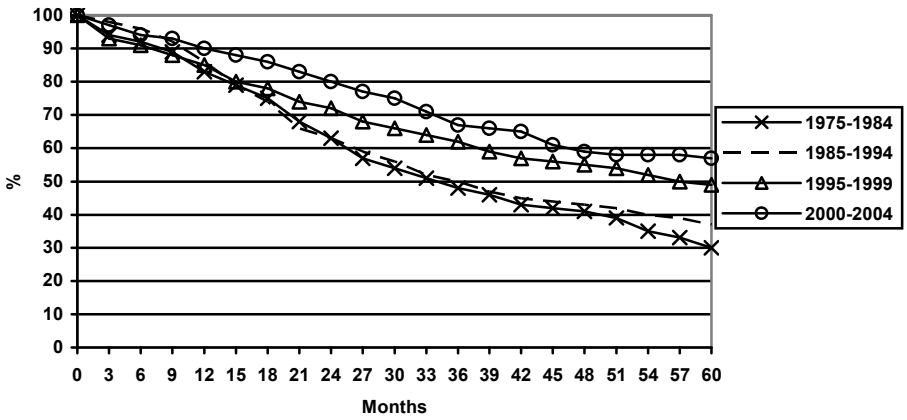


Figure 4h. Relative survival among patients with stage IV rectal cancer.

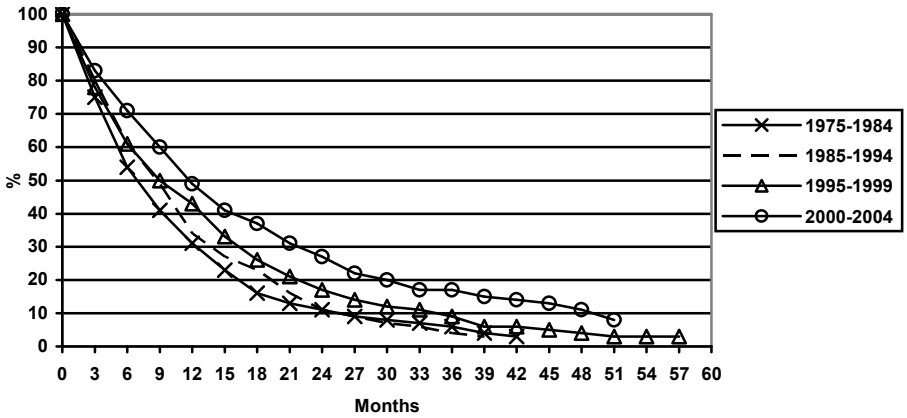


Table 4i. Relative survival among patients with colon cancer, all stages, younger than 70 years.

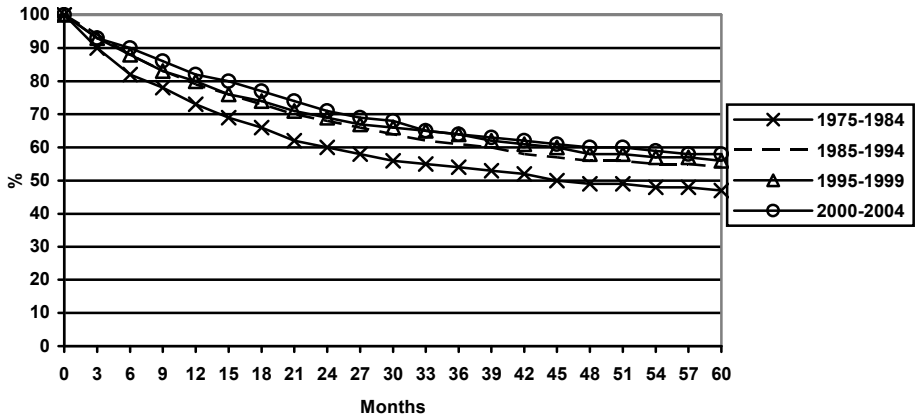


Table 4j. Relative survival among patients with colon cancer, all stages, 70 years or older.

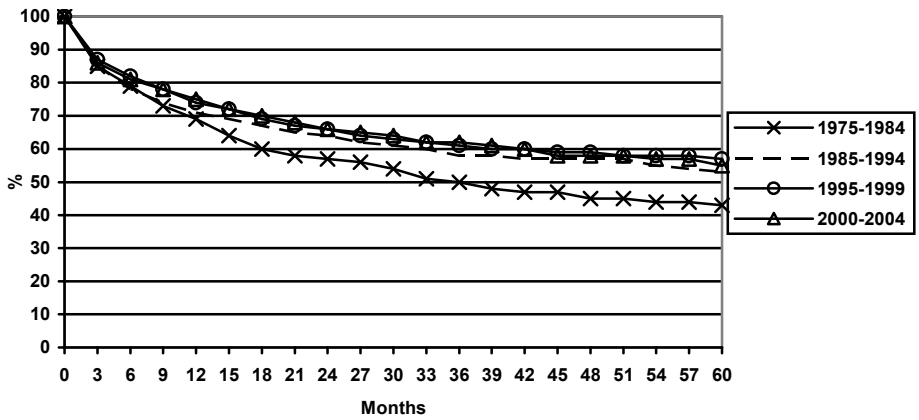


Table 4k. Relative survival among patients with rectal cancer, all stages, younger than 70 years.

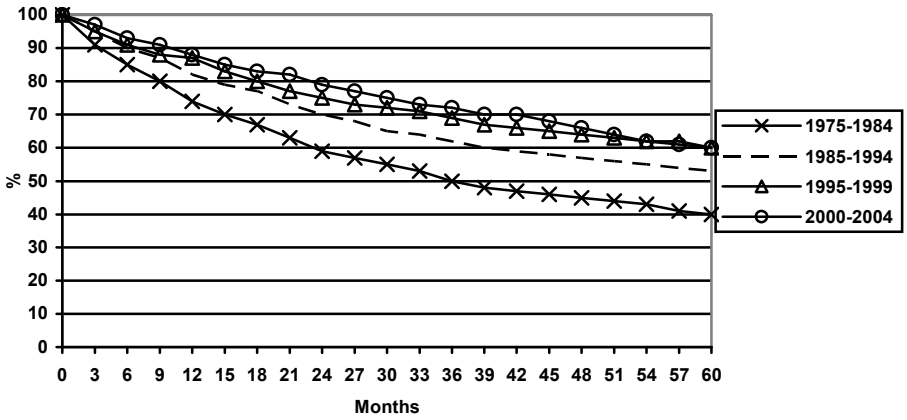


Table 4l. Relative survival among patients with rectal cancer, all stages, 70 years or older.

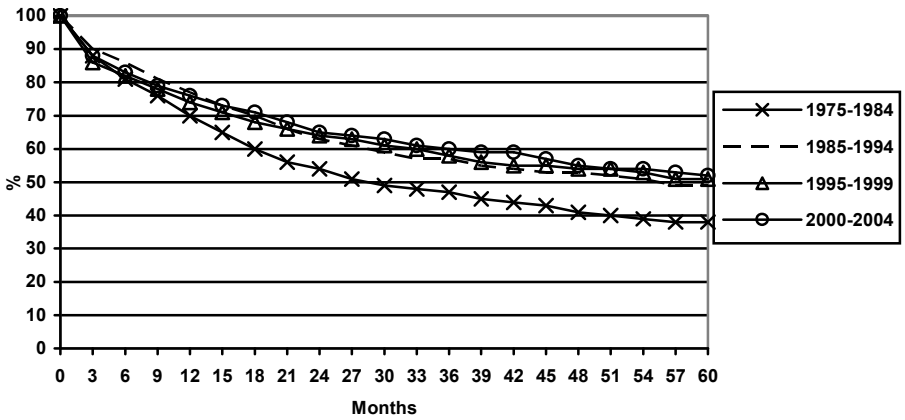


Table 4m. Relative survival among patients with colon cancer, all stages and ages.

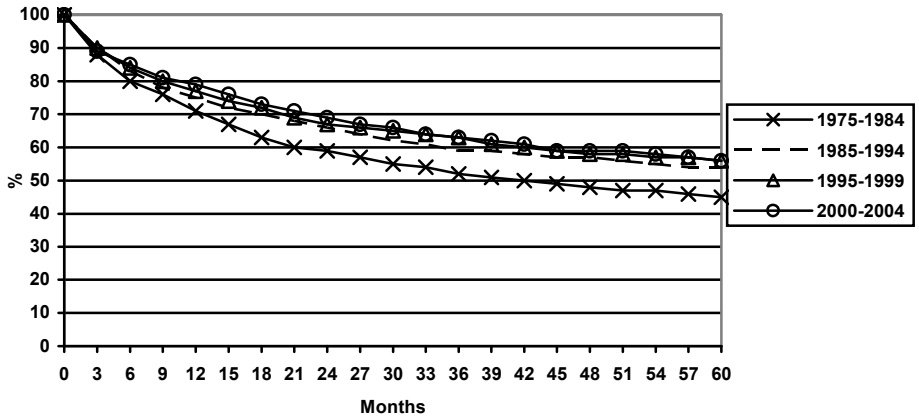
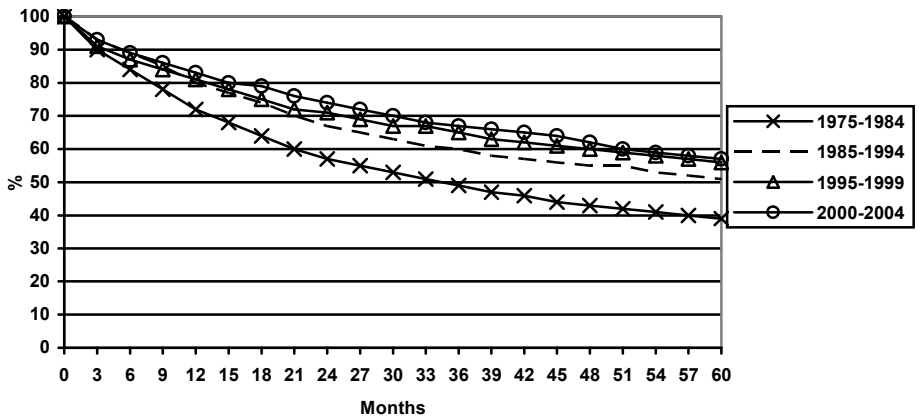


Table 4n. Relative survival among patients with rectal cancer, all stages and ages.



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 2004. 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, this means an increase from 800 colorectal cancer patients per hospital to almost 1300 patients.

Discussion

The epidemiology of CRC has changed strikingly in the south of the Netherlands during the period 1975 to 2004. First of all, there has been a gradual increase in incidence, which was most marked among males and for proximal tumours. Furthermore, survival increased dramatically, especially among patients younger than 70 years. This went together with changes in treatment; particularly since the mid-1990's, a growing proportion of predominantly younger patients underwent adjuvant chemo- or radiotherapy. The advances in survival led in turn to decreased mortality rates, and consequently to increased prevalence rates. The changes in stage distribution suggested improved staging procedures over time, without 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 [2, 193-195]. Changes in major risk factors such as life style, including physical activity, diet and obesity may account for the rising trend (van Steenbergen et al, submitted for publication). These trends are however in contrast to patterns found in the USA, where overall incidence rates have been steadily declining over the past two decades [196]. One explanation for this reversed trend may be the more extensive implementation of opportunistic CRC screening in the latter country [196]. 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 more proximal tumour site was observed [197-201]. This has been related to the use of sigmoidoscopy (and related polypectomy) as a screening tool [197, 202]. 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 [15-20, 22, 27, 203-205].

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

		Model excl. treatment[1]		Model incl. treatment[1]	
		Hazard ratio	**p-value**	**Hazard ratio**	**p-value**
Colon, stage III, <70 yrs	Period of diagnosis				
	1975-1984	1.42	0.02	1.10	0.34
	1985-1994	1.0		1.0	
	1995-1999	0.83	0.04	1.08	0.44
	2000-2004	0.64	<0.0001	1.02	0.18
	Treatment				
	Surgery	-		1.0	
	Surgery + adjuvant chemotherapy	-		0.50	<0.0001
Colon, stage III, 70+ yrs	Period of diagnosis				
	1975-1984	1.26	0.02	1.27	0.02
	1985-1994	1.0		1.0	
	1995-1999	0.94	0.46	1.05	0.59
	2000-2004	0.84	0.04	0.99	0.88
	Treatment				
	Surgery	-		1.0	
	Surgery + adjuvant chemotherapy	-		0.50	<0.0001
Rectum, stage II/III, <70 yrs	Period of diagnosis				
	1975-1984	1.37	0.0002	1.37	0.0003
	1985-1994	1.0		1.0	
	1995-1999	0.70	<0.0001	0.70	<0.0001
	2000-2004	0.58	<0.0001	0.54	<0.0001
	Treatment				
	Surgery	-		1.0	
	Surgery + any adjuvant therapy	-		1.03	0.98
Rectum, stage II/III, 70+ yrs	Period of diagnosis				
	1975-1984	1.19	0.07	1.15	0.18
	1985-1994	1.0		1.0	
	1995-1999	0.86	0.05	0.84	0.04
	2000-2004	0.81	0.02	0.77	0.007
	Treatment				
	Surgery	-		1.0	
	Surgery + any adjuvant therapy	-		0.93	0.33

[1] Adjusted for age, gender, subsite, and variables shown

There was a vast improvement in 5-year relative survival for both colon and rectal cancer, especially among stage III patients. The current study demonstrated that the increase in survival was more pronounced among patients younger than 70. For stage III colon cancer patients, the increased use of effective adjuvant chemotherapy regimens for these patients probably largely accounted for this improvement. Among elderly stage III patients, survival increased more moderately. Adjuvant chemotherapy was administered to only 36% of patients aged 70-79 years and only 4% of those aged

Table 3b. Multivariable analysis of patients with stage IV colorectal cancer.

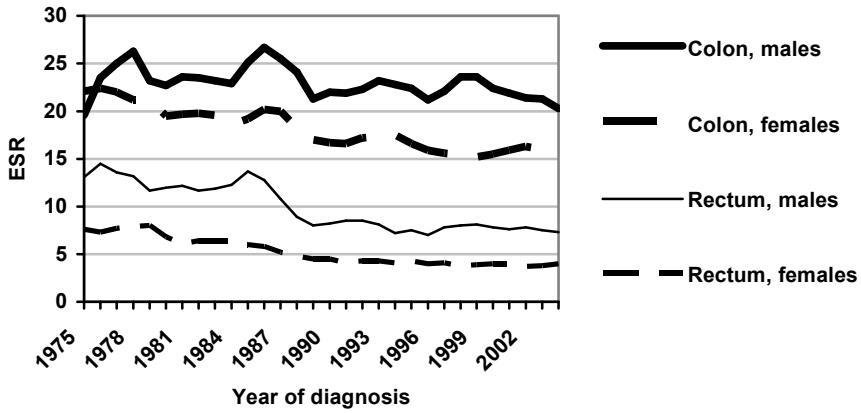
		Model excluding treatment[1]		Model including treatment[1]	
		Hazard ratio	p-value	Hazard ratio	p-value
Colorectum, stage IV, <70 yrs	Period of diagnosis				
	1975-1984	1.17	0.03	1.18	0.03
	1985-1994	1.0		1.0	
	1995-1999	0.84	0.006	0.90	0.09
	2000-2004	0.68	<0.0001	0.76	<0.0001
	Treatment				
	No systemic therapy	-		1.0	
	Systemic therapy	-		0.76	<0.0001
Colorectum, stage IV, 70+ yrs	Period of diagnosis				
	1975-1984	0.85	0.27	0.86	0.10
	1985-1994	1.0		1.0	
	1995-1999	0.95	0.84	0.98	0.81
	2000-2004	0.86	0.46	0.96	0.56
	Treatment				
	No systemic therapy	-		1.0	
	Systemic therapy	-		0.64	<0.0001

[1] Adjusted for age, gender, site, and variables shown

80 or older in the period 2000-2004, although several studies have demonstrated the benefit of this therapy at higher ages [141, 206]. Besides age as well as hospital, also comorbidity, gender, and socio-economic status influenced administration of adjuvant chemotherapy in the south of the Netherlands [139]. Survival improved also among stage IV CRC patients, and among rectal cancer patients. Although a 2003 study did not detect a significant survival improvement among elderly rectal cancer patients in the south of the Netherlands, the present study shows an improvement in this group of patients [47]. This may be explained by the fact that survival of elderly patients especially improved during the most recent years (2000-2004) which were not included in the previous study. 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 [47, 89, 207]. The increase in survival for rectal cancer in general was large, when also taking into account the survival in the period 1965-1974 (33%), the relative improvement in survival was the largest among all adult tumours [1]. For stage IV CRC patients, higher resection rates and an increased use of and changes in chemotherapy could be noted. 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 stage III colon cancer patients, in our multivariable analyses the survival improvements for stage II/III rectal cancer patients could not be explained by the increased use of adjuvant treatment. Therefore, also changes in surgery, more accurate staging procedures by surgeon and pathologist, perioperative care, and the

establishment of multidisciplinary teams have probably contributed to the improved survival of rectal carcinoma.

Figure 5. Age-standardized mortality of CRC in the south of the Netherlands (3-year moving average), according to gender and tumour site.



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 [80]. 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, specific knowledge of CRC care of the elderly, while lagging behind the treatment of younger patients, is beginning to emerge. Informed by recent trials, the approach towards elderly patients is shifting towards more aggressive treatment and multimodal therapy, as partly confirmed by our data.

In recent years, the limited armamentarium of fluoruracil-based chemotherapy has been replenished by new systemic treatments agents [208]. Oxaliplatin in combination with conventional 5-fluoruracil/leucovorin is now considered standard therapy for stage III colon cancer in the Netherlands. Targeted therapies directed at the vascular endothelial growth factor pathway and the epidermal growth factor pathway have also become key players in the treatment of CRC [209]. However, the high costs of these new agents have to be taken into consideration, at the same time bearing in mind the rising number of CRC patients [209]. Of importance to note here is that high-risk stage II colon cancer patients with a low number of lymph nodes examined, are nowadays also often offered adjuvant chemotherapy [210]. Nevertheless, evidence confirming the benefit of this procedure among stage II patients stems from the preliminary results from one

randomised study only, which to date has not published the complete results [211]. Priority should be given to increase adequacy of nodal examination, which has been shown to be sub-optimal in the south of the Netherlands [212].
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 5 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 [4]. 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, and they have also an excess risk of developing a subsequent primary cancer [213].

Table 4. Ten-years prevalence (ESR) of patients with CRC at 1st of January 1984, 1994, and 2004, respectively, in the south of the Netherlands.[1]

		Prevalence (ESR)		
		01-01-1984	**01-01-1994**	**01-01-2004**
Males	Colon	101	138	167
	Rectum	70	104	128
Females	Colon	96	118	145
	Rectum	51	59	75

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

The strength of the current study is the availability of long-term, high quality population-based data [54, 214]. 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 presumably the same. Nevertheless, this study demonstrated large improvements in management and survival of CRC patients between 1975 and 2004. Progress can still be made, principally regarding management of older patients and early detection of CRC.

Chapter 5

Discussion

Chapter 5.1

Introduction to the discussion

This thesis described the clinical epidemiology of colorectal cancer in the South of the Netherlands, a region of 2.4 million people served by the Comprehensive Cancer Centre South (CCCS). The studies included in this thesis gave an overview of daily clinical practice, with results which were expected (comorbidity influencing treatment and survival), unexpected (the large variation in administration of adjuvant chemotherapy and of lymph node examination between institutions), and desirable (improvement in survival). It answered many questions, but even more questions were raised and remained unanswered. In this chapter, we will address several of these answered and unanswered questions in more detail; first we will address the trends in incidence and survival of colorectal cancer patients. Then we will focus on one of the main topics discussed in this thesis: treatment and survival of older colorectal cancer patients. Afterwards we will go deeper into the impact of comorbidity, and discuss guideline adherence and variation. We will end the discussion with a paragraph on future perspectives.

Chapter 5.2

Incidence and survival

The incidence of colon cancer increased since 1975 while rectal cancer incidence remained relatively stable (chapter 4.1). The differential increase in incidence for colon and rectal cancer in both genders is probably due to changed lifestyle factors. Epidemiological studies confirm the importance of lifestyle in colorectal cancer. Excessive intake of energy, red and processed meat, dietary fat, alcohol, smoking, as well as obesity and reduced physical activity are known risk factors for CRC [14-23]. There was no major improvement in stage distribution during the last decades. Probably, this reflects the relatively low uptake of (opportunistic) screening activities. Currently available screening tests, if applied to the general population, could substantially reduce colorectal cancer incidence and mortality [215]. Apart from this, there was already a large and continuing increase in survival in the south of the Netherlands, since the 1970s, for both colon and rectal cancer. The increase in rectal cancer survival was the largest of all tumours among adults. Changes in detection and treatment are largely accountable for the improvement for colorectal cancer survival: imaging techniques, surgery, and adjuvant chemo- and radiotherapy have all undergone major changes, as described in chapter 4.1. Survival increased more among patients younger than 75 years, but during more recent years also among elderly patients an improvement in survival could be noted.

The increased incidence and survival rates led to a large increase in the prevalence of patients with colorectal cancer. Most of these patients will require follow-up, and part of these patients will need extra care, i.e. because of a permanent stoma or incontinence, and the excess risk of developing a subsequent primary cancer [213, 216, 217]. This, together with increasing incidence rates, the demographic changes of the Dutch population, and the likely future implementation of colorectal cancer mass screening will necessitate enlarged provision of service.

Chapter 5.3

Management and survival of colorectal cancer in the elderly; an overview of population-based studies

Reprinted from European Journal of Cancer: J. Faivre, V.E.P.P. Lemmens, V. Quipourt, A.M. Bouvier. Management and survival of colorectal cancer in the elderly; an overview of population-based studies. Paper in press.

Summary

Colorectal cancer is a major problem in elderly patients. Most data on the management and survival of colorectal cancer has been provided by specialised hospital units and as such cannot be used as reference because of unavoidable selection bias. Cancer registries recording data on treatment and survival at a population level represent the best valuable resource to assess the management of patients. However, there is a paucity of reports published in the literature due to the difficulty to routinely collect such data. Relative survival rates in the elderly were lower than in younger patients. However, the gap that has separated younger from elderly patients is closing. Stage at diagnosis remains the major determinant of prognosis. There is also large variation in survival within countries: survival rates being dramatically lower in Eastern European countries, compared to Western European countries. Comorbidity, which is particularly frequent in the elderly increases the complexity of cancer management and affects survival.

Substantial improvement in the care of colorectal cancer in the elderly has been achieved (increase in the proportion of patients resected for cure, decrease in operative mortality, improvement in stage at diagnosis). Surgery should not be restricted on the basis of age alone. Further improvements can be made, in particular with respect to adjuvant therapy.

Introduction

Colorectal cancer is predominantly a problem of the elderly: 30 to 40% of the cases occur in subjects aged 75 or older [2]. The ageing of the population and the rise in life expectancy, as well as the increasing incidence of colorectal cancer, have led to a growing number of affected patients. Over the past 25 years important advances have occurred in the management of colorectal cancer [218]. However, diffusion of treatment that has proven beneficial among elderly patients is not well known. Most data on management and survival of colorectal cancer in the elderly is provided by specialised hospital units and as such cannot be used as reference because of unavoidable selection bias. Furthermore, crude survival rates overestimate cancer-specific mortality among elderly patients since mortality due to other causes is high. Relative survival, defined as the ratio of observed survival to expected survival in a population of the same age and sex distribution, provides an estimation of patient survival which is corrected for non-colorectal cancer cause of death [192]. Population-based studies, recording all cases diagnosed in a well-defined population, represent the best way to assess improvements in management or prognosis of colorectal cancer in the elderly (defined in this paper as patients aged 75 years or older). Such studies are rare, because they require accurate and detailed data collection, which is difficult to achieve for many cancer registries. The purpose of this report is to describe colorectal cancer management and survival in the elderly and to explore the factors involved using community-based statistics.

Surgery for colorectal cancer

Colorectal cancer is managed by surgical resection of the primary tumour whenever possible. This is the only possibility for cure of the cancer, with the exception of endoscopic polypectomy of a malignant adenoma, which by itself can be a sufficient treatment. A review of 28 independent studies, involving a total of 34,194 patients, has reported a lower resection rate in elderly patients compared to younger patients [81] (Table 1). This difference between age groups is multifactorial. It may be because of later presentation, poor performance status, presence of comorbidities or an expectation of poorer outcome in elderly patients. However, the gap between age groups is closing.

Table 1: Aggregate data on treatment and stage at diagnosis for colorectal cancer according to age, in 28 studies

	65-74 years	**75-84 years**	**≥ 85 years**
Resection for cure	75%	73%	67%
No operation	6%	11%	21%
Emergency surgery	15%	18%	29%
TNM stage 1	15%	14%	10%
TNM stage 4	21%	22%	25%

Recent data suggest that the resection rate for colon cancer is now similar in all age groups up until 85 and becomes lower only in the very old age group [81, 219]. The age-related decreased resection rate appears earlier among patients with rectal cancer, just after the age of 80 [219]. This can be explained by the fact that rectal surgery is generally more complex. Several reports from France indicate that there was a major improvement in the proportion of resected cases until the 1990s, after which it levelled out [123, 218, 220]. A similar trend has also been reported in Denmark [221]. The absence of a recent improvement in the proportion of resected cases can be related to the fact that it is not far from the optimum: 90% for colon cancer and 85% for rectal cancer up until 85 years of age [219]. The observed trend shows a change in the habits and opinions of surgeons and anaesthetists over the years. It is now well established that the quality of surgery is of particular importance in rectal cancer. Total mesorectal excision decreases local recurrence. However, it has been shown that total mesorectal excision was performed less often in elderly patients than in younger patients [80]. This treatment must be recommended whatever the age. The importance of appropriate treatment does not diminish with age. Age in itself should not be a limiting factor in the treatment of patients with colorectal cancer. A comprehensive geriatric assessment for determining operative risk should assist in selection of patients who otherwise appear unlikely to benefit from surgery.

It is important to underline that the increase in the proportion of patients resected from their cancer is associated with an improvement in the stage at diagnosis [222]. Several explanations can be put forward: earlier consultation, more frequent and more rapid referral for investigations by general practitioners, a more forceful attitude of surgeons and also because among non-resected cases in the past, there were patients with early-stage disease which are now identified as such.

The objectives of surgery in elderly patients are to improve life expectancy with a minimal risk of operative mortality and loss of autonomy. A Canadian study compared quality of life of patients over 80 years old who had undergone surgery for colorectal cancer, with a younger group composed of patients under 70 [223]. Patients were surveyed by mail using the EORTC quality-of-life scales specific to cancer (EORTC – C30) and colorectal cancer (EORTC – CR38). The two groups scored similarly except for physical functioning and stoma-related problems. Most patients did not require special assistance or alternative living arrangements after discharge from the hospital and were able to return to their preoperative level of functioning. This study suggests that elderly patients who are selected for surgery have a quality of life comparable to younger patients in most respects. It is well established that elderly patients have an increased frequency, compared with younger patients, of comorbid conditions such as diabetes, hypertension, chronic obstructive pulmonary disease or cardiovascular and cerebrovascular disease [80, 224]. In a population-based study in the Netherlands the proportion of patients with comorbidity varied from almost 40% in patients aged 50-64 years to more than 70% in those aged 80 years or older [80]. However, the proportion of patients undergoing surgery was not affected by comorbidity. Elderly patients constitute a heterogeneous group. Post-operative morbidity increases progressively with age, as well as the duration of hospital stay. An increasing frequency of thrombo-

embolism, respiratory and cardiovascular complications was reported in relation to age [224]. Some comorbid conditions at the time of diagnosis predict complications after surgery. This is particularly the case of chronic obstructive pulmonary disease and deep-vein thrombosis [225]. However, anastomotic leak rates were unchanged. Available population-based data indicate that the outcomes of surgery, even in the oldest age groups, can be good. It can be concluded that if an elderly patient is believed to be fit for surgery, then a standard surgical procedure with primary anastomosis can be tolerated without excessive risk of surgical complications.

Non-surgical treatments

Randomized controlled trials published in the 1990s established that 5-FU-based chemotherapy reduces the crude risk of colon cancer recurrence and mortality by as much as 10% [53]. These publications led to a progressive change in practices. In France, it took only 4 years in patients under 65, and 6 years in those aged 65-74, to reach almost optimum values (15). Although there was some improvement over time, few patients over the age of 75 received adjuvant chemotherapy for stage III colon cancer (24%, 1997-1998 period) (15). Data from Europe and Australia suggest that in the year 2000, only 20-25% of elderly patients received adjuvant chemotherapy (15-20), in comparison to 40-50% in the US (21-29) (Table 2). More frequent use of adjuvant chemotherapy in elderly patients would reduce death from colorectal cancer. Data from the SEER program suggested that, in patients older than 65 years old, treatment with 5-FU in node positive colon cancer was associated with a 34% reduction in mortality, a difference similar to that described in randomized studies (30). Elderly patients have been under-represented in clinical trials, so it can be difficult to determine whether the benefits shown among trial participants pertain to older patients. However, a review of 7 randomised trials indicated that the benefits of 5-FU-based chemotherapy in elderly people diminished only slightly with increasing age, and there was only a small increase in toxicity (in particular mucite) (31, 32). So, greater toxicity is an insufficient explanation for the decline in usage observed with advancing age. Elderly patients themselves may choose not to receive chemotherapy. However, when studied, older patients were just as likely as younger patients to accept chemotherapy, although after choosing to receive treatment they were less likely to accept major toxicity in exchange for added survival (33). Furthermore they have indicated that the primary determinant of their decision regarding chemotherapy was their physician's advice (34). The physician's attitude may explain the low utilisation of adjuvant chemotherapy, in particular in Europe.
Some elderly patients may be unsuitable for chemotherapy due to pre-existing comorbidity. In a US study among patients 75 to 84 years of age, 53% received chemotherapy in the absence of co-morbidity, 47% if there was one-comorbid condition and 37% if there were two (25) (Table 2). The corresponding percentages for patients aged 85 and older were 19%, 9% and 2%. In the Netherlands, 28% of patients aged 75 to 79 years old without comorbidity received adjuvant chemotherapy, compared to 15% of patients in this age group with comorbidity (16). However, despite

the fact that chronic conditions appear to be a strong barrier to the receipt of adjuvant chemotherapy, there is a paucity of studies that were able to link specific comorbid conditions to outcome for colorectal cancer. A recent cohort study did not find any between adjuvant chemotherapy and heart-failure, diabetes, and chronic pulmonary obstructive disease, regarding all-cause, condition-specific, or toxicity-related hospitalisation (28).

Table 2: Proportions of elderly stage III colon cancer patients treated with adjuvant chemotherapy; population-based data [a].

		Age group			Comorbidity score		
Author	**All cases (75+ y)**	**75-79 y**	**80-84 y**	**85+ y**	**0**	**1**	**2+**
Morris et al	17% [64%]	-	-	-	-	-	-
Phelip et al	18%	-	-	-	-	-	-
Faivre-Finn et al	24%	52%	10%	3%	-	-	-
Fietkau et al	29%	-	-	-	-	-	-
Lemmens et al	-	20%	-	-	28%	16%	15%
Potosky et al	35%	47%	24%		-	-	-
Schrag et al	38%	58%	34%	8%	-	-	-
Dobie et al	-	56% [74%][b]	30% [68%][c]	8% [65%][d]	59% [79%]	48% [77%]	47% [74%]
Sundararayan et al	52%	58%	32%	15%	59%	57%	33%
Ayanian et al	39%	48%		11%	53%[e] 19%[f]	47%[e] 9%[f]	37%[e] 2%[f]
Gross et al	-	63%[b]	38%[c]	11%[d]	69%	55%[g]	39%[h]
Neugut et al	-	54% [63%]	21% [51%][i]	-	56% [68%]	44% [61%]	39% [57%]
Cronin et al	52%	-	-	-	-	-	-
Jessup et al	-	69%[j]	39%		-	-	-
Bouchardy et al	13%[k]	-	-	-	-	-	-

[a] In square brackets: rate of adjuvant chemotherapy completion
[b] Age group 76-80 y
[c] Age group 81-85 y
[d] Age group 86+ y
[e] Age group 75-84 y
[f] Age group 85+ y
[g] 1-2 comorbid conditions
[h] 3+ comorbid conditions
[i] Age group 80+ y
[j] Age group 70-79 y
[k] Age group 70+ y

In view of the generally relatively low toxicity of chemotherapy in colon cancer and the increase in life expectancy, it can be concluded that a larger proportion of elderly patients, who are healthy enough to be operated on, could benefit from this treatment. The treatment decision for an individual patient should be based on the known benefit as opposed to the side effects and the impact on quality of life. In this context, discussion of the medical file within multidisciplinary consultancy meetings including a geriatrician is important. A recent survey in France indicated that multidisciplinary

consultancy meeting has yet to be fully developed, particularly for the elderly (35). The importance that patients place on the physician's opinion makes it imperative for clinicians to fully inform their patients of the potential benefit of chemotherapy.
Local recurrence, following curative resection for rectal cancer, remains a substantial problem. A population-based study has reported a 5-year local recurrence rate of 25% (1976-2000) (36). These results demonstrate the importance of effective adjuvant treatment in addition to surgery. Adjuvant radiotherapy for rectal cancer has been shown to reduce local recurrence, and preoperative radiotherapy was found to be more effective than postoperative radiotherapy. The effectiveness of preoperative radiotherapy has also been demonstrated after optimal surgery including total mesorectal excision (37).
Current guidelines for patients with rectal cancer include adjuvant or neoadjuvant radiotherapy. Some data are available on the practice of radiotherapy in the elderly at a population level. They indicate that elderly patients are being undertreated compared to younger patients: 35% vs 79% in Burgundy over the 1994-1996 period (38). There were some variations between countries: treatment among elderly patients stood at 36%-40% among SEER registries in the US (1992-1996 period) (25, 27, 39), 35% in France (1994-1996) (38), 36% in Germany (1999-2000) (20), and 20%-50% in the Netherlands (1980-2000, 2000-2004) (40-42, Lemmens, this thesis) (Table 3).

Table 3: Proportions of elderly stage I-III rectal cancer patients treated with pre- or postoperative radiotherapy; population-based data

Author	All cases (75+ y)	Age group 75-79 y	80-84 y	85+ y
Faivre-Finn et al	35%	35%	36%	34%
Fietkau et al	36%	-	-	-
Martijn et al	20%	-	-	-
Shahir et al	36%[a]	-	-	-
Vulto et al	-	55%[b,c]	23%	
Lemmens et al	-	58%[d]	42%	
Neugut et al	37%	48%	35%	17%
Ayanian et al	40%	47%	14%	
Cronin et al	36%	-	-	-

[a] Age group 70+ y
[b] Age group 65-79 y
[c] Declining from 65% in absence of comorbidity, to 45% in presence of 2 or more comorbid conditions
[d] Age group 70-79 y

In the US, adjuvant treatment consisted of postoperative radiotherapy administered concurrently with chemotherapy. In France and in the Netherlands, preoperative radiotherapy has become the standard treatment regimen. Although radiotherapy is not always indicated in elderly patients because of severe comorbidity, it has not reached full implementation in this age group. The need for transportation between the home and the few radiotherapy centres can limit its use for elderly patients, although this aspect seems to be less important for patients receiving short-course preoperative radiotherapy (5 x 5 Gray). It has also been shown that elderly patients who underwent

surgery plus operative radiotherapy develop more complications than patients undergoing surgery alone (especially pneumonia and cardiac complications). It is possible that after use of total mesorectal surgery, the added value of radiotherapy among the elderly is limited (41). In order to optimise the risk benefit ratio for elderly patients a comprehensive geriatric assessment is of critical importance.

Survival

In a review of the literature, postoperative mortality, i.e. mortality within 30 days of surgery, was 3 times higher in patients aged 75-84 and over 6 times more common in those aged 85 and over, compared with patients under 65 years of age (5). The increase in postoperative mortality with advancing age may be partly explained by comorbidity. An increasing frequency of respiratory, cardiovascular and tromboembolic complications has been reported in relation to age (9). However a steady reduction in operative mortality has been reported over time (43,44), even though it is still higher than in younger patients. This is all the more noticeable as the proportion of patients who were offered surgery has increased. This has been achieved by improvement in the perioperative management of elderly patients, through evaluation and preoperative correction of associated medical conditions and by improvement of postoperative resuscitation.
The 5-year mean relative survival rate for elderly patients, reported in the EUROCARE-3 study, covering the period 1990-1994 (45), was 43%, higher for colon cancer (46%) than for rectal cancer (39%). The rate was similar in males (43%) and in females (44%). It was lower in younger patients since the 5-year relative survival rate was 57% in patients under 45, and 51% in patients aged 65 to 74. A slight improvement in survival in elderly patients was reported in the EUROCARE study. For colon cancer, the 5-year relative survival rates were 40% (1983-1985) and 48% (1992-1994). The corresponding rates for rectal cancer were 35% and 40%. The gap that has separated younger from elderly patients is decreasing. In France, among patients over 80, 5-year relative survival rates for colon cancer increased from 27.0% (1978-1981) to 47.8% (1995-1997), and for rectal cancer from 18.1% to 41.7% (5). Also in the Netherlands a clear improvement in relative survival could be noted among these patients: from 39% (1975-1984) to 45% (2000-2004) for colon cancer, and from 29% to 49% for rectal cancer (Lemmens, personal communication). The improvement in survival can be attributed to the decrease in operative mortality and to the increase in proportion of patients resected for cure, which is associated with earlier diagnosis. The excess mortality rate is mainly observed during the first months after diagnosis (46, 47). The older persons who survive the first year have a prognosis similar to younger ones. Late diagnosis, and comorbidities or physiological impairment can explain an early prognostic disadvantage. These impose limits on the use of potentially curative treatment. Comorbidity was shown to be an independent prognostic factor (9). Previous malignancy, cardiovascular diseases, chronic obstructive pulmonary disease, hypertension and diabetes decreased 5-year survival. Comorbidity also led to less frequent use of adjuvant therapy, thus contributing to its impact on survival rates. In

contrast, older patients who are in good health, and who can undergo the same therapies as younger patients, have the same chances of survival.
There were also large variations in survival between countries among elderly patients (Table 4). Survival rates were dramatically lower in Eastern European countries compared to Western European countries (46). Stage at diagnosis remained the major determinant of prognosis. In Burgundy, the 5-year relative survival rate in elderly patients was 85% for stage I, 65% for stage II, 35% for stage III and 4% for stage IV (1991-2000). This is probably the major determinant of survival differences between countries. In a study involving three European cancer registries, differences in rectal cancer survival were no longer significant after adjusting for stage (48). It has also been shown that survival is related to the level of health investment (49). Effective diagnosis and conditions of treatment depend on macroeconomic determinants, including total national expenditure on health.

Table 4: 5-year relative survival rates for colon and rectum cancers in Europe (EUROCARE – 3 data)

	COLON		**RECTUM**	
	all ages	**≥ 75 y**	**all ages**	**≥ 75 y**
France	59	52	58	45
Switzerland	56	53	57	54
Netherlands	54	51	55	53
Sweden	53	53	55	48
Finland	54	51	51	43
Italy	53	45	49	36
Portugal	47	45	43	44
England	46	44	46	42
Denmark	46	43	44	35
Slovakia	43	41	31	19
Slovenia	40	31	36	28
Estonia	40	31	32	23
Poland	30	21	29	21

Conclusions

There is growing interest in the management of CRC in the elderly. Although improvements have been achieved, in particular an improvement in resection rate and a decrease in operative mortality, there is evidence that there is still room for

improvement in the use of adjuvant treatments. Comorbidities, which are particularly frequent in the elderly increase the complexity of cancer management and affect survival. The comprehensive geriatric assessment and multidisciplinary consultations need to be put in place to select those who can benefit from standard treatment.

Chapter 5.4

Comorbidity

As described in chapter 5.3, colorectal cancer affects a large number of people who, because of their age, are likely to have other chronic disabling, life-shortening conditions. This thesis showed that the proportion of Dutch patients with comorbidity varied from almost 40% among patients aged 50-64 years to more than 70% among those aged 80 or older (chapter 2.1). Using the registration of chronic conditions in the Eindhoven Cancer Registry (which required extensive training and validation), the most common concomitant conditions among all age groups together were cardiovascular diseases (15%), hypertension (13%), and previous malignancies (9%). Comorbidity did not influence the proportion of patients undergoing surgery for colorectal cancer. On the other hand, it did influence adjuvant treatment; the use of adjuvant chemotherapy in patients with stage III colon cancer was especially lower among patients with a previous malignancy and chronic obstructive pulmonary disease (COPD). Adjuvant radiotherapy among rectal cancer patients was negatively influenced by the presence of hypertension together with diabetes. From the treating physician point of view, the main reason for refraining from adjuvant therapy among these patients might be the perception of a short life-expectancy, or the fear of an increased risk of – potentially life-threatening- side effects/toxicity. However, one might argue why other serious concomitant diseases did not cause the physician to refrain from adjuvant treatment. There is yet no clear evidence to what degree it is beneficial or harmful for the patient with comorbidity to receive standard adjuvant treatment. These questions were not specifically addressed and therefore not answered by this thesis. More detailed information about the general condition of the patient, the seriousness and stage of the comorbid condition(s), treatment complications (prospectively), the exact reason why the physician chose not to treat certain patients, patient preferences, and social conditions has to be collected in order to provide any answer. In 2007, two 3-year projects funded by the Dutch Cancer Society will focus in the CCCS region on better implementation of new insights in daily treatments in this region served only by community hospitals, and on the differences that exist between patients older than 75 years treated and non-treated according to guidelines with respect to patient characteristics, complication rate, and recurrence free, progression free and cancer specific survival.

The results presented in chapter 2.3 justified the fact that comorbidity hardly affected colorectal cancer resection rates. There was no relation between comorbidity in general and surgical complications. It showed although that extra attention is needed for certain patients before, during, and after surgery: patients with COPD or deep vein thrombosis at time of cancer diagnosis were at higher risk of developing surgical complications.

The studies in this thesis also showed that comorbidity negatively affected survival of patients with colorectal cancer (chapters 2.1, 2.2, and 3.2). Colon cancer patients without comorbidity aged 65-79 years old had a 5-year overall survival rate of 55%, decreasing to 44% in presence of 1 comorbid condition, and to 38% in presence of 2 comorbid conditions. After adjustment for relevant patient and tumour characteristics, previous malignancies and COPD had the largest influence on survival. Among rectal cancer patients aged 65-79 years, the 5-year survival rate decreased from 33% for patients without comorbidity to 19% for patients with 2 or more concomitant conditions. COPD and hypertension had the largest impact on survival after adjustment for patient and tumour characteristics. It was shown that the adverse effects of increasing age and comorbidity on survival appeared to be independent of cancer treatment, so less aggressive treatment could not (fully) account for the observed differences in survival.

Comorbidity is a multidimensional variable, which means that diseases that affect life expectancy may not be the same as those influencing function or tolerance to treatment. Although there is general agreement on the prognostic importance of comorbidity, there is no consensus about the types of diseases that should be included, or about the weighing of the conditions. Several scales for measuring comorbidity have been developed and validated. The most commonly used comorbidity indices are the Charlson Comorbidity index, the cumulative index rating scale, and the Kaplan-Feinstein index. [72, 78, 226-228] When measuring comorbidity, the scale should be carefully chosen, because the prevalence of comorbidity varies qualitatively and quantitatively between different scales. For example, in a lung cancer study comorbidity influenced survival when measured with the cumulative index rating scale but not with the Charlson scale.[226] The Charlson scale is a relatively restrictive way to assess comorbidity, and may result in underestimation of prevalence of (less severe?) comorbidity. Recently, the Adult Comorbidity Evaluation-27 (ACE-27) was developed, based on previous classification systems, especially the Kaplan-Feinstein Index. [78, 227] This index has been validated and has been shown to discriminate expected complications and survival in elderly cancer patients. [73] In some recent studies this comorbidity index has shown to discriminate expected complications and prognosis in elderly patients. [78, 229-233] Until now, elderly are often not included in clinical trials, and evidence-based guidelines are often based on results of treatment in middle-aged patients without serious comorbidity. [140, 234, 235] Forthcoming studies will have to describe treatment difficulties and outcome in unselected elderly patients, to indicate whether it is reasonable to extend the present treatment guidelines to the elderly, and to indicate relevant subgroups for which prospective clinical trials can be initiated.

Chapter 5.5

Guideline adherence and variation

Promoted by concerns regarding practice variations, the standard of care for colorectal cancer in the Netherlands is formulated in clinical practice guidelines since the mid 1990s. Clinical practice guidelines are defined as 'systematically developed statements to assist both practitioner and patient decisions about appropriate health care for specific clinical circumstances' [125]. Recommendations in guidelines are not always followed; this was well documented by several studies presented in this thesis (chapters 3.1, 3.2 and 3.3).

There might be well established 'good' clinical reasons to refrain from adjuvant chemotherapy in case of severe comorbidity (chapters 3.1, 3.2, and 3.3). This thesis however also showed that females and patients with a low socio-economic status received less often adjuvant chemotherapy than their counterparts, even after adjustment for age and comorbidity. Possible reasons for this were described in chapter 3.2. At first sight, there seems to be no clinical reason for this undertreatment. However, maybe the lack of a supportive partner among elderly women makes the choice for not treating her with adjuvant chemotherapy the right one; patients with a low socio-economic status might cope less well with the effects of chemotherapy [63, 69, 161, 162]. Furthermore, patient preferences were not taken into account, while these may be of significant importance. Among rectal cancer patients, there were large differences between hospitals in the rate of referral for radiotherapy (Cox S et al, submitted for publication). Here, a remarkable difference could be observed between the east part and the west part of the CCCS region, although this has decreased over time. Nevertheless, this suggests that clinical 'tradition' can still play a large role within medical practice.

The central question remains: when is deviance from standard treatment guidelines inferior clinical practice, and when does this reflect good quality of care? Individualisation of treatment, especially among older cancer patients, is often considered to be beneficial. In many instances this might lead to an alternative treatment or even withholding treatment. If this prevents treatment related complications without exposing the patient to a disproportionate risk of tumour recurrence or death, this might be considered good quality of care.

For rectal cancer, it is argued that preoperative radiotherapy may be omitted in patients with perfect mesorectal excision [236]. However, results from the CRO7 trial show that even with perfect surgery there is added value of preoperative radiotherapy [237]. An ongoing Scandinavian study investigates the effect of delaying surgery after a short course of radiotherapy [238]. The study goal is to see whether delay leads to downsizing and staging for the tumour. It could be that after a waiting period of 6-12 weeks the patient recovers from the radiotherapy and avoids the double jeopardy of

radiotherapy and a major surgical trauma. Nutritional, metabolic, cardiac, or pulmonary disorders may be optimised in the waiting period. In the study described in chapter 2.2, we also found significantly less complications among patients who, for any reason, had a longer interval between end of radiotherapy and surgery (subgroup analysis of small sample of patients, therefore these results were not shown in chapter 2.2).
The dogma for diagnosis of colorectal cancer is the same as it is for treatment: when does deviating from standard guidelines reflect diminished quality of care, or when does it reflect the opposite? For example, this thesis showed that the proportion of colon cancer patients who underwent a complete colonoscopy amounted to only 60% (chapter 3.1). However, often there were good reasons not to perform pancolonoscopy; for example serious discomfort as indicated by the patient, and the inability to pass a malignant structure. The latter was confirmed by our finding that especially patients with larger, more penetrating tumours underwent less often a full colonoscopy. A recent study suggested a large variation in practice between gastroenterologists, reason why in 2007 in the CCCS region a study will be performed to investigate variation in colonoscopy practice [239].
This thesis revealed low adherence to treatment guidelines concerning lymph node examination (chapter 3.3). In the present guidelines, a minimum of 12 examined nodes is required for adequate staging. A median number of 6 nodes was examined among patients with stage I-III colon carcinoma in the period 1999-2002 in the CCCS region. This median number ranged from 3 to 8 between the six departments of pathology in the region. After correction for relevant patients and tumour characteristics, this variation remained, and led to significant differences in stage distribution between the departments. A higher yield of lymph nodes was correlated with improved survival, and indeed survival was worse for patients who had their lymph nodes examined in the departments of pathology with the lowest median number of nodes examined. There may be substantial inter-individual variation concerning the number of lymph nodes that can be found, depending on i.e. tumour site, neoadjuvant treatment, and the immune response [147, 167, 183]. For the latter, we could not control in our analyses, but it is highly unlikely that there are geographically differential patterns in this respect within the CCCS region. Therefore, the variation had to be due to the either the thoroughness of the surgical lymphadenectomy, and/or the diligence of the pathologist's examination. Our study indicated that the diligence of the pathologist's examination probably contributed more strongly to both the low number of examined nodes and the variation between the departments. This was supported by the interesting finding that there was no difference in the number of lymph nodes examined between the hospitals covered by one and the same department of pathology, while there was a significant difference in the number of nodes between two departments of pathology serving one and the same hospital within the study period. Although lymph node examination partly explained survival differences between the various departments, differences –not related to nodal evaluation- remained. This indicates that other relevant clinical features differ between institutions, in addition to the determinants we assessed in our analyses.

In one of the Dutch National Cancer Society projects starting in 2007, surgical procedures for colon cancer will be recorded in detail, together with the implementation of a method for improving the lymph node yield. This method, developed by dr. Rutten (surgeon, Catharina Hospital Eindhoven) and dr. van Lijnschoten (pathologist, PAMM), consists of 3 key points: firstly, injection of 0.5cc of blue dye by the surgeon into the mesocolon (ex vivo!), without opening the specimen; secondly, fixation in formalin for 48 hours instead of the commonly used 24 hours; and thirdly, opening the specimen by transverse slicing, according to the method described by Quirke [240]. The results of a pilot study in 4 hospitals during spring and summer 2007 already showed a dramatically increased yield of lymph nodes, without increasing procedure time for the pathologist. Implementation of this method on a wide scale would ensure adequate nodal staging of colon cancer patients. There might however also be other approaches to enhance lymph node examination [174, 241, 242]. In the new, evidence-based colon cancer treatment guidelines, high-risk stage II colon cancer patients are considered eligible for adjuvant chemotherapy. High-risk comprises patients with non-adequate lymph node sampling (less than 10), T4 tumours, and/or poorly differentiated tumours. In the present situation, this would mean that the majority of stage II patients would indeed have to receive adjuvant chemotherapy. By increasing the proportion of patients who were adequately staged, for example by using the new method described above, many patients (about 20%) do not unnecessarily have to go through treatment with chemotherapy. This even gains importance in view of the new, and, although effective, expensive chemotherapeutics.

Chapter 5.6

Future perspectives

Prevention and screening

As shown in chapter 1, a large range of risk factors is described in literature. Besides modifications in life-style, which requires large changes in the individuals' behaviour and the Western societal environment in general, several nutrients and chemopreventive agents have been subject of study. Promising are vitamin D and calcium, and Cox-2 inhibitors, such as certain non-steroidal anti-inflammatory drugs [28, 243-245]. For the first two, fortification of foods might be a safe and effective option to increase daily amounts ingested, but regarding COX-2 inhibitors it will be first necessary to identify inhibitors with lower risks of cardiovascular adverse effects [246]. Prognostic molecular signatures of individuals at high risk of developing colorectal cancer and predictive markers of response to preventive agents have to be addressed in further studies [247].

It has been estimated that widespread application of screening technologies that address the whole colon could decrease colorectal cancer incidence by as much as 60% to 70% and reduce colorectal cancer deaths by up to 80% [247]. Varying levels of clinical evidence exist for the effectiveness of available colorectal cancer screening options, and most guidelines offer a panel of acceptable screening options including fecal occult blood testing, sigmoidoscopy, and colonoscopy. The question is when, and using which (combination of) screening instrument(s), mass screening for colorectal cancer will be implemented in the Netherlands. This will also depend on the outcome of three large trials which are now underway in the Netherlands. However, raising awareness among both health care professionals and members of the general public about the fact that colorectal cancer can be prevented or detected early remains a crucial goal. Moreover, endoscopy capacity will have to be increased.

To circumvent the invasiveness, time, and cost of colonoscopy, several techniques have been developed including computed tomography (CT) and colography (virtual colonoscopy). Virtual colonoscopy has been shown to be safe and well tolerated by patients [247]. Indications for virtual colonoscopy include screening for polyps, incomplete or failed colonoscopy, and preoperative assessment of the colon proximal to an obstructive cancer that cannot be endoscopically traversed. Virtual colonoscopy may increase patient participation in screening programs, leading to early diagnosis of colorectal cancer. Although virtual colonoscopy seems a potentially attractive screening method for colorectal cancer, its cost-effectiveness is yet to be determined [248]. Other emerging technologies for colorectal cancer screening include fecal immunochemical testing, stool DNA mutational analysis, and proteomic analysis of serum [247].

Encouraging the rapid evaluation of new approaches to colorectal cancer screening at different levels are important research goals for the near future.

Diagnostics and staging

In colorectal cancer, methylation likely represents a third disease pathway in addition to the established genetic pathways of chromosomal and microsatellite instability [247, 249-251]. One form of epigenetic methylation that has been shown to have a potential role in risk evaluation and stratification is loss of imprinting, an epigenetic form of gene silencing that occurs in the gamete and results in hemizygosity and decreased gene expression. It was reported that loss of imprinting of *IGF2* occurred in greater percentages of colorectal adenoma and cancer patients compared with controls [252]. Epigenetic markers also show considerable promise and should be considered in addition to genetic and proteomic markers in studies of colorectal cancer risk and progression [247].

As long as conventional detection is the norm, it will be of utmost importance to increase adequacy of lymph node examination for adequate staging of colon cancer, for example by the method described in chapter 5.5. This peri-operative staging may also be of relevance in rectal cancer, but staging in rectal cancer is of at least equal importance in the preoperative setting. Magnetic resonance imaging (MRI) has the best overall results, with better imaging of the circumferential resection margin compared to sonography and CT [253]. There are no clear differences between MRI, CT, and sonography concerning preoperative lymph node staging [254]. Further advances in staging may be achieved with novel magnetic resonance contrast agents (such as superparamagnetic iron oxide particles) and positron emission tomography scanning [247].

Treatment

In a recent review including stage II colon cancer patients, adjuvant FU therapy was associated with a disease-free survival benefit, but the benefit was small and not necessarily associated with improved overall survival [255]. In another study, adding oxaliplatin to infusional FU plus leucovorin (FOLFOX4) resulted in an advantage in disease-free survival for stage II patients that was comparable to that in stage III patients compared with the use of FU plus leucovorin alone [256]. Despite these results, surgery alone remains the primary option of treatment until better techniques of identifying high-risk stage II patients are developed.

Promising strategies for further improvement of treatment of stage III colon cancer, besides the addition of oxaliplatin which is already considered standard in the Netherlands, are targeted therapies with monoclonal antibodies bevacizumab or cetuximab. It will be of high importance to develop genetic markers that will be able to predict response to chemotherapy, such as thymidylate synthase [257].

As said, surgical resection will undoubtedly remain the cornerstone of colorectal cancer treatment. One of the main changes in colon cancer surgery will be the more widespread use of laparoscopic surgery, which has been proven to be safe in a recent meta-analysis [258]. Total mesorectal excision is likely to remain the basis of rectal cancer management. Accurate radiological staging, optimal surgery and detailed histopathological assessment together with consideration of a preoperative adjuvant strategy will remain the basis for current treatment and future research in rectal cancer [259].

Elderly

We are still unable to discern fully from current evidence why doctors chose not to treat their patients or why patients chose not to be treated or to discontinue treatment. Treatment decisions will have to be individualized to fit the needs of each older patient as much as possible. In the adjuvant setting, even the reduction in the risk of cancer recurrence offered by chemotherapy may not be as important to older patients as their quality of life. Despite a growing body of data, a lot of work is still needed to establish optimal strategies to care for patients diagnosed with cancer later in life [206]. It is also important to our understanding of how to communicate risk and benefit to older patients and their families (de Vries M. et al, Eur J Cancer, in press).

Chapter 5.7

Concluding remarks

In this thesis we gave an overview of clinical epidemiology of colorectal cancer in the in the South of the Netherlands, covering a period of more than 40 years. We could demonstrate large increases in incidence and improvements in management and survival of colorectal cancer patients. Progress can however still be made, especially regarding management of older patients, early detection and staging of colorectal cancer.

Many aspects of the clinical epidemiology of colorectal cancer were only marginally or not at all discussed in this thesis. Stage IV colorectal cancer, intra-operative radiation, laparoscopic surgery, transanal microscopic microsurgery, management of familial cancer, quality-of-life-related issues, stoma care, and many more items were not addressed or shed insufficient light on. Among others, a broad coalition of forces and a higher awareness of colorectal cancer in the population are necessary. This means that, although this thesis is finished now, the work continues. Besides further work on the issues described in this thesis, priorities include studies on early detection, diagnosis (involve family doctors), treatment of recurrences and metastases, and palliative care.

Summary

This thesis presented studies on different aspects of the clinical epidemiology of colorectal cancer in the south of the Netherlands, with an emphasis on elderly cancer patients. The Eindhoven Cancer Registry (ECR) was used as the main data source.

The influence of age and comorbidity on clinical care of colorectal cancer was described in chapter 2.1. The prevalence of comorbid conditions increased with age. Of patients aged 50 to 64 years, 29% had 1 comorbid disease, compared to 35% of patients aged 65 to 79 years, and 34% of patients over the age of 80. Fourteen percent of patients aged 50 to 64 years old suffered of 2 or more comorbid conditions, compared to 29% of patients aged 65 to 79, and 37% of patients older than 80 years. For all age groups the most frequent single concomitant diseases were hypertension (9% of patients, however decreasing with age), previous malignancy (7%, increasing with age) and cardiovascular disease (6%, increasing with age). The most frequent combination of comorbid conditions was cardiovascular disease plus hypertension (3%).
Age and comorbidity did not influence resection rates, but clearly decreased the proportion of patients receiving adjuvant therapy, even after controlling for relevant factors. Five-year survival was largely influenced by comorbidity. Crude 5-year survival rates for patients with colon carcinoma aged 65 to 79 years old decreased from 55% among patients without comorbidity, to 44% among patients with one comorbid condition, and to 38% among patients with 2 or more concomitant diseases. For patients with rectal carcinoma, 5-year survival decreased from 54%, to 44%, and to 33%, respectively. Also after controlling for other prognostic factors such as age, stage, and treatment, the influence of comorbidity on survival remained. Previous malignancy, cardiovascular disease and COPD had the largest impact on survival.

In a previous ECR study it was shown that survival of rectal cancer patients had been improving between 1980 and 2000, but that this improvement was restricted to patients younger than 75 years. The goal of the study presented in chapter 2.2 was to investigate whether the absence of improvement in the elderly was related to a higher complication rate.
Of stage I-III patients aged 70 or older, 36% underwent adjuvant radiotherapy, compared to 49% of patients aged 60 to 69. Fifty-one percent of patients aged 60-69 years old had any complication within one year of diagnosis compared to 65% of patients aged 70 or older. Elderly suffered more from cardiac complications and pneumonia. The presence of comorbidity also increased the risk of complications, especially among patients older than 70. Compared to patients who received surgery alone, the risk of developing complications was larger among those treated with adjuvant radiotherapy. Local recurrence rate did however not differ between those who were operated on with or without adjuvant radiotherapy. In a multivariable analysis, age, comorbidity, and the presence of 2 or more complications had a negative impact on survival.
Elderly had a relatively higher risk of complications, which may partly explain the status quo in survival among elderly rectal cancer patients.

An accurate preoperative assessment is important, especially in view of the growing proportion of elderly patients. In chapter 2.3 the influence of specific comorbid conditions on the development of postoperative surgical complications was investigated among stage I-III colorectal carcinoma patients.
Older patients, patients with a tumour located in the rectum, and patients operated on in an emergency setting more often developed postoperative complications. The presence of COPD at time of cancer diagnosis among patients with colon carcinoma increased the risk of developing a pneumonia (18% vs. 2%) or haemorrhage (9% vs. 1%) postoperatively compared to patients who did not have any comorbidity. Patients with a tumour located in the rectum who suffered from COPD more frequently had any surgical complication (73% vs. 46%). Although the number of patients with deep vein thrombosis (DVT) at time of cancer diagnosis was relatively small (N=15), it seemed to lead to an increased frequency of postoperative complications.
This study showed that especially among patients with preoperative COPD or probably also DVT extra attention has to be paid to preventing and anticipating surgical complications.

In chapter 3.1 the level of adherence to clinical guidelines for colorectal cancer in the ECR region in 2002 was investigated. Adherence to guidelines was determined for diagnostic assessment, pathology, and treatment.
Surgical procedures and referral for preoperative radiotherapy were carried out largely conform the recommendations. Although all patients should undergo a complete colonoscopy according to the guidelines, the number of performed colonoscopies among colon cancer patients amounted up to only 60%; contrast enemas after incomplete colonoscopy were performed in only 27% of patients. The median number of examined lymph nodes was only six for patients with colon cancer and five for rectal cancer, while a minimum number of 12 was mentioned in the guidelines. The administration of adjuvant chemotherapy for patients with stage III colon cancer decreased from 95% of patients younger than 70 years to 48% of patients over 70. Adherence to clinical guidelines was not optimal, although in some cases there were apparent reasons to deviate from guidelines, such as not performing a complete colonoscopy in case of patient discomfort or in presence of a malignant structure in the bowel. Especially nodal assessment and adjuvant treatment among older patients have to be studied in more detail to reveal reasons for non-compliance.

In relation with the results presented in the previous chapter, the determinants of receiving adjuvant chemotherapy among stage III colon carcinoma patients aged 65 to 79 years old were examined in chapter 3.2, including their influence on survival.
The proportion of elderly patients receiving adjuvant chemotherapy increased from 19% in 1995 to 50% in 2001, but large inter-hospital variation remained. In a multivariable analysis, females, patients with comorbidity, and patients with a low socio-economic status (SES) had a lower chance of receiving adjuvant chemotherapy. The fact that older patients or patients with comorbidity were treated less often with adjuvant chemotherapy might be due to uncertainty on the side of the treating physician about the risk-benefit ratio of adjuvant treatment in those patients. There seems to be however no obvious rationale for the undertreatment of women and patients with a low SES. Previous studies reported that older women are more prone to decline adjuvant chemotherapy when offered, but unfortunately we did not have data on patient preferences. Patients with a low SES might communicate in a less assertive

way with their physician, and have a lower self-rated health, which may all affect clinical decision making.
Even after adjustment for adjuvant chemotherapy, there was a clear improvement in survival for stage III colon carcinoma patients between 1995 and 2001, which may point at other improvements besides the increased treatment with adjuvant chemotherapy. Patients treated with adjuvant chemotherapy had a better survival than patients who did not receive this treatment; however, even after adjusting for comorbidity and age, there still might be a bias due to selection of the 'fitter' patient by the treating physician. Unfortunately, we did not have information on the performance status of the patient.

Also chapter 3.3 was based on the study described in chapter 3.1. An adequate lymph node examination is important for correct staging. The factors influencing lymph node examination and survival were studied among stage I-III colon carcinoma patients diagnosed between 1999 and 2002.
A median number of 6 lymph nodes was examined, while the guidelines in that period mentioned a minimum number of 12. There was a large variation between the pathology departments in the number of examined nodes, ranging from a median number of 3 to 8. The number of examined nodes also depended on age, comorbidity, tumour localisation, tumour size, and nodal status. After adjustment for these variables, the variation between the departments of pathology remained. This variation led to differences in stage distribution, which was correlated with the number of examined nodes. Patients who had more lymph nodes evaluated had a better 5-year survival.
Future research has to demonstrate whether the low number of examined nodes, including the variation between the departments, persists. Probably, new methods for nodal detection should be implemented which enables the pathologist to increase the yield of nodal examination.

In chapter 4.1 the clinical and epidemiological trends in colorectal cancer in the ECR region from 1975 to 2004 were described. Large changes have taken place in this period. First of all, there has been a gradual increase in incidence, which was most marked for males and proximal tumours. Furthermore, survival increased dramatically, especially among patients younger than 70 years. This was at least partly due changes in treatment; particularly, since the mid-1990s, a growing proportion of patients underwent adjuvant chemo- or radiotherapy. Also large changes in rectal cancer surgery took place. The advances in survival led in turn to decreased mortality rates, and consequently to increased prevalence rates. An increase in stage III patients suggested improved nodal staging procedures over time, but there was no evidence that patients diagnosed more recently were diagnosed at an earlier stage of the disease (I or II).
The results of this study showed that the workload of all clinicians involved will keep increasing considerably in the near future. The steady increase in age-adjusted incidence, the demographic changes in the Dutch population and the likely future implementation of colorectal cancer mass screening will necessitate investments related to education, recruitment, materials and infrastructure. In many other European countries, the situation is presumably the same. Nevertheless, this study demonstrated large improvements in management and survival of patients with colorectal cancer between 1975 and 2004.

In chapter 5, the results presented in this thesis were commented, and some questions which were not answered within this thesis were discussed. The future perspectives of a number of aspects of the clinical epidemiology of colorectal cancer were reviewed.

The overall conclusion of this thesis is that age and comorbidity are important predictors of treatment and outcome of colorectal cancer. Patients with comorbidity are treated less aggressively and have a dismal prognosis, which is only partly explained by the less aggressive treatment. Although large improvements could be noted in survival, there remains room for improvement in view of the inter-institutional variation regarding staging and treatment.

Samenvatting

Dit proefschrift beschrijft de klinische epidemiologie van dikkedarmkanker in Nederland, met een nadruk op de oudere patiënt. Voor alle studies werd gebruikgemaakt van de Kankerregistratie van het Integraal Kankercentrum Zuid (IKZ) te Eindhoven. De hoofdvragen waren: a) welke factoren zijn van invloed op behandeling, complicaties van behandeling, en overleving van dikkedarmkanker, met de nadruk op de oudere patiënt? b) in hoeverre heeft de behandeling van dikkedarmkanker plaatsgevonden volgens de richtlijnen, en bestond er variatie tussen de ziekenhuizen? en c) wat waren de trends in vóórkomen, behandeling, stadiumverdeling, en overleving van dikkedarmkanker in de IKZ-regio?

Voor een goed begrip: met coloncarcinoom wordt een tumor in het eerste 2/3de deel van de dikke darm bedoeld, met rectumcarcinoom of endeldarmkanker een tumor in het laatste 1/3de deel van de dikke darm. Indien gesproken wordt over dikkedarmkanker, wordt de gehele darm (colon plus rectum) bedoeld.

In hoofdstuk 2.1 werd het vóórkomen van potentieel ernstige co-morbiditeit (bijkomende ziekten naast de kanker) bij patiënten met dikkedarmkanker beschreven. Er is een duidelijke toename van co-morbiditeit met een stijgende leeftijd; bij patiënten van 50 tot en met 64 jaar heeft 45% co-morbiditeit, bij patiënten van 80 jaar en ouder is dit al ruim 70%. De meest voorkomende co-morbiditeit is hoge bloeddruk, gevolgd door een eerdere kwaadaardige tumor, en hart- en vaatziekten. Co-morbiditeit was, evenals leeftijd, van invloed op de adjuvante behandeling van dikkedarmkanker-patiënten. Bij patiënten met stadium III (patiënten met uitzaaiingen in de lymfeklieren) coloncarcinoom ontvingen vooral zij met eerdere tumoren of chronisch obstructieve longziekte (COPD) minder vaak chemotherapie na de operatie (adjuvante chemotherapie). Patiënten met een rectumcarcinoom ondergingen minder vaak adjuvante radiotherapie in aanwezigheid van co-morbiditeit. Naast de aanwezigheid van co-morbiditeit verkleinde ook hogere leeftijd de kans op adjuvante behandeling. De overleving van patiënten met co-morbiditeit was slechter dan die van patiënten zonder co-morbiditeit. De ruwe 5-jaarsoverleving voor patiënten met coloncarcinoom in de leeftijd van 65 tot en met 79 jaar nam af van 55% voor patiënten zonder bijkomende ziekten tot 38% voor patiënten met 2 of meer bijkomende ziekten; voor patiënten met een rectumcarcinoom nam dit af tot 33%.

In een eerdere studie van het IKZ is beschreven dat de overleving voor patiënten met een rectumcarcinoom aanzienlijk is toegenomen tussen 1980 en 2000, met uitzondering van patiënten ouder dan 75 jaar. In hoofdstuk 2.2 werd nagegaan of leeftijd en co-morbiditeit van invloed waren op de effectiviteit van behandeling. Hoewel patiënten ouder dan 70 jaar weliswaar minder vaak verwezen werden voor adjuvante radiotherapie, bleek deze behandeling gepaard te gaan met een grotere kans op complicaties bij deze ouderen ten opzichte van chirurgie zonder radiotherapie. Ook de aanwezigheid van co-morbiditeit en een hogere leeftijd vergrootten de kans op het ontwikkelen van complicaties. Het percentage lokale recidieven bleek niet groter in de groep bestraalde patiënten dan in de groep patiënten welke alleen geopereerd werden.

Een hogere leeftijd, co-morbiditeit, en het optreden van 2 of meer complicaties ging gepaard met een hogere sterftekans.
Ouderen bleken dus vaker behandelingsgerelateerde complicaties te ontwikkelen dan jongere patiënten, hetgeen voor een deel het uitblijven van verbeteringen in prognose zou kunnen verklaren.

De preoperatieve beoordeling van het risico op postoperatieve chirurgische complicaties is van groot belang, juist in de groeiende groep oudere patiënten. In hoofdstuk 2.3 werd middels statusonderzoek bij dikkedarmkankerpatiënten (exclusief patiënten met uitzaaiingen op afstand) bepaald welke specifieke bijkomende ziekten van invloed waren op het optreden van postoperatieve complicaties. De aanwezigheid van COPD op het moment van diagnose bleek de kans op postoperatieve pneumonie en bloedingen bij patiënten met een coloncarcinoom te verhogen. Bij patiënten met een rectumcarcinoom en COPD kwamen complicaties in het algemeen vaker voor. Verder nam het risico op postoperatieve complicaties toe bij aanwezigheid van diep veneuze trombose (DVT) op het moment van diagnose, hoewel het hier slechts om een klein aantal patiënten ging (N=15).
De resultaten van dit onderzoek laten zien dat men vooral bij patiënten met preoperatieve COPD en mogelijk bij DVT in verhoogde mate alert moet zijn op chirurgische complicaties, en waar mogelijk deze complicaties trachten te voorkomen.

In hoofdstuk 3.1 werd nagegaan in hoeverre de behandelingsrichtlijnen voor dikkedarmkanker in 2002 werden opgevolgd in de IKZ-regio. Er werd onderscheid gemaakt tussen diagnostiek, behandeling, en pathologie.
Chirurgische procedures (voor zover na te gaan in het medisch dossier), en verwijzing voor radiotherapie gebeurden grotendeels in overeenstemming met de richtlijnen. Hoewel de richtlijn complete colonoscopie voorschrijft, werd dit bij 40% niet gedaan, echter vaak met goede redenen zoals discomfort bij de patiënt of een obstruerende tumor. Adjuvante chemotherapie werd, zoals ook al gezien in hoofdstuk 2.1, minder vaak voorgeschreven bij oudere patiënten met een stadium III coloncarcinoom. Een belangrijke bevinding was dat het mediaan aantal onderzochte lymfeklieren bedroeg 6 voor patiënten met een coloncarcinoom, en 5 voor patiënten met een rectumcarcinoom, terwijl de richtlijn een minimum van 12 voorschrijft.
Het merendeel van de procedures werd conform de richtlijn uitgevoerd; indien hiervan af werd geweken waren daar vaak goede redenen voor. Echter, het minder vaak toepassen van adjuvante behandeling bij ouderen dient nader onder de loep genomen te worden (zie hoofdstuk 3.2). Ook een hernieuwde evaluatie van het lymfeklieronderzoek is gewenst (zie hoofdstuk 3.3).

Op basis van de in hoofdstuk 3.1 beschreven bevindingen, werd in hoofdstuk 3.2 onderzocht welke factoren van invloed zijn op het al dan niet ontvangen van adjuvante chemotherapie bij stadium III coloncarcinoom, en in hoeverre deze factoren samenhangen met overleving. Data van patiënten in de leeftijd van 65 tot en met 79 jaar, gediagnosticeerd tussen 1995 en 2001 in de IKZ-regio werden hiervoor gebruikt. Tussen 1995 en 2001 was er een toename in behandeling van 19% tot 50%. Er was echter een behoorlijke variatie tussen de ziekenhuizen, zelfs nog in 2001. De resultaten van een multivariabele analyse lieten zien dat behalve patiënten met een hogere leeftijd en co-morbiditeit, ook vrouwelijke patiënten (ten opzichte van mannen) en patiënten met een lage sociaal-economische status (SES) (ten opzichte van patiënten met een hoge SES) minder vaak adjuvante chemotherapie kregen. Voor deze laatste

bevindingen lijkt er geen voor de hand liggende verklaring te zijn. Echter, uit de literatuur blijkt dat oudere – vaker alleenstaande- vrouwen vaker adjuvante chemotherapie weigeren, maar helaas hadden we in deze studie geen informatie over patiëntvoorkeuren. Patiënten met een lagere SES communiceren wellicht minder assertief met de behandelende arts, en beoordelen de eigen gezondheid vaak slechter, wat vervolgens weer op de klinische beslissing van invloed kan zijn. Het minder vaak behandelen van patiënten met hoge leeftijd of co-morbiditeit lijkt te wijzen op onzekerheid bij de behandelende arts met betrekking tot de gunsten-baten verhouding van adjuvante behandeling in deze groep.
De overleving voor patiënten met een stadium III coloncarcinoom steeg tussen 1995 en 2001, zelfs na correctie voor de toename in gebruik van adjuvante chemotherapie. Dit duidt erop dat behalve de toegenomen adjuvante behandeling ook op andere vlakken verbeteringen optraden. Patiënten die chemotherapie ondergingen hadden ten opzichte van patiënten die alleen geopereerd werden een gunstigere overleving, ook wanneer rekening werd gehouden met leeftijd en co-morbiditeit; dit is waarschijnlijk voor een deel te verklaren door het feit dat de behandelende arts bij een 'fittere' patiënt eerder geneigd zal zijn om deze chemotherapie toe te dienen. Helaas ontbrak de mogelijkheid om de functionele status van de patiënt in dit onderzoek mee te nemen.

Ook hoofdstuk 3.3 heeft de bevindingen van hoofdstuk 3.1 als uitgangspunt, namelijk het lage aantal onderzochte lymfeklieren bij coloncarcinoom. Een adequaat lymfklieronderzoek, met een voldoende aantal klieren, is van belang om het juiste stadium van de tumor vast te stellen. Dat laatste is dan weer van invloed op de behandelingskeuze. In de literatuur is ook een relatie met overleving aangetoond. De tijdens de studieperiode (1999-2002) geldende richtlijn ging uit van een minimum aantal van 12 klieren. Of dit aantal wordt gehaald is van vele factoren afhankelijk, maar is in ieder geval afhankelijk van zowel de chirurg, die voldoende lymfeklieren moet wegsnijden en aanleveren bij de patholoog, en laatstgenoemde die de lymfeklieren in het resectiepreparaat moet vinden en onderzoeken op aanwezigheid van eventuele uitzaaiingen van de tumor. In de hier beschreven studie werd bij stadium I-III coloncarcinoom-patiënten bestudeerd welke factoren van invloed waren op het aantal onderzochte lymfeklieren, en of er een relatie tussen deze factoren en de 5-jaarsoverleving kon worden aangetoond.
Er bleek variatie te bestaan tussen de 6 pathologielaboratoria (PA-labs) in de IKZ-regio; het mediaan aantal onderzochte klieren varieerde tussen 3 en 8. Het aantal onderzochte klieren was ook afhankelijk van leeftijd, geslacht, co-morbiditeit, tumorlokalisatie, tumorgrootte, en klierstatus. De variatie tussen de PA-labs bleek niet te verklaren door verschillen in een van deze factoren . Deze variatie vertaalde zich ook in een verschil in stadiumverdeling tussen de PA-labs, hetgeen gecorreleerd was met het aantal onderzochte lymfeklieren. Patiënten met een groter aantal onderzochte klieren hadden een betere overleving.
Vervolgstudies zullen kunnen aantonen of deze variatie in en de lage opbrengst van lymfeklieronderzoek bleef bestaan. Het ligt voor de hand om nieuwe methoden toe te passen welke de patholoog in staat stelt meer klieren te detecteren en te onderzoeken, zonder evenredige verhoging van de werklast.

In hoofdstuk 4.1 werden de klinische en epidemiologische trends in het zuiden van Nederland (de IKZ-regio) van de afgelopen 30 jaar beschreven (1975-2004). Er deden zich in deze periode grote veranderingen voor; zo was er een forse toename in het

vóórkomen van dikkedarmkanker, met name bij mannen. Dikkedarmkanker bevond zich steeds vaker in het begin (het opstijgend deel) van de dikke darm. Verder was er een verbetering in overleving; deze was het grootst bij rectumcarcinoom en stadium III coloncarcinoom. Hieraan gingen veranderingen in de behandeling vooraf, zoals de reeds uitgebreid beschreven adjuvante chemotherapie bij stadium III coloncarcinoom, de verschuiving van post- naar preoperatieve radiotherapie bij rectumcarcinoom, de introductie van nieuwe chirurgische technieken als de Total Mesorectal Excision (TME). In feite was de verbetering in overleving van rectumcarcinoom de meest aanzienlijke van alle tumoren. De stijging in zowel incidentie als overleving leidde ertoe dat de prevalentie (het aantal patiënten in leven dat ooit is gediagnosticeerd met de ziekte) gestaag toenam.
Een degelijke beschrijving van veranderingen in risico en prognose, waarvoor de data van de Kankerregistratie van het IKZ zeer geschikt zijn, kan aanwijzingen geven over de invloed van veranderingen in leefstijl, stagering en behandeling. Ook kan het, door middel van bijvoorbeeld het aantonen van variatie in diagnostiek en behandeling, demonstreren waar nog verbetering te behalen valt. Het kan al met al ook zeer behulpzaam zijn bij het anticiperen op de ontwikkelingen in de nabije toekomst.

In hoofdstuk 5 werden de resultaten zoals beschreven in dit proefschrift bediscussieerd, en werd ingegaan op enkele nog niet beantwoorde vragen, evenals een bespreking van een aantal toekomstige klinische aspecten.

Concluderend: leeftijd en co-morbiditeit bleken belangrijke voorspellers van behandeling en behandelingsuitkomst. Patiënten met co-morbiditeit werden minder agressief behandeld, en hebben een slechtere overleving, hetgeen niet volledig wordt verklaard door de minder agressieve behandeling. Hoewel de 5-jaarsoverleving duidelijk is verbeterd blijft er ruimte voor verbetering, gezien de variatie in stagering en behandeling.

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Curriculum vitae

Valery Lemmens werd geboren te Heerlen op 26 april 1972. In 1990 behaalde hij het VWO-diploma aan de Scholengemeenschap Sint Michiel te Geleen. Na enkele jaren aan de wielersport gewijd te hebben, begon hij aan de studie Gezondheidwetenschappen, richting Biologische Gezondheidskunde aan de Universiteit van Maastricht, welke hij in 2002 afrondde. Als keuze-onderwijs volgde hij het traject 'Methoden en Technieken van Wetenschappelijk Onderwijs' (Epidemiologie). Begin 2003 begon hij bij het Integraal Kankercentrum Zuid te Eindhoven als junior-onderzoeker, waar hij zich onder andere bezig hield met studies naar de effecten van comorbiditeit op behandeling en overleving van oudere kankerpatiënten, en met patterns-of-care studies op het gebied van dikkedarmkanker. Van februari 2006 tot en met juli 2007 was hij verbonden aan de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC te Rotterdam, waar hij als post-doc werkte op het Eurocadet project, een Europees project dat zich richt op preventie van kanker. Vanaf augustus 2007 is hij weer terug als onderzoeker bij het Integraal Kankercentrum Zuid te Eindhoven, waar hij werkt op 2 door het KWF gefinancierde projecten: 'Treatment and outcome for cancer patients aged 75 years or older: a national population-based study', en 'Impact on mortality of improving quality of colorectal cancer care in the South of the Netherlands, preceding mass screening'. Sinds 2003 is hij getrouwd met Ella.