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

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# 2.2
# Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in the Netherlands 1989-2006

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# Abstract

**Background**

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

**Methods**

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

**Results**

The administration of adjuvant chemotherapy in stage III patients <75 years increased from 19% in 1989-1993 to 79% in 2004-2006 and from 1% to 19% in stage III patients ≥75 years. Among stage IV patients, resection rates of the primary tumour decreased from 72% to 63%, while chemotherapy administration increased from 23% to 64% in those <75 years. Survival increased from 52% to 58% in males and from 55% to 58% among females. Stage III patients with adjuvant chemotherapy exhibited a relative excess risk of 0.4 (95% confidence interval 0.4-0.4) compared with those without. Among stage IV patients, resection of primary tumour, palliative chemotherapy, and metastasectomy were important prognostic factors.

**Conclusions**

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

# Introduction

Colon cancer is one of the most frequent cancers in the Netherlands with >7000 new cases annually of whom ~60% are aged >70 years.[1] It is the second most frequent cause of cancer death in the Netherlands with >3700 deaths in 2008 of whom 68% are aged >70 years.[2] According to the evidence-based Dutch clinical practice guidelines, developed by a multidisciplinary working group of medical specialists, patients without distant metastasis should undergo curative resection. Administration of adjuvant chemotherapy for stage III colon cancer patients is recommended in the guidelines since the early 1990s and for high-risk stage II colon cancer patients since 2005.[3] High-risk patients were defined as patients with pT4 or poorly differentiated tumours, tumours with angioinvasion, or patients with <10 lymph nodes evaluated.[3]

Since the mid-1980s, improvement in survival has been achieved in randomised clinical trials, in particular due to advances in chemotherapy.[4] The role of adjuvant chemotherapy with 5-fluorouracil (5-FU)-based chemotherapy for stage III colon cancer patients is well established,[5] in more recent years in combination with oxaliplatin.[6] However, many elderly patients with stage III colon cancer do not receive adjuvant chemotherapy,[7;8] despite the fact that they also benefit from 5 FU-based chemotherapy.[9;10] The administration of chemotherapy to patients with metastatic colon cancer increased in Southern Netherlands from 14% in 1990-1994 to 44% in 2003-2004. Subsequently, survival of unselected patients with metastatic colon cancer increased significantly from 26 (95% CI 22-32) weeks in 1990-1994 to 39 (95% CI 31-48) weeks in 2003-2004.[11] However, the nationwide level of implementation of these treatments and its impact on population-based survival is unknown. Therefore, in this study, the changes in treatment of colon cancer over time are described, as well as the influence of these changes on survival in the Netherlands in the period 1989-2006.

# Methods

**Data collection**

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

tumour characteristics such as date of diagnosis, subsite (International Classification of Diseases for Oncology[12]), histology, stage (TNM (tumour-node-metastasis) classification[13]), grade, and primary treatment, are obtained routinely from the medical records ~9 months after diagnosis.[14] The quality of the data is high due to thorough training of the registrars and computerised consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[15] Vital status of all patients was obtained actively on a regular basis from the integrated database of the municipal registry and from the database of deceased persons of the Central Bureau for Genealogy. For the current analyses, the criteria of the International Association of Cancer Registries for multiple primaries were applied.[12]

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

**Statistical analyses**

Trends in incidence and mortality of colon cancer were described per 100,000 person-years, standardised according to the European Standard Population (European Standardised Rate, ESR). Treatment was given as percentages per age group and period. Differences in treatment over time were tested by the Cochran-Armitage trend test. Follow-up was calculated as the time from diagnosis to death or 1 January 2008. Relative survival was used as an estimation of disease-specific survival. It reflects survival of cancer patients, adjusted for survival in the general population with the same structure for age and gender. Relative survival is calculated as the ratio of the observed rates in cancer patients to the expected rates in the general population using the Ederer method.[16] Patients were censored at age 100 years, since follow-up of the very old might be incomplete. For the period 1989-2003, cohort analysis was used. Since follow-up data were only available until January 2008, 5-year follow-up was not feasible for the

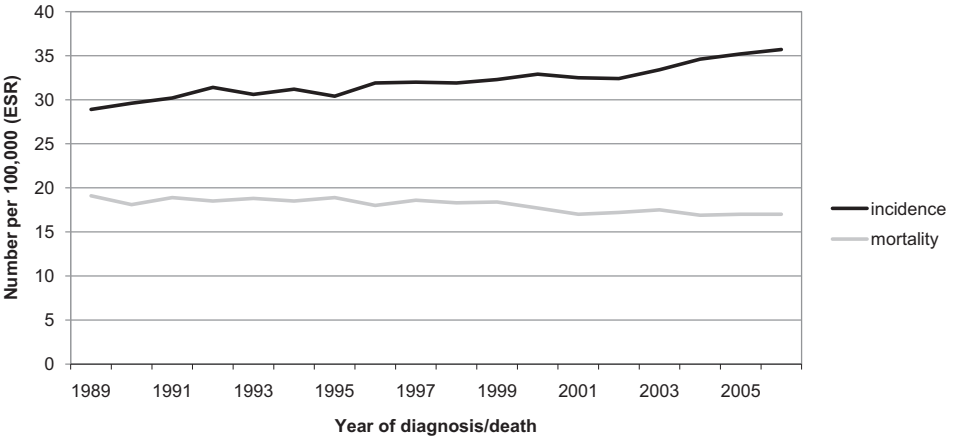


*Figure 1 Age-standardised incidence and mortality rates of colon cancer in the Netherlands, 1989-2006 ((ESR) European standardised rate)*

period 2004-2006, and period analysis was conducted for this period. Survival trends were quantified as the mean annual percentage change within 1989-2006 estimated by a linear regression model. A positive value of the mean annual change implies an upward trend in survival (i.e. improving) and a negative value implies a negative trend (i.e. deterioration). This calculation assumes that the rates increased or decreased at a constant rate over the entire period. Multivariable relative survival analyses, using Poisson regression modelling,[17] were carried out to estimate relative excess risk (RER) of dying adjusted for follow-up interval. For stage III disease patients, the multivariable relative survival analysis was stratified for adjuvant chemotherapy use since there was significant interaction between period of diagnosis and adjuvant chemotherapy use. In the multivariable relative survival analysis for stage IV disease patients, the treatment variables 'chemotherapy', 'resection of primary tumour', and 'metastasectomy' were added to investigate the effect of therapy on the RER of period of diagnosis. (SAS system 9.1, SAS Institute, Cary, NC).

## Results

The incidence rate (ESR) of colon cancer increased from 29 in 1989 to 36 per 100,000 person-years in 2006 (annual change 1.02 (95% CI 0.84; 1.20)), while the mortality rate (ESR) decreased from 19 in 1989 to 17 per 100,000 person-years in 2007 (annual change -0.64 (95% CI -0.83; -0.45)) (Figure 1). The age distribution was stable, with 40% of patients aged ≥75 years. The male to female ratio increased from 0.8 to 1.0

over time. No significant changes were seen in the distribution of tumour subsite, although the proportion of tumours in the proximal colon increased slightly. The proportion of patients with stage III disease increased from 22% in 1989-1993 to 25% in 2004-2006, while the proportion of patients with stage II disease decreased from 37% to 33% in the same periods. The proportion of patients with stage IV disease was constant with 19% in the periods 1989-1993 and 1994-1998 and increased significantly to 22% in 2004-2006 (Table 1).

*Table 1 Descriptives of all patients diagnosed with colon cancer in the Netherlands from 1989 to 2006 (N=103,744)*

| | 1989-1993 | | 1994-1998 | | 1999-2003 | | 2004-2006 | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Gender | | | | | | | | |
| Male | 11,218 | 46 | 13,132 | 48 | 14,880 | 49 | 10,612 | 50 |
| Female | 13,342 | 54 | 14,144 | 52 | 15,743 | 51 | 10,674 | 50 |
| Age (yrs) | | | | | | | | |
| <75 | 14,751 | 60 | 16,548 | 61 | 18,301 | 60 | 12,537 | 59 |
| ≥75 | 9,809 | 40 | 10,728 | 39 | 12,322 | 40 | 8,748 | 41 |
| Tumour site | | | | | | | | |
| Proximal[1] | 13,402 | 55 | 14,849 | 54 | 16,855 | 55 | 11,679 | 55 |
| Distal[2] | 10,424 | 42 | 11,583 | 43 | 12,905 | 42 | 8,948 | 42 |
| Other/NOS | 734 | 3 | 844 | 3 | 863 | 3 | 658 | 3 |
| Stage | | | | | | | | |
| I | 3,593 | 15 | 4,022 | 15 | 4,261 | 14 | 3,072 | 14 |
| II | 9,149 | 37 | 9,802 | 36 | 10,735 | 35 | 6,980 | 33 |
| III | 5,283 | 22 | 6,399 | 23 | 7,446 | 24 | 5,218 | 25 |
| IV | 4,668 | 19 | 5,175 | 19 | 6,202 | 20 | 4,615 | 22 |
| Unknown | 1,867 | 8 | 1,878 | 7 | 1,979 | 6 | 1,400 | 7 |
| Total | 24,560 | | 27,276 | | 30,623 | | 21,286 | |

[1] Including the coecum, appendix, ascending colon, and hepatic flexure
[2] Including the descending colon and sigmoid
NOS, not otherwise specified

**Treatment**

During the whole study period, almost all patients with stages I-III colon cancer underwent resection of their primary tumour. For patients with stage IV colon cancer, the resection rate decreased over time: for the younger patients (<75 years) from 72% in 1989-1993 to 63% in 2004-2006 and among elderly patients (≥75 years) from 66% to 56% in 2004-2006.

Administration of adjuvant chemotherapy increased over time among patients with stage II colon cancer <75 years from 4% in 1989-1993 to 10% in 2004-2006. Virtually, none of the stage II patients ≥75 years received adjuvant chemotherapy. There was a steep increase in the administration of adjuvant chemotherapy in stage III disease patients in both age groups: from 19% in 1989-1993 to 79% in 2004-2006 in those aged <75 years, although it seems to level off in 2004-2006. The proportion of elderly (≥75 years) stage III disease patients who received adjuvant chemotherapy was much lower, with proportions of 1% in 1989-1993 to 19% in 2004-2006. Chemotherapy administration in patients with stage IV colon cancer increased over time, with a much lower proportion of elderly (≥75 years) patients receiving chemotherapy (Table 2).

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

| Treatment | Age (yrs) | 1989-1993 | | 1994-1998 | | 1999-2003 | | 2004-2006 | | P trend |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % | |
| Resection, stages I-III | | | | | | | | | | |
| | <75 | 10,651 | 98 | 12,126 | 99 | 13,094 | 98 | 8,904 | 99 | 0.001 |
| | ≥75 | 7,062 | 98 | 7,771 | 98 | 8,946 | 98 | 6,128 | 98 | 0.002 |
| Adjuvant chemotherapy, stage II | | | | | | | | | | |
| | <75 | 194 | 4 | 263 | 5 | 426 | 7 | 392 | 10 | <0.001 |
| | ≥75 | 5 | 0 | 21 | 1 | 28 | 1 | 22 | 1 | <0.001 |
| Adjuvant chemotherapy, stage III | | | | | | | | | | |
| | <75 | 642 | 19 | 1,914 | 47 | 3,422 | 74 | 2,564 | 79 | <0.001 |
| | ≥75 | 21 | 1 | 152 | 6 | 386 | 14 | 367 | 19 | <0.001 |
| Resection, stage IV | | | | | | | | | | |
| | <75 | 2,229 | 72 | 2,460 | 71 | 2,876 | 68 | 1,923 | 63 | <0.001 |
| | ≥75 | 1,033 | 66 | 1,117 | 66 | 1,139 | 59 | 857 | 56 | <0.001 |
| Metastasectomy, stage IV | | | | | | | | | | |
| | <75 | 41 | 1 | 148 | 4 | 235 | 6 | 253 | 8 | <0.001 |
| | ≥75 | 10 | 1 | 26 | 2 | 37 | 2 | 46 | 3 | <0.001 |
| Chemotherapy, stage IV | | | | | | | | | | |
| | <75 | 731 | 23 | 1,151 | 33 | 2,223 | 52 | 1,965 | 64 | <0.001 |
| | ≥75 | 35 | 2 | 89 | 5 | 210 | 11 | 332 | 40 | <0.001 |

**Survival**

Five-year relative survival from colon cancer in males increased from 52% in 1989-1993 to 58% in 2004-2006 (annual change: +0.38% (95% CI 0.21; 0.56)), while in females, the 5-year survival increased from 55% to 58% in the same period (annual change +0.18% (95% CI 0.04; 0.32)). In 1989-1998, 5-year relative survival was better in females than in males, but this discrepancy disappeared after 1998. Survival decreased with increasing stage of disease, with the 5-year relative survival of ~94% for stage I

disease in the entire period 1989-2006, while the 5-year relative survival rates for stages II, III and IV disease were respectively, ~77%, 53% and 6% in the entire study period. No significant improvement over time was seen in survival from stage I colon cancer, while survival from stage II colon cancer increased significantly (annual change males +0.36% (95% CI 0.07; 0.66) and females +0.37% (95% CI 0.13; 0.60)). Survival improved most in patients with stage III colon cancer: an increase from 46% in 1989-1993 to 59% in 2004-2006 (annual change +0.97% (95% CI 0.59; 1.34)) was seen in male patients and from 48% in 1989-1993 to 60% in 2004-2006 (annual change +0.88% (95% CI 0.65; 1.12)) in female patients. Patients with stage III disease who received adjuvant chemotherapy had a 5-year relative survival of 67%, whereas patients with stage III disease who did not receive adjuvant chemotherapy had a 5-year relative survival of 44% (Figure 2). The 5-year relative survival of patients with stage IV colon cancer increased in males from 5% in 1989-1993 to 7% in 2004-2006 (annual change +0.15% (95% CI 0.02; 0.28)), while it was stable at ~6% in female patients. Increases in 5-year relative survival seemed more pronounced for younger males (<60 years), while this increase was not seen for younger females. Five-year relative survival in female patients aged ≥75 years was stable at 56%, but rose in men from 52% to 58% (annual change +0.45% (95% CI 0.13; 0.77)). In males, survival was somewhat better in distally located tumours compared with proximally located tumours (Table 3).

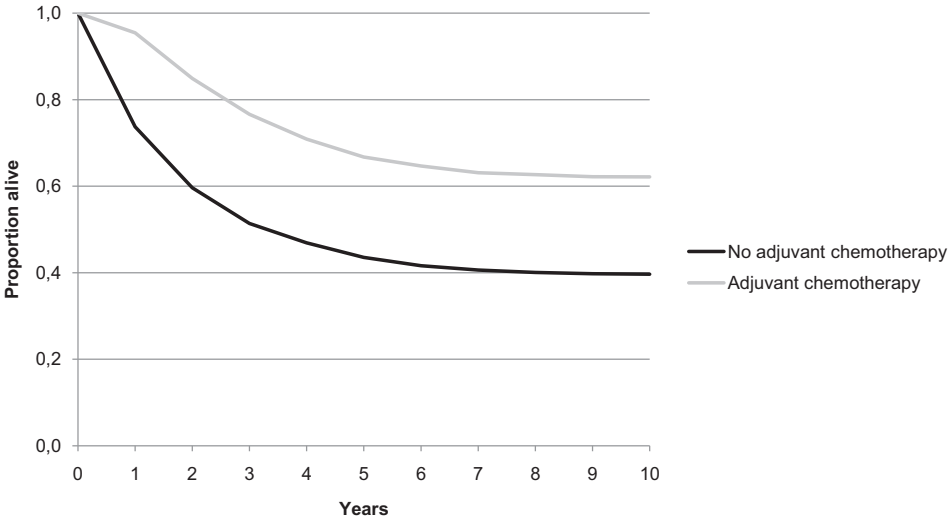


*Figure 2 Relative survival of colon cancer stage III patients according to adjuvant chemotherapy administration*

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

| | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1989-1993 | 1994-1998 | 1999-2003 | 2004-2006[1] | Annual change (95% CI) | 1989-1993 | 1994-1998 | 1999-2003 | 2004-2006[1] | Annual change (95% CI) |
| Total | 52 (0.9) | 54 (0.6) | 57 (0.5) | 58 (0.7) | +0.38 (0.21; 0.56)* | 55 (0.8) | 56 (0.6) | 57 (0.5) | 58 (0.6) | +0.18 (0.04; 0.32)* |
| Stage | | | | | | | | | | |
| I | 92 (2.3) | 91 (1.4) | 94 (1.2) | 94 (1.5) | +0.21 (-0.05; 0.46) | 96 (1.7) | 94 (1.2) | 94 (1.1) | 92 (1.4) | -0.28 (-0.59; 0.02) |
| II | 74 (1.6) | 74 (1.0) | 78 (0.9) | 78 (1.1) | +0.36 (0.07; 0.66)* | 75 (1.4) | 76 (0.9) | 80 (0.8) | 80 (1.0) | +0.37 (0.13; 0.60)* |
| III | 46 (1.9) | 49 (1.2) | 56 (1.1) | 59 (1.3) | +0.97 (0.59; 1.34)* | 48 (1.6) | 50 (1.1) | 57 (1.0) | 60 (1.2) | +0.88 (0.65; 1.12)* |
| IV | 5 (0.7) | 5 (0.5) | 5 (0.5) | 7 (0.7) | +0.15 (0.02; 0.28)* | 6 (0.8) | 5 (0.5) | 6 (0.5) | 7 (0.7) | +0.14 (-0.05; 0.33) |
| Age (yrs) | | | | | | | | | | |
| ≤44 | 59 (3.4) | 66 (2.5) | 70 (2.2) | 66 (2.9) | +0.63 (-0.08; 1.34) | 67 (3.2) | 69 (2.3) | 64 (2.2) | 66 (2.9) | -0.02 (-0.61; -0.58) |
| 45-59 | 54 (1.8) | 55 (1.2) | 58 (1.1) | 60 (1.3) | +0.42 (0.08; 0.76)* | 55 (1.8) | 58 (1.2) | 60 (1.0) | 59 (1.3) | +0.27 (-0.07; 0.62) |
| 60-74 | 52 (1.3) | 54 (0.8) | 55 (0.7) | 57 (0.9) | +0.36 (0.12; 0.60)* | 55 (1.2) | 57 (0.8) | 58 (0.7) | 61 (0.9) | +0.36 (0.11; 0.62)* |
| ≥75 | 52 (1.3) | 54 (1.4) | 57 (1.2) | 58 (1.4) | +0.45 (0.13; 0.77)* | 56 (1.5) | 53 (1.0) | 56 (0.9) | 55 (1.1) | 0.00 (-0.21; 0.22) |
| Tumour location | | | | | | | | | | |
| Proximal[2] | 50 (1.3) | 54 (0.8) | 55 (0.8) | 55 (0.9) | +0.36 (0.13; 0.59)* | 54 (1.1) | 56 (0.7) | 57 (0.7) | 58 (0.8) | +0.21 (-0.04; 0.46) |
| Distal[3] | 56 (1.4) | 57 (0.9) | 60 (0.8) | 61 (0.9) | +0.40 (0.17; 0.62)* | 59 (1.3) | 58 (0.9) | 60 (0.8) | 60 (1.0) | +0.14 (-0.08; 0.36) |
| Other/NOS | 43 (5.5) | 31 (2.9) | 33 (2.7) | 40 (3.7) | n.a. | 30 (4.2) | 36 (3.0) | 30 (2.5) | 31 (3.1) | n.a. |

[1] Based on period analysis
[2] Including the coecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure
[3] Including the descending colon and sigmoid
* P<0.05
95% CI, 95% confidence interval; NOS, not otherwise specified; n.a., not applicable

The multivariable relative survival analyses for stage II colon cancer patients showed a decreased risk of death for those with a younger age (<60 years), a tumour in the proximal colon, more recent period of diagnosis, female gender, and administration of adjuvant chemotherapy (Table 4). Omitting adjuvant chemotherapy from the model led to similar results (data not shown). Patients with stage III colon cancer who received adjuvant chemotherapy had a significantly lower risk of dying compared to stage III patients who received no chemotherapy (RER 0.4 (95% CI 0.4-0.4)). Among stage III patients not receiving adjuvant treatment, those diagnosed in the period 1989-1993 had a worse survival compared with patients diagnosed after 1994. Furthermore, patients aged <60 years had a decreased risk of dying, as well as female patients, while a proximal tumour increased the risk of dying. Among stage III disease patients who received adjuvant chemotherapy, survival increased over time, with the RER being 0.5 (95% CI 0.4-0.6) in 2004-2006 compared with 1989-1993. An increased risk of dying for stage III disease patients with a tumour in the proximal colon was found, while no decreased risk of dying was found among younger (<60 years) patients (Table 5). Among patients with stage IV colon cancer, the risk of death decreased over time, which only remained significant for

*Table 4 Multivariable relative survival analysis, colon cancer stage II*

| | Multivariate model[1] | |
|---|---|---|
| Variable | RER | 95% CI |
| Period of diagnosis | | |
| 1989-1993 | 1.0 | |
| 1994-1998 | 1.0 | 0.9-1.1 |
| 1999-2003 | 0.8* | 0.8-0.9 |
| 2004-2006 | 0.8* | 0.8-0.9 |
| Gender | | |
| Male | 1.0 | |
| Female | 0.9* | 0.9-1.0 |
| Age group (yrs) | | |
| ≤44 | 0.4* | 0.4-0.6 |
| 45-59 | 0.8* | 0.8-0.9 |
| 60-74 | 1.0 | |
| ≥75 | 1.4* | 1.4-1.5 |
| Subsite | | |
| Proximal colon | 0.8* | 0.8-0.9 |
| Distal colon | 1.0 | |
| Other/NOS | 1.7* | 1.4-2.0 |
| Adjuvant chemotherapy | | |
| No | 1.0 | |
| Yes | 0.8* | 0.7-1.0 |

[1] Adjusted for follow-up interval, gender, age group, subsite, and adjuvant chemotherapy
* P<0.05
RER, relative excess risk; 95% CI, 95% confidence interval; NOS, not otherwise specified

*Table 5 Multivariable relative survival analysis, colon cancer stage III*[1]

| | No adjuvant chemotherapy | | Adjuvant chemotherapy | |
|---|---|---|---|---|
| Variable | RER | 95% CI | RER | 95% CI |
| Period | | | | |
| 1989-1993 | 1.0 | | 1.0 | |
| 1994-1998 | 1.1* | 1.0-1.2 | 0.8* | 0.7-0.9 |
| 1999-2003 | 1.2* | 1.1-1.3 | 0.6* | 0.5-0.7 |
| 2004-2006 | 1.2* | 1.1-1.3 | 0.5* | 0.4-0.6 |
| Gender | | | | |
| Male | 1.0 | | 1.0 | |
| Female | 0.9* | 0.9-1.0 | 1.0 | 0.9-1.1 |
| Age group (yrs) | | | | |
| ≤44 | 0.8* | 0.6-0.9 | 0.9 | 0.7-1.0 |
| 45-59 | 0.9* | 0.8-1.0 | 0.9 | 0.8-1.0 |
| 60-74 | 1.0 | | 1.0 | |
| ≥75 | 1.0 | 0.9-1.1 | 0.8* | 0.6-1.0 |
| Subsite | | | | |
| Proximal colon | 1.2* | 1.1-1.3 | 1.4* | 1.3-1.6 |
| Distal colon | 1.0 | | 1.0 | |
| Other/NOS | 1.5* | 1.2-1.8 | 1.8* | 1.3-2.4 |

[1] Adjusted for follow-up interval, gender, age group, and subsite
* P<0.05
RER, relative excess risk; 95% CI, 95% confidence interval; NOS, not otherwise specified

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

## Discussion

In this population-based study covering the entire Netherlands over a period of 17 years, we observed substantial changes in treatment of colon cancer in the period 1989-2006. Use of adjuvant chemotherapy in patients with stage III disease and to a lesser extent stage II colon cancer increased steeply over time, while resection rates remained stable for curative colon cancer patients. Among metastatic colon cancer patients, the resection rate of primary tumour decreased, while administration of chemotherapy increased. Survival increased over time, particularly in patients with stage III colon cancer.

The changes in treatment and improvements in survival of colon cancer found in this first study using national data covering the entire Netherlands are in line with results

*Table 6 Multivariable relative survival analysis, colon cancer stage IV*[1]

| | Multivariate model 1 | | Multivariate model 2[2] | |
|---|---|---|---|---|
| Variable | RER | 95% CI | RER | 95% CI |
| Period | | | | |
| 1989-1993 | 1.0 | | 1.0 | |
| 1994-1998 | 1.0 | 0.9-1.0 | 1.0 | 1.0-1.1 |
| 1999-2003 | 0.9* | 0.8-0.9 | 1.0 | 0.9-1.0 |
| 2004-2006 | 0.7* | 0.7-0.8 | 0.8* | 0.8-0.9 |
| Gender | | | | |
| Male | 1.0 | | 1.0 | |
| Female | 1.0 | 1.0-1.1 | 1.0* | 1.0-1.1 |
| Age group (yrs) | | | | |
| ≤44 | 0.8* | 0.7-0.9 | 0.9* | 0.8-1.0 |
| 45-59 | 0.9* | 0.8-0.9 | 0.9* | 0.9-1.0 |
| 60-74 | 1.0 | | 1.0 | |
| ≥75 | 1.4* | 1.3-1.5 | 1.1* | 1.1-1.2 |
| Subsite | | | | |
| Proximal colon | 1.3* | 1.2-1.3 | 1.2* | 1.2-1.3 |
| Distal colon | 1.0 | | 1.0 | |
| Other/NOS | 1.9* | 1.8-2.1 | 1.4* | 1.3-1.5 |
| Chemotherapy | | | | |
| No | | | 1.0 | |
| Yes | | | 0.6* | 0.6-0.6 |
| Resection of primary tumour | | | | |
| No | | | 1.0 | |
| Yes | | | 0.4* | 0.4-0.4 |
| Metastasectomy | | | | |
| No | | | 1.0 | |
| Yes | | | 0.4* | 0.3-0.4 |

[1] Adjusted for follow-up interval, gender, age group, and subsite
[2] Additionally adjusted for chemotherapy, resection of primary tumour, and metastasectomy
* P<0.05
RER, relative excess risk; 95% CI, 95% confidence interval; NOS, not otherwise specified

from a previous Dutch study covering the southern part of the Netherlands.[18] Our finding that almost all colon cancer patients with stages I-III disease underwent resection of their tumour is similar to the results reported in a French population-based study.[19] The increase in palliative chemotherapy in metastatic colon cancer patients is also in line with a previous regional Dutch study.[11]

The large increase in adjuvant chemotherapy among stage III disease patients, and to a lesser extent among stage II disease patients is influenced by the results of randomised clinical trials conducted in the 1990s, among which was one Dutch trial, published in 2001.[20-24] During this period, there was no consensus about the effect of adjuvant chemotherapy in stages II and III disease patients in the Netherlands, hindering the

introduction of adjuvant chemotherapy. Our findings as well as those in previous studies show that elderly patients receive adjuvant chemotherapy less often than younger patients.[7;25] Several reasons are given in literature to explain why elderly patients are less likely to receive adjuvant chemotherapy, including the presence of concomitant diseases, frailty, the absence of supportive caregivers, and a decrease in the patients' general condition and cognitive ability.[26] Elderly patients seem less willing to accept the negative effects of treatment with adjuvant chemotherapy compared to younger patients,[27;28] resulting in more patient refusal. In addition, the decision of the medical oncologist, which is based on clinical experience, plays a role in the choice of adjuvant chemotherapy administration. However, several studies have shown that elderly patients may equally benefit from adjuvant chemotherapy treatment with similar toxicity levels.[9;10] In addition, the benefit of adjuvant chemotherapy is strongest in the first 2 years after treatment.[4] In this light, it is important to note that the life expectancy of 80-year-old Dutch men is still 7 years and even higher for a Dutch woman.[2]

According to the current Dutch treatment guidelines, adjuvant chemotherapy is not recommended for stage II colon cancer patients.[3] However, those with a T4 tumour, with perforation or obstruction at presentation, with <10 lymph nodes examined, or with angioinvasion are considered high-risk patients since survival of these patients is similar to stage III patients with colon cancer. These patients should therefore nowadays be considered for treatment with adjuvant chemotherapy.[3] This explains the increase in adjuvant chemotherapy in stage II disease patients. Tumours of the proximal colon are usually detected at a late stage.[29] When a proximal tumour lead to symptoms, the tumour can be detected at an earlier stage, resulting in a better survival compared with more distally located tumours as found in our study. The survival of more advanced proximal tumours is worse compared with distal tumours, which is in line with literature.[30]

The considerable improvement in survival of patients with stage III colon cancer is likely to be attributed to the increased administration of adjuvant chemotherapy regimens in these patients. There might be other factors associated with treatment allocation not controlled for in the analysis. Therefore, we do not know the extent to which the prognostic impact observed in this study for treatment factors estimate the real impact on survival due to selection bias. Stage-migration is likely to have occurred since evaluation of lymph nodes has become more adequate in the Netherlands during the study period[31] and imaging techniques have been developing over time detecting smaller metastases, which would have remained undetected otherwise.[32;33] The lack of effect of age on survival in stage III disease patients who received adjuvant chemotherapy reflects that elderly patients who receive adjuvant chemotherapy have a similar survival as their younger counterpart.

For metastatic colon cancer, survival improved as well, probably due to an increased use of and changes in chemotherapy, and probably a more adequate selection of patients eligible for surgery.[11] In the most recent years, there has been a regionalisation of the surgical expertise for treating liver metastases. This could have resulted in improved surgery, leading to a better survival in stage IV colon cancer patients in 2004-2006 compared with the previous periods.

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

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

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