

# Earlier stages of colorectal cancer detected with immunochemical faecal occult blood tests

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## ABSTRACT

**Background:** The aim of colorectal cancer screening is to improve prognosis by the detection of early cancer and precursor stages. We compared the stage distribution of asymptomatic colorectal cancer patients detected by a positive immunochemical or guaiac-based faecal occult blood test (FOBT) with symptomatic colorectal cancer patients.

**Methods:** In a longitudinal cohort study tumour stages were assessed in 144 symptomatic (mean age 69.3 years, 56% male) and 41 asymptomatic colorectal cancer patients (mean age 64.9 years, 56% male) of which 11 were detected with guaiac FOBTs (G-FOBT, Hemoccult-II<sup>®</sup>) and 30 with immunochemical FOBTs (I-FOBT, OCSensor<sup>®</sup>). Stage distributions were used to calculate average stage specific predicted five-year survival rates and to analyse group differences with Wilcoxon log-rank test.

**Results:** Colorectal cancer was detected in significantly earlier stages in symptomatic compared with asymptomatic patients ( $p < 0.0001$ ). Average stage specific predicted five-year survival was 59.1% in symptomatic and 76.6% in asymptomatic patients. Compared with the symptomatic patients the stage distribution for colorectal cancer patients detected with Hemoccult-II was not significantly different ( $p = 0.29$ ), whereas colorectal cancer was detected at significantly earlier stages with the OCSensor ( $p < 0.0001$ ). Treatment could be confined to colonoscopy in 27% of the asymptomatic patients compared with 3% of the symptomatic patients ( $p < 0.0001$ ). Cancer distribution over the colon was comparable between symptomatic and asymptomatic patients ( $p = 0.3$ ).

**Conclusions:** Compared with symptomatic patients, patients detected by FOBT and especially immunochemical

FOBT, presented significantly more often at earlier stages suggesting increased survival. Additionally treatment could more often be confined to colonoscopy.

## KEY WORDS

Colorectal cancer, faecal occult blood test, mass screening, survival

## INTRODUCTION

Colorectal cancer is, after breast cancer, the second most frequent cancer in women, and after lung and prostate cancer, the third most frequent cancer in men in the Netherlands. The lifetime risk of developing colorectal cancer is approximately 6% ([www.IKCnet.nl](http://www.IKCnet.nl)). In 2003, colorectal cancer was responsible for more than 56,000 life-years lost and for 70,000 disability adjusted life-years in the Netherlands. Total costs for management of colorectal cancer patients amounted to 230 million euros.<sup>1</sup> The ageing population will have an enormous impact on the incidence of colorectal cancer and costs in the near future. Until 2025, the incidence of colorectal cancer will gradually increase by 40% in the Netherlands and medical costs for colorectal cancer patients will considerably increase due to growing application of biologicals.<sup>2</sup> When colorectal cancer is detected as a result of symptoms, the prognosis is still rather poor with an average five-year survival between 50 to 60% ([www.IKCnet.nl](http://www.IKCnet.nl)).<sup>3</sup> In order to improve the prognosis of colorectal cancer, colorectal

cancer should be detected in earlier stages or even precursor stages. Colorectal cancer is a heterogeneous disease arising from a complex series of molecular events. The successive evolution of normal colonic mucosa to a benign adenoma, then to an adenomatous polyp containing cancer, and then to a potentially life-threatening invasive cancer is associated with a series of genetic events occurring over a period of approximately ten years.<sup>4</sup> So, many years pass before colorectal cancer becomes clinically manifest and therefore there is an opportunity to improve prognosis by early detection of colorectal cancer with screening.

In 2006, colorectal cancer screening studies were started in the Netherlands randomly employing two different types of faecal occult blood tests (FOBTs): guaiac-based FOBTs and immunochemical FOBTs. In order to verify if prognosis of colorectal cancer is improved by FOBT screening and if improvement depends on the type of FOBT, we compared the stage distribution of colorectal cancer patients detected as a result of FOBT screening with colorectal cancer patients detected because of symptoms.

## MATERIALS AND METHODS

Between July 2006 and March 2007, asymptomatic subjects with a positive FOBT were invited for colonoscopy. These subjects were recruited from two colorectal cancer screening studies in the Netherlands with a comparable design, registered at Current Controlled Trials (ISRCTN57917442). All invited participants were asymptomatic, between 50 and 75 years of age and without apparent family history of colorectal cancer. Data from the largest of the two studies comparing the performance of two types of FOBTs, supported by the Netherlands Organisation for Health Research and Development (ZonMW: number 50-50115-98-060, project 63000004), were published previously.<sup>5</sup> From the patients with colorectal cancer detected in these studies, the following data were collected: age, gender, location of the tumour, surgical or endoscopic treatment and TNM classification. These data were also collected from 144 consecutive symptomatic colorectal cancer patients without a family history of colorectal cancer in the same region in the Netherlands and in the same period, from July 2006 to March 2007. Tumour staging was performed according to the American Joint Committee on Cancer (AJCC) system, also called the TNM system, which describes stages using Roman numerals I through IV. Three experienced pathologists staged all the detected colorectal cancers of both the symptomatic and the asymptomatic patients. According to data from the Surveillance, Epidemiology, and End Results (SEER) programme, each stage has an average stage specific five-year survival (table 1).<sup>6</sup> The follow-up

**Table 1.** Stage specific average five-year survival rates for colorectal cancer

| T      | N      | M  | Dukes | Stage | 5-year survival* |
|--------|--------|----|-------|-------|------------------|
| Tis    | No     | Mo | -     | 0     | 98%              |
| T1     | No     | Mo | A     | I     | 93%              |
| T2     | No     | Mo | A     | I     | 93%              |
| T3     | No     | Mo | B1    | IIA   | 85%              |
| T4     | No     | Mo | B2    | IIB   | 72%              |
| T1,2   | N1     | Mo | C1    | IIIA  | 83%              |
| T3,4   | N1     | Mo | -     | IIIB  | 64%              |
| Each T | N2     | Mo | C2    | IIIC  | 44%              |
| Each T | Each N | M1 | D     | IV    | 8%               |

\*According to data from the Surveillance, Epidemiology, and End Results (SEER) programme.

after our study was too short to measure actual five-year survival and furthermore actual five-year survival would have to be corrected for over-diagnosis and lead-time bias, the extent of which is largely unknown. Therefore the stage specific average five-year survival rates were used to predict the five-year survival of the patients in our study group. For each colorectal cancer stage we assumed that the five-year survival would eventually prove to be identical for symptomatic or asymptomatic patients and identical to the SEER data. Of course this approximation method has certain drawbacks, but also advantages, which we will discuss in the discussion.

In the asymptomatic patients participating in the colorectal cancer screening study, the type of FOBT was also registered.<sup>5</sup> Two types of FOBT were used, a guaiac-based FOBT (Hemoccult-II<sup>®</sup>) and an immunochemical based FOBT (OCSensor<sup>®</sup>). A specific advantage of the OCSensor<sup>®</sup> is that the test is quantitative allowing the cut-off value for positivity to be changed. As threshold for positivity, the manufacturer recommends a cut-off value of 100 ng/ml, applied in several studies.<sup>7-12</sup> The literature as well as data provided by the manufacturer show that the test results of the OCSensor<sup>®</sup> are reliable in the range from 50 ng/ml to 2000 ng/ml.<sup>13</sup> In the previous publication in Gastroenterology we compared the guaiac FOBT Hemoccult-II<sup>®</sup> with the I-FOBT OCSensor<sup>®</sup>. In that publication, for generalisability with the previous studies, we presented data for the I-FOBT with a cut-off value of 100 ng/ml. However, we invited all patients for colonoscopy with an I-FOBT result of  $\geq 50$  ng/ml, corresponding to about 10  $\mu$ g haemoglobin per gram faeces.<sup>14</sup> In the current study we use the data of all invited patients with a cut-off value of 50 ng/ml.

With immunochemical faecal occult blood tests, as little as 0.3 ml of daily blood loss in the stool can be detected.<sup>15</sup> In contrast, the Hemoccult-II<sup>®</sup> test is a qualitative test in which the minimal amount of blood that can be

detected in faeces is probably about ten times higher than immunochemical FOBTs.<sup>15,16</sup> Therefore, we speculated that the immunochemical FOBT OCSensor® detects colorectal cancer at earlier stages.

We calculated descriptive statistics of the symptomatic and asymptomatic study populations. We used nonparametric analysis with the Wilcoxon log-rank test to compare the stage distribution between the two groups. Statistical significance was accepted if the level of probability of a type I error was ≤5% (p<0.05). Statistical analyses were performed with SAS system for windows, software version 8.02 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

Colonoscopies in the asymptomatic group with a positive FOBT revealed in total 41 patients with colorectal cancer (23 male, 18 female; mean age 64.9 years, range 53 to 75 years). Nine of the tumours were located in the rectum, 19 in the sigmoid, three in the descending colon, one in the splenic flexure, two in the transverse colon, one in the hepatic flexure, four in the ascending colon, and two in the caecum (table 2). Twenty of the tumours were classified as stage I, six as stage IIA, three as stage IIIA, five as stage IIIB, four as stage IIIC, and three as stage IV (table 3). The average predicted five-year survival deduced from the TNM staging system and SEER programme (table 1) in this group of 41 patients was 76.6 (SD 25%). In 11 (27%) of these 41 patients tumour treatment could be confined to endoscopy. Tumours were found in 11 patients with a positive Hemoccult-II® and in 30 patients with a positive OCSensor®. The predicted five-year survival for the patients with a positive Hemoccult-II® test was 60.5 (SD 37%), and for the patients with a positive OCSensor® 82.4 (SD 16%).

**Table 2.** Location of colorectal cancer in symptomatic and asymptomatic patients

| Colorectal cancer location | Symptomatic patients<br>N=144* (%) | Asymptomatic patients<br>N=41 (%) |
|----------------------------|------------------------------------|-----------------------------------|
| Rectum                     | 61 (42%)                           | 9 (22%)                           |
| Sigmoid colon              | 33 (23%)                           | 19 (46%)                          |
| Descending colon           | 3 (2%)                             | 3 (7%)                            |
| Splenic flexure            | 3 (2%)                             | 1 (2%)                            |
| Transverse colon           | 5 (3%)                             | 2 (5%)                            |
| Hepatic flexure            | 5 (3%)                             | 1 (2%)                            |
| Ascending colon            | 17 (12%)                           | 4 (10%)                           |
| Caecum                     | 15 (10%)                           | 2 (5%)                            |
| Unknown                    | 4 (3%)                             | - (0%)                            |

\*Two patients had two concurrent colorectal tumours.

**Table 3.** Staging of colorectal cancer in symptomatic and asymptomatic patients

| Colorectal cancer stage | Symptomatic patients<br>N=144 (100%) | Asymptomatic patients<br>N=41 (100%) |
|-------------------------|--------------------------------------|--------------------------------------|
| I                       | 6 (4%)                               | 20 (49%)                             |
| IIA                     | 23 (16%)                             | 6 (15%)                              |
| IIB                     | 43 (30%)                             | 0 (0%)                               |
| IIIA                    | 15 (10%)                             | 3 (7%)                               |
| IIIB                    | 12 (8%)                              | 5 (12%)                              |
| IIIC                    | 13 (9%)                              | 4 (10%)                              |
| IV                      | 32 (22%)                             | 3 (7%)                               |

Colonoscopies performed in subjects referred with symptoms, such as visible blood loss and changed bowel habits, revealed 144 patients with colorectal cancer (81 male, 63 female; mean age 69.3 years, range 32 to 93 years). Sixty-one of the tumours were located in the rectum, 33 in the sigmoid, three in the descending colon, three in the splenic flexure, five in the transverse colon, five in the hepatic flexure, 17 in the ascending colon, 15 in the caecum and for four tumours the specific location was uncertain (table 2). Two patients had a double tumour and these patients were staged according to the most advanced carcinoma. Six of the patients were classified as stage I, 23 as stage IIA, 43 as stage IIB, 15 as stage IIIA, 12 as stage IIIB, 13 as stage IIIC, and 32 as stage IV (table 3). The predicted five-year survival for this group of 144 patients was 59.1 (SD 29%). In four (3%) of these 144 patients tumour removal could be confined to endoscopy.

Colorectal cancer was detected significantly earlier in symptomatic patients compared with asymptomatic patients (p<0.0001). Average stage specific predicted five-year survival was 59.1% in symptomatic and 76.6% in asymptomatic patients. Additionally, treatment for colorectal cancer could be confined to colonoscopy in 27% of the asymptomatic patients compared with 3% of the symptomatic patients (p<0.0001). Ten (24%) of the colorectal cancer tumours in asymptomatic patients and 45 (31%) of the colorectal cancer tumours in symptomatic patients were located proximal of the descending colon (p=0.3).

Compared with the symptomatic patients the stage distribution for colorectal cancer patients detected with Hemoccult-II was not significantly different (p=0.29), whereas colorectal cancer was detected significantly earlier in patients detected with OCSensor compared with the symptomatic patients (p<0.0001). The average predicted five-year survival was 82.4% for the asymptomatic patients detected with the OCSensor® and 60.5% for the patients detected with the Hemoccult-II®.

## DISCUSSION

In this study we demonstrated that colorectal cancer in asymptomatic persons aged between 50 and 75 years with a positive FOBT is on average detected at a significantly earlier stage compared with symptomatic subjects with colorectal cancer diagnosed in the same time period and in the same geographical region. In addition, treatment of colorectal cancer could significantly more often be confined to colonoscopy in the asymptomatic screening group than in the symptomatic group. The most important finding in this study was that, compared with symptomatic patients, colorectal cancer was detected in significantly earlier stages for the patients detected with the I-FOBT, but not for patients detected with the G-FOBT.

We have compared the data from our study with data from a German study by Hüppe *et al.* For easy comparison with our study we calculated the gain in predicted five-year colorectal cancer survival according to stage distribution from the data in their study in 5066 asymptomatic patients (participating in colonoscopy screening) and in 4099 symptomatic patients.<sup>17</sup> The 18% gain in survival from their data compares well with the 22% gain in average predicted survival we observed with FOBT screening. In addition Hüppe *et al.* had followed up their population for up to five years (on average 33 months). Up to the time of their publication no subjects in the screening group had died compared with 20% of the symptomatic colorectal cancer patients, confirming the predicted gain in five-year survival according to stage distribution.<sup>17</sup> We propose this indicates that the stage distribution of colorectal cancer detected by primary colonoscopy screening is comparable with the stage distribution of colorectal cancer detected by faecal occult blood testing. Additionally the follow-up data by Hüppe *et al.* indicate that colorectal cancer survival predicted by stage distribution might on average correlate well with actual survival. We think this is interesting for policy makers who are considering implementing colorectal cancer screening with either primary colonoscopy or FOBT.

Another important finding of our study was the difference that we observed in the stage distribution between subjects with colorectal cancer detected after a positive Hemoccult-II® test, compared with a positive OCSensor® test. Both the Hemoccult-II® test and the OCSensor® test are developed to detect haemoglobin in faeces. In contrast to the Hemoccult-II® test, the OCSensor® test is specific for human haemoglobin and the test is quantitative, allowing the cut-off values for positivity to be shifted. The Hemoccult-II® test is probably at least ten times less sensitive to haemoglobin compared with the OCSensor® test.<sup>15,16</sup> The stage distribution of colorectal cancer patients detected with the OCSensor® in this study was significantly better than the stage distribution in the

symptomatic patients. In contrast, the stage distribution of colorectal cancer patients detected with the Hemoccult-II® was not significantly different from the symptomatic patients. Therefore we propose that colorectal cancer patients detected by a positive OCSensor® can probably on average expect to have an increased five-year survival compared with those with a positive Hemoccult-II®. Although slightly more proximal colorectal cancers were detected in the symptomatic patients compared with the asymptomatic patients, this difference was not statistically significant. Therefore, tumours in the proximal colon are also detected by FOBT. For the OCSensor® this was confirmed in a recent study, where it was shown that the amount of blood in the stool detected in patients with proximal colorectal cancer is lower than in distal colorectal cancer, but never below the cut-off value of 50 ng/ml that we used in our study population.<sup>14</sup> In another study with a different immunochemical FOBT (Magstream 1000®), a lower sensitivity for proximal compared with distal colorectal cancer was reported, but this difference was not statistically significant.<sup>18</sup> Wexner *et al.* demonstrated there was no difference in colorectal cancer location for Hemoccult-II® negative and Hemoccult-II® positive colorectal cancer patients.<sup>19</sup> Fujita *et al.* also failed to detect any differences in colorectal cancer distribution over the colon in asymptomatic patients screened with guaiac slides compared with symptomatic patients.<sup>20</sup>

## CONCLUSION

We demonstrated that colorectal cancer is detected at significantly earlier stages in asymptomatic patients by a positive FOBT compared with symptomatic patients. In addition, treatment of colorectal cancer could be confined to colonoscopy in significantly more asymptomatic patients with a positive FOBT than in the symptomatic group. Furthermore, there was no difference in distribution of colorectal cancer over the colon between the asymptomatic and symptomatic colorectal cancer patients, indicating that tumours in the proximal colon are also detected by FOBT. Colorectal cancer was not detected at significantly earlier stages in patients detected with the Hemoccult-II compared with symptomatic patients. However, colorectal cancer was detected in significantly earlier stages in patients detected with the OCSensor compared with symptomatic patients.

## NOTE

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## REFERENCES

1. Slobbe L, Kommer G, Smit J, Groen J, Meerding W, Polder J. Costs of illness in the Netherlands 2003 (Dutch). RIVM report. 2006(270751010).
2. De Gramont A, Tournigand C, Andre T, Larsen AK, Louvet C. Adjuvant therapy for stage II and III colorectal cancer. *Semin Oncol.* 2007;34(2 Suppl 1):S37-40.
3. Gondos A, Bray F, Brewster DH, et al. Recent trends in cancer survival across Europe between 2000 and 2004: A model-based period analysis from 12 cancer registries. *Eur J Cancer.* 2008;44:1463-75.
4. Cappell MS. The pathophysiology, clinical presentation, and diagnosis of colon cancer and adenomatous polyps. *Med Clinics North Am.* 2005;89(1):1-42, vii.
5. Van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology.* 2008;135:82-90.
6. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst.* 2004;96(19):1420-5.
7. Fenocchi E, Martinez L, Tolve J, et al. Screening for colorectal cancer in Uruguay with an immunochemical faecal occult blood test. *Eur J Cancer Prev.* 2006;15(5):384-90.
8. Chiang CH, Jeng JE, Wang WM, Jheng BH, Hsu WT, Chen BH. A comparative study of three fecal occult blood tests in upper gastrointestinal bleeding. *Kaohsiung J Med Sciences.* 2006;22(5):223-8.
9. Castiglione G, Grazzini G, Miccinesi G, et al. Basic variables at different positivity thresholds of a quantitative immunochemical test for faecal occult blood. *J Medical Screen.* 2002;9(3):99-103.
10. Sohn DK, Jeong SY, Choi HS, et al. Single immunochemical fecal occult blood test for detection of colorectal neoplasia. *Cancer Res Treat.* 2005;37(1):20-3.
11. Rubeca T, Rapi S, Confortini M, et al. Evaluation of diagnostic accuracy of screening by fecal occult blood testing (FOBT). Comparison of FOB Gold and OC Sensor assays in a consecutive prospective screening series. *Int J Biol Markers.* 2006;21(3):157-61.
12. Grazzini G, Castiglione G, Ciabattini C, et al. Colorectal cancer screening programme by faecal occult blood test in Tuscany: first round results. *Eur J Cancer Prev.* 2004;13(1):19-26.
13. Vilkin A, Rozen P, Levi Z, et al. Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *Am J Gastroenterol.* 2005;100(11):2519-25.
14. Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. *Ann Int Med.* 2007;146(4):244-55.
15. Rockey DC. Occult gastrointestinal bleeding. *New Engl J Med.* 1999;341(1):38-46.
16. Stroehlein JR, Fairbanks VF, McGill DB, Go VL. Hemoccult detection of fecal occult blood quantitated by radioassay. *Am J Dig Dis.* 1976;21(10):841-4.
17. Huppe D, Hartmann H, Felten G, et al. [Effectiveness of screening colonoscopy in a community-based study]. *Gastroenterology.* 2008;46(2):193-200.
18. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology.* 2005;129(2):422-8.
19. Wexner SD, Brabbee GW, Wichern WA Jr. Sensitivity of hemoccult testing in patients with colorectal carcinoma. *Dis Colon Rectum.* 1984;27(12):775-6.
20. Fujita M, Sugiyama R, Kumanishi Y, et al. Evaluation of effectiveness of mass screening for colorectal cancer. *World J Surg.* 1990;14(5):648-52; discussion 52-3.