# Survival in patients with colorectal cancer diagnosed by screening colonoscopy

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**Background:** In Germany, screening colonoscopy was first established in 2002 as part of the national cancer screening program.

**Objective:** To evaluate whether colorectal cancer (CRC) survival differs when CRC is diagnosed by screening colonoscopy (S-CRC) versus diagnostic colonoscopy (D-CRC).

**Design:** Long-term, retrospective, multicenter, observational study.

**Setting:** Study centers: 10 private gastroenterology practices in Germany.

**Patients:** A total of 60 patients diagnosed with CRC during screening colonoscopy and 252 patients during diagnostic colonoscopy in 2002, 2003, and 2004.

**Interventions:** Colonoscopy.

**Main Outcome Measurements:** Survival of patients up to December 2013.

**Results:** Mean (± standard deviation [SD]) follow-up time was 81.0 (± 40.1) months. Union Internationale Contre le Cancer (UICC) stages I and II were found more often in S-CRC (81.6%) compared with D-CRC (59.9%; $P < .002$). Kaplan-Meier analysis showed significantly reduced overall survival for patients with D-CRC (mean [± SD] 86.9 [± 3.0] months; 95% confidence interval [CI], 81.0-92.8) compared with S-CRC (mean [± SD] 107.1 [± 4.9] months; 95% CI, 97.4-116.9; $P = .003$). When deaths not related to CRC were excluded, survival was still shorter for D-CRC patients (mean [± SD] 89.4 [± 3.0] months; 95% CI, 83.5-95.4) compared with S-CRC (mean [± SD] 109.6 [± 4.7] months; 95% CI, 100.2-119.0; $P = .004$).

**Limitations:** Retrospective study design.

**Conclusion:** In this long-term, retrospective study, patients with CRC diagnosed during screening colonoscopy lived significantly longer when compared with patients with CRC diagnosed during diagnostic colonoscopy. (Gastrointest Endosc 2015;82:133-7.)

In 2002, screening colonoscopy was introduced to the German national cancer screening program as an alternative to the fecal occult blood test (FOBT). Every public health insurant aged 55 years or older has a choice of screening method (screening colonoscopy or FOBT). Several European countries and the United States implemented colonoscopy as part of colorectal cancer (CRC) screening programs because it is believed to reduce

*Abbreviations: CRC, colorectal cancer; D-CRC, CRC diagnosed by diagnostic colonoscopy; FOBT, fecal occult blood test; S-CRC, CRC diagnosed by screening colonoscopy; UICC, Union Internationale Contre le Cancer.*

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CRC-related mortality. Indeed, numerous studies have shown that colonoscopic removal of adenomatous polyps prevents CRC development and CRC-associated deaths.[1-4] A German, single-center study reported a 2.43% CRC prevalence during diagnostic colonoscopy (presence of symptoms indicative of CRC or a positive FOBT result before colonoscopy) and 0.9% during screening colonoscopy (absence of symptoms indicative of CRC). The benefit of screening colonoscopy is attributed to polyp resection, but data on long-term follow-up of patients diagnosed with CRC during screening colonoscopy are limited. Ten years after the implementation of screening colonoscopy to the German cancer screening program, we sought to investigate whether survival rates of patients with CRC differed, based on whether CRC was diagnosed during screening or diagnostic colonoscopy.

## METHODS

This was a retrospective, multicenter, observational study investigating the influence of screening colonoscopy on survival of patients with CRC. Patients diagnosed with CRC in 2003, 2004, or 2005 were classified, based on indication for the examination (screening vs diagnostic colonoscopy) and followed until 2013. According to the 2002 German CRC guideline, patients aged ≥55 years can choose between 2 CRC screening methods: screening colonoscopy or FOBT. Patients with positive FOBT results underwent colonoscopy, which was considered diagnostic colonoscopy. Besides positive FOBT results, patients with symptoms indicative of CRC such as abdominal pain, iron deficiency anemia, weight loss, changes in bowel habits, or rectal bleeding were considered for diagnostic colonoscopy. Therefore, screening colonoscopy is defined as the absence of these symptoms, and any FOBT performed must have negative results. No patient had undergone colonoscopy before the examination that diagnosed CRC. All patients diagnosed with CRC received endoscopic follow-up care, which included colonoscopy within 3 years after surgical intervention followed by 5-year colonoscopy intervals if first colonoscopy after surgery was without pathologic findings. Patients not treated surgically received radiologic abdominal imaging at regular intervals.

Ten private gastroenterology practices already established in 2003 and located within a 50-mile radius of our center were asked to participate. Clinical data during follow-up were obtained by contacting the treating physician, the hospital responsible for tumor treatment, and registry authorities. We identified basic clinical parameters, initial tumor stage, time of survival, and cause of death. Initial tumor stage was determined according to the international classification of the Union International Contre le Cancer (UICC) in stages I through IV. Patients were followed until December 2013. The study was approved by the Ethics Committee of the University of Heidelberg and carried out in accordance with the declaration of Helsinki in its present form.

Descriptive data are presented as mean ± standard deviation (SD). Statistics were calculated with the use of the paired *t* test and the chi-square test when appropriate. The actuarial survival rate was estimated by the Kaplan-Meier method. Differences between the actuarial estimates were analyzed by using the log-rank test and presented as mean ± SD with 95% confidence interval (CI). All statistical computations were performed by using SPSS version 21 (IBM Germany, Ehningen, Baden-Wuerttemberg, Germany).

## RESULTS

### Study setting

All 10 private gastroenterology practices agreed to participate. A total of 372 patients were diagnosed with CRC in the years 2003, 2004, or 2005 at the 10 practices. Follow-up was complete in 312 patients; these patients were the cohort for further analysis, based on the study protocol. Reasons for loss of follow-up were inability to contact (n = 34), withdrawal of consent (n = 7), and incomplete data collection (n = 19). Mean (± SD) follow-up time was 81.0 (± 40.1) months.

### Patient cohort

A total of 125 of the 312 patients were female (40.1%). Mean (± SD) age at diagnosis of CRC was 66.1 (± 10.5) years (women: mean [± SD] 66.6 [± 11.2] years; men: mean [± SD] 65.7 [± 10.1] years). Overall, 7980 screening colonoscopies and 20,664 diagnostic colonoscopies were performed from 2003 to the end of 2005. A total of 60 patients were diagnosed with CRC during screening colonoscopy (S-CRC) and 252 patients during diagnostic colonoscopy (D-CRC). Therefore, the CRC-detection rate for screening colonoscopy was 0.75% and 1.12% for diagnostic colonoscopy.

A total of 101 (32.4%) of the CRCs were rectal, 100 (32.1%) were in the sigmoid colon, 17 in the descending colon (5.4%), 31 in the transverse colon (9.9%), 45 in the ascending colon (14.4%), and 18 were cecal (5.8%). Therefore, the majority of CRC were left sided (n = 223; 71.5%). There was no difference in age at diagnosis of CRC between patients with D-CRC (mean [± SD] 66.2 [± 11.2] years) or S-CRC (mean 65.8 [± 7.1] years; $P = .783$). Sex distribution was similar (Table 1). Of all patients diagnosed with CRC, we observed no post-colonoscopy, missed CRCs during the course of follow-up.

### UICC stages

A total of 104 patients were diagnosed with UICC stage I (33.3%), 96 with stage II (30.8%), 102 with stage III

**TABLE 1. Patient cohort**

| Variable | Screening CRC | Diagnostic CRC | *P* value |
|---|---|---|---|
| Age, mean (± SD), y | 65.8 (± 7.1) | 66.2 (± 11.2) | .783* |
| Female/male, no. | 26/34 | 99/153 | .565† |
| Death during follow-up, no. (%) | 14 (23.3) | 113 (44.8) | .002† |
| Tumor-associated death, no. (%) | 12 (20.0) | 101 (40.0) | .004† |

*CRC,* Colorectal cancer; *SD,* standard deviation.
**P* values were calculated by using the *t* test.
†*P* values were calculated by using the chi-square test.

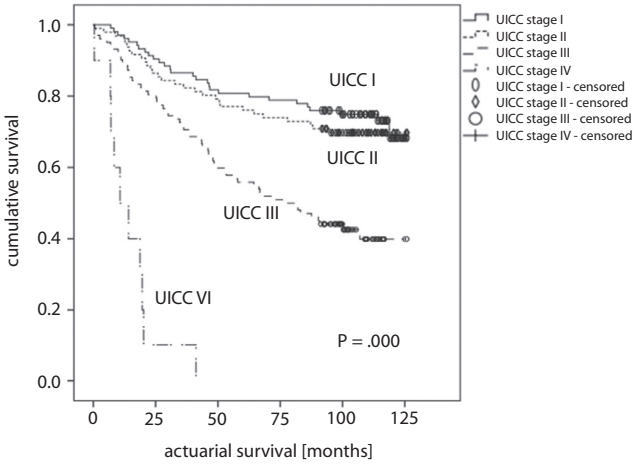


**Figure 1.** Survival analysis based on UICC stage Kaplan-Meier analysis of all patients (n = 312) according to UICC stages. There were 29 events in 104 patients with UICC stage I, 29 events in patients with UICC stage II, 59 events in UICC stage III, and 10 events in 10 patients with UICC stage IV ($P = 0.000$).

(32.7%), and 10 with stage IV (3.2%). CRC stages I and II were more frequent, with S-CRC (81.6%) compared with D-CRC (59.9%) ($P < .002$).

## Symptoms before D-CRC

A total of 58 (23.0%) D-CRC patients received colonoscopy because of positive FOBT results, 177 (70.2%) D-CRC patients had symptoms indicative of CRC, and 17 (6.7%) patients had symptoms indicative of CRC plus a positive FOBT result. The presence of CRC-indicative symptoms plus a positive FOBT result was more often found (94.1%) in UICC stages III and IV compared with patients with CRC-indicative symptoms but no positive FOBT result (36.1%).

## Survival analysis

As expected, CRC stage had a highly significant impact on overall survival: stage I (n = 104; mean [± SD] 104.3 [± 3.9] months; 95% CI, 96.6-111.9), stage II (n = 96; mean [± SD] 99.7 [± 4.4] months; 95% CI, 91.0-108.4) stage III (n = 102; mean [± SD] 76.1 ± 4.6 months; 95% CI, 66.9-85.3), stage IV (n = 10; mean [± SD] 14.7 ± 3.5 months; 95% CI, 7.7-21.7) ($P = .000$) (Fig. 1).

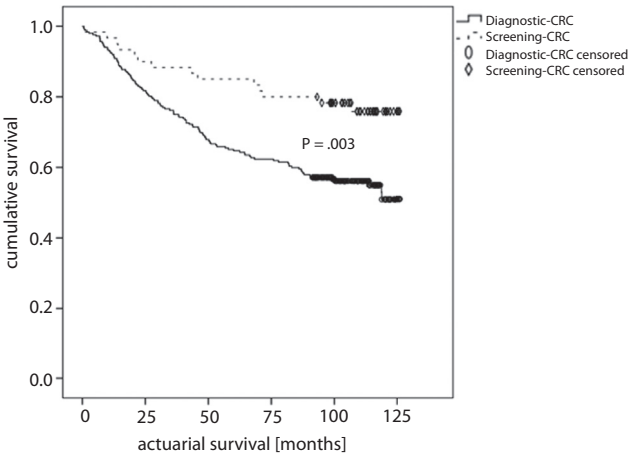


**Figure 2.** Survival analysis based on diagnostic-CRC or screening-CRC Kaplan-Meier analysis of patients with diagnostic-CRC (n = 252) or screening-CRC (n = 60). There were 113 events patients with diagnostic-CRC and 14 events in patients with screening-CRC resulting in a highly significant difference of actuarial survival ($P = .003$).

Kaplan-Meier survival analysis did not show an impact of CRC site when we compared left-sided CRC (n = 223; mean [± SD] 91.5 [± 3.1] months; 95% CI, 85.4-97.7) with right-sided CRC (n = 89; mean [± SD] 88.4 [± 4.9] months; 95% CI, 78.7-98.1) ($P = .646$).

The absence of symptoms indicative of CRC resulted in significantly prolonged survival (n = 60; mean [± SD] 107.1 [± 4.9] months; 95% CI, 97.4-116.9) compared with patients with positive FOBT results (n = 58; mean [± SD] 90.7 [± 6.1] months; 95% CI, 78.7-102.7) or patients with symptoms indicative of CRC (n = 194; mean [± SD] 85.8 [± 3.4] months; 95% CI, 79.0-92.5) ($P = .008$). Interestingly, survival did not differ statistically when we compared patients with CRC-indicative symptoms plus positive FOBT results (n = 17; mean [± SD] 82.4 [± 13.0] months; 95% CI, 56.8-108.0) compared with patients with CRC-indicative symptoms and the absence of a positive FOBT result (n = 177; mean [± SD] 85.8 [± 3.5] months; 95% CI, 78.8-92.8) ($P = .865$).

A total of 113 of 252 (44.8%) D-CRC patients and 14 of 60 (23.3%) S-CRC patients died during follow-up ($P = .02$). Kaplan-Meier analysis showed that actuarial survival was reduced with D-CRC (mean [± SD] 86.9 [± 3.0] months; 95% CI, 81.0-92.8) compared with S-CRC (mean [± SD] 107.1 [± 4.9] months; 95% CI, 97.4-116.9; Fig. 2; $P = .003$).

## CRC-associated survival

Of the 131 D-CRC patients who died during follow-up, 12 died from causes not associated with CRC. Of the 14 S-CRC patients who died during follow-up, 2 died from causes not associated with CRC ($P = .537$). A total of 13

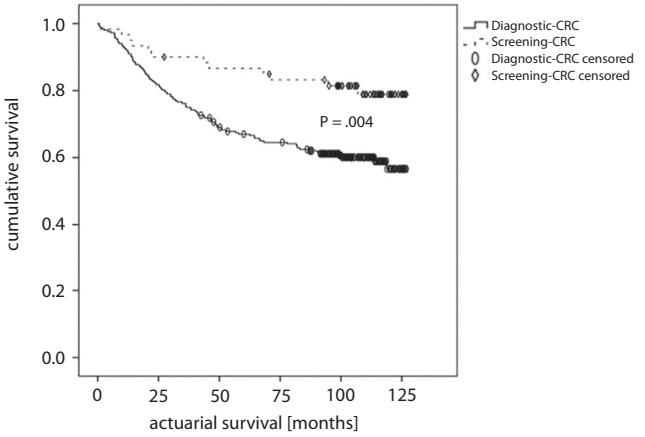


**Figure 3.** CRC-associated survival based on diagnostic-CRC or screening-CRC Kaplan-Meier analysis of patients with diagnostic-CRC (n = 252) or screening-CRC (n = 60) when only defining CRC-related deaths as events. There were 101 events patients with diagnostic-CRC and 12 events in patients with screening-CRC resulting in a highly significant difference of actuarial survival ($P$ = .004).

of the deaths not related to CRC (92.8%) occurred within UICC stage I, whereas 1 death not related to CRC occurred within UICC stage II. Reasons for deaths not related to CRC were cardiovascular events (57.1%), non-CRC malignancy (14.2%), pulmonary emphysema (14.2%), end-stage liver disease (7.1%), and septic pulmonary infection (7.1%). After we removed deaths not associated with CRC from Kaplan-Meier analysis, CRC-associated survival was impaired for D-CRC patients (89.4 ± 3.0 months; 95% CI, 83.5-95.4) compared with S-CRC patients (109.6 ± 4.7 months; 95% CI, 100.2-119.0) (Fig. 3) ($P$ = .004).

## DISCUSSION

Screening colonoscopy was established in Germany in 2002 as part of the national cancer screening program. Screening colonoscopy is associated with a stage-shift of CRC toward UICC stages I and II, suggesting that screening colonoscopy might improve survival of CRC patients.[5] The aim of the present study was to investigate this hypothesis a decade after the introduction of the screening colonoscopy program in Germany.

The detection of early stage CRC previously has been associated with reduced mortality.[6-8] In the present study, we found that CRC survival is longer in patients with lower UICC stages compared with patients with higher UICC stages at diagnosis ($P$ = .000; Fig. 1). In 2012, a study investigating more than 2 million screening colonoscopies concluded that the German screening program is highly efficient because screening colonoscopy achieves a stage shift of CRC diagnosis toward lower UICC stages. This stage shift was even more pronounced than in other large, population-based programs, with UICC stage I and II cancers found in about 70% of CRC patients.[9] Notably, 81.6% of CRCs detected in the present study during screening colonoscopy were within UICC stage I and II, compared with 59.9% of CRCs diagnosed during diagnostic colonoscopy (Table 2; $P$ = .002).

**TABLE 2. UICC stages based on Screening-CRC and Diagnostic-CRC**

| UICC stage, no. (%)* | Screening CRC | Diagnostic CRC | *P* value |
|---|---|---|---|
| I | 32 (53.3) | 72 (28.6) | .002† |
| II | 17 (28.3) | 79 (31.3) | |
| III | 9 (15.0) | 93 (36.9) | |
| IV | 2 (3.3) | 8 (3.1) | |

*UICC*, Union International Contre le Cancer; *CRC*, colorectal cancer.
*UICC stage I (T1/T2, N0, M0), stage II (T3/T4, N0, MO), stage III (any T, N1/N2, M0), stage IV (any T, any N, M1) *T*, tumor; *N*, node; *M*, metastasis.
†*P* value was calculated by using the chi-square test when we compared UICC stages I and II with UICC stages III and IV of screening colonoscopy with diagnostic colonoscopy.

Importantly, we demonstrated that patients diagnosed with CRC during screening colonoscopy lived 20.2 months longer than patients diagnosed during diagnostic colonoscopy (Fig. 2). We attribute this survival benefit to the lower UICC stages found in the S-CRC group compared with the D-CRC group. This finding is in line with studies investigating screening sigmoidoscopy[10-12] also showing a significant reduction of CRC mortality by screening methods.

The term *screening* generally applies to colonoscopy when the procedure is undertaken in asymptomatic patients who have either not had FOBTs or had negative FOBT results. Diagnostic colonoscopies are those performed in patients with symptoms or who have positive screening test results other than colonoscopy. The various colorectal symptoms differ in their predictive value for cancer at colonoscopy.[13] For example, bleeding symptoms including hematochezia, iron deficiency anemia, melena with a negative upper endoscopy, and positive FOBT results all predict a higher prevalence of cancer at colonoscopy compared with patients who have either no symptoms or who have non-bleeding symptoms such as abdominal pain or a change in bowel habit.[14,15] Patients with positive FOBT results and no symptoms have an increased prevalence of cancer, but the cancers have earlier stages compared with patients with symptoms.[16] In our study, we included patients with positive FOBT results in the diagnostic category per the usual convention. Despite including the patients with positive FOBT results in the diagnostic colonoscopy category and the strong association of positive FOBT results with early stage cancers, we still found that screening colonoscopy was associated with better survival than diagnostic colonoscopy.

A strength of this study is the long follow-up period up to 10 years after CRC diagnosis, whereas its key limitations is the retrospective design. A prospective, multinational, randomized, controlled trial is currently ongoing to test

CRC screening effectiveness in the general population, with a screening and a non-screening control group.[17] However, the results of this study will not be available for >10 years. Although CRC-screening methods differ between nations, our main finding of prolonged survival in cancers diagnosed at screening colonoscopy likely applies to screening colonoscopy in other countries.

Through detection and removal of pre-cancerous polyps, screening colonoscopy decreases the incidence of CRC[18] and prevents death from colorectal cancer.[1] In this long-term observational study, we showed that patients with CRC detected by screening colonoscopy have better survival than occurs in patients with CRC detected during colonoscopy performed for diagnostic indications. This effect in screening colonoscopy occurs independent of polypectomy.

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