

Predicting return to work among patients with colorectal cancer

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Background: The increase in prevalence of colorectal cancer among young patients coupled with an older retirement age in developed countries means that more patients are being diagnosed with colorectal cancer while still at work. The aim of this study was to develop prediction models for return to work by 1 and 2 years after the start of sick leave.

Methods: This was a retrospective registry-based cohort study of data from a nationwide occupational health service in the Netherlands. Only employed patients with colonic or rectal cancer treated with curative intent were included. Two predictor variable models were developed using multivariable logistic regression with backward selection. Calibration, discrimination and explained variance were used to assess model performance, and internal validation by bootstrapping was performed.

Results: Median time to return to work for 317 included patients was 423 (95 per cent c.i. 379 to 467) days. Two-thirds of patients had returned to work by 2 years after the start of the sick leave. Presence of metastases, adjuvant treatment, stoma, emotional distress and postoperative complications were predictors of not returning to work in the 1-year model. In the 2-year model, presence of metastases, emotional distress, postoperative complications, company size and the trajectory of the return-to-work process were predictors.

Conclusion: Almost 70 per cent of patients with colorectal cancer in this population returned to work within 2 years after the start of sick leave. The models can be used to guide patients early in colorectal cancer treatment about the likelihood of returning to work, and to identify and modify barriers that could facilitate this.

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Introduction

Improvements in colorectal cancer management have led to more patients being diagnosed at an early stage, with improved survival^{1–7}. As a result, more patients with colorectal cancer will resume normal life after treatment, including a return to work⁸. The increased incidence of colorectal cancer in young patients, coupled with the increasing retirement age in many countries, will lead to more patients being diagnosed with colorectal cancer while still in work^{9,10}.

Ability to return to work and to stay at work is important both to the patient and society in general^{11–15}. The impact of colorectal cancer on a patient's ability to return to work has not been studied extensively^{16,17}. Psychosocial and occupational factors, such as self-efficacy or workplace environment, may have an impact on return to work after

a cancer diagnosis in general^{18,19}. Previous research has mainly concentrated on other cancer types, where other disease-specific factors may play a role^{20,21}. Factors influencing rates of return to work among patients with colorectal cancer may be modifiable, such as workplace environment, or non-modifiable, such as age, (neo)adjuvant therapy and co-morbidity^{21–27}.

Reported return-to-work rates for patients with colorectal cancer range from 60 to 89 per cent^{26–30}. The average duration of sick leave for patients with colorectal cancer in the Netherlands is unknown^{31,32}. More evidence is required about the modifiable and non-modifiable barriers for patients to return to work^{19,20}. The aim of this study was to develop and internally validate prediction models for return to work by 1 and 2 years after the start of the sick leave among patients with colorectal cancer.

Methods

This was a retrospective registry-based cohort study. Data were extracted from the nationwide Dutch Occupational Health Service (ArboNed) registry³³. Data were collected from the medical records of occupational health physicians providing sickness guidance to employees of 70 000 contracted companies from a variety of economic sectors. The database included more than 1 million employees in the Netherlands. This study was approved by the Medical Ethical Committee of the Amsterdam University Medical Centres, VU University Amsterdam (registration number 2016.092). The TRIPOD checklist was used to ensure transparent reporting of these prediction models³⁴.

Study population

Included patients were sourced from the ArboNed registry. Inclusion criteria were being at least 18 years old with colonic or rectal cancer treated with curative intent, between January 2012 and December 2014. This included patients with potentially curable metastatic disease. Exclusion criteria were: patients with a diagnosis of recurrent colonic or rectal cancer, and those with another cancer diagnosis during the sick leave.

Sick leave regulation in the Netherlands

Regulation and guidance regarding sick leave for employees is mostly coordinated by Occupational Health Services in the Netherlands. An occupational health physician should be consulted within 6 weeks of starting sick leave, but the responsibility for return to work resides with the employer and employee. During the first 2 years of sick leave, the occupational health physician reviews the patient every 6 weeks to monitor recovery and potential for return to work, and to give advice. Employers are obliged to pay at least 70 per cent of the salary of the sick employee during these 2 years. After 2 years, if a return to work has not been possible, the employee is eligible for a disability pension from the social security agency of the Netherlands. The employer is then no longer responsible for payments^{35,36}.

Outcome measures

Return to work was calculated as a dichotomous outcome (did or did not return to work) by 1 and 2 years after the start of the sick leave. Return to work was defined as full and sustainable, which means at least 28 days of full work resumption after the sick leave ended with no loss of earning capacity.

Predictors of return to work

Potential predictors of return to work were selected based on clinical knowledge and previous studies, and also whether the data were available from the occupational health physician registry. All consultations were reviewed by the researcher and all candidate predictors were scored based on the information from these consultations. A second reviewer scored 10 per cent of all patients independently. All disagreements were resolved by discussion. Candidate predictors of return to work were categorized as person-, disease- or treatment-, or occupation-related factors. Person-related factors included: age (continuous)^{16,21–23}, sex (male, female)^{22,23}, marital status (married, single, widower, co-habiting)^{22,23} and medical history (no, yes)^{16,21–23}. Disease- or treatment-related factors included: type of diagnosis (colonic, rectal)^{22,23,27}, presence of metastases (curative treatment without metastases, curative treatment with metastases)²⁷, neoadjuvant treatment (no, yes)^{16,21–23}, adjuvant treatment (no, yes)^{16,21–23}, stoma (no, yes)^{22,23}, emotional distress (no, yes)^{22,23}, fatigue (no, yes)^{22,23}, pain (no, yes) and postoperative complications (no, yes)^{16,22,23,27}. Occupation-related factors included: type of work (physical, not physical, combination)³⁷, type of contract (full-time (36 h or more per week), part-time (less than 36 h but more than 12 h per week), flexible)³⁸, type of employment (permanent, temporary contract), company size (micro (fewer than 10 employees), small (11–50 employees), medium (51–250 employees), large (251 or more employees))³⁹, relationship with employer (bad, good) and the trajectory of the return to work (direct, phased).

Missing data

Before data extraction it was decided that, if no information regarding neoadjuvant therapy, adjuvant therapy, stoma, emotional distress or postoperative complications was available in the medical records, these factors would be scored as 'not reported' and included in the analysis as not present. This is in line with routine practice, as confirmed by the involved occupational health physicians, not to specifically record the absence of each of these variables. For all other predictors not reported in the medical record, the assumption was made that data were missing. To ensure the quality of the applied models, given the approach taken for the five predictors specified above, all other predictors with missing values were excluded from the analysis.

Statistical analysis

Analyses were performed using SPSS® version 22.0 (IBM, Armonk, New York, USA) unless indicated otherwise.

Table 1 Characteristics of the study population	
	No. of patients* (n = 317)
Age (years)†	54.4(7.7)
Sex ratio (F : M)	105 : 212
Diagnosis	
Colonic cancer	175 (55.2)
Rectal cancer	142 (44.8)
Aim of treatment	
Curative (no metastases)	260 (82.0)
Curative (metastases present)	57 (18.0)
Neoadjuvant therapy	
No	4 (1.3)
Yes	124 (39.1)
Not reported	189 (59.6)
Adjuvant therapy	
No	48 (15.1)
Yes	117 (36.9)
Not reported	152 (47.9)
Stoma	
No	37 (11.7)
Yes	164 (51.7)
Not reported	116 (36.6)
Emotional distress	
No psychological distress	75 (23.7)
Psychological distress	90 (28.4)
Not reported	152 (47.9)
Postoperative complications	
No	28 (8.8)
Yes	128 (40.4)
Not reported	161 (50.8)
Type of work	
Physical	90 (28.4)
Non-physical	126 (39.7)
Combination	101 (31.9)
Type of employment contract	
Part time	90 (28.4)
Full time	187 (59.0)
Flexible/0 h	40 (12.6)
Company size (no. of employees)	
< 10	97 (30.6)
10–50	154 (48.6)
51–250	56 (17.7)
≥ 251	10 (3.2)
Trajectory of return to work	
Direct	130 (41.0)
Phased	187 (59.0)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.).

Model development

Two prediction models were developed: return to work by 1 year and by 2 years after the start of sick leave. Collinearity between co-variables was tested based on the correlation between candidate predictors. The candidate predictor type of diagnosis was excluded from the

Fig. 1 Return to work for all 317 patients with colorectal cancer

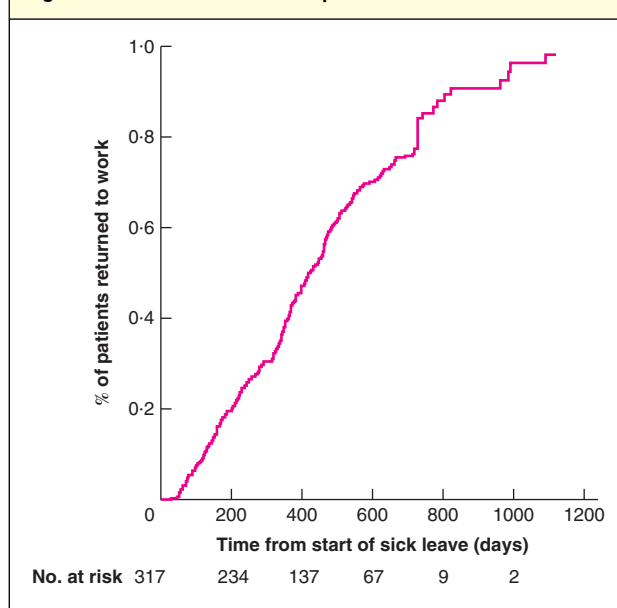


Table 2 Median time until return to work and reasons for not returning

	No. of patients (n = 317)*
Time until full return to work (days)†	423 (379, 467)
Time until first day of return to work (days)†	273 (239, 307)
Returned or did not return to work after total sick leave period	
Returned to work	233 (73.5)
Full and sustainable	223 (70.3)
Partial	10 (3.2)
Did not return to work	84 (26.5)
Registered work disabled	18 (5.7)
Contract terminated	32 (10.1)
Retired	12 (3.8)
Termination of contract of occupational health service with employer	11 (3.5)
Died	2 (0.6)
Reason unknown	9 (2.8)
1-year follow-up	
Returned to work	118 (37.2)
Not returned to work	199 (62.8)
2-year follow-up	
Returned to work	214 (67.5)
Not returned to work	103 (32.5)

*With percentages in parentheses unless indicated otherwise; †values are median (95 per cent c.i.).

Table 3 Results of univariable logistic regression analysis for return to work by 1 and 2 years

	Return to work by 1 year		Return to work by 2 years	
	Odds ratio	P	Odds ratio	P
Patient-related factors				
Sex (M versus F)	1.43 (0.88, 2.31)	0.145	0.87 (0.54, 1.46)	0.631
Age (per year)	0.99 (1.00, 1.03)	0.742	0.98 (0.95, 1.01)	0.280
Disease- and treatment-related factors				
Presence of metastases (yes versus no)	0.34 (0.17, 0.69)	0.003	0.38 (0.21, 0.69)	0.001
Neoadjuvant therapy (yes versus no)	0.62 (0.39, 1.01)	0.053	1.02 (0.63, 1.65)	0.943
Adjuvant therapy (yes versus no)	0.34 (0.20, 0.56)	< 0.001	0.78 (0.48, 1.27)	0.323
Stoma (yes versus no)	0.37 (0.23, 0.59)	< 0.001	0.76 (0.48, 1.22)	0.259
Emotional distress (yes versus no)	0.44 (0.26, 0.76)	0.003	0.42 (0.25, 0.70)	0.001
Postoperative complications (yes versus no)	0.51 (0.32, 0.83)	0.006	0.68 (0.43, 1.10)	0.118
Occupation-related factors				
Type of work				
Physical versus not physical	0.78 (0.45, 1.35)	0.372	1.02 (0.56, 1.85)	0.959
Physical versus combination	0.61 (0.34, 1.10)	0.097	0.60 (0.33, 1.09)	0.092
Type of contract				
Part-time versus full-time	0.86 (0.51, 1.44)	0.558	0.84 (0.49, 1.45)	0.531
Part-time versus flexible	0.81 (0.37, 1.75)	0.589	0.61 (0.28, 1.33)	0.213
Company size (no. of employees)				
10–50 versus < 10	0.87 (0.52, 1.47)	0.612	0.84 (0.49, 1.47)	0.548
51–250 versus < 10	0.83 (0.42, 1.63)	0.583	0.73 (0.36, 1.47)	0.380
≥ 251 versus < 10	0.37 (0.08, 1.85)	0.226	0.41 (0.11, 1.51)	0.179
Trajectory of return to work (direct versus phased)	0.69 (0.44, 1.10)	0.119	2.87 (1.77, 4.66)	< 0.001

Values in parentheses are 95 per cent confidence intervals.

analysis owing to the assumed correlation with neoadjuvant therapy and adjuvant therapy. There was no assumption of correlation for all other candidate predictors. The variable age was tested for linearity by means of spline curves and was subsequently considered as a continuous variable in the analysis⁴⁰. All candidate predictors were analysed in a separate univariable analysis. Then, multivariable logistic regression modelling with backward selection of variables with $P \leq 0.100$ was undertaken. Odds ratios and 95 per cent confidence intervals were calculated for the predictors in the models before and after internal validation.

Model performance

Calibration was assessed visually using a smooth calibration curve, and statistically using the Hosmer and Lemeshow goodness-of-fit test. Predicted probabilities were calculated for return to work by 1 and 2 years for each patient by using the linear predictor⁴¹. Discrimination was estimated using the area under the receiver operating characteristic (ROC) curve (AUC) (C-index of the model), which indicated the model's ability to discriminate between patients with a high versus low probability of returning to

work. AUC values of 0.70–0.79 were considered to indicate acceptable discrimination, 0.80–0.89 as excellent and 0.90 or more as outstanding discrimination⁴¹. Finally, the explained variance was calculated in terms of Nagelkerke's R^2 value.

Validation

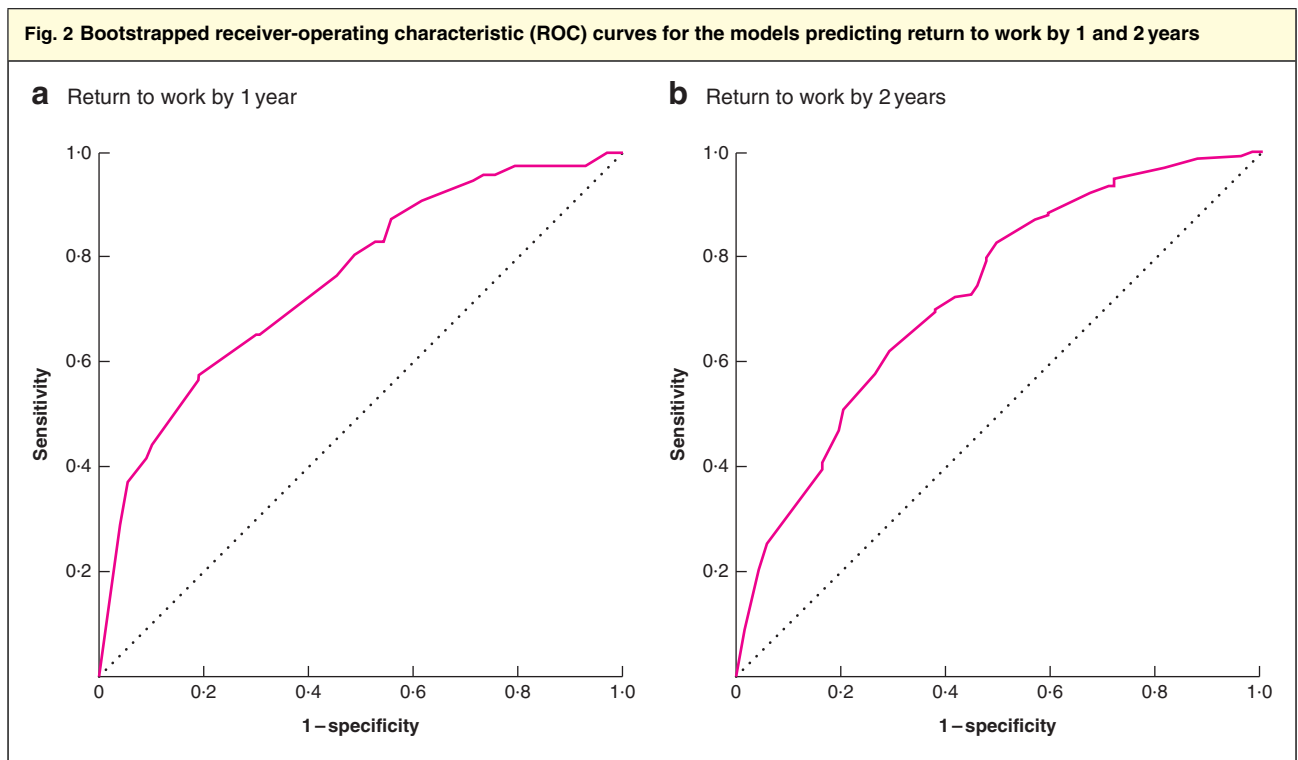
Internal validation by bootstrapping was done using Stata[®] version 14 (StataCorp, College Station, Texas, USA). The modelling process was repeated in 250 bootstrap samples. Testing the 250 bootstrap models for the original data and calculating the linear predictor slope established the overoptimism of the models developed in this study. The average difference between the linear predictor slope in the bootstrap samples and the original data was used as a shrinkage factor to correct the regression coefficients of the original model, and report the optimism-corrected AUC and Nagelkerke's R^2 value⁴².

Results

Some 317 patients with colorectal cancer were identified in the registry, 175 patients with colonic and 142 with rectal cancer. Patient characteristics are summarized in

	Before internal validation			After internal validation		
	Regression coefficient	Odds ratio	P	Regression coefficient	Odds ratio	P
Presence of metastases (yes versus no)	-0.84	0.43 (0.20, 0.94)	0.034	-0.84	0.43 (0.18, 1.04)	0.062
Adjuvant therapy (yes versus no)	-1.56	0.21 (0.11, 0.39)	<0.001	-1.56	0.21 (0.11, 0.40)	<0.001
Stoma (yes versus no)	-1.30	0.27 (0.15, 0.49)	<0.001	-1.30	0.27 (0.15, 0.49)	<0.001
Emotional distress (yes versus no)	-0.75	0.47 (0.26, 0.86)	0.010	-0.75	0.47 (0.25, 0.89)	0.020
Postoperative complications (yes versus no)	-0.52	0.60 (0.34, 1.06)	0.068	-0.52	0.60 (0.35, 1.01)	0.055
Constant		1.16			1.16	
P (Hosmer and Lemeshow test)		0.736				
Nagelkerke's R ²		0.26			0.16	
AUC		0.76 (0.70, 0.81)			0.73 (0.67, 0.78)	

Values in parentheses are 95 per cent confidence intervals. AUC, area under the curve.



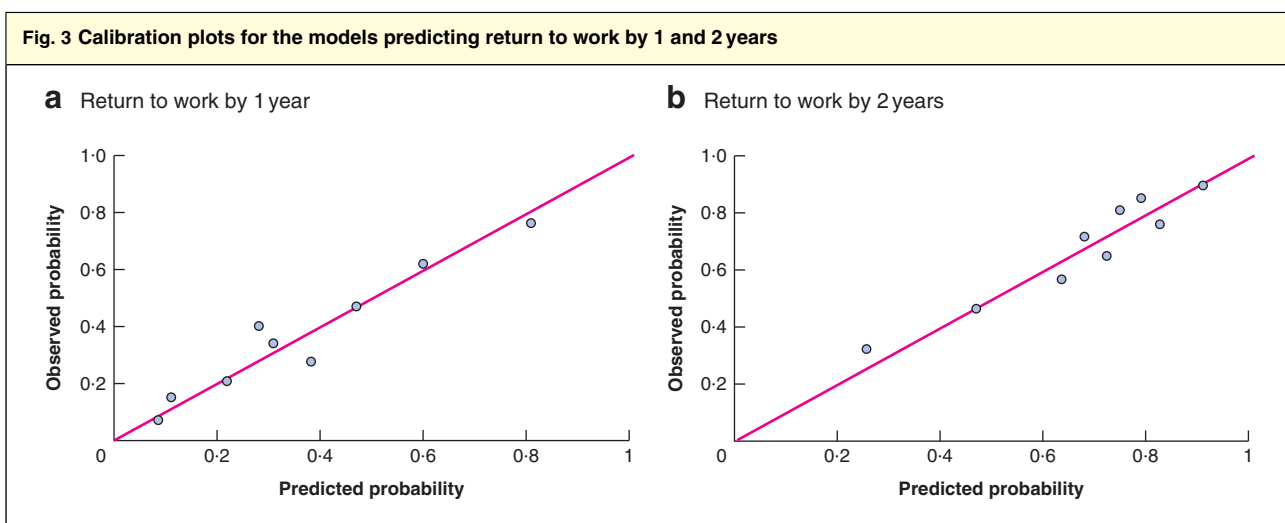
Return to work by **a** 1 year and **b** 2 years.

Table 1. These characteristics were also selected as candidate predictors for development of the prediction models. The other candidate predictors with missing values were not selected for analysis; the percentage of missing values for each excluded variable is shown in *Table S1* (supporting information). The median time until return to full-time and sustainable work was 423 (95 per cent c.i. 379 to 467) days (*Fig. 1*) and that until the first day of return to work was 273 (239 to 307) days. In total, 223 patients with colorectal cancer (70.3 per cent) returned to work fully.

Return to work rates by 1 and 2 years, and reasons for not returning to work after 2 years are shown in *Table 2*.

Univariable analysis

Table 3 shows the results of univariable analysis for return to work by 1 and 2 years. The candidate predictors presence of metastases, adjuvant therapy, stoma, emotional distress and postoperative complications predicted not returning to work by 1 year. Presence of metastases, emotional distress



Return to work by a 1 year and b 2 years.

	Before internal validation			After internal validation		
	Regression coefficient	Odds ratio	P	Regression coefficient	Odds ratio	P
Presence of metastases (yes versus no)	-0.95	0.39 (0.21, 0.72)	0.003	-0.95	0.39 (0.22, 0.67)	0.001
Emotional distress (yes versus no)	-0.95	0.39 (0.22, 0.67)	0.001	-0.95	0.39 (0.22, 0.67)	0.001
Postoperative complications (yes versus no)	-0.60	0.55 (0.32, 0.93)	0.026	-0.60	0.55 (0.31, 0.97)	0.039
Company size (no. of employees)						
10–50 versus < 10	-0.28	0.76 (0.41, 1.38)	0.362	-0.28	0.76 (0.39, 1.46)	0.403
51–250 versus < 10	-0.60	0.55 (0.25, 1.18)	0.125	-0.60	0.55 (0.24, 1.27)	0.162
≥ 251 versus < 10	-1.31	0.27 (0.07, 1.12)	0.070	-1.31	0.27 (0.07, 1.11)	0.069
Trajectory of return to work (direct versus phased)	1.26	3.52 (2.07, 6.00)	< 0.001	1.26	3.52 (1.52, 5.62)	0.001
Constant		1.08			1.08	
P (Hosmer and Lemeshow test)		0.513				
Nagelkerke's R²		0.20			0.12	
AUC		0.73 (0.67, 0.79)			0.71 (0.65, 0.77)	

Values in parentheses are 95 per cent confidence intervals. AUC, area under the curve.

and the trajectory of the return predicted not returning to work by 2 years.

Prediction model for return to work by 1 year

Multivariable analysis identified the following variables as independent predictors of not returning to work by 1 year: presence of metastases, adjuvant therapy, stoma, emotional distress and postoperative complications (Table 4). The *P* value for the Hosmer and Lemeshow test was 0.736. Before internal validation, the AUC of the model was 0.76 (95 per cent c.i. 0.70 to 0.81) and Nagelkerke's *R*² was 0.26. After internal validation with bootstrapping (250 samples), the AUC of the model was 0.73 (0.67 to 0.78) and Nagelkerke's *R*² was 0.16. The bootstrapped

ROC curve is shown in Fig. 2a and the calibration plot of this model in Fig. 3a. A worked example using the 1-year prediction model for return to work is available in Appendix S1 (supporting information).

Prediction model for return to work by 2 years

Multivariable analysis revealed that the following variables predicted return to work by 2 years: presence of metastases, emotional distress, postoperative complications, company size and the trajectory of the return to work (Table 5). The *P* value for the Hosmer and Lemeshow test was 0.513. Before internal validation, the AUC of the model was 0.73 (95 per cent c.i. 0.67 to 0.79) and Nagelkerke's *R*² was 0.20. After internal validation with bootstrapping (250

samples), the AUC of the model was 0.71 (0.65 to 0.77) and Nagelkerke's R^2 was 0.12. The bootstrapped ROC curve and calibration plot for this model are shown in *Figs 2b* and *3b* respectively. Calculation of the probability of return to work by 2 years for a fictitious patient is shown in *Appendix S1* (supporting information).

Discussion

Return to work after cancer treatment can be considered a surrogate marker of recovery in general. The ability to work is rated as the third most important aspect of quality of life^{43,44}. The present study has developed two models that can be used in daily practice to advise patients very early during treatment for colorectal cancer about their likelihood of returning to work by 1 and 2 years after diagnosis. Early identification of barriers that may prevent a return to work could allow employment modification of the barrier to allow a return to work that may have otherwise been impossible.

Disease- and treatment-related factors were found to play a role in return to work within the first year, which is not surprising as this interval coincides with the treatment period. Thereafter, occupation-related factors influenced return to work. It has been found previously that psychosocial and other occupation-related factors such as beliefs and expectations about long-term illness influence return to work for cancer survivors^{18,45–49}. There were insufficient data available to analyse all these factors fully in the present study, which may explain the low variance of these models. However, acceptable discrimination before and after internal validation was seen for both prediction models^{41,50}.

In the present study, only 37.2 per cent of included patients had returned to work by 1 year, which is lower than reported previously. This may be a result of different definitions of return to work^{26–30}. Alternatively, the lower rate of return to work by 1 year may be explained by differences in sick-leave regulations between countries. Patients may be less motivated to return to work when state-funded welfare is available, and so the importance of patient motivation should not be underestimated⁵¹. In the UK, for example, employers must provide Statutory Sick Pay for up to 28 weeks; thereafter, the state is responsible for at least 70 per cent of the compensation⁵¹. In the Netherlands, the employer is obliged to pay the salary of the sick employee for 2 years after the start of sick leave. The rate of return to work of 67.5 per cent at 2 years after the start of the sick leave in the present study is comparable to results in other countries (60–83 per cent)^{52,53}.

This study was limited by a relatively small data set, which can cause overfitting of prediction models, resulting in

underestimation of the probability of an event for low-risk patients and overestimation for high-risk patients^{42,54}. However, the use of internal validation by bootstrap resampling addresses the stability and quality of selected predictors, such that the risk of overfitting of these models is decreased. Another potential limitation was that the data were not originally collected for research purposes. This resulted in poorer data quality, meaning that some candidate predictors could not be assessed adequately and were therefore not included in the analysis. In addition, for some candidate predictors it was assumed that no reference in the occupational health medical report meant that this factor was not present. The occupational health physicians involved in this study indicated that it is routine practice not to specifically record the absence of each of these variables. This assumption may have had an impact on the results, and collection of longitudinal data for research purposes is recommended in future prospective studies. Furthermore, most categorical predictors were scored as dichotomous variables, resulting in less distinct information within the variable. However, dichotomization of variables makes the models more user-friendly, allowing quicker assessment of the likelihood of return to work.

An evidence-based guideline for recovery after colorectal cancer treatment in the Netherlands has been developed. Potential benefits and harms of the use of the screening tools in this study population need to be evaluated by others in future studies and external validation of these models performed. These studies should also include relevant occupational factors and patients' own expectations regarding ability to work. It would also be useful to develop separate models for colonic and rectal cancer to reflect the different characteristics and treatment options for tumours at each site.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.