One-year mortality of colorectal cancer patients: development and validation of a prediction model using linked national electronic data

Running title: Prediction of one-year colorectal cancer mortality

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Abstract

Background: The existing literature does not provide a prediction model for mortality of all colorectal cancer patients using contemporary national hospital data. We developed and validated such a model to predict colorectal cancer death within 90, 180, and 365 days after diagnosis.

Methods: Cohort study using linked national cancer and death records. The development population included 27 480 patients diagnosed in England in 2015. The test populations were diagnosed in England in 2016 (*n*=26 411) and Wales in 2015-16 (*n*=3814). Predictors were age, gender, socioeconomic status, referral source, performance status, tumour site, TNM stage, and treatment intent. Cox regression models were assessed using Brier scores, *c*-indices, and calibration plots.

Results: In the development population, 7.4%, 11.7%, and 17.9% of patients died from colorectal cancer within 90, 180, and 365 days after diagnosis. T4 versus T1 tumour stage had the largest adjusted association with the outcome (HR 4.67; 95% CI: 3.59–6.09). *C*-indices were 0.873–0.890 (England) and 0.856–0.873 (Wales) in the test populations, indicating excellent separation of predicted risks by outcome status. Models were generally well calibrated.

Conclusions: The model was valid for predicting short-term colorectal cancer mortality. It can provide personalised information to support clinical practice and research.

Background

In 2018, colorectal cancer was the third most incident cancer and caused the second largest number of cancer deaths in high-income countries.[1,2] It is a heterogeneous disease with varied presentations and large differences in prognosis. Considering the cancer stage alone, one-year net survival for localised and metastatic cancer varies from 96% to 55%, respectively, in the United States.[3]

Clinical prediction models combine multiple prognostic factors to estimate individualised risks of outcomes for each patient.[4,5] These risk predictions have many uses. In colorectal cancer research, prediction models have been used to examine prognosis in clinical trials,[6] to control for confounding in observational studies,[7] and to assess the added prognostic value of biomarkers.[8] In clinical practice, they may be used to inform treatment decisions and to communicate prognosis to patients, in line with the aims of personalised medicine and shared decision-making.[9]

In the absence of high-quality prediction models, clinicians' predictions of cancer survival may be inaccurate, non-transparent, and difficult to explain to patients.[10-12] Existing models for colorectal cancer mortality have focused on selected populations recruited to clinical trials (such as stage III and IV groups)[6,13,14], risks after surgery or chemotherapy,[15,16] or long-term survival using primary care data.[17] A recent systematic review[18] did not identify any models to predict mortality for all colorectal cancer patients using contemporary national hospital data.

In this study, our objective was to develop and validate a prediction model for death from colorectal cancer within three, six, and twelve months after diagnosis. To do this, we analysed national electronic hospital records linked to official mortality data from England and Wales.

Methods

Study populations

The National Bowel Cancer Audit collects data on adults (aged 18 years or over) newly diagnosed with colorectal cancer (International Classification of Diseases 10th Revision (ICD-10) codes: C18-20[19]) in England and Wales.[20] These data are entered into electronic record systems by hospital staff and later combined into a pooled national dataset by the National Health Service (NHS). We analysed data for patients whose date of diagnosis was from January 2015 to December 2016.

We defined one population to develop the prediction model and two separate populations to test the performance of this model. The eligible population used for model development included patients who were diagnosed in England in 2015 (*n*=28 505 patients). The first test population included patients who were diagnosed in England in 2016 (*n*=28 216 patients). The second test population included patients who were diagnosed in Wales in 2015 or 2016 (*n*=3861 patients).

Outcome

The outcome was death from colorectal cancer as identified from official death records provided by the Office for National Statistics.[21] We defined death from colorectal cancer using relevant ICD-10 codes recorded as the 'underlying cause of death' (see Supplement S1). The underlying cause is 'the disease or injury which initiated the train of morbid events leading directly to death'.[22]

Time to death was defined as the number of days between the date of diagnosis (as recorded in the National Bowel Cancer Audit dataset) and the date of death from colorectal cancer (as recorded in Office for National Statistics mortality data). The date of diagnosis was 'the date when cancer was confirmed or diagnosis agreed', which is typically the date of the pathology report that confirmed cancer. Patients who died from other causes were censored on the date of death. Patients alive as of 1 January 2018 were censored on that date, providing at least 365 days of follow-up for all patients.

Records from the National Bowel Cancer Audit and Office for National Statistics datasets were combined using deterministic linkage based on each patient's unique NHS number, date of birth, gender, and postcode. From the 60 582 eligible patients (in both development and test sets), the final sample size was 57 705 patients (27 480 in the development population; 26 411 in the England test population; and 3814 in the Wales test population). Supplement S2 provides the sample flow chart. Distributions of variables were similar for the linked and unlinked patients (Supplement S3).

Predictor variables

We used ten variables from the National Bowel Cancer Audit dataset as predictor variables: age, gender, socioeconomic status, source of referral, performance status, tumour site, TNM (tumour, node, metastasis) stage at diagnosis, and treatment intent. All variables were recorded in electronic data systems around the time of the first meeting between clinicians to discuss patients' treatment after diagnosis. We selected these predictors *a priori* to include variables recorded around the time of diagnosis that had relatively complete data (≥80% of values non-missing).

Patient age was coded as a continuous variable defined as the number of complete years between the dates of birth and diagnosis. Gender was male/female. Socioeconomic status was defined as the national rank of a patient's area of residence according to the Index of Multiple Deprivation[23]; the mean population size of these areas was 1500.[23] To aid interpretation, these ranks were linearly rescaled to have a median of zero and lower and upper quartiles of -1 and +1 respectively.[24]

The source of referral for investigation of suspected cancer had five categories: emergency hospital admission, urgent care/emergency department visit, primary care, national screening programme, and 'other' (e.g. a separate outpatient clinic). Performance status was defined by five categories of the Eastern Cooperative Oncology Group score (ranging from 'fully active' to 'completely disabled').[25] Tumour site was one of nine ICD-10 codes indexed under C18-20. T, N, and M stages of the cancer were defined by the TNM Classification of Malignant Tumours 5th Edition.[26] The treatment intent had three categories: curative, non-curative, and no active cancer treatment.

All ten predictor variables were defined using the National Bowel Cancer Audit dataset. The original (incomplete) data were used to calculate descriptive statistics for each variable. To account for missing values of predictors, we used multiple imputation with chained equations to generate 40 complete datasets (see Supplement S4 for details). All analysis of associations between the outcome and predictors was done using these 40 imputed datasets. We pooled model estimates and performance measures across the datasets to produce the final results.[27]

Statistical analysis

We used Cox proportional hazards regression[28] to estimate associations between predictor variables and the hazard of colorectal cancer death. Deaths from other causes were treated as censoring events. All predictors entered the regression model simultaneously. We fitted linear associations with the outcome for age and socioeconomic status, as non-linear transformations fitted by a multivariable fractional polynomial algorithm[29-31] were well approximated by linear relationships.

We assessed model performance at 90, 180, and 365 days after diagnosis. Overall model performance was measured using Brier scores.[32] These scores were calculated from the mean squared differences between predicted probabilities of colorectal cancer death within a given time period and the observed death status. We scaled these scores from 0–100% (0% if non-informative and 100% if perfect).[33]

To assess discrimination, we calculated the *c*-index.[34] This indicates the proportion of all pairs of patients whose survival times could be ordered such that the patient with the lower predicted risk of colorectal cancer death survived longer.[24] *C*-indices equal one for perfect models and 0.5 for random predictions. To assess model calibration, we plotted the predicted risks of colorectal cancer death against the actual observed risks, using the loess smoother to estimate the calibration curve.[24]

We assessed the internal validity of the model using 10-fold cross-validation and calculated mean values of the performance measures across the ten folds. We tested the performance of the model in two other populations: patients diagnosed in England in 2016 and in Wales in either 2015 or 2016.

Sensitivity analyses

Three sensitivity analyses tested the specification of the model and its performance, as detailed in Supplement S5. These added interaction terms between key predictors, added a comorbidity score and the number of unplanned admissions in the past year as predictor variables, and assessed whether censoring of surviving patients at 365 days affected the associations estimated.

Data preparation was done using Stata (v15) and R (v3.5) was used for all statistical analysis.

Results

In the population used to develop the prediction model, the percentages of patients who died from colorectal cancer were 7.4% (within 90 days), 11.7% (180 days), and 17.9% (365 days). These percentages were similar in the England test population but slightly greater in the Wales test population (Table 1). The Wales population had greater percentages of patients who were referred for diagnostic investigations after an emergency admission (29.0% *vs.* 13.0% in the development population) and who had metastases (25.6% *vs.* 22.1%). Most patients in each population were treated with curative intent (73.3% to 74.1%) (Table 2).

Missing values were most common for the performance status of the patient (16.8%) and the T and N-stages of the cancer (19.2% and 17.0%; Table 2). Data fields were complete across all variables for 61.5% of patients. These patients were more likely to be treated with curative intent (76.6% *vs.* 67.5%) and to survive until the end of follow-up (70.6% *vs.* 61.5%) than patients who had at least one predictor variable with a missing value (Supplement S6).

After multiple imputation of missing values, risks of colorectal cancer death were greatest for patients who had metastatic disease, had a treatment plan with non-curative intent or no active cancer treatment, or had an unfavourable performance status (Table 3). The risk of cancer death within 365

days was more than 50% for three patient groups: patients in the two worst performance status categories (50.3% and 58.3%) and patients with a non-curative treatment intent (51.9%).

In the multivariable model including all predictor variables, the greatest relative difference in the hazard of colorectal cancer death was between the T4 and T1 stages (hazard ratio (HR) = 4.67; 95% confidence interval (CI): 3.59 to 6.09). Compared to patients with a curative treatment intent, the hazard of colorectal cancer death was 3.85 times greater for patients whose treatment plan was non-curative (HR = 3.85, 95% CI: 3.60 to 4.11) or did not include active cancer treatment (HR = 3.85, 95% CI: 3.52 to 4.21). Outcomes were similar between the non-curative and no active cancer treatment groups (HR = 1.00, 95% CI: 0.92 to 1.09) (Table 3).

Predicted probabilities of colorectal cancer death varied widely within treatment intent categories. In the England test population, the 10th and 90th percentiles of predicted risks within 365 days were 1.7% and 12.9% for patients treated with curative intent, 23.8% and 88.8% for patients with a non-curative intent, and 16.3% and 89.6% for patients with no active cancer treatment planned.

Model performance

The probabilities of colorectal cancer death predicted by the model were well-calibrated with the observed proportions of patients that died, in both England and Wales test populations (Figure 1).

The model typically predicted very low risks of colorectal cancer death for patients who did not experience this outcome (Figure 2). The predicted risks were generally much greater for patients who did die from colorectal cancer, particularly for the 365-day outcome period. As a result, the predicted probabilities of colorectal cancer death were well separated between patients who did and did not have this outcome (Figure 2). This was reflected in large values of the *c*-index, ranging from 0.873 to 0.890 and 0.856 to 0.873 in the England and Wales test populations, respectively (Table 4).

The overall performance of the model as measured by the scaled Brier score was best for the 365-day period, followed by the 180 then 90-day periods (Table 4). For the 365-day period in the England test

population, the Brier score was improved by 40.0% compared to if the overall risk of colorectal cancer death had been used as the predicted probability for all patients, indicating a large improvement in prediction ability when using the model (versus no model).

Sensitivity analyses

In the sensitivity analyses, interaction terms between patient age, M-stage, and treatment intent did not improve model performance (maximum absolute difference in *c*-index or Brier score *vs.* main analysis = 0.001). Results were also similar when each patient's history of comorbidities and unplanned hospitalisations were added as predictors (maximum absolute difference = 0.002). When patients who were alive 365 days after diagnosis were censored at this time point, predictor effects were similar to those in the main analysis (range of relative differences in HRs: 0.97 to 1.08).

Discussion

The model developed was valid for predicting death from colorectal cancer within three, six, and twelve months after diagnosis in England and Wales. The model discriminated very well between patients who did and did not die from colorectal cancer, such that the former group typically had much higher predicted probabilities of death. These predictions were well calibrated with observed outcomes. The T-stage of the tumour had the largest adjusted association with the risk of death, followed by the treatment intent and performance status of the patient.

No single variable alone had a high positive predictive value for colorectal cancer death. For example, just over half of patients (51%) who did not have a curative treatment intent died within 365 days. Predicted risks of death varied widely across patients who did not have a curative intent. This wide variation also existed for patients who did have a curative treatment plan.

Strengths and limitations

We used large, national datasets to develop a new model and examine its temporal and geographic validity in whole populations from two countries. The data used for predictor variables were entered as part of routine care processes and therefore represent information available to clinicians in practice around the time of decision-making. We used cause of death information from official death records to distinguish colorectal cancer deaths from other deaths, and we were able to measure these outcomes for at least one year after diagnosis for all patients. Though the patients in the test sets were similar to those in the development set, the differences in the type of referrals and TNM stages between England and Wales provided a reasonable test of external validity.

The model would likely be improved if further information about the cancer was available, such as the sites of any metastases or possibly molecular data, as well as additional characteristics of patients (such as frailty) and their cancer care. This may help to predict greater probabilities of colorectal cancer death for patients who experienced this outcome. Some uncertainty in prognosis may reflect the biological development of cancer and the possibility of treatment-related complications.

Detailed assessment of patients' overall morbidity, particularly for older patients, could be used to contextualise predictions of cancer mortality in terms of overall life expectancy. However, the overall risk of dying from causes other than colorectal cancer within one year after diagnosis was only 4%, so other causes of mortality in this period may be less relevant to treatment decisions for most patients.

Differences in data collection or population characteristics may limit the generalisability of the model to other countries. Estimates of one-year survival for colorectal cancer can differ markedly between high-income countries, such as 78% in England and 84% in Sweden in 2010-12.[35] The model may need to be re-calibrated when used elsewhere if the survival differences are unexplained by differences in the distributions of predictors. However, despite survival in Wales being somewhat worse than in England in the current study, model calibration remained acceptable. Most predictors

used have standard international definitions. We rescaled the measure of socioeconomic status so that it might approximate similarly rescaled measures in other settings.

In order to avoid the possibility that any racial biases in access to treatment are reinforced by the prediction model, we did not consider patient ethnicity as a predictor.[36] This is in line with most clinical prediction models.[37] Prognostic factors such as lymphovascular invasion, surgical margin status, and definitive treatment were not included in the model as they are typically unknown around the time of diagnosis and were not relevant to all patients (some of whom do not receive surgery).

Missing data will have biased results if data were 'missing not at random', which multiple imputation cannot address. The extent of this bias cannot be ascertained from observed data, but each predictor had less than 20% of values missing, thus reducing the potential bias. National Bowel Cancer Audit records could not be linked to Office for National Statistics death records for 4.4% of eligible patients; distributions of predictor variables were similar between the linked and unlinked groups of patients but some bias due to linkage problems cannot be ruled out.

The 5th edition of the TNM system used in the analysis has been superseded by the 8th edition in the U.K., which will affect the N stage of some (but relatively few) patients.

Relation to existing literature

A previous study[17] used primary care records and cancer registry data to develop a prediction model for longer-term survival (1, 5, and 10-year) of colorectal cancer patients in England. This model did not include several variables that are routinely recorded in clinical team meetings shortly after diagnosis such as the referral source, performance status, separate TNM stages, and treatment intent. The *c*-index of 0.873 attained by our model for predicting 365-day cancer mortality in England is much greater than that reported for one-year mortality (from all causes) in the previous study (0.795 for men and 0.807 for women[17]). This indicates a large increase in performance (closer to the perfect *c*-index of 1), especially as *c*-indices are relatively insensitive to improvements in model fit.[38]

A systematic review[18] reported several prediction models developed for mortality in subgroups of colorectal cancer patients, such as patients with stage III[6] or metastatic[13,14] cancer, or for post-treatment mortality.[15,16] None of these models were developed to predict mortality for all colorectal cancer patients using contemporary national hospital data. A previous study[7] by our group used linked National Bowel Cancer Audit and Office for National Statistics death records to develop a risk-adjustment model for 90-day postoperative mortality. This model used similar predictors to the model presented here and showed good discrimination (*c*-index=0.799) and calibration; the *c*-index may have been lower in this surgical cohort partly due to the population being more homogeneous.

Implications for research and practice

The predictor information used in the model is recorded electronically as part of routine practice in England and Wales, typically during clinical team meetings where patient care is planned. Patients' risks of death within three, six, and twelve months could be automatically calculated in these meetings without additional data entry. Supplement S7 gives the formula for calculating predicted probabilities of colorectal cancer death within 90, 180, and 365 days after diagnosis.

The external validity of the model should be tested further before being used outside of England and Wales, possibly in combination with well-established methods for updating prediction models when used in new settings.[39] Ideally, the effects of the model on decision-making and patient outcomes would also be evaluated in future research (though such impact studies are rare[40]).

The model's predictions could be used to provide accurate prognostic information to patients, so that they can make informed decisions together with clinicians. The risk predictions may also help to prioritise patients for specialist palliative care services,[41,42] given the wide range of predicted risks for patients without a curative treatment intent. The predictions also varied widely for those with a curative intent, which may help to inform the intensity of related treatment. Finally, the model could also be relevant to various clinical, epidemiological, and biomarker studies.

Additional information

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Author contributions: T.E.C., J.B., and J.v.d.M. conceived the study. T.E.C. conducted the data analysis. T.E.C., A.B., J.B., K.W., A.K., S.G., A.A., M.B., L.D.S., and J.v.d.M. contributed to the design of the study, the interpretation of results, revisions of manuscripts drafted by T.E.C., and approved the final version to be published.

Ethics approval and consent to participate: As the National Bowel Cancer Audit involves analysis of data for service evaluation, it is exempt from UK National Research Ethics Committee approval. Section 251 approval was obtained from the Ethics and Confidentiality Committee for the collection of personal health data without the consent of patients. The study was performed in accordance with the Declaration of Helsinki.

Consent to publish: Not applicable.

Data availability: The data used in this study are available from NHS Digital and Public Health England's Office for Data Release but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. We do not have permission to share the patient-level records used in our analysis.

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Tables

Table 1. Descriptive statistics for the outcome variable and follow-up time

	Development population	**Test population - England**	**Test population - Wales**
Number of patients	27 480	26 411	3814
CRC death within, *n* (%)			
90 days	2024 (7.4)	1862 (7.1)	362 (9.5)
180 days	3210 (11.7)	2978 (11.3)	540 (14.2)
365 days	4926 (17.9)	4659 (17.6)	820 (21.5)
Other death within, *n* (%)			
90 days	483 (1.8)	467 (1.8)	83 (2.2)
180 days	762 (2.8)	677 (2.6)	117 (3.1)
365 days	1139 (4.1)	1039 (3.9)	158 (4.1)
Median follow-up (IQR), days*	908 (818 to 999)	544 (452 to 636)	705 (527 to 906)

CRC colorectal cancer, *IQR* interquartile range
*Calculated using the reverse Kaplan-Meier method

Table 2. Descriptive statistics for predictor variables

	Development population (*n*=27 480)	**Test population – England (*n*=26 411)**	**Test population – Wales (*n*=3814)**
Median age (years; IQR)*	72 (63 to 80)	72 (63 to 80)	72 (64 to 80)
Gender, *n* (%)			
Male (*vs.* female)	15 505 (56.4)	15 101 (57.2)	2209 (57.9)
Missing	7	12	0
Median socioeconomic status (IQR)†	0.2 (-0.8 to 1.1)	0.3 (-0.7 to 1.1)	-1.9 (-1.9 to -1.8)**
Referral source, *n* (%)			
Emergency admission	3542 (13.0)	3224 (12.4)	1092 (29.0)
Urgent care/ED visit	741 (2.7)	768 (3.0)	55 (1.5)
Screening	2701 (10.0)	2749 (10.6)	398 (10.6)
Primary care	15 227 (56.1)	14 549 (56.0)	1871 (49.6)
Other	4943 (18.2)	4689 (18.1)	354 (9.4)
Missing	326	432	44
Performance status, *n* (%)‡			
0 (fully active)	10 014 (43.9)	10 234 (45.8)	1217 (42.5)
1	7166 (31.4)	6770 (30.3)	924 (32.2)
2	3505 (15.4)	3285 (14.7)	462 (16.1)
3	1793 (7.9)	1729 (7.7)	234 (8.2)
4 (completely disabled)	340 (1.5)	313 (1.4)	29 (1.0)
Missing	4662	4080	948
Tumour site, *n* (%)			
Caecum	4087 (14.9)	3885 (14.7)	574 (15.1)
Ascending colon	3043 (11.1)	2908 (11.0)	416 (10.9)
Hepatic flexure	1083 (3.9)	1059 (4.0)	167 (4.4)
Transverse colon	1783 (6.5)	1725 (6.5)	232 (6.1)
Splenic flexure	688 (2.5)	671 (2.5)	104 (2.7)
Descending colon	946 (3.4)	980 (3.7)	118 (3.1)
Sigmoid colon	6364 (23.2)	6189 (23.4)	842 (22.1)
Rectosigmoid junction	1545 (5.6)	1477 (5.6)	226 (5.9)
Rectum	7941 (28.9)	7517 (28.5)	1135 (29.8)
Missing	0	0	0
T-stage, *n* (%)			
1	1338 (6.1)	1291 (6.0)	142 (4.3)
2	4387 (20.0)	4275 (20.0)	630 (19.2)
3	11 399 (51.9)	11 081 (51.8)	1670 (50.9)
4	4847 (22.1)	4731 (22.1)	840 (25.6)
Missing	5509	5033	532
N-stage, *n* (%)			
0	10 790 (47.8)	10 554 (48.0)	1532 (46.1)
1	7657 (33.9)	7566 (34.4)	1108 (33.4)
2/3	4137 (18.3)	3865 (17.6)	682 (20.5)
Missing	4896	4426	492
M-stage, *n* (%)			
0	17 975 (77.9)	17 853 (78.6)	2413 (74.4)
1	5094 (22.1)	4861 (21.4)	832 (25.6)
Missing	4411	3697	569
Treatment intent, *n* (%)			
Curative	19 078 (73.3)	18 089 (73.7)	2406 (74.1)
Non-curative	5440 (20.9)	4869 (19.8)	722 (22.2)
No active cancer treatment	1508 (5.8)	1601 (6.5)	118 (3.6)
Missing	1454	1852	568

ED emergency department, IQR interquartile range

Number of patients with no missing values across all populations = 35 472 (61.5%).

*Age range was 18 to 104. †Rescaled national rank of the area in which a patient resided (0 is the median; -1 is the lower quartile, more deprived; 1 is the upper quartile, less deprived). ‡Measured on the Eastern Cooperative Oncology Group (ECOG) scale. **Values not comparable to England values due to differences in scales

Table 3. Univariable and multivariable associations between the outcome and predictor variables in the development population, estimated using Cox regression

	CRC death within 90 days (%)	CRC death within 180 days (%)	CRC death within 365 days (%)	Univariable associations, HR (95% CI)	Multivariable associations, HR (95% CI)
Age (per 10 years)	-	-	-	1.39 (1.37 to 1.42)	1.21 (1.18 to 1.23)
Gender					
Male	6.8	11.0	16.8	1	1
Female	8.0	12.6	19.3	1.09 (1.05 to 1.14)	1.02 (0.98 to 1.07)
Socioeconomic status*	-	-	-	0.92 (0.90 to 0.93)	0.96 (0.95 to 0.98)
Referral source					
Emergency admission	18.1	25.0	34.5	1	1
Primary care	6.0	10.3	16.8	0.47 (0.44 to 0.49)	0.73 (0.69 to 0.78)
Urgent care/ED visit	15.6	22.0	31.1	0.88 (0.78 to 0.99)	0.98 (0.86 to 1.12)
Screening	0.7	1.3	2.2	0.09 (0.08 to 0.11)	0.33 (0.29 to 0.39)
Other	6.2	10.4	16.3	0.46 (0.43 to 0.49)	0.75 (0.69 to 0.81)
Performance status†					
0 (fully active)	2.3	4.5	8.5	1	1
1	5.2	9.3	15.9	1.73 (1.63 to 1.84)	1.20 (1.13 to 1.28)
2	11.3	17.8	26.9	2.95 (2.76 to 3.15)	1.53 (1.42 to 1.66)
3	28.3	39.7	50.3	6.99 (6.51 to 7.51)	2.34 (2.14 to 2.55)
4 (completely disabled)	39.7	48.8	58.3	10.04 (8.68 to 11.60)	3.37 (2.87 to 3.96)
Tumour site					
Caecum	11.0	16.7	25.1	1	1
Ascending colon	7.8	12.4	19.9	0.77 (0.71 to 0.84)	0.92 (0.84 to 1.00)
Hepatic flexure	9.9	15.4	23.4	0.92 (0.82 to 1.03)	1.14 (1.01 to 1.29)
Transverse colon	10.0	16.3	23.0	0.89 (0.81 to 0.98)	1.08 (0.98 to 1.19)
Splenic flexure	9.3	12.5	18.2	0.73 (0.63 to 0.84)	0.88 (0.76 to 1.03)
Descending colon	10.3	14.2	18.9	0.77 (0.68 to 0.88)	0.92 (0.80 to 1.05)
Sigmoid colon	6.7	10.7	16.1	0.66 (0.62 to 0.71)	0.81 (0.75 to 0.87)
Rectosigmoid junction	7.3	11.9	18.3	0.73 (0.66 to 0.81)	0.85 (0.76 to 0.94)
Rectum	4.5	7.7	12.9	0.61 (0.57 to 0.65)	0.79 (0.73 to 0.85)
T-stage					
1	0.8	1.4	2.1	1	1
2	2.5	3.8	6.1	2.93 (2.24 to 3.84)	2.03 (1.55 to 2.66)
3	6.2	9.9	15.8	7.30 (5.66 to 9.41)	3.02 (2.32 to 3.93)
4	16.0	25.2	37.2	17.80 (13.80 to 22.96)	4.67 (3.59 to 6.09)
N-stage					
0	4.2	6.5	10.4	1	1
1	8.4	13.4	20.5	1.98 (1.87 to 2.10)	1.15 (1.08 to 1.23)
2/3	13.5	21.5	32.1	3.34 (3.15 to 3.56)	1.52 (1.42 to 1.64)
M-stage					
0	3.0	5.0	8.7	1	1
1	22.6	34.9	49.9	7.45 (7.09 to 7.82)	2.81 (2.62 to 3.02)
Treatment intent					
Curative	1.5	2.7	5.9	1	1
Non-curative	23.0	36.3	51.9	10.74 (10.22 to 11.28)	3.85 (3.60 to 4.11)
No active cancer treatment	23.8	34.1	45.3	8.41 (7.80 to 9.06)	3.85 (3.52 to 4.21)

CI confidence interval, CRC colorectal cancer, ED emergency department, HR hazard ratio
*National rank of the area in which a patient resided (1 unit increase equals difference between quartiles of ranks)
†Measured on the Eastern Cooperative Oncology Group (ECOG) scale

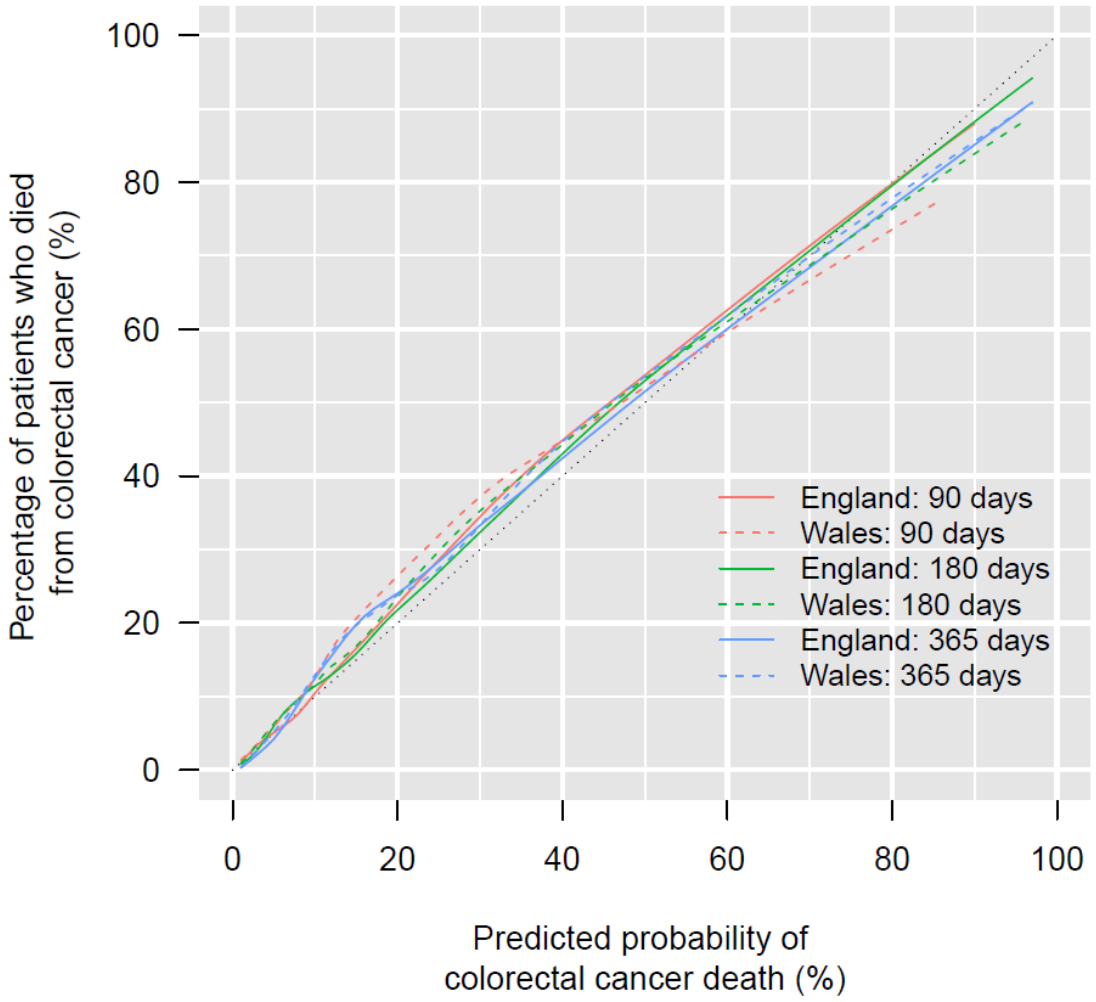
Table 4. Overall model performance and discrimination in the development and test populations

	Development population	**Test population - England**	**Test population - Wales**
Scaled Brier score (%)			
90 days	23.5	23.7	24.1
180 days	32.6	32.4	32.1
365 days	39.5	40.0	40.1
***c*-index**			
90 days	0.885	0.890	0.873
180 days	0.882	0.885	0.867
365 days	0.870	0.873	0.856

Scaled Brier scores range from 0% to 100% with larger scores indicating better performance
C-indices range from 0.5 (random predictions) to 1 (perfect discrimination)

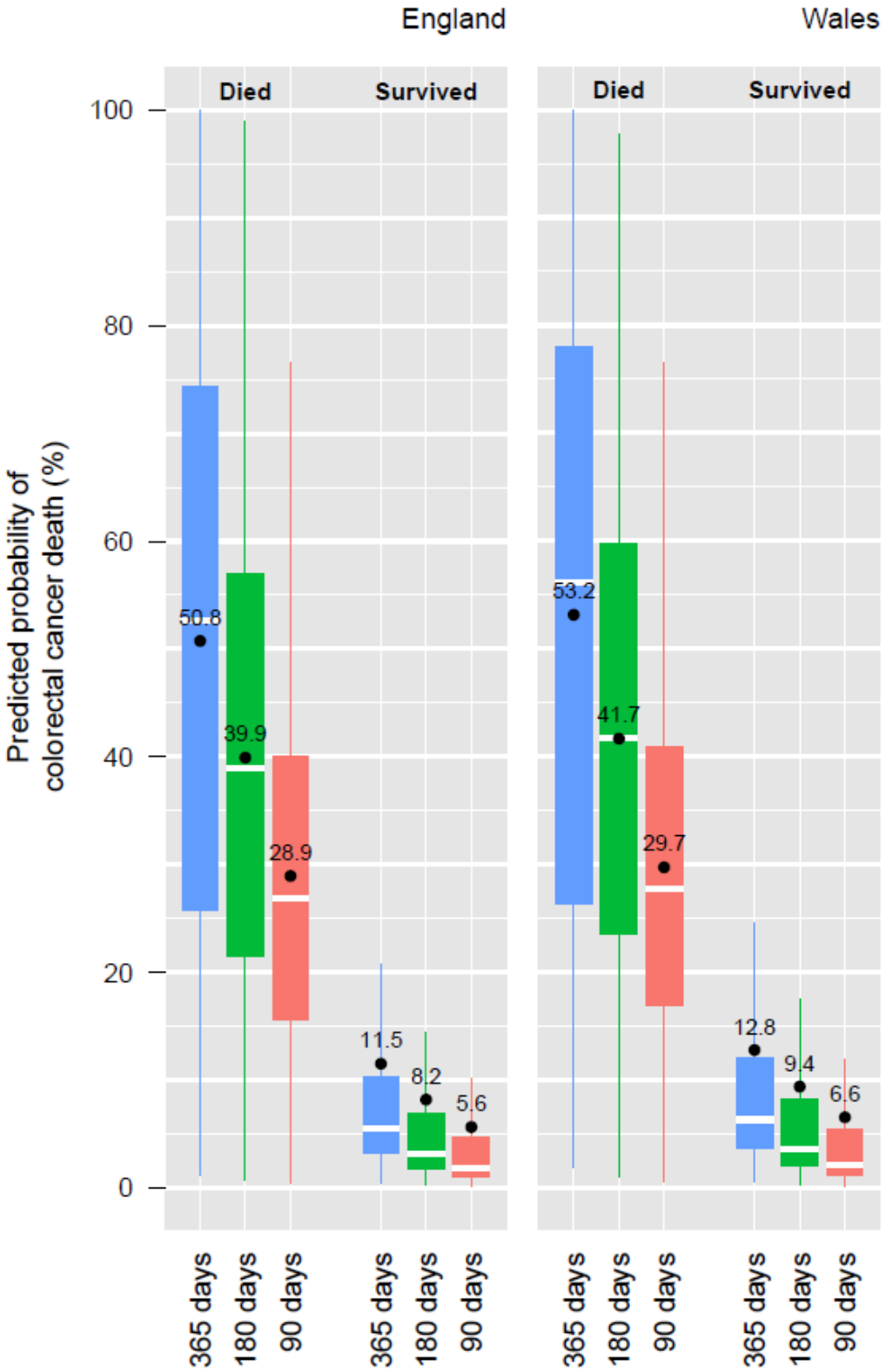
Figures

Figure 1. Calibration plots for predicted probabilities of colorectal cancer death within 90, 180, and 365 days after diagnosis, in the England and Wales test populations



Note: The coloured lines represent the smoothed relationships between the observed and predicted risks of colorectal cancer death. The black dotted 45° line represents the ideal relationship showing perfect calibration.

Figure 2. Boxplots comparing predicted probabilities of colorectal cancer death by outcome status within 90, 180, and 365 days after diagnosis, in the England and Wales test populations



Note: Boxes are drawn from the lower to upper quartile of predicted probabilities with a white horizontal line at the median value. Annotated values and black dots correspond to mean values. Whiskers are drawn to the most extreme predicted probabilities that are no more than 1.5 times the interquartile range from the box.

Supplementary Information

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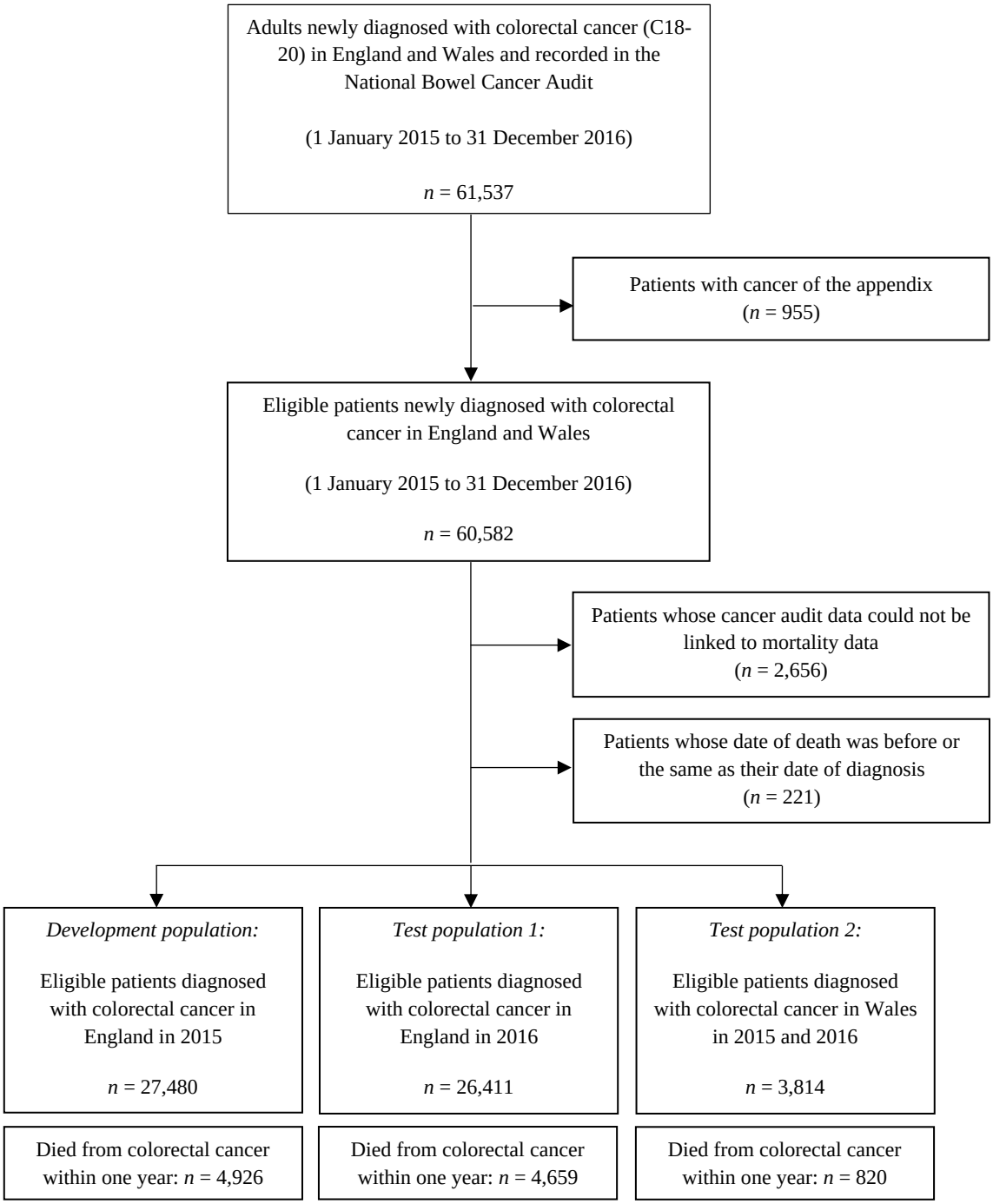
Supplement S1. ICD-10 codes used to identify deaths from colorectal cancer

ICD-10 code	Description
C18	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C26.0	Malignant neoplasm of other and ill-defined digestive organs: intestinal tract, part unspecified
C26.9	Malignant neoplasm of other and ill-defined digestive organs: ill-defined sites within the digestive system
C76.2	Malignant neoplasm of other and ill-defined sites: abdomen
C77	Secondary and unspecified malignant neoplasm of lymph nodes
C78	Secondary malignant neoplasm of respiratory and digestive organs
C79	Secondary malignant neoplasm of other and unspecified sites
D37.4	Neoplasm of uncertain or unknown behaviour of oral cavity and digestive organs: colon
D37.5	Neoplasm of uncertain or unknown behaviour of oral cavity and digestive organs: rectum
D37.7	Neoplasm of uncertain or unknown behaviour of oral cavity and digestive organs: other digestive organs

Supplement S2. Flow diagram of study population



Supplement S3. Descriptive statistics for predictor variables by linkage of the National Bowel Cancer Audit and Office for National Statistics death records

	Linked patients (*n*=57 926)	**Unlinked patients (*n*=2656)**
Median age (years; IQR)*	72 (63 to 80)	73 (65 to 80)
Gender (%)		
Male (*vs.* female)	56.9	54.3
Median socioeconomic status (IQR)†	0.1 (-1.0 to 1.1)	0.1 (-0.8 to 1.0)
Referral source (%)		
Emergency admission	13.9	14.4
Urgent care/ED visit	2.8	2.6
Screening	10.2	9.1
Primary care	55.5	55.8
Other	17.6	18.1
Performance status‡ (%)		
0 (fully active)	44.6	43.0
1	30.9	31.6
2	15.2	15.7
3	7.9	7.8
4 (completely disabled)	1.5	1.9
Tumour site (%)		
Caecum	14.8	16.6
Ascending colon	11.0	10.8
Hepatic flexure	4.0	4.2
Transverse colon	6.5	6.9
Splenic flexure	2.6	3.3
Descending colon	3.5	4.0
Sigmoid colon	23.2	22.5
Rectosigmoid junction	5.6	5.2
Rectum	28.7	26.5
T-stage (%)		
1	5.9	6.1
2	19.9	19.9
3	51.7	51.6
4	22.4	22.5
N-stage (%)		
0	47.8	47.9
1	34.1	35.1
2/3	18.1	17.0
M-stage (%)		
0	77.9	78.4
1	22.1	21.6
Treatment intent (%)		
Curative	73.4	75.7
Non-curative	20.6	18.1
No active cancer treatment	6.0	6.2

*Age range was 18 to 104. †Rescaled national rank of the area in which a patient resided (0 is the median; -1 is the lower quartile; 1 is the upper quartile). ‡Measured on the Eastern Cooperative Oncology Group (ECOG) scale. ED: emergency department.

Supplement S4. Methods for imputed datasets

We applied multiple imputation using chained equations to predict missing values of predictor variables.[1] For each of these variables, all other predictors, colorectal cancer death status and the Nelson-Aalen estimate of the cumulative baseline hazard were included in the imputation model.[2] The imputation method was predictive mean matching for continuous variables, logistic regression for binary variables, and polytomous regression for categorical variables with more than two categories. We generated 40 complete imputed datasets for each population, following guidance to use at least as many imputed datasets as the percentage of observations with incomplete data.[3] Imputation was done separately for each population to avoid introducing artificial correlations across populations.

Estimates from Cox proportional hazards regression in each imputed dataset were pooled using Rubin's rules.[4] When assessing the internal validity of the model using 10-fold cross-validation, we calculated the medians of the cross-validated estimates of the Brier score and *c*-index in each imputed dataset.[5] As there were 40 complete imputed datasets for the development population and each test population, there were 1,600 (40 x 40) unique combinations of datasets for each test population. When assessing external validity, we tested model performance for each of these combinations, then calculated the medians of the Brier score and *c*-index across the 1,600 combinations.

For the calibration plots, we calculated the mean of the complementary log-log transformation of the probability estimated for each patient across the 1,600 combinations.[5] The back-transformed means were then plotted against the observed risks.

References:

1. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software* 2011;45(3):67.

2. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med* 2009;28(15):1982-98.

3. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30(4):377-99.

4. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York: Wiley; 1987.

5. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol* 2009;9:57.

Supplement S5. Sensitivity analyses

We examined whether adding an interaction term between patient age and M-stage improved model performance, as this interaction was predictive of 90-day postoperative mortality in a similar dataset.[1] We also added interactions between age and treatment intent and between M-stage and treatment intent in this model, to allow treatment to moderate key patient characteristics.

We assessed the benefit of adding two extra variables as predictors: a comorbidity score and the number of unplanned hospital admissions in the year before diagnosis. These variables were limited to sensitivity analyses as they are not available from the same dataset as the other predictors so would be more difficult to implement practically. The comorbidity score was a weighted number of comorbidities, based on 28 non-cancer comorbidities[2] and their established weights.[3] To generate the scores, we linked National Bowel Cancer Audit records to routine hospital records of inpatient admissions (Hospital Episode Statistics[4]). We used ICD-10 codes[5] to identify each comorbidity in the year before diagnosis. The number of unplanned admissions was derived from the same dataset.

The Cox proportional hazards model assumes that the hazard ratios are constant over the follow-up period. We explored whether different follow-up periods affected the hazard ratios estimated by censoring survival times beyond 365 days at 365 days and re-estimating the model.

References:

1. Walker K, Finan PJ, van der Meulen JH. Model for risk adjustment of postoperative mortality in patients with colorectal cancer. *Br J Surg* 2015;102(3):269-80.

2. Elixhauser A, Steiner C, Harris DR, Coffey RN. Comorbidity measures for use with administrative data. *Med Care* 1998;36(1):8-27.

3. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A Modification of the Elixhauser Comorbidity Measures into a Point System for Hospital Death Using Administrative Data. *Med Care* 2009;47(6):626-33.

4. NHS Digital. *Hospital Episode Statistics (HES)*. Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics.

5. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43(11):1130-9.

Supplement S6. Comparison of patients with completely observed data for all variables and patients with missing data for one or more variables

	Completely observed data	**Missing data**
Number (%) of patients	35 472 (61.5)	22 233 (38.5)
Median survival/follow-up time (IQR)	597 (406 to 823)	563 (318 to 816)
Status at follow-up end, *n* (%)		
Survived	25 053 (70.6)	13 679 (61.5)
Colorectal cancer death	8524 (24.0)	6861 (30.9)
Other death	1895 (5.3)	1693 (7.6)
Median age (years; IQR)*	72 (63 to 80)	73 (64 to 81)
Gender, *n* (%)		
Male (*vs.* female)	20 480 (57.7)	12 335 (55.5)
Median socioeconomic status (IQR)†	0.1 (-1.0 to 1.1)	0.0 (-1.0 to 1.0)
Referral source, *n* (%)		
Emergency admission	4297 (12.1)	3561 (16.6)
Urgent care/ED visit	772 (2.2)	792 (3.7)
Screening	3704 (10.4)	2144 (10.0)
Primary care	20 706 (58.4)	10 941 (51.1)
Other	5993 (16.9)	3993 (18.6)
Performance status, *n* (%)‡		
0 (fully active)	16 366 (46.1)	5099 (40.7)
1	10 985 (31.0)	3875 (30.9)
2	5309 (15.0)	1943 (15.5)
3	2425 (6.8)	1331 (10.6)
4 (completely disabled)	387 (1.1)	295 (2.4)
Tumour site, *n* (%)		
Caecum	5069 (14.3)	3477 (15.6)
Ascending colon	3974 (11.2)	2393 (10.8)
Hepatic flexure	1386 (3.9)	923 (4.2)
Transverse colon	2198 (6.2)	1542 (6.9)
Splenic flexure	857 (2.4)	606 (2.7)
Descending colon	1225 (3.5)	819 (3.7)
Sigmoid colon	7639 (21.5)	5756 (25.9)
Rectosigmoid junction	2057 (5.8)	1191 (5.4)
Rectum	11 067 (31.2)	5526 (24.9)
T-stage, *n* (%)		
1	2088 (5.9)	683 (6.1)
2	7174 (20.2)	2118 (19.0)
3	18 476 (52.1)	5674 (50.9)
4	7734 (21.8)	2684 (24.1)
N-stage, *n* (%)		
0	16 276 (45.9)	6600 (53.1)
1	12 621 (35.6)	3710 (29.9)
2/3	6575 (18.5)	2109 (17.0)
M-stage, *n* (%)		
0	28 312 (79.8)	9929 (73.2)
1	7160 (20.2)	3627 (26.8)
Treatment intent, *n* (%)		
Curative	27 176 (76.6)	12 397 (67.5)
Non-curative	6740 (19.0)	4291 (23.4)
No active cancer treatment	1556 (4.4)	1671 (9.1)

*Age range was 18 to 104. †Rescaled national rank of the area in which a patient resided (0 is the median; -1 is the lower quartile, more deprived; 1 is the upper quartile, less deprived). ‡Measured on the Eastern Cooperative Oncology Group (ECOG) scale. ED: emergency department; IQR: interquartile range.

Supplement S7. How to calculate probabilities of colorectal cancer death within 90, 180, and 365 days of diagnosis from the prediction model

The probability of colorectal cancer death by time *t* equals: $1 - S_0(t)^{\exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p)}$.

where $S_0(t)$ is the baseline survival probability at time *t*, β are the regression coefficients from the estimated Cox proportional hazards regression model, *X* are predictor variables, and p is the number of predictor variables.

The value of $S_0(t)$ for an individual with all risk factors equal to zero** is:

- For the 90 days period: 0.9983142
- For the 180 days period: 0.9969342
- For the 365 days period: 0.9941971

The values of β for each predictor variable are:

	β
Age (per 10 years)*	0.18802794
Gender	
Male	0
Female	0.02453517
Socioeconomic status†	-0.03625044
Referral source	
Emergency admission	0
Urgent care/ED visit	-0.01889659
Screening	-1.09412094
Primary care	-0.31258302
Other	-0.28886696
Performance status‡	
0 (fully active)	0
1	0.18617150
2	0.42744336
3	0.84882276
4 (completely disabled)	1.21503157
Tumour site	
Caecum	0
Ascending colon	-0.08209810
Hepatic flexure	0.13092154
Transverse colon	0.07391412
Splenic flexure	-0.12596959
Descending colon	-0.08558521
Sigmoid colon	-0.21539719
Rectosigmoid junction	-0.16826741
Rectum	-0.23575824
T-stage	
1	0
2	0.70853229
3	1.10545928
4	1.54166050
N-stage	
0	0
1	0.14132215
2/3	0.42053813
M-stage	
0	0
1	1.03367028
Treatment intent	
Curative	0
Non-curative	1.34685236
No active cancer treatment	1.34679083

*Age range was 18 to 104. †Rescaled national rank of the area in which a patient resided (0 is the median; -1 is the lower quartile, more deprived; 1 is the upper quartile, less deprived). ‡Measured on the Eastern Cooperative Oncology Group (ECOG) scale. ED: emergency department. **Baseline survival probabilities assume age zero and median socioeconomic status.