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Colorectal cancer recurrence and its impact on survival after curative surgery: An analysis based on multistate models

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ABSTRACT

Aim: To investigate the usefulness of multistate models (MSM) for determining colorectal cancer (CRC) recurrence rate, to analyse the effect of different factors on tumour recurrence and death, and to assess the impact of recurrence for CRC prognosis.

Methods: Observational follow-up study of incident CRC cases disease-free after curative resection in 2006–2013 ($n = 994$). Recurrence and mortality were analyzed with MSM, as well as covariate effects on transition probabilities.

Results: Cumulative incidence of recurrence at 60 months was 13.7%. Five years after surgery, 70.3% of patients were alive and recurrence-free, and 8.4% were alive after recurrence.

Recurrence has a negative impact on prognosis, with 5-year CRC-related mortality increasing from 3.8% for those who are recurrence-free 1-year after surgery to 33.6% for those with a recurrence.

Advanced stage increases recurrence risk (HR = 1.53) and CRC-related mortality after recurrence (HR = 2.35). CRC-related death was associated with age in recurrence-free patients, and with comorbidity after recurrence.

As expected, age≥75 years was a risk factor for non-CRC-related death with (HR = 7.76) or without recurrence (HR = 4.26), while its effect on recurrence risk was not demonstrated.

Conclusions: MSM allows detailed analysis of recurrence and mortality in CRC. Recurrence has a negative impact on prognosis. Advanced stage was a determining factor for recurrence and CRC-death after recurrence.

1. Introduction

Worldwide, colorectal cancer (CRC) remains the fourth most commonly diagnosed cancer and the fifth leading cause of cancer-related death [1]. Survival rates for CRC patients have improved significantly in recent decades, and now exceed 50% at 5 years from diagnosis [2,3]. According to EUROCARE-5 data, European age-standardised 5-year survival rates were 57% and 55.8% for colon and rectal tumours, respectively [4]. This improvement in survival may be due to improvements in disease diagnosis, treatment, and surgical techniques.

However, CRC prognosis depends heavily on the stage at diagnosis [5]. Surgical resection (with or without adjuvant or neoadjuvant chemoradiotherapy) is the primary curative treatment for 80% of non-metastatic CRC patients [6,7]. However, more than 40% of patients eligible for potentially curative resection develops recurrent disease during the follow-up [8]. Patients who develop recurrence are known to have a significantly increased risk of death, so better knowledge of recurrence risk could improve the follow-up of patients who have undergone curative surgery, allowing clinicians to select more appropriate therapies or treatments based on the patient's estimated risk of recurrence.

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The Cox proportional hazards model is the most commonly used model to analyse survival data in cancer epidemiology [9]. Some CRC prognostic factor studies have used a Cox regression model including recurrence as a time-dependent covariate to assess its effect on mortality [10–13]. However, this methodology assumes that the effect of a baseline prognostic variable on mortality is the same in patients with or without a recurrence. This could be avoided by including interactions between covariates and recurrence as a time-dependent variable. However, the Cox regression model is limited to a single event (mortality) and does not allow for different transitions between health states (such as recurrence and mortality), so the effect of baseline prognostic factors on the risk of recurrence and death cannot be assessed simultaneously. These limitations are overcome by multistate models (MSM), which allow the effects of prognostic factors on different clinical endpoints to be separated [11,14–18].

Darcourt et al. [13] showed the advantages of MSM to study the course of CRC progression and the role of recurrence in this process, comparing them with conventional survival models. However, although that study included a long follow-up, it was conducted on a cohort of patients diagnosed before 1984 and only a few prognostic factors (age, sex, site and stage at diagnosis) were analysed. Despite their potential usefulness, few recent studies have explored the use of MSM to analyse the prognosis of patients with CRC [19–22]. In 2015, Gilard-Pioc et al. [20] applied MSM to explore the impact of age, gender, and cancer stage on mortality and recurrence in a large registry of CRC patients who underwent curative surgery. More recently, Khaniki et al. [21] modelled the risk of local recurrence and death after initial treatment using MSM, adjusting for other prognostic factors. Finally, Alfachi et al. [22] jointly modelled recurrence and death, taking into account the probability of being apparently cured after resection using a so-called multi-state cure model.

The results of using this methodology to analyse the prognosis of patients with CRC are therefore still scarce and limited to series with small numbers of patients in which only a few prognostic factors are analysed. In particular, the differences between colon and rectal tumours have not been studied in this way. On the other hand, the prognosis of CRC patients should be studied by independently analysing cancer-specific and non-cancer-specific mortality. A high proportion of these patients are elderly or have associated comorbidities that make them more susceptible to competing events (death from other causes), especially in long-term follow-up. In this context, a competing risk approach is recommended to correctly identify prognostic factors that may be differentially associated with CRC-related and non-CRC-related death [23].

The aim of this study is to investigate the usefulness of MSM to determine the recurrence rate in a large prospective cohort of CRC patients, to analyse the impact of different prognostic factors, including location, on tumour recurrence and cancer-specific death, and to assess the importance of recurrence as an intermediate event for the prognosis of CRC patients.

2. Material and methods

2.1. Design and study population

This is an observational, ambispective follow-up study of incident cases of CRC. Consecutive adult (≥18 years) patients with a histopathological diagnosis of CRC (International Disease Classification 153-154) were recruited at the Complexo Hospitalario Universitario A Coruña (north-west Spain), between 2006 and 2013. Prevalent or recurrent cases, cases with multiple cancers, cases treated only in private hospitals, cases detected by CRC screening, and cases diagnosed in another hospital were excluded. For the purpose of this study, only patients who underwent resection with curative intent and were disease-free after surgery and adjuvant or neoadjuvant chemoradiotherapy were included ($n = 994$ patients).

Part of this cohort was included in a multicentre project (DECCIRE I and DECCIRE II studies [24,25]). Informed patient consent and ethical review board approval was obtained (Galician Clinical Research Ethics Committee codes 2004/159, 2009/160 and 2020/090).

2.2. Data collection

Cases were identified through the Pathological Anatomy Department. Each patient was then contacted by the specialist responsible for their follow-up, who explained the aims of the study and their possible inclusion. After informed consent, data for the study were obtained from patient interviews conducted by trained nurses and from review of clinical records.

2.3. Measurements

The data analysed included socio-demographic factors. family history of cancer and comorbidity (Charlsonś score). Several variables related to CRC at diagnosis were registered, including tumour location, histological grade, TNM stage [26], and carcinoembryonic antigen (CEA) level.

Primary outcomes were recurrence and death. Recurrence was defined as a composite of local recurrence and/or distant metastasis, whichever occurred first. Information on vital status and cause of death, according to the International Classification of Diseases 10th revision (ICD-10), was obtained from clinical records and the Galician Mortality Registry. Death was classified as CRC-related for ICD-10 codes C18-C20. Otherwise, the death was attributed to another cause.

2.4. Statistical analyses

Descriptive and univariate analyses were performed to determine differences in sociodemographics, comorbidity, and clinical variables according to tumour location. Quantitative variables were compared using Student's *t*-test or Mann–Whitney *U test*, after assessing normality using the Komogorov-Smirnov test. Categorical characteristics were compared using chi-squared statistics.

The cumulative incidence of recurrence, CRC-related death, and non-CRC-related death was estimated by competing risk survival analysis [27], stratified by tumour location and stage. Follow-up started on the date of surgery and ended on the date of death or the last time an individual was known to be alive. Follow-up was extended to November 2019.

MSM were used to separate the effects of prognostic factors on the risk of recurrence from their effects on the risk of death [10,15,16]. A MSM was implemented with the following four states: (1) initial state, alive without recurrence, (2) transition state, alive with recurrence, and two absorbing states, (3) CRC-related death and (4) non-CRC-related death as a competing event (Fig. 1). For this study, the most relevant transitions were: transition from alive and recurrence-free to recurrence; from alive and recurrence-free to CRC-related death, and from recurrence to CRC-related death.

First, the transition probabilities and state occupation probabilities were estimated in this nonparametric model for all patients using the Markovian estimator (Aalen-Johansen estimator) [14,28–30]. Cumulative transition hazards were calculated for each of the possible transitions. To examine the effect of covariates, the stratified Cox proportional hazards model was used to calculate the empirical cumulative hazard by covariate for each transition. A transition-specific Cox model was considered to estimate the regression coefficients of the covariates for each transition. This ap-

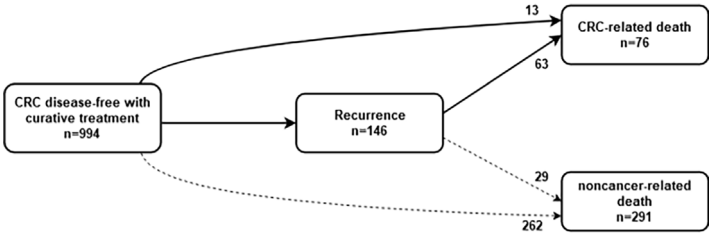

Fig. 1. Multistate model of colorectal cancer recurrence and mortality.

Table 1
Clinical characteristics and prognosis of the patients included.

	Total n = 994	Colon n = 682	Rectum n = 309	p
Age at diagnosis (years), mean±SD	69.7 ± 10.8	70.8 ± 10.4	67.3 ± 11.3	<0.001
Charlson's comorbidity index, median (IQR)	1 (0–2)	1 (0–2)	0 (0–1)	0.100
Gender, male	600 (60.4%)	404 (59.2%)	193 (62.5%)	0.337
Family history of cancer	113 (11.7%)	80 (12.0%)	32 (10.7%)	0.541
TNM Stage				0.054
In situ	12 (1.3%)	9 (1.4%)	3 (1.0%)	
I	230 (24.5%)	153 (23.8%)	77 (26.5%)	
II	400 (42.6%)	293 (45.5%)	106 (36.4%)	
III	276 (27.8%)	175 (27.2%)	99 (34.0%)	
IV	20 (2.1%)	14 (2.2%)	6 (2.1%)	
Histological grade				0.124
G1 (well differentiated)	198 (21.0%)	141 (21.7%)	57 (19.7%)	
G2 (moderately differentiated)	665 (70.6%)	448 (68.9%)	215 (74.4%)	
G3-G4 (poorly differentiated)	79 (8.4%)	61 (9.4%)	17 (5.9%)	
CEA at diagnosis, median (IQR)	1.6 (0.9–3.1)	1.6 (0.9–3.0)	1.8 (0.9–3.1)	0.202
Surgery type				<0.001
Hemicolectomy	611 (61.7%)	587 (86.0%)	24 (8.0%)	
Subtotal/Total colectomy	46 (4.6%)	43 (6.3%)	1 (0.3%)	
Rectal resection	299 (30.2%)	34,0 (5.0%)	264,0 (87.7%)	
Endoscopic polypectomy	34 (3.4%)	18 (2.6%)	12 (4.0%)	
Adyuvant chemotherapy	409 (41.1%)	245 (36.5%)	162 (55.1%)	<0.001
Time of follow-up from surgery (months), median (IQR)	91.5 (66.9–112.8)	91.4 (66.9–111.8)	91.6 (67.3–115.1)	0.704
Recurrence	146 (14.7%)	88 (12.9%)	58 (18.8%)	0.016
Local recurrence	43 (29.4%)	32 (36.4%)	11(19.0%)	
Distant metastasis	91 (62.3%)	50 (56.8%)	41 (70.7%)	
Local recurrence and metastasis	12 (8.2%)	6 (6.8%)	6 (10.3%)	
Time from surgery to recurrence (months), median (IQR)	23.2 (16.7–38.2)	20.7 (14.7–31.1)	27.7 (20.4–42.9)	0.006
Death	367 (36.9)	256 (37.5%)	110 (35.6%)	0.558
CRC-related death	76 (20.7)	49 (19.1%)	27 (24.5)	
Non-CRC-related death	291 (79.3)	207 (80.9%)	83 (75.5%)	

proach allows us to specify separate baseline transition hazards for each transition. The semi-parametric model included the following prognostic factors: age at diagnosis (classified as <65, 65–75 or ≥75 years of age), sex, TNM stage, histological grade, tumour location, and CEA. Other factors such as adjuvant chemotherapy and type of surgery were also examined. A sensitivity analysis was performed combining CRC-related and non-CRC-related death. Finally, the analysis was also repeated by excluding cases with metastases at diagnosis. To avoid over-adjustment bias, it was decided not to adjust for variables related to treatment received, that are only presented in the Supplementary Material.

All statistical analyses were performed using SPSS 24.0 and R 3.5.1, in addition to the *cmprsk, mstate,* and *survival* packages. Bilateral p-values<0.05 were considered statistically significant.

3. Results

A total of 994 CRC patients were included in the study (mean age at diagnosis: 69.7 ± 10.8 years; 60.4% male). Tumours were located in the colon in 67.2% of patients and in the rectum in 32.8%. TNM stage and other clinical features are shown in Table 1

Patients were followed for 85.5 ± 36.5 months (median follow-up=91.5 months) after curative surgery. One hundred and forty six (14.7%) developed local recurrence or metastasis after curative treatment, of whom 92 (63.0%) died (63 CRC-related deaths). Median time to recurrence was 23.2 months (IQR=16.7–38.2). 275 (27.7%) patients died without having previously developed local recurrence or metastasis (13 CRC-related deaths). A total of 627 patients were alive at the end of the follow-up (Fig. 1).

The cumulative incidence of recurrence was 1.6% at 12 months after surgery, 7.5% at 24 months, 10.8% at 36 months, and 13.7% at 60 months, with a significantly higher incidence in rectal than in colon tumours (p = 0.024) (Fig. 2a) and in more advanced stages (p < 0.001) (Fig. 2b). There were no differences in recurrence rates between the different types of surgery, or between patients who received adjuvant chemotherapy and those who did not. More than 60% of the recurrences were diagnosed between 12 and 36 months after surgery. At 60 months of follow-up, the cumulative incidence of CRC-related and non-CRC-related death was 4.0% and 17.3%, respectively. For stage IV tumours, the 60-month CRC-related death rate was 10.5% (Fig. 2c). Overall survival at 5-years was 78.7%, with no difference between colon and rectal tumours (Fig. 2d).

Occupation probabilities, defined as the probability that a patient is in a given state at any given time after curative surgery, and some specific transition probabilities between states, are shown in Fig. 3 and Table 2. Numeric results show that 93.0% of the patients are alive and relapse-free 1-year after surgery; 77.9% and 70.3% are alive and relapse-free at 3 and 5-years, respectively. At the same time points, 1.6%, 8.8% and 8.4%, respectively, are alive after being diagnosed with a recurrence. Recurrence has a negative

Table 2
State occupation probabilities (probability that a patient be in a specific state at a given time from surgery) and transition probabilities between states.

State/Transition	From time (s) (months)	To time (t) (months)	Probability	95% CI
Alive, recurrence-free	0	12	0.930	0.914–0.946
	0	24	0.841	0.818–0.864
	0	36	0.779	0.754–0.805
	0	48	0.730	0.702–0.758
	0	60	0.703	0.674–0.731
Recurrence	0	12	0.016	0.008–0.024
	0	24	0.070	0.055–0.086
	0	36	0.088	0.070–0.105
	0	48	0.092	0.074–0.109
	0	60	0.084	0.066–0.101
CRC-related dead	0	12	0.000	0–0
	0	24	0.002	0–0.005
	0	36	0.015	0.008–0.023
	0	48	0.026	0.016–0.036
	0	60	0.040	0.028–0.053
Non-CRC-related dead	0	12	0.054	0.040–0.068
	0	24	0.086	0.069–0.104
	0	36	0.118	0.098–0.138
	0	48	0.152	0.130–0.174
	0	60	0.173	0.150–0.197
Alive, recurrence-free -> Recurrence	6	60	0.085	0.067–0.103
	12	60	0.082	0.065–0.099
	24	60	0.052	0.038–0.065
	36	60	0.029	0.019–0.040
	48	60	0.012	0.005–0.020
Alive, recurrence-free -> CRC-related Dead	6	60	0.041	0.028–0.053
	12	60	0.038	0.026–0.050
	24	60	0.022	0.013–0.030
	36	60	0.010	0.004–0.015
	48	60	0.003	0.000–0.006
Recurrence -> CRC-related Dead	6	60	0.336	0.210–0.462
	12	60	0.336	0.210–0.462
	24	60	0.285	0.201–0.369
	36	60	0.203	0.127–0.278
	48	60	0.133	0.066–0.201

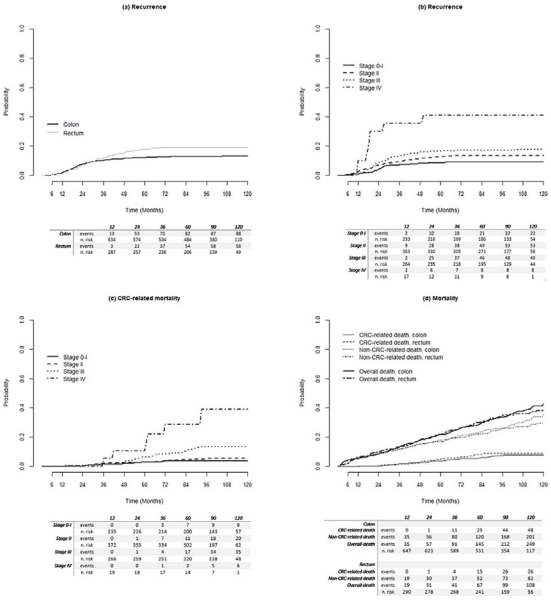

Fig. 2. Cumulative incidence of colorectal cancer (CRC) recurrence, CRC-related, and non-CRC-related mortality in patients undergoing curative resection, according to tumor location and stage.

impact on the CRC prognosis, with the 5-year CRC-related mortality increasing from 3.8% to 33.6% when moving from those who are alive and recurrence-free one year after surgery to those who have had a recurrence by that time. These figures are 1.0% and 20.3% respectively when comparing a patient alive and recurrence-free with a patient alive after CRC-recurrence 3-years after surgery.

The effects of covariates on the transition probabilities estimated from a transition-specific Cox model are shown in Table 3. A similar analysis was also performed considering CRC-related and non-CRC-related deaths together (Supplemental Table 1), as well as deleting from analysis those patients diagnosed with metastasis (Supplemental Table 2). Of all the variables examined, only stage III-VI (HR = 1.53; $p = 0.022$) significantly increased the hazard of recurrence, although this effect disappear after adjusting for adjuvant chemotherapy (Supplemental Table 3).

Furthermore, advanced age was significantly associated with an increase in non-CRC-related mortality, whether there was a recurrence during follow-up or not, although the effect of age on the risk of non-related death appears to be weaker after a recurrence diagnosis (age≥75 years: HR = 4.26 vs. HR = 7.76). Non-CRC-related death was also significantly associated with higher Charlson comorbidity scores (HR = 1.43; $p < 0.001$) in patients without local recurrence or metastases. In both patients with and without recurrence, women tended to be associated with a lower risk of death, although the differences were not statistically significant (Table 3). In addition, after adjustment for adjuvant chemotherapy, this treatment also appears to be associated with higher non-CRC-related mortality (Supplemental Table 3).

In contrast, in patients without a recurrence, the only variable that significantly increased the risk of CRC-related mortality was age ≥75 years (HR = 8.48; $p = 0.049$). After a recurrence, the risk of CRC-related death significantly increased in stages III-IV (HR = 2.35; $p = 0.004$) and with higher comorbidity scores (HR = 1.54; $p = 0.003$). After adjustment for potential confounders, no differences were found in the cumulative inci-

Table 3
Results of Cox models to analyze the association of different prognostic factors on recurrence and mortality. Multistate Markov proportional regression model.

	Alive, recurrence-free -> Recurrence					
	HR	95 % CI(HR)	*p*			
Age at diagnosis						
[65, 75) years vs (<65 years)	0.84	0.54–1.32	0.453			
≥ 75 years vs (<65 years)	1.11	0.72–1.71	0.638			
Gender						
Female vs Male	0.88	0.61–1.27	0.479			
TNM Stage						
III, IV vs In situ, I or II	1.53	1.06–2.21	0.022			
Localitation						
Rectum vs Colon	1.31	0.90–1.89	0.156			
Histological grade						
G2 (moderately differentiated) vs G1	1.11	0.71–1.75	0.645			
G3-G4 (poorly differentiated) vs G1	0.38	0.13–1.11	0.076			
Charlson's comorbidity index	0.84	0.69–1.01	0.068			
CEA	1.01	0.99–1.02	0.280			
	Alive, recurrence-free -> CRC-related Dead			Recurrence -> CRC-related Dead		
	HR	95 % CI(HR)	*p*	HR	95 % CI(HR)	*p*
Age at diagnosis						
[65, 75) years vs (<65 years)	2.95	0.30–28.8	0.353	0.90	0.44–1.84	0.769
≥ 75 years vs (<65 years)	8.48	1.00–71.69	0.050	1.18	0.60–2.33	0.633
Gender						
Female vs Male	1.32	0.39–4.47	0.653	1.05	0.56–1.95	0.890
TNM Stage						
III, IV vs In situ, I or II	2.15	0.62–7.48	0.229	2.35	1.31–4.20	0.004
Location						
Rectum vs Colon	1.09	0.28–4.23	0.899	0.76	0.42–1.37	0.359
Histological grade						
G2 (moderately differentiated) vs G1	0.56	0.14–2.31	0.427	1.32	0.62–2.83	0.470
G3-G4 (poorly differentiated) vs G1	0.51	0.05–5.36	0.579	0.61	0.13–2.95	0.540
Charlson's comorbidity index	1.20	0.72–1.99	0.490	1.54	1.16–2.04	0.003
CEA	0.93	0.75–1.16	0.524	1.02	0.99–1.04	0.146
	Alive, recurrence-free -> Non-CRC-related Dead			Recurrence -> Non-CRC-related Dead		
	HR	95 % CI(HR)	*p*	HR	95 % CI(HR)	*p*
Age at diagnosis						
[65, 75) years vs (<65 years)	2.82	1.63–4.87	<0.001	0.89	0.23–3.47	0.866
≥ 75 years vs (<65 years)	7.76	4.63–12.99	<0.001	4.26	1.29–14.10	0.018
Gender						
Female vs Male	0.76	0.57–1.02	0.071	0.34	0.11–1.11	0.073
TNM Stage						
III, IV vs In situ, I or II	0.93	0.68–1.27	0.649	0.84	0.34–2.06	0.707
Localitation						
Rectum vs Colon	1.17	0.86–1.59	0.332	0.93	0.37–2.38	0.883
Histological grade						
G2 (moderately differentiated) vs G1	1.24	0.86–1.80	0.251	1.00	0.35–2.86	0.997
G3-G4 (poorly differentiated) vs G1	1.08	0.59–1.97	0.798	0.00	0.00-Inf	0.988
Charlson's comorbidity index	1.43	1.29–1.58	<0.001	1.27	0.81–2.01	0.299
CEA	1.00	0.99–1.02	0.628	1.01	0.97–1.05	0.671

dence of recurrence or survival between colon and rectal tumours (Table 3).

Finally, the differential impact of local recurrence and distant metastasis on both CRC-related and non-CRC-related death was examined. As expected, distant metastasis significantly increased the risk of CRC-related death compared with local recurrence (Supplemental Table 4).

4. Discussion

This study verified the usefulness of MSM for analysing CRC recurrence and death risk and associated factors in CRC disease-free patients after curative surgical resection. Although other authors have shown the advantages of these statistical models in this context [13], there are still few studies that have used this methodology [20–22]. In contrast to the work of Darcourt et al., which years ago already demonstrated the advantages of MSM over other methodological approaches to study CRC progression and the role of recurrence in this process, this study provides a new analysis in a contemporary cohort, including prognostic factors not analysed in that manuscript. Moreover, it provides current estimates of the CRC recurrence rate and the transition probabilities between different states (alive without recurrence, alive without recurrence, or dead), while separately analysing factors associated with CRC-related and non-CRC-related mortality.

MSM overcome, as it was previously introduced, the limitations of other analytical approaches. Thus, some studies have analysed prognostic factors for recurrence using logistic regression [31], ignoring differences in the length of follow-up between patients. The impact of recurrence on survival has also been analysed using Cox models, ignoring that it is a time-dependent covariate and introducing the so-called lead-time bias.

To our knowledge, this is the first study to estimate the probability of a CRC patient being in a given situation (alive without recurrence, alive after a recurrence, or dead) at different times. The few works that have also employed MSM to analyse CRC prognosis have mainly used them to determine the impact of relapse on survival and its associated risk factors; without providing an overall

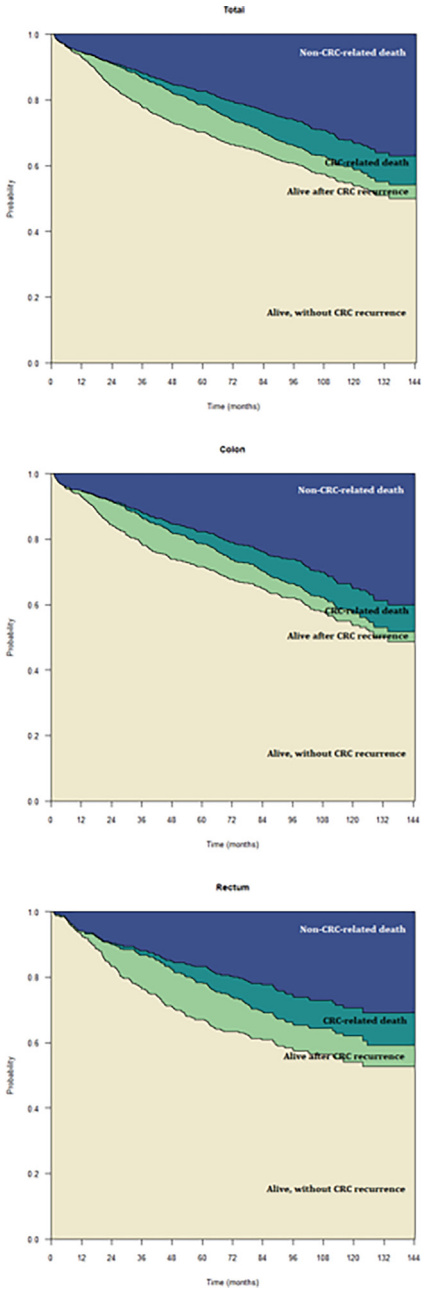

Fig. 3. Stacked plot of state occupation probabilities of being alive free from recurrence, being alive after recurrence and CRC-related or non-CRC-related death as a function of time since curative surgery.

view of the probability of different prognostic pathways [20–22]. This information during the follow-up could be very useful both to improve patient communication, postoperative follow-up planning and clinical decision-making.

Our study confirms the overall good prognosis of CRC patients undergoing curative surgery, with nearly 75% surviving 5-years without recurrence, both for colon and rectal tumours. These values are similar to those reported in other geographical contexts [32], but higher than those reported for 5-year overall survival in a recent review [33]. This review found European rates of 42.9% [34] for CRC as a whole, and of 46.3% for colon and 46.9% for rectum in Spain [35]. The present study excludes patients who are not candidates for curative surgery, which justifies the higher figures. Other works [33–35] included patients diagnosed at a much earlier period. This increase in survival may be related to improvements in the preoperative, intraoperative and postoperative management [36].

The cumulative recurrence incidence was 13.7%, with most of the recurrences occurring in the first 2–3 years. This figure is lower than that reported in a recent review, which concluded that recurrence after curative surgery occurs in 30–50% of cases [32,37–39], but agrees that the first two years after surgery is the period with the highest rate of recurrence. Studies including patients with stages II-IV [38,39] reported higher incidences. Stage I patients accounted for 24.5% of our series, which may favour a decrease in the incidence. It should be noted that studies [40–42] with more recent series including stage I reported incidences close to ours. Moreover, most studies showed a higher recurrence rate in rectum cancer.

Secondly, this study confirms the negative impact of recurrence on prognosis in terms of overall survival and cancer-specific mortality. Thus, transition probabilities obtained from MSM estimate that the probability of dying from the tumor at 5-years is only 3.8% for patients who remain without recurrence 1-year after surgery and 33.6% for a patient who has recurred in the first 12 months. These results highlight the need for close follow-up in the first 2–3 years after surgery, where 60% of detected recurrences are concentrated. These results are supported by other studies [43,44].

Third, MSM have allowed separate analysis of the impact of some prognostic factors on different outcomes. Even some studies [45] analyse survival only in CRC patients after recurrence. The impact of simple variables such as age, gender, stage at diagnosis or histological grade, on the prognosis of CRC patients has been well studied [42,46–49]. However, their impact has been analysed independently on recurrence or survival, and few studies have analysed the differential impact on survival according to whether the patient has a recurrence or not [13,20–22,38]. Moreover, CRC-specific mortality is not always analysed [13,20,22].

As in previous studies, no differences in prognosis were found according to CRC location. Although a higher cumulative incidence of recurrence was found in rectal tumours, these differences were not maintained in the multivariate analysis and are probably related to a higher percentage of stage III-IV rectal tumours (36.1% vs. 29.4%). Another work based on MSM revealed that tumour location was not associated with recurrence [21].

Stage was the only variable associated with recurrence. Most publications agree that stage is a risk factor for overall mortality and, in particular, mortality after recurrence [13,42]. Not surprisingly, stage is not associated with non-cancer mortality [48]. Similar results were reported by Darcourt et al. [13], who concluded that information on baseline stage is of only limited interest when patients are monitored for recurrence. Other studies concluded that stage III was associated with recurrence [43] and a higher probability of death after recurrence [13,22], although other authors did not support this finding [38]. However, the cause of death was not considered in these studies. Gilard-Pioc et al. [20] and Huszti et al. [50] determined that higher cancer stage is an obvious predictor of specific death with and without recurrence in CRC using a multistate approach. Although the significant impact of tumor stage on recurrence risk disappears after adjusting for adjuvant chemotherapy, this could be attributed to the so-called over-adjustment bias [51]. This phenomenon may also explain why a role for adjuvant chemotherapy in reducing recurrence rates has not been confirmed. On the other hand, adjuvant chemotherapy resulted significantly associated with non-cancer mortality, as seen in other tumors, probably related to its high toxicity [52].

Age resulted not significantly associated with recurrence, as reported by other authors [20,22,39,41], but is inconsistent with studies focusing on patients with stage I-II CRC [13,37]. Age was not associated with CRC-related death, whilst was a significant risk factor for non-CRC-related mortality. These findings are consistent

with those of other authors [13,20], who also note how the impact of age became less important after recurrence.

In our results, as in another study [43], no association was observed between comorbidity at diagnosis and CRC recurrence. In contrast, a higher risk of CRC-related death after recurrence and non-CRC-related death without recurrence was observed in patients with higher comorbidity scores. Other studies suggest that comorbidity is associated with risk of recurrence and poor survival [37,53,54]. Differences could be associated to different definitions of comorbidity, with some authors analysing the impact of specific comorbidities such as overweight/obesity [21] or diabetes mellitus [45].

Our study did not find an association between sex, grade of differentiation and preoperative CEA levels with CRC prognosis. Published results on differences in recurrence risk between males and females are contradictory [13,20–22,32,33,37,41,46], whereas a systematically higher survival rate in women has been described [36,38]. Regarding the degree of differentiation, our study does not allow us to verify the findings of previous analyses, according to which poor differentiation was associated with an increased risk of recurrence in patients with stage I-III colon cancer [37] or worse survival after recurrence [44]. Finally, some studies [32,55] have reported a good correlation between CEA levels and CRC recurrence and survival. In our work, CEA levels at diagnosis were considered, so it would be interesting for future studies to include post-surgery CEA levels.

This study has several limitations. First, it is a single-centre study, which may limit the generalisability of our findings. However, the data collection was simplified and the procedures, measures and variables collected were more homogeneous. Secondly, some of the measures were obtained from clinical records, so information bias could not be discarded. Other measures were based on interview data, so there was a risk of recall bias. Thirdly, this is an old series of patients, which could lead to changes in patient management. On the other hand, it allows us to have a long-term follow-up period. Fourth, recurrence was defined as a composite of local recurrence and/or distant metastasis, whichever came first. However, it should be taken into account that the prognostic differences between local and metastasis are not fully comparable. Finally, some factors for CRC recurrence or survival, such as chemotherapy, adjuvant therapy, surgery type or treatment, were not analysed.

The main strength of this study is that it was based on a prospective dataset of incident CRC cases with a long follow-up time. Unlike most publications, this study analysed the impact of recurrence on survival by considering CRC-related deaths and non-CRC-related deaths separately. Finally, we would like to highlight the use of a statistical methodology that allows us to disaggregate the complex temporality between recurrence and death.

In conclusion, this study demonstrate the usefulness of MSM to analyse in detail the prognosis, and its associated factors, in CRC disease-free patients after curative resection. It confirms the negative impact of recurrence as an intermediate event on survival, and analyse separately the influence of simple prognostic factors on recurrence, CRC-related mortality and non-CRC-related mortality.

Conflict of interest

None.

What does this study adds to the literature?

Although the limitations of conventional methods for survival analysis are well known, few studies have used multistate models (MSM) for the analysis of colorectal cancer (CRC) prognosis. This study employed MSM to analyse in detail the timing of recurrence and death, and associated factors, in CRC disease-free patients after curative resection.

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Authors contribution

V.B.B., S.P.D., C.G.M. and T.S.P. contributed to the study conceptualization, data curation, formal analysis, and methodology of the study. Funding acquisition, project administration and supervision was carried out by SPD. Investigation process was performed by T.G.R., R.P.P. and L.Y.G.D. Visualization and writing of the first draft were done by SPD and V.V.B. All authors participated in the critical review and editing of the final manuscript.

Ethical approval

The manuscript complies with the ethical standard guidelines of the journal. Informed patient consent and ethical review board approval was obtained (Galician Clinical Research Ethics Committee codes 2004/159, 2009/160, 2020/090), in accordance with current legislation.

Formal consent

Informed consent was obtained from all the patients included in the study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.11.041.

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