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Multi-state relative survival modelling of colorectal cancer progression and mortality☆

Séverine Gilard-Pioc [a,b], Michal Abrahamowicz [c,d,e], Amel Mahboubi [a,b], Anne-Marie Bouvier [b,f], Olivier Dejardin [g,h], Ella Huszti [i], Christine Binquet [b], Catherine Quantin [a,j,*]

[a] Teaching Hospital, Department of Biostatistics and Medical Informatics (DIM), Dijon F-21000, France
[b] Inserm, U866, University of Burgundy, Dijon F-21000, France
[c] McGill University, Department of Epidemiology, Biostatistics and Occupational Health, Montreal, Canada
[d] Universite de l'océan Indien, Ile de la Reunion, France
[e] CHU de La Reunion, Centre d'Etudes Périnatales de l'Océan Indien, 97 448 Saint-Pierre Cedex, France
[f] University Hospital Dijon, Digestive Cancer Registry of Burgundy, Inserm U866, University of Burgundy, Dijon F-21079, France
[g] CHU de Caen, Département de recherche épidémiologique et d'évaluation, Caen, France
[h] University Hospital of Caen, U1086 INSERM UCBN "Cancers & Preventions", France
[i] Campbell Family Institute for Breast Cancer Research, Princess Margaret Cancer Center, 610 University Avenue, Toronto, ON M5G 2M9, Canada
[j] INSERM, CIC 1432, Dijon, France Dijon University Hospital, Clinical Investigation Center, Clinical Epidemiology/Clinical Trials Unit, Dijon, France

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ABSTRACT

Accurate identification of factors associated with progression of colorectal cancer remains a challenge. In particular, it is unclear which statistical methods are most suitable to separate the effects of putative prognostic factors on cancer progression vs cancer-specific and other cause mortality. To address these challenges, we analyzed 10 year follow-up data for patients who underwent curative surgery for colorectal cancer in 1985–2000. Separate analyses were performed in two French cancer registries. Results of three multivariable models were compared: Cox model with recurrence as a time-dependent variable, and two multi-state models, which separated prognostic factor effects on recurrence vs death, with or without recurrence. Conventional multi-state model analyzed all-cause mortality while new relative survival multi-state model focused on cancer-specific mortality. Among the 2517 and 2677 patients in the two registries, about 50% died without a recurrence, and 28% had a recurrence, of whom almost 90% died. In both multi-state models men had significantly increased risk of cancer recurrence in both registries (HR = 0.79; 95% CI: 0.68–0.92 and HR = 0.83; 95% CI: 0.71–0.96). However, the two multi-state models identified different prognostic factors for mortality without recurrence. In contrast to the conventional model, in the relative survival analyses gender had no independent association with cancer-specific mortality whereas patients diagnosed with stage III cancer had significantly higher risks in both registries (HR = 1.67; 95% CI: 1.27–2.22 and HR = 2.38; 95% CI: 1.29–3.27). In conclusion, relative survival multi-state model revealed that different factors may be associated with cancer recurrence vs cancer-specific mortality either after or without a recurrence.

1. Introduction

Colorectal cancer (CRC) has high incidence and is associated with high case fatality [1]. In France, the 5-year survival, pooled across all cancer stages at diagnosis, ranges from 57% in men to 60% in women [2]. About one third of patients diagnosed with CRC will develop a metachronous recurrence during the following years [3]. It is of paramount importance to accurately identify factors associated with the increased risk of progression and death, in order to develop effective follow-up and treatment strategies. However, to accurately assess the role of patients' specific

☆ Relative survival multi-state model deal with two difficulties, i.e. to account for possibly different effect of prognostic factors on death versus recurrence, and unknown causes of death. It provide to clinicians more precise information on patients' profiles and their risks of recurrence or death. Applied to colorectal cancer: (1) a considerable proportion of deaths among patients who had no recurrence may represent mortality due to natural causes and (2) women have a similar risk of recurrence-free death than men.

* Corresponding author at: Centre Hospitalier Universitaire de Dijon, Service de biostatistique et d'Informatique Médicale (DIM), BP 77908, 21079 Dijon Cedex, France.
E-mail address: catherine.quantin@chu-dijon.fr (C. Quantin).

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characteristics in the progression of cancer several methodological challenges need to be overcome [4].

One difficulty, common to prognostic studies of cancer, concerns the need to separate the effects of prognostic factors on different clinical endpoints, such as disease recurrence vs recurrence-free death [5]. Some published prognostic studies of CRC used a Cox regression model that included recurrence as a time-dependent covariate, to assess the impact of recurrence on mortality, and to adjust for recurrence when estimating the effects of other prognostic factors on mortality. However, the Cox model is limited to the assessment of the effects of covariates on a *single* endpoint, such as death. This limitation is overcome by multi-state models, that make it possible to model alternative pathways of disease progression and to assess the impact of prognostic factors on both (i) mutually-exclusive events, such as recurrence-free death vs death after recurrence, and (ii) a sequence of events, such as recurrence followed by death [6,7].

Another difficulty, encountered in prognostic studies, is that the cause of death is not available or not accurately coded [8]. Yet, some patients are likely to die of causes not related to the disease of primary interest, especially in cancers with longer survival and in those that affect older subjects [9–11]. The effects of prognostic factors estimated with Cox model, or classic multi-state models, are not able to discriminate between their effects on the mortality due to cancer of primary interest vs natural mortality [12,13]. However, age is a very strong predictor of overall mortality, but is not systematically associated with higher cancer-specific mortality [14]. Simulations demonstrated that Cox model yields biased estimates of the effects of those prognostic factors whose impact on disease-specific mortality is quite different from their impact on all-cause mortality [15]. To deal with this difficulty, many prognostic studies use relative survival methods. Indeed, this approach has been developed to make it possible to estimate the effects of prognostic factors on disease-specific survival, even in the absence of causes of death [12,13,16–18]. The general idea is to use the mortality tables for the relevant general population to estimate survival corrected for the expected natural mortality, due to other causes of death [13].

Until recently, the existing statistical methodology was not able to simultaneously, deal with both difficulties, i.e. to account for (i) possibly different effects of prognostic factors on death vs recurrence, and (ii) unknown causes of death. However, this challenge has been addressed by the recent development of the Markov relative survival model (MRS) [19], which extends the Markov multi-state model [20] to incorporate relative survival modelling. Simulations demonstrate that MRS is able to accurately estimate different effects of prognostic factors on the risk of each of several events, including separate effects on disease-specific vs other causes of death [19]. To date, the MRS had not been applied in clinical or epidemiological studies.

The aim of this study was to assess the potential advantages of the new multi-state relative survival model (MRS), proposed by Huszti et al. [19], in a prognostic cancer study. To this end, we compared the MRS results with those obtained with two more conventional analyses, based on Cox's proportional hazards model [21], and the multi-state Markov model proposed by Alioum and Commenges [20]. The three models were applied to explore the impact of prognostic factors on cancer-specific mortality and recurrence, in a large population-based French registry of colorectal cancer, with up to 25 years of follow-up.

2. Material and methods

2.1. Study population

The study population was derived from the digestive cancer registries of two French administrative areas (Côte-d'Or and Calvados, with a total population about 1,155,000 inhabitants according to the 1999 census). All patients with TNM stage I, II or III colorectal adenocarcinoma [22], who underwent resection with a curative intent between 1985 and 2000 were included. The two registries have been working together for many years and use identical standardized data collection, recording and validation procedures. The linkage of several data sources (pathology laboratories, practitioners in the private and public sectors, teaching hospitals, comprehensive cancer centres, public and private hospitals, physicians employed by the Social Security department and death certificates) ensures the exhaustive collection of data. The quality of the data collection, as well as its completeness is regularly evaluated by the National Committee on Population-based-registries and by the National Institute of Health and Medical Research (INSERM).

The beginning of follow-up corresponded to the date of curative surgery. Routinely collected data included information related to diagnostic strategies, treatment, stage at diagnosis and follow-up of the patients. Information about all local recurrences and metastases that occurred up to 10 years after the initial diagnosis was obtained from all physicians (specialists and general practitioners) involved in the management and the follow-up of these patients.

The vital status of the patients was ascertained from the "Répertoire National d'Identification des Personnes Physiques" (RNIPP) and, in cases of failure, from the City Hall of the place of birth. If the place of birth was unknown, medical records, Health Insurance files and the Town Hall of the place of residence (small communities) were consulted.

The main exclusion criteria were recurrence within the first 6 months after diagnosis, considered as synchronous event, and a death within 30 days after surgery, as such short-term mortality was likely due to post-surgical complications [5].

2.2. Prognostic factors

Prognostic factors, evaluated at the time of cancer diagnosis, included gender, age and cancer stage. Age at diagnosis was categorized in three classes: $<$65 years; 65–74 years; $\geq$75 years. Cancer stage was categorized in two classes: (i) in situ, I, II and (ii) stage III at diagnosis according to the TNM classification.

2.3. Outcomes

The two outcomes of primary interest were death and recurrence. For death, the exact date was known, but the cause was not recorded. Recurrence was defined as a first diagnosis of either local recurrence or distant metastasis, implying that a subsequent recurrence was not considered as a transition to a new health state. Date of the first diagnosis of recurrence was established through a retrospective chart review, and corresponded to the date of histological or complementary investigation, at which the recurrence was identified.

2.4. Statistical models

To assess the robustness of our findings and conclusions, we carried out separate analyses of the data from each of the two registries (Côte d'Or and Calvados), and compared their results.

Preliminary analyses included estimation of the Kaplan–Meier survival curves for all-cause mortality, stratified by gender and stage at diagnosis and the logrank testing of the differences in survival between the respective strata.

Main analyses relied on three different multivariable regression models, as outlined below and adjusted for colorectal subsite. All three models included the same prognostic factors, and used the

same information on the timing of deaths and recurrences. In all models, the patients were censored at the time they were lost to follow-up or at the end of the study, in December 2011.

First, we estimated the Cox's proportional hazards model [21], to assess the prognostic factors effects on all-cause mortality. In Cox's model, recurrence was represented by a binary time-dependent covariate, which changed the value from 0 to 1 at the time the first recurrence was diagnosed. Whereas the above Cox's model allows us to estimate the impact of cancer recurrence on the hazard of all-cause mortality, it is unable to (a) separate the effects of prognostic factors on the risk of recurrence from their effects on the risk of mortality, and (b) account for possible differences in the effects of the same prognostic factors on the hazards of (i) recurrence-free death vs (ii) death after recurrence [5].

To overcome the above limitations of the Cox's model, we then employed the multi-state Markov piecewise constant intensities model (MKVPCI), developed by Alioum and Commenges [20]. Similar to other Markov multi-state models, the MKVPCI model generalizes the single-endpoint survival analytical models, such as Cox's model, to allow *simultaneous* estimation of the effects of prognostic factors on the hazard of transitions between all clinically relevant health states. Accordingly, a single MKVPCI analysis of the entire study cohort permits estimating the separate associations with each of the events of interest, including both mutually exclusive events (e.g. recurrence vs recurrence-free death) and events that follow some earlier events (e.g. death after recurrence) [20]. The MKVPCI model has been previously shown to be able to separate the effects of prognostic factors on recurrence from their effects on mortality, both in the analyses of real-life cancer progression studies [5] and in simulations [23]. Furthermore, simulations showed that by simultaneously estimating the effects of prognostic factors on all transitions, MKVPCI model avoids potentially important biases due to non-random censoring [23].

In our study, we modelled transitions between three states: (1) initial state, at CRC diagnosis, alive without recurrence, (2) alive with recurrence, and (3) death (see Fig. 1). Multi-state MKVPCI model allowed us to estimate separate effects of each prognostic factors (i) recurrence (transition (1–2)), (ii) death without recurrence (1–3), and (iii) death after recurrence (2–3) (notice that this piecewise-constant intensities model assumed different intensities (i.e. hazard rates) (i) in the first year of follow-up, and (ii) after the first year, with constant hazard within each of the two time intervals [20]). In the estimation process, it was assumed that all cohort members were initially at risk of either transition (1–2) or transition (1–3), until the time of their recurrence (state 2), recurrence-free death (state 3) or censoring at the end of follow-up (if they remained in state 1). An individual who had a cancer

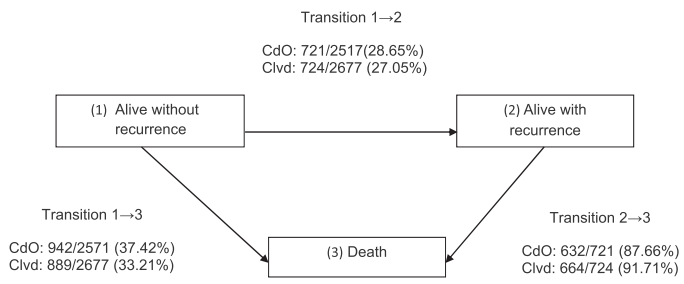

Fig. 1. Markov multi-state model of cancer progression and mortality. Three possible states are considered: (1) alive without recurrence, (2) alive with recurrence, (3) death. Number (%) of patients for each transition: "CdO", Côte d'Or area; "Clvd", Calvados area for transition 2–3 (death after recurrence), the percent is calculated using the number of patients who previously reached state 2 (recurrence).

recurrence (i.e. transitioned from state 1–2) at time t, was not considered anymore at risk of transition (1–3) after t, but was then considered at risk of transition (2–3), i.e. of a death after recurrence. In contrast, individuals who died without recurrence and, thus, whose first transition was (1–3), were considered at risk of recurrence (transition 1–2) until that time, but had their follow-up terminated at time of death, and where not at risk of transition (2–3). Notice that the MKVPCI estimates for transitions (1–3) and (2–3) should be interpreted as effects on all-cause mortality [19].

The third multivariable model used in our analyses was the new multi-state Markov relative survival model (MRS), proposed by Huszti et al. [19]. MRS extends the original MKVPCI model of Alioum and Commenges [20] by incorporating relative survival modelling to account for unknown causes of death [19]. MRS uses the relative survival methods [12] to account for expected natural mortality in the general population, from which the cancer cases were drawn. In (non homogeneous) MRS model, we assumed piecewise constant intensities, using the same time intervals (i) before vs (ii) after 1 year of follow-up, as in the MKVPCI analyses. In our MRS analyses of CRC progression, natural all-cause mortality was obtained from mortality life tables for the general populations for each of the two areas (Côte d'Or and Calvados, France), stratified by gender, age, and calendar year of death. Accordingly, MRS allowed us to estimate separate effects of prognostic factors on each of the three transitions shown in Fig. 1, while accounting for unknown causes of deaths. Specifically, the MRS estimates of the effects for transitions (1–3) and (2–3) should be interpreted in terms of the prognostic factors effects on the hazard of CRC-specific mortality [19], in contrast to MKVPCI model, which estimates the effects on all-cause mortality.

Based on the MRS results, we then estimated the absolute risks of alternative transitions, conditional on different covariate vectors, i.e. the cumulative probability that a given transition will occur before time t for a subject with specific characteristics. To this end, we first reconstructed the transition-specific conditional hazards by multiplying the baseline hazard, estimated for a given transition, by the hazard ratios corresponding to the specific characteristics. These calculations were performed separately for the two time intervals defined by the piecewise intensity model, as described above. We then converted the resulting conditional hazard estimates into the cumulative probabilities by using the cumulative distribution function of a piecewise exponential distribution.

To assess the robustness of the MRS findings, we used the split-sample (internal) validation in the Cote d'Or database. Specifically, we repeated 10 times the following steps: (1) we randomly divided the database into two subsamples of equal size; (2) we estimated the MRS model in each of the two subsamples; (3) we then compared the corresponding point estimates and their statistical significance (at $\alpha = 0.05$), for each prognostic factor and each transition.

3. Results

We reviewed a series of 2517 patients in Côte d'Or and 2677 in Calvados, who were all resected for cure for colorectal adenocarcinoma between 1985 and 2000. Table 1 describes patients' characteristics at the time of CRC diagnosis. The mean age was 70.5 years (SD = 12 years) and 69.5 years (SD = 11.9 years) respectively, and in both areas men represented a slight majority of patients. Stage at diagnosis was in situ, I or II, for 71% of patients in Côte d'Or and 66% in Calvados (Table 1).

Patients were followed for up to 25 years after diagnosis. During the first 10 years of follow-up, 1574 (63%) patients in Côte d'Or and 1553 (58%) in Calvados had died, with a median survival of 3.5 years and 4.2 years, respectively. The numbers of locoregional

Table 1
Baseline characteristics and results of multivariable Cox regression analyses for all-cause mortality with recurrence as a time-dependent variable: in Côte d'Or (left part) and Calvados (right part).

Variables	Côte d'Or				Calvados			
	N	%	HR	95% CI	*N*	%	HR	95% CI
Age	2541				2677			
<65 years[a]	742	29.20	1		834	31.15	1	
[65–75]	743	29.24	1.26**	1.12–1.41	851	31.79	1.38**	1.23–1.55
≥75 years	1056	41.56	2.60**	2.33–2.89	992	37.06	2.51**	2.26–2.79
Gender								
Female	1136	44.71	0.83**	0.76–0.90	1266	47.3	0.82**	0.75–0.89
Male[a]	1405	55.29	1		1411	52.7	1	
Stage								
In situ, I & II[a]	1783	70.84	1		1772	66.19	1	
III	734	29.16	1.69**	1.55–1.85	905	33.81	1.61**	1.48–1.76
Recurrence								
No[a]	1796	71.35	1		1953	72.95	1	
Yes	721	28.65	4.17**	3.78–4.60	724	27.05	4.89**	4.44–5.39

Adjusted for colorectal subsite. *Abbreviations:* CI: confidence interval; HR, adjusted hazard ratio.
** $p \leq 0.001$
[a] Reference category.

recurrences were 229 and 272, respectively, in Côte d'Or and Calvados, and the corresponding numbers of metastases were 466 and 441. In both areas, slightly less than 30% of all patients had a recurrence during the follow-up, of whom about 90% subsequently died (last row of Table 1). Median time to recurrence was 1.75 years in both areas (Interquartile Range [IQR]: 12.7–38.5 months in Côte d'Or and IQR: 12.3–36 months in Calvados). The response rate of the survey for recurrences was 87%. For all these patients we had all the information needed to validate the recurrence.

Fig. 2 shows the Kaplan Meier survival curves, for all-cause mortality, for gender and stage at diagnosis, for the two areas. As expected, in univariate analyses, survival was significantly lower for patients with stage III at diagnosis ($p < 0.0001$ in both areas).

Table 1 shows the results of the multivariable Cox model analyses with recurrence as a time-dependent variable. The estimated effects of all prognostic factors on the hazard of all-cause mortality are very similar for both areas. After recurrence, the risk of death increased dramatically, by a factor of about four, relative to patients with the same baseline values of other

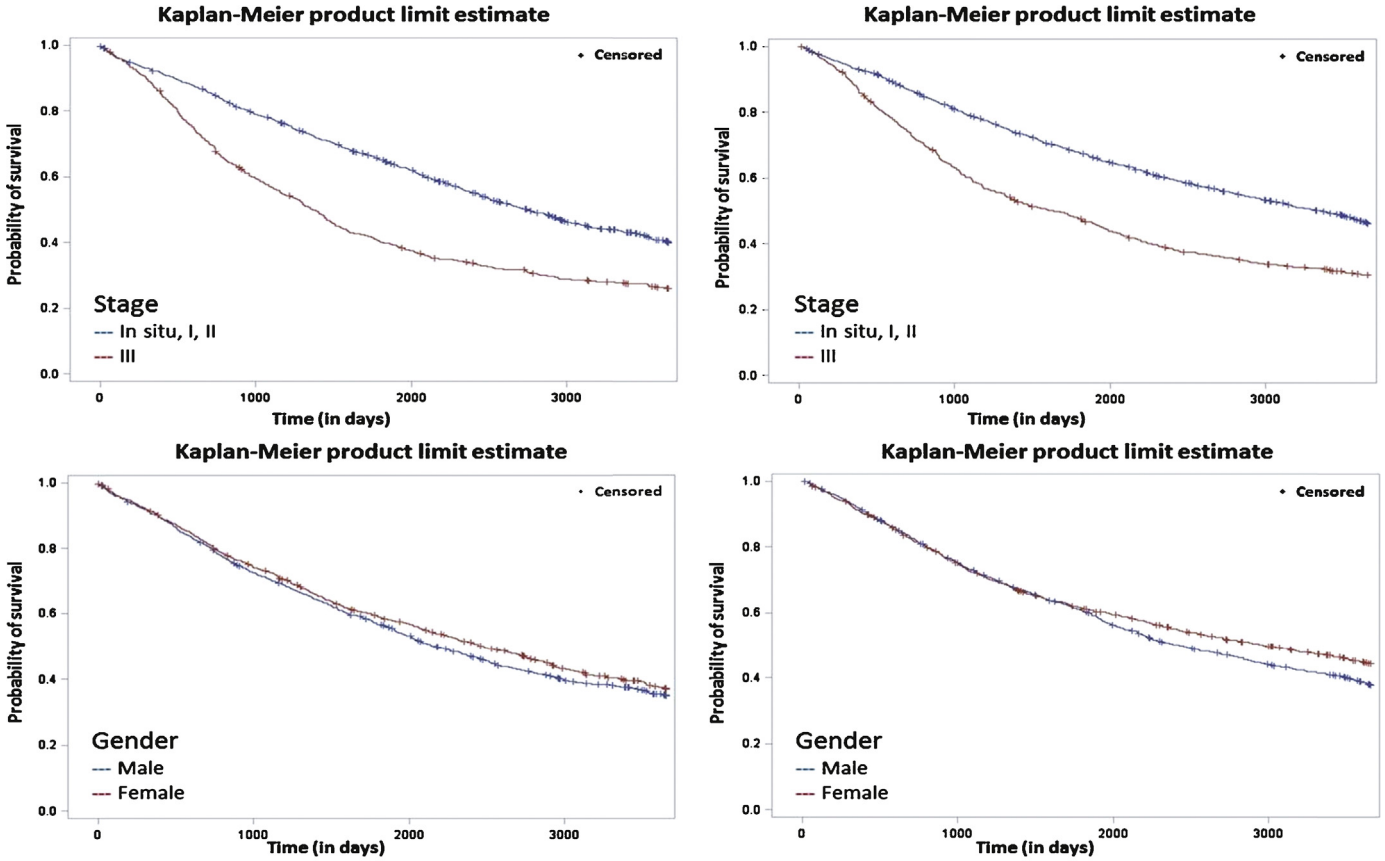

Fig. 2. Kaplan Meier survival curves (left panels: Côte d'Or, right panels: Calvados) stratified by gender (log rank test: $p = 0.17$ and $p = 0.005$, respectively for each of the two areas) and stage at diagnosis ($p < 0.0001$ for both areas).

prognostic factors who had no recurrence. When adjusted for recurrence, both more advanced cancer stage III and older age were associated with statistically significantly worse survival, with the hazard of all-cause mortality for the oldest group (aged > 75 years at diagnosis) being more than twice higher than for subjects aged < 65 years (HR = 2.60, 95% CI: 2.33–2.89 in Côte d'Or). On the other hand, women had a significantly albeit only slightly lower mortality than men diagnosed at the same cancer stage and the same age (HR = 0.83, 95% CI: 0.76–0.90). However, the interpretation of the above results should take into account some limitations of the Cox model. Firstly, while the estimates in Table 1 do account for the recurrences that occurred during the follow-up, it is assumed that the effect of a given baseline prognostic factor is the same on mortality for (i) subjects who had a recurrence and (ii) those who had no recurrence. Secondly, by including recurrence as a time-dependent covariate, Cox model demonstrates the major impact of recurrence on mortality but does not allow us to assess if some baseline characteristics are associated with an increased risk of recurrence. Both limitations are relevant in our analyses because Fig. 1 shows that almost 30% of patients had a recurrence, and a several hundred of deaths occurred both among subjects with and those without recurrence.

Multi-state Markov modelling allowed us to overcome the above limitations of the Cox model, by including recurrence as an intermediate state in the disease progression. Accordingly, in the multi-state analyses, we were able to estimate separate effects of the baseline prognosis factors on each of the three transitions shown in Fig. 1. Table 2 shows the results of the two separate multi-state models.

We first present the results of the conventional MKVPCI multi-state model which, in the absence of the individual causes of death, for transitions 1 → 3 and 2 → 3, estimates the effects of prognostic factors on the hazard of all cause-mortality. Interestingly, there are some important differences between the effects of some prognostic factors on all-cause mortality between (a) patients who had a recurrence (transition 2 → 3) vs (b) those without a recurrence (transition 1 → 3). Firstly, the protective effect of female gender is limited to recurrence-free deaths (1 → 3). Secondly, the impact of older age is much stronger for recurrence-free deaths than for death after recurrence. In contrast, the impact of advanced cancer stage III on mortality becomes weaker, in both areas, and loses its statistical significance in Calvados, for patients, for patients who had no recurrence (Table 2). On the other hand, multi-state MKVPCI analyses allowed us to identify stage III at CRC diagnosis as a major prognostic factor for recurrence, with a three-fold risk increase relative to patients diagnosed at less advanced stages. Finally, while the risk of recurrence is lower for women, it is not associated with age in Côte d'Or (Table 2).

For each prognosis factor and each transition, Table 2 compares the effects estimated with (i) the conventional MKVPCI multi-state model (left columns) vs (ii) the relative survival multi-state model MRS (right columns). The two multi-state models yielded almost identical estimates of the effects of different variables on the hazard of recurrence (transition 1 → 2). This was expected, because the only difference between the two models concerns the way they handle the data on mortality, in the absence of individual causes of death. Whereas the conventional MKVPCI model estimates the effects of prognosis factors on the hazard of all-causes mortality, the MRS uses the relative survival methods to estimate their effects on mortality due specifically to colorectal cancer. Interestingly, this analytical difference had no marked impact on the estimated effects for deaths after recurrence (transition 2 → 3), where the estimates obtained with the two multi-state models are very similar (right most part of Table 2).

In contrast, the results of the MKVPCI and the MRS models do differ substantially for recurrence-free mortality (transition 1 → 3 in Table 2). First, the estimated effects of both demographic factors, age and sex, on mortality without recurrence are much weaker when related to cancer-specific deaths only (MRS estimates) that when related to all-cause mortality (MKVPCI estimates). Specifically, in the relative survival multi-state MRS analyses, female gender loses its significant protective effect, and the adjusted hazard ratios (HR) for risk increases associated with older age, while still significant, are much smaller than the corresponding HR's from the MKVPCI analyses (Table 2). For example, for the oldest group (>75 years at diagnosis) in Côte d'Or area, the HR decreases from 5.62 (95% CI: 4.59–6.90) for all-cause mortality without recurrence to 3.48 (2.45–4.93) for CRC-specific mortality without recurrence, with the 95% confidence intervals that barely overlap, and the corresponding difference is even larger in the Calvados area (6.58 in MKVPCI vs 2.84 in MRS). On the other hand, the MRS estimate for recurrence-free deaths (transition 1 → 3) indicates a much stronger impact of the stage III cancer stage on CRC-specific mortality (HR = 1.67; 1.27–2.22 in Côte d'Or)

Table 2
Results of Multi-state Markov modelling prognostic factor's effects on recurrence, and death either without recurrence or after recurrence, in colorectal cancer in Côte d'Or and Calvados areas, estimated with MKVPCI and MRS models.

Transitions	Recurrence 1 → 2		Death without recurrence 1 → 3		Death after recurrence 2 → 3	
	MKVPCI (a) HR (95% CI)	MRS (b) HR (95% CI)	MKVPCI (a) HR (95% CI)	MRS (b) HR (95% CI)	MKVPCI (a) HR (95% CI)	MRS (b) (HR 95%-IC)
<65 years[a]	1	1	1	1	1	1
[65–75] vs <65 years						
Côte d'Or	0.98 (0.82–1.18)	0.98 (0.82–1.18)	2.10** (1.67–2.64)	1.70* (1.15–2.50)	1.03 (0.84–1.25)	0.99 (0.80–1.22)
Calvados	0.99 (0.82–1.18)	0.98 (0.82–1.18)	2.41** (1.91–3.04)	1.92* (1.08–3.73)	1.33* (1.10–1.62)	1.31* (1.07–1.60)
−75 years vs <65 years						
Côte d'Or	1.13 (0.95–1.35)	1.13 (0.95–1.35)	5.62** (4.59–6.90)	3.48** (2.45–4.93)	2.61** (2.16–3.16)	2.46** (2.01–3.01)
Calvados	1.25* (1.04–1.49)	1.25* (1.04–1.49)	6.58** (5.32–8.14)	2.84* (1.73–5.82)	1.97** (1.64–2.37)	1.78** (1.47–2.19)
Female vs male						
Côte d'Or	0.83* (0.71–0.96)	0.83* (0.71–0.96)	0.78** (0.68–0.89)	0.92 (0.70–1.21)	0.91 (0.78–1.07)	0.94 (0.79–1.11)
Calvados	0.79* (0.68–0.92)	0.79* (0.68–0.92)	0.74** (0.65–0.85)	1.25 (0.75–1.96)	0.97 (0.83–1.13)	1.00 (0.84–1.18)
Stage III vs in situ, I, II						
Côte d'Or	3.33** (2.87–3.86)	3.33** (2.87–3.86)	1.23* (1.06–1.44)	1.67** (1.27–2.22)	1.35** (1.15–1.59)	1.38** (1.16–1.63)
Calvados	3.15** (2.72–3.65)	3.15** (2.72–3.65)	1.11 (0.96–1.29)	2.38* (1.29–3.27)	1.38** (1.18–1.61)	1.41** (1.19–1.66)

Adjusted for colorectal subsite. *Abbreviations*: (a) MKVPCI: Markov model with piecewise constant intensities; proposed by Alioum and Commenges [22]. HR's for transition 1–3 and 2–3 represent prognostic factors effects on the hazard of all-causes mortality. (b) MRS, Multi-state Markov Relative Survival model proposed by Huszti et al. [21]. HR's for transitions 1–3 and 2–3 represent prognostic factors effects on the hazard of mortality due to colorectal cancer. CI, confidence interval; HR, adjusted hazard ratio.

* $p \leq 0.05$.

** $p \leq 0.001$.

[a] Reference category.

Table 3
Probabilities of transitions between the 3 health states for selected follow-up durations, for patients with different characteristics (Estimated with the MRS model for Cote d'Or).

Sex	Age	Transition	1→2	1→2	1→2	1→2	1→3	1→3	1→3	1→3	2→3	2→3	2→3	2→3
		Time since diagnosis (year)	0.5	1	2	3	0.5	1	2	3	0.5	1	2	3
		Cancer stage												
M	<65	I, II	0.03	0.06	0.11	0.15	0.02	0.03	0.06	0.08	0.35	0.57	0.73	0.83
M	65–75	I, II	0.03	0.06	0.11	0.15	0.03	0.05	0.10	0.14	0.34	0.57	0.72	0.82
M	>75	I, II	0.04	0.07	0.12	0.17	0.06	0.11	0.19	0.26	0.65	0.88	0.96	0.99
M	<65	III	0.10	0.20	0.32	0.42	0.03	0.05	0.09	0.13	0.44	0.69	0.83	0.91
M	65–75	III	0.10	0.19	0.31	0.41	0.05	0.09	0.13	0.17	0.44	0.68	0.83	0.91
M	>75	III	0.12	0.22	0.35	0.46	0.09	0.17	0.29	0.39	0.76	0.94	0.99	1.00
F	<65	I, II	0.03	0.05	0.09	0.13	0.02	0.03	0.05	0.08	0.33	0.55	0.70	0.81
F	65–75	I, II	0.03	0.05	0.09	0.12	0.03	0.05	0.09	0.13	0.33	0.55	0.70	0.80
F	>75	I, II	0.03	0.06	0.10	0.14	0.05	0.10	0.17	0.24	0.63	0.86	0.95	0.98
F	<65	III	0.09	0.17	0.27	0.36	0.03	0.05	0.09	0.12	0.42	0.67	0.81	0.90
F	65–75	III	0.09	0.16	0.27	0.36	0.04	0.08	0.14	0.20	0.42	0.66	0.81	0.89
F	>75	III	0.10	0.19	0.30	0.40	0.08	0.16	0.27	0.37	0.74	0.93	0.98	1.00

than its impact on all-cause mortality (HR = 1.23; 1.06–1.44), estimated with MKVPCI. The corresponding change is even bigger in Calvados, where the effect of stage III on recurrence-free mortality is statistically non-significant and very weak in the MKVPCI analyses (HR = 1.11; 0.96–1.29) but becomes significant and clinically important in the relative survival MRS model (HR = 2.38; 1.29–3.27).

Split-sample validation, based on 10 random splits of the Cote d'Or dataset (see Section 2), confirmed the robustness of the main findings of the MRS analyses. For all associations which were statistically significant in the full dataset (see Cote d'Or results in Table 2), the corresponding log HR's, estimated from two independent subsamples, were of similar magnitude, with their absolute differences being systematically much lower than the point estimates (data not shown). Furthermore, the empirical standard deviations of the 20 log HR's were uniformly very close to the estimated standard errors. Finally, the conclusions regarding the statistical significance of the associations between individual prognostic factors and hazards of different transitions were also quite robust. For all associations which were non-significant in the full Cote d'Or dataset ($p > 0.05$ in Table 2), the results remained non-significant in 90–100% of the 20 subsamples. Similarly, all the associations which were highly significant in MRS analyses of the full dataset ($p < 0.001$ in Table 2), were also identified as significant ($p < 0.05$) in 85–100% of the subsamples (data not shown). The only two exceptions regard the two marginally significant associations ($0.001 < p < 0.05$ in Table 2), with HR's relatively close to 1 in the full dataset, for the effects of (i) sex on cancer recurrence (HR = 0.83, 95% CI: 0.71–0.96), and (ii) middle age category (65–75 years) on recurrence-free death (HR = 1.70, 1.15–2.50). These two associations were significant in, respectively, 30% and 45% of the subsamples, which likely reflects the inadequate power of split-sample analyses for testing weaker effects, due to 50% reduction of the sample size.

Table 3 helps assess how the absolute risks of different transitions vary depending on the prognostic factors. It reports the MRS-based estimates of the cumulative probabilities that each of the three transitions will occur before selected follow-up times of $t = 0.5, 1, 2$ and 3 years after diagnosis, for patients with different combinations of sex, age and cancer stage. These estimates may help identify subgroups of patients with high risk of specific endpoints. For example, the contrast between risks of the 'competing', mutually exclusive transitions (1–2) vs (1–3) varies considerably depending on the patient characteristics. Those in the youngest subgroup, aged < 65 years, are much more likely to have a cancer recurrence [1,2] than a recurrence-free death, especially if they are diagnosed at advanced stage III (for 3 years of follow-up: 0.42 vs 0.13 for men and 0.36 vs 0.12 for women, Table 3). In contrast, for patients diagnosed with stage I or II at age > 75 years, recurrence-free death is more likely than recurrence for men and almost as likely for women (Table 3). On the other hand, after a cancer recurrence all subgroups of patients have very high probability of death related to colorectal cancer (transition 2–3), within the next 2–3 years (rightmost part of Table 3).

Table 4 compares the baseline hazards for each transition, separately for the first year after cancer diagnosis and the latter period, after 365 days of follow-up, estimated with the two models MKVPCI and MRS. Consistent with results in Tables 2 and 3, the baseline hazard estimates for transitions 1–2 and 2–3 are very similar (Table 4). In contrast, the relative survival MRS model yields much lower hazard estimates for recurrence-free death (transition 1–3), which represents only cancer-specific mortality in MRS vs all-cause mortality in MKVPCI.

4. Discussion

Cox's proportional hazards regression model [21] has become the most popular method for analysing survival data in cancer epidemiology [4]. In this study, we used two large population-based colorectal cancer registries to illustrate how multi-state modelling [6,7,20,24] and its recent extension to relative survival [19] may help addressing specific challenges related to (i) the need to account for cancer recurrence, and (ii) the absence of information on individual causes of death. Comparison of the results obtained, in two registries allowed us to assess the robustness of our clinical and methodological conclusions.

Table 4
Comparison of baseline hazards for the 3 transitions, for two time intervals, between the two multi-state models: MKVPCI vs MRS.

Transitions	1→2 (recurrence)		2→3 (death after recurrence)		1→3 (recurrence-free death)	
Time intervals	<365 days	>365 days	<365 days	>365 days	<365 days	>365 days
MKVPCI	0.0657	0.0484	0.8833	0.4804	0.0621	0.0581
MRS	0.0657	0.0484	0.8505	0.4475	0.0329	0.0264

The first challenge is related to the fact that different patients may follow different pathways of cancer progression. In particular, recurrence is an important event in the evolution of cancer, that may act as an intermediate clinical endpoint, as well as both a risk factor and a modifying effect for subsequent death. The conventional Cox model is limited in that it allows assessing the effects of prognostic factors on the time to a *single* endpoint. Specifically, by including recurrence as a time-dependent covariate, we could only confirm that the risk of all-cause mortality increases dramatically after a recurrence, and adjust the estimated effects of prognostic factors on mortality for recurrence.

To address more complex issues, we applied Markov multi-state modelling, as recommended by Kay [24] and done by several other authors [5,25–28]. Both multi-state models identified, advanced cancer stage III as a major risk factor for recurrence and indicated that females had about 20% lower risk of recurrence than men with the same cancer stage and age. Some colorectal cancer studies have identified female gender as a protective factor of recurrence [29–32]. Differences in adherence to treatment, gender variation in treatment efficacy or physiological factors could also interact on the development of recurrence. Further studies are needed to disentangle between these potential factors. In contrast, older age had only a marginal impact on the risk of recurrence. Equally important, multi-state analyses revealed that the effects of some prognostic factors did differ depending on whether a patient had recurrence or not. In particular, the effects of both older age and male gender were much stronger with recurrence-free mortality than with mortality after a recurrence, for which females had similar risk to men (Table 2). Notice that Cox model yielded the hazard ratios (Table 1) that represented an 'average' of the corresponding two estimates obtained with the multi-state model. For example, the Cox estimate of the adjusted HR for patients aged >75 years in Calvados was 2.51 (95% CI: 2.26–2.79), which represents an average between the very strong effect on recurrence-free mortality (HR = 6.58; 5.32–8.14 in MKVPCI model in Table 2) and a much weaker effect (HR = 1.97; 1.64–2.37) for mortality after a recurrence.

The source of the second methodological challenge is that, even after taking recurrence into account, the estimated effects of some factors on mortality may represent a compound of their associations with (a) mortality specific to the primary cancer, and (b) 'natural mortality' due to all other causes. But, similar to many other cancer registry-based prognostic studies [33] we had no information on individual causes of death. Markov relative survival multi-state model (MRS) was developed to allow estimating effects specific to mortality due to the cancer of primary interest [19]. Because the only difference between the MRS and MKVPCI models concerns handling of deaths, the two models yielded identical results for predictors of recurrence (Table 2). However, our finding that the two multi-state models produced also very similar estimates for mortality after recurrence (transition 2 → 3 in Table 2) was less predictable a priori. Our tentative, a posteriori, interpretation of this finding is that almost all deaths among patients who had a cancer recurrence were due to colorectal cancer. This conjecture is supported by the fact that almost all patients who had a recurrence died soon after, with a median time from recurrence to death of only less than two years, which is reflected by the uniformly very high absolute risks of this transition (Table 3). This implies that the risk of transition 2–3 is only moderately affected by patient characteristics, which explains a relatively weak, even if statistically significant, impact of advanced cancer stage on the hazard of a colorectal cancer-related death after recurrence.

In contrast, the relative survival approach incorporated in the MRS model did result in marked changes in the estimated effects of all prognostic factors on the risk of a recurrence-free death. Firstly, the MRS estimates of the impact of older age on mortality without recurrence are much lower than the corresponding conventional MKVPCI estimates. Secondly, in contrast to a significant protective effect of female gender in conventional multi-state analyses, MRS results indicate that women have a similar risk of recurrence-free death than men, diagnosed with colorectal cancer at the same stage and the same age.

Both these differences can be explained by the analytical differences between the two multi-state models, together with the fact that both older age and male gender are well established 'generic' risk factors for all-cause mortality. Our MRS analyses indicate that men and women have similar risk of dying due to colorectal cancer without having a recurrence, while older patients have moderate, statistically significant increase of this risk. On the other hand, the conventional crude MKVPCI multi-state model yields the estimates that represent an average of the possibly different effects of the same factors on the two types of death. The differences between the estimates from the two models indicate that, as expected, a considerable proportion of deaths among patients who had no recurrence may represent mortality due to natural causes, which increases for older subjects and men.

The same analytical difference between the two multi-state models explains why the impact of stage III colorectal cancer on recurrence-free mortality is much stronger in the relative survival MRS analyses. Higher cancer stage at diagnosis is an obvious predictor of increased cancer-related mortality, but is unlikely to be related to 'natural' mortality due to other causes. By not being able to separate the two different effects of advanced cancer stage of diagnosis, the conventional multi-state model largely underestimates its important impact on recurrence-free mortality due to colorectal cancer.

Overall, MRS model [19] allowed us to identify important differences between the pathways disease progression and mortality among different subgroups of patients diagnosed with colorectal cancer. Age at diagnosis is not associated with the risk of recurrence, but older patients have increased risk of mortality due to colorectal cancer both without recurrence and, to a lesser extent, after recurrence. In contrast, women have lower risk of recurrence than men diagnosed at the same age and the same cancer stage, but their risk of cancer-related mortality either before or after a recurrence is not significantly different from men. Thus, given that recurrence is itself a major risk factor for death, the impact of male gender on colorectal cancer progression and mortality is mostly mediated through the increased risk of recurrence. Finally, advanced colorectal cancer stage III at diagnosis is associated with high risk of recurrence and also with important increases in cancer-related mortality both before and after a recurrence.

The relative survival Markov (MRS) model assessed an excess risk of mortality among patients diagnosed with colorectal cancer, compared to the general population [12,13]. Accordingly, "deaths due to colorectal cancer" (transitions 1–3 and 2–3) represent a surplus of deaths over what would be expected for subjects of the same age and sex in the general population of the same area. Among patients who had no cancer recurrence during the follow-up, such additional deaths might have occurred for several reasons. Firstly, some deaths could be related to late complications of initial treatments of cancer, which may affect mortality up to one year after the initial resection [34]. Secondly, some 'generic' risk factors for all-cause mortality were found to be associated with the occurrence of colorectal cancer, including exposure to alcohol, tobacco or diabetes [35] and, thus, may be more frequent in this population. Because we could not adjust for these risk factors, they might have acted as unmeasured confounders and, thus, might have partly accounted for the observed excess mortality. Furthermore, it is possible that the occurrence of a second cancer [36], or even a cancer recurrence could not be diagnosed (subclinical

recurrence) before the time of death. Finally, patients with a particularly aggressive disease might have died very early, before they had a recurrence diagnosed.

Some limitations of our study have to be recognized. Firstly, locoregional recurrence and metastasis were considered as the same event. Whereas the MRS and MKVPCI models are able to handle additional states, simulations and empirical results reported by Huszti et al. [19] suggest that the estimates based on the resulting, more complex analyses could be numerically unstable, especially if some transitions are relatively rare. An interesting alternative approach was recently proposed by Belot et al. [37], who modelled local recurrence, distant metastasis and excess recurrence-free death as three separate events using a competing risks excess hazard method. Competing risks methods, however, can only model mutually-exclusive events, and cannot account for a sequence of events, such as recurrence followed by death after recurrence. Secondly, in our MRS analyses, we focused only on the risk of death related to the cancer of interest, an approach common to relative survival analyses [12,13,16–18]. Eloranta et al. [38] proposed an alternative method that is able to distinguish between excess mortality in deaths related to the cancer of interest and deaths related to a common complication of this cancer. Such information could be of interest for patients and clinicians, as it could help reducing the excess mortality caused, for example, by the side effects of the treatment. Future research should consider combining this approach with multi-state modelling. Furthermore, in our study, all of the variables were recorded at the time of the diagnosis. Both MKVPCI and MRS models impose the conventional proportional hazards assumption, inherited from the Cox model. This implies that the impact of a predictor on survival does not change during the follow-up [12]. However, previous analyses of both all-cause mortality and relative survival in different cancers, including colorectal cancer, indicated that the impact of cancer stage at diagnosis may decrease with increasing follow-up and the effect of age may also change over time [16–18,39–42]. Future research should use similar methods to extend multi-state models to incorporate flexible modelling of time-dependent effects of prognostic factors. Current software for implementation of either MKVPCI or MRS models does not allow us to incorporate flexible modelling of likely non-linear effects of a continuous variable representing age at diagnosis [19,20]. Therefore, to avoid the incorrect linearity assumption [16,17], and make our results more comparable with published prognostic studies of colorectal cancer, we categorized age, using cut-offs commonly used in cancer epidemiology [5,34,43]. Future research should expand the existing multi-state models to include flexible modelling of non-linear effects of continuous prognostic factors, using fractional polynomials [44] or splines [42]. Finally, the modern methods for assessing models' goodness of fit, such as pseudo-residuals for traditional (single-endpoint) survival analyses [45] or methods developed specifically for relative survival analyses [46], should be adapted to relative survival multi-state models. Current software for MRS and MKVPCI models does not allow an accurate assessment of goodness-of-fit. Future research should adapt recent approaches for assessing goodness-of-fit, such as pseudo-residuals for traditional (single-endpoint) survival analyses [45] or methods developed specifically for relative survival analyses [46], to relative survival multi-state models. On the other hand, the robustness of our MRS model results is suggested by the similarity of the point estimates, and consistency of their statistical significance, obtained in both (i) the independent analyses of two cancer registries, and (ii) and the split-sample validation.

In conclusion, our analyses demonstrate how relative survival multi-state modelling [19] can offer new important insights regarding recurrence and disease-specific mortality in colorectal cancer. This approach allowed us to fully account for the role of cancer recurrence, which is an important event in the evolution of cancer. It also helped us separating effects of prognostic factors on (a) recurrence vs mortality before or after recurrence, and (b) cancer-specific vs natural, all-causes mortality. These results provide clinicians with more precise information on patients' profiles and their risks of recurrence or death and, thus, may help improve prognosis, therapeutic approaches and follow-up procedures. We believe that relative survival multi-state modelling [19] may help refining future prognostic studies of other cancers. Finally, this approach could allow to estimate the effects of biomarkers, potential marker of the efficacy of a treatment, on cancer-specific mortality.

Conflict of interest statement

None.

Authorship contribution

Co-authors: Séverine Gilard-Pioc performed statistical analyses, interpreted the data and wrote the paper. Amel Mahboubi performed the statistical analyses and contributed to revised the manuscript draft. Michal Abrahamowicz contributed of the conception of the study, participated in the interpretation of the results and contributed to writing the manuscript. Anne-Marie Bouvier critically reviewed and revised the manuscript drafts and participated in the interpretation of the results. Olivier Dejardin revised the manuscript drafts. Ella Huszti created the statistical model used in this study. Christine Binquet and Catherine Quantin conceptualized and designed the study, participated in the interpretation of the results and critically reviewed and revised the manuscript drafts.

All authors accept responsibility for the paper as published.

Contributors: Philip Bastable edited the manuscript.

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References

[1] Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917.
[2] Roche L, Danieli C, Belot A, Grosclaude P, Bouvier A-M, Velten M, et al. Cancer net survival on registry data: use of the new unbiased Pohar-Perme estimator and magnitude of the bias with the classical methods. Int J Cancer 2013;132:2359–69.
[3] Bülow S, Svendsen LB, Mellemgaard A. Metachronous colorectal carcinoma. Br J Surg 1990;77:502–5.
[4] Altman DG, De Stavola BL, Love SB, Stepniewska KA. Review of survival analyses published in cancer journals. Br J Cancer 1995;72:511–8.
[5] Dancourt V, Quantin C, Abrahamowicz M, Binquet C, Alioum A, Faivre J. Modeling recurrence in colorectal cancer. J Clin Epidemiol 2004;57:243–51.
[6] Andersen PK, Keiding N. Multi-state models for event history analysis. Stat Methods Med Res 2002;11:91–115.

[7] Commenges D. Multi-state models in epidemiology. Lifetime Data Anal 1999;5:315–27.
[8] Karremann M, Rausche U, Roth D, Kühn A, Pietsch T, Gielen GH, et al. Cerebellar location may predict an unfavourable prognosis in paediatric high-grade glioma. Br J Cancer 2013;109:844–51.
[9] Wæhre H, Vlatkovic L, Cvancarova M, Paus E, Fosså SD, Danielsen HE. Fifteen-year mortality after radical prostatectomy: which factors are available for patient counselling? Scand J Urol 2013;48:123–30.
[10] Epstein MM, Edgren G, Rider JR, Mucci LA, Adami H-O. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst 2012;104:1335–42.
[11] Noon AP, Albertsen PC, Thomas F, Rosario DJ, Catto JWF. Competing mortality in patients diagnosed with bladder cancer: evidence of undertreatment in the elderly and female patients. Br J Cancer 2013;108:1534–40.
[12] Estève J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. Stat Med 1990;9:529–38.
[13] Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med 2004;23:51–64.
[14] Schellerer V, Croner R, Langheinrich M, Hohenberger W, Merkel S. Colorectal carcinoma in young patients – is age a prognostic factor? Zentralbl Chir 2015. in press.
[15] Le Teuff G, Abrahamowicz M, Bolard P, Quantin C. Comparison of Cox's and relative survival models when estimating the effects of prognostic factors on disease-specific mortality: a simulation study under proportional excess hazards. Stat Med 2005;24:3887–909.
[16] Remontet L, Bossard N, Belot A, Estève J. French network of cancer registries FRANCIM. An overall strategy based on regression models to estimate relative survival and model the effects of prognostic factors in cancer survival studies. Stat Med 2007;26:2214–28.
[17] Mahboubi A, Abrahamowicz M, Giorgi R, Binquet C, Bonithon-Kopp C, Quantin C. Flexible modeling of the effects of continuous prognostic factors in relative survival. Stat Med 2011;30:1351–65.
[18] Giorgi R, Abrahamowicz M, Quantin C, Bolard P, Esteve J, Gouvernet J, et al. A relative survival regression model using B-spline functions to model non-proportional hazards. Stat Med 2003;22:2767–84.
[19] Husztı E, Abrahamowicz M, Alioum A, Binquet C, Quantin C. Relative survival multi-state Markov model. Stat Med 2012;31:269–86.
[20] Alioum A, Commenges D. MKVPCI: a computer program for Markov models with piecewise constant intensities and covariates. Comput Methods Progr Biomed 2001;64:109–19.
[21] Cox DR. Regression models and life tables. 34e éd. 1972;187–220.
[22] Obrocea FL, Sajin M, Marinescu EC, Stoica D. Colorectal cancer and the 7th revision of the TNM staging system: review of changes and suggestions for uniform pathologic reporting. Rom J Morphol Embryol 2011;52:537–44.
[23] Husztı E, Abrahamowicz M, Alioum A, Quantin C. Comparison of selected methods for modeling of multi-state disease progression processes: a simulation study. Commun Stat – Simul Comput 2011;40:1402–21.
[24] Kay R. A Markov model for analysing cancer markers and disease states in survival studies. Biometrics 1986;42:855–65.
[25] Bantema-Joppe EJ, van den Heuvel ER, de Munck L, de Bock GH, Smit WGJM, Timmer PR, et al. Impact of primary local treatment on the development of distant metastases or death through locoregional recurrence in young breast cancer patients. Breast Cancer Res Treat 2013;140:577–85.
[26] Porta N, Calle ML, Malats N, Gómez G. A dynamic model for the risk of bladder cancer progression. Stat Med 2012;31:287–300.
[27] Liao C-S, Yang K-C, Yen AM-F, Chen L-S, Chen TH-H. Remission, relapse, and metastasis/death of small hepatocellular carcinoma treated with percutaneous ethanol injection. Cancer J Sudbury Mass 2006;12:194–200.
[28] De Bock GH, Putter H, Bonnema J, van der Hage JA, Bartelink H, van de Velde CJ. The impact of loco-regional recurrences on metastatic progression in early-stage breast cancer: a multi-state model. Breast Cancer Res Treat 2009;117:401–8.
[29] Van Enckevort CCG, de Graaf APJ, Hollema H, Sluiter WJ, Kleibeuker JH, Koornstra JJ. Predictors of colorectal neoplasia after polypectomy: based on initial and consecutive findings. Neth J Med 2014;72:139–45.
[30] Martínez ME, Baron JA, Lieberman DA, Schatzkin A, Lanza E, Winawer SJ, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology 2009;136:832–41.
[31] De Jonge V, Sint Nicolaas J, van Leerdam ME, Kuipers EJ, Veldhuyzen van Zanten SJO. Systematic literature review and pooled analyses of risk factors for finding adenomas at surveillance colonoscopy. Endoscopy 2011;43:560–72.
[32] Van Heijningen E-M, Lansdorp-Vogelaar I, Kuipers EJ, Dekker E, Lesterhuis W, Ter Borg F, et al. Features of adenoma and colonoscopy associated with recurrent colorectal neoplasia based on a large community-based study. Gastroenterology 2013;144:1410–8.
[33] Huh JW, Lee JH, Kim HR, Kim YJ. Prognostic significance of lymphovascular or perineural invasion in patients with locally advanced colorectal cancer. Am J Surg 2013;206:758–63.
[34] Dekker JWT, Gooiker GA, Bastiaannet E, van den Broek CBM, van der Geest LGM, van de Velde CJ, et al. Cause of death the first year after curative colorectal cancer surgery; a prolonged impact of the surgery in elderly colorectal cancer patients. Eur J Surg Oncol 2014;40:1481–7.
[35] Boyle T, Fritschi L, Tabatabaei SM, Ringwald K, Heyworth JS. Smoking, alcohol, diabetes, obesity, socioeconomic status, and the risk of colorectal cancer in a population-based case-control study. Cancer Causes Control 2014;25:1659–68.
[36] Birgisson H, Wallin U, Holmberg L, Glimelius B. Survival endpoints in colorectal cancer and the effect of second primary other cancer on disease free survival. BMC Cancer 2011. http://dx.doi.org/10.1186/1471-2407-11-438.
[37] Belot A, Remontet L, Launoy G, Jooste V, Giorgi R. Competing risk models to estimate the excess mortality and the first recurrent-event hazards. BMC Med Res Method 2011;11(78):1–27.
[38] Eloranta S, Lambert PC, Andersson TML, Czene K, Hall P, Björkholm M, et al. Partitioning of excess mortality in population-based cancer patient survival studies using flexible parametric survival models. BMC Med Res Methodol 2012. http://dx.doi.org/10.1186/1471-2288-12-86.
[39] Quantin C, Abrahamowicz M, Moreau T, Bartlett G, MacKenzie T, Tazi MA, et al. Variation over time of the effects of prognostic factors in a population-based study of colon cancer: comparison of statistical models. Am J Epidemiol 1999;150:1188–200.
[40] Gagnon B, Abrahamowicz M, Xiao Y, Beauchamp M-E, MacDonald N, Kasymjanova G, et al. Flexible modeling improves assessment of prognostic value of C-reactive protein in advanced non-small cell lung cancer. Br J Cancer 2010;102:1113–22.
[41] Bolard P, Quantin C, Esteve J, Faivre J, Abrahamowicz M. Modelling time-dependent hazard ratios in relative survival: application to colon cancer. J Clin Epidemiol 2001;54:986–96.
[42] Abrahamowicz M, MacKenzie TA. Joint estimation of time-dependent and non-linear effects of continuous covariates on survival. Stat Med 2007;26:392–408.
[43] Landreau P, Drouillard A, Launoy G, Ortega-Deballon P, Jooste V, Côme L, et al. Incidence and survival in late liver metastases of colorectal cancer. J Gastroenterol Hepatol 2014. http://dx.doi.org/10.1111/jgh.12685.
[44] Royston P, Sauerbrei W. Interactions between treatment and continuous covariates: a step toward individualizing therapy. J Clin Oncol 2008;26:1397–9.
[45] Perme MP, Andersen P. Checking hazard regression models using pseudo-observations. Stat Med 2008;27:5309–28.
[46] Stare J, Pohar M, Henderson R. Goodness of fit of relative survival models. Stat Med 2005;24(24):3911–25.