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How to Identify Patients Less Likely To Have Metachronous Neoplasms After A Colon Cancer: A Predictive Model.

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Acronyms

CI: Confidence Interval
CRC: colorectal cancer
FAP: familial adenomatous polyposis
HNPCC: hereditary nonpolyposis colorectal cancer
LS: Lynch Syndrome
RCT: Randomized Controlled Trial

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ABSTRACT

Background & Aims: Patients with prior colon cancer have increased risk of metachronous colorectal neoplasms, therefore endoscopic surveillance is indicated. Current recommendations are not risk-stratified. Aim was to find predictive factors for colorectal neoplasms to build a model to spare colonoscopies for low-risk patients.

Methods: Multicenter retrospective study including patients who underwent surgery for colon cancer from 2001 to 2008 (derivation cohort) and from 2009 to 2013 (validation cohort). A predictive model for neoplasms occurrence at 2nd surveillance colonoscopy was developed and validated.

Results: 421 and 203 patients were included in derivation and validation cohort, respectively. At 2nd surveillance colonoscopy, 112 (26.6%) and 55 (27.1%) patients with metachronous neoplasms were found in derivation and validation group; three cancers were detected in the latter. History of left-sided colon cancer (OR 1.65,95%CI 1.03-2.66), ≥1 advanced adenoma at index colonoscopy (OR 1.90,95%CI 1.05-3.42), and ≥1 adenoma at first surveillance colonoscopy (OR 2.06,95%CI 1.29-3.27) were independently predictive of metachronous colorectal neoplasms at 2nd surveillance colonoscopy. Considering patients without such risk factors, the diagnostic accuracy parameters were: 89.3% (95%CI,82-94.3%) and 78.2% (95%CI,65-88.2%) sensitivity, and 28.5% (95%CI,23.5-33.9%) and 33.8% (95%CI,26.2-42%) specificity in derivation and validation group, respectively. No cancer would be missed.

Conclusions: subjects with prior left-sided colon cancer or ≥1 advanced adenoma at index colonoscopy or ≥1 adenoma at 1st surveillance colonoscopy are significantly more prone to neoplasms at 2nd surveillance colonoscopy, whereas subjects without such factors have much lower risk and could safely skip that colonoscopy. Nevertheless, a prospective, multicenter validation study is needed.

INTRODUCTION

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with 1.4 million new cases and almost 694,000 deaths estimated to have occurred in 2012, and with a 5-year survival rate of 65% [1]. Patients with a prior history of curative colon resection for cancer are at increased risk for developing recurrent and/or metachronous neoplasms [2]. Thus, colonoscopy-based surveillance protocols have been established in order to prolong survival by diagnosing recurrent and metachronous cancers at a curable stage, and to prevent metachronous cancer by detecting and removing precancerous lesions [3,4]. Current guidelines recommend performing surveillance colonoscopy 1 year after surgery; in case of negative results, the interval to the next colonoscopy should be 3 years and if negative, 5 years; subsequent colonoscopies should occur at 5-year intervals [3,4]. However, current surveillance recommendations are mostly based on outdated studies [5–7], despite treatment modalities for colon cancer have evolved over time, and they might not stand the test of time. Thus, it may be argued that current surveillance protocols could entail a considerable waste of resources, and attempts to stratify the risk of metachronous neoplasms may result in more cost-effective strategies.

In a recent multicenter retrospective study conducted in 441 patients with history of colonic resection for cancer, we found that patients with a prior left-sided colon cancer were at significantly increased risk of developing metachronous colorectal adenomas than subjects with a history of right-sided colon cancer, at the second surveillance colonoscopy [8]. However, this study had several limitations as it did not consider additional potentially relevant information, such as findings at index colonoscopy (i.e. the examination performed at the cancer diagnosis) and at first surveillance colonoscopy.

Aim of the present study was to identify predictive factors of metachronous neoplasms in the residual colon at the second post-operative colonoscopy in patients with a history of colon cancer. We developed and validated a predictive model to identify low-risk patients that could safely skip the second surveillance colonoscopy.

METHODS

This multicenter retrospective study was performed at seven institutions in Italy (Bologna, Brescia, Como, Milano, Napoli, Ravenna, and Reggio-Emilia). Consecutive patients with a diagnosis of colon carcinoma who had undergone surgical resection from January 1st, 2001 to December 31st, 2008 were eligible to be included in the derivation cohort. Patients who underwent surgical resection from January 1st, 2009 to December 31st, 2013 were eligible to be included in the validation group. Given the retrospective design, not all the centers included patients for the entire length of the two timeframes considered in the derivation and validation cohort.

The following inclusion criteria had to be satisfied: (i) previous proximal or distal colon cancer (considering the splenic flexure as the border between proximal and distal colon); (ii) availability of the index colonoscopy report; (iii) availability of reports of the first and second surveillance colonoscopy, conducted after the surgical intervention; (iv) complete colonoscopy to the cecum or ileo-colonic anastomosis, explicitly defining the quality of bowel cleansing as adequate; in details, bowel cleansing was reported according to Aronchick scale and Boston bowel preparation score, and was judged as adequate when Aronchick scale was “good” or “fair”, or Boston bowel preparation score was ≥2 for each colonic segment; (v) age ≥ 18 years at the time of the diagnosis of colon carcinoma. All the involved centers adopted the same surveillance recommendations [9].

Patients had to undergo a perioperative cleansing colonoscopy, either at the time of diagnosis or performed within six months after the surgical resection. In case the cleansing colonoscopy was performed after the resection, this colonoscopy was not considered as the first surveillance colonoscopy.

Patients with colonic resection for diseases different from colon cancer, rectal resection or diagnosis of hereditary cancer predisposing syndromes (i.e. familial adenomatous polyposis, FAP, or Lynch syndrome, LS) were excluded from the study.

The following data were extracted for each patient: gender, age at diagnosis, colon cancer staging, site of colon cancer (i.e. proximal or distal to the splenic flexure), number and location of adenomas found during index colonoscopy and during the first two surveillance colonoscopies after the surgical intervention.

The primary outcome of the study was the occurrence of metachronous colorectal neoplasms (i.e. adenoma, advanced adenoma or cancer) at the second surveillance colonoscopy. Advanced adenoma was defined if one of the following was satisfied: (i) ≥1 cm in size, (ii) tubulovillous or villous histology, (iii) high-grade dysplasia [10].

A predictive model was developed to derive the probability of finding ≥1 metachronous neoplasm at the 2nd surveillance colonoscopy in the derivation cohort, then validated in the validation group following the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) recommendations [11,12]. In order to develop the predictive model, patients with cancer at 1st surveillance colonoscopy were excluded from the analysis as they would restart their surveillance protocol after surgery for recurrent CRC. We provided the TRIPOD checklist as **Supplementary Table 1**.

The study was approved by the Institutional Review Board of the coordinating center (S. Orsola-Malpighi- Hospital, University of Bologna, Bologna, Italy; approved: 05/12/2015; protocol number: 1538/2015) and, thereafter, by the Ethics Committee of each participating centers.

Statistical analysis

Results are presented as absolute frequency and percentage with 95% confidence interval (95%CI) for categorical variables, and mean with standard deviation (SD) or median with interquartile range (IQR) for normally or not-normally distributed continuous variables, respectively. A multivariate logistic regression analysis was performed in order to identify predictive factors of neoplasms at the second surveillance colonoscopy. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were estimated for endoscopic findings at index and first surveillance colonoscopy, adjusted for age, gender, and stage of index cancer. A predictive model was subsequently developed. The diagnostic accuracy of our model was explored by computing sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for absence of risk factors and presence of each of them. The model derived in the derivation cohort was therefore validated in the validation cohort. Analyses were conducted using R statistical software (The R Project for Statistical Computing, Vienna, Austria) and STATA software (Stata Corp, College Station, TX).

Sample size

The sample size estimation was based on deriving a predictive model for metachronous neoplasm occurrence at 2nd surveillance colonoscopy. Estimating that a model based on logistic regression would increase the probability of finding ≥1 metachronous neoplasm from 22% to 35% (odds ratio = 1.91), with 80% power and one-sided 5% alpha level, we computed a sample size of 373 patients in the derivation cohort. We assumed a binomial distribution of covariate and $R^2 = 0.2$. Sample size calculation was conducted using G*power v3.1 for Mac [13,14].

RESULTS

Study population

Derivation cohort

A total of 431 patients with prior curative surgery for colon cancer between 2001 and 2008 were included (**Figure 1A**). Ten (2.4%) patients had a cancer at 1st surveillance colonoscopy and were excluded from the analysis, giving 421 patients in the derivation cohort. The time interval elapsed from surgery to 1st surveillance colonoscopy was 365 days (IQR, 273-504). A history of left-sided colon cancer was documented in 253 (60.1%) patients. Mean age was 62.3 (SD, 9.2) years, and 224 (53.2%) subjects were females. At index and 1st surveillance colonoscopy, 171 (40.6%) and 136 (32.3%) patients had ≥1 adenoma, of which 61 (14.5%) and 21 (5.0%) had ≥1 advanced adenoma, respectively. At the second surveillance colonoscopy, no colorectal cancers were discovered, while ≥1 adenoma was found in 112 (26.6%) patients, and ≥1 advanced adenoma was found in 22 (5.2%) patients, respectively (**Table 1**). The time interval elapsed from surgery to 2nd surveillance colonoscopy was 960 days (IQR, 726-1386).

Validation cohort

Between 2009 and 2013, a total of 209 patients with prior curative surgery for colon cancer were included (**Figure 1B**). Six (2.9%) patients had a cancer at 1st surveillance colonoscopy and were excluded from the analysis, giving 203 patients in the validation cohort. The time interval elapsed from surgery to 1st surveillance colonoscopy was 388 days (IQR, 335-500). A history of left-sided colon cancer was reported in 104 (51.2%) patients. Mean age was 63.4 (SD, 11.3) years, and 104 (51.2%) subjects were female. At index and 1st surveillance colonoscopy, 70 (34.5%) and 70 (34.5%) patients had ≥1 adenoma, of which 35 (17.2%) and 25 (12.3%) had ≥1 advanced adenoma, respectively. At the second surveillance colonoscopy, one metachronous colon cancer and two anastomotic recurrences were found, whereas ≥1 adenoma was found in 55 (27.1%) subjects, and ≥1 advanced adenoma was found in 20 (9.9%) patients (**Table 1**). The time interval elapsed from surgery to 2nd surveillance colonoscopy was 1088 days (IQR, 803-1444).

Predictive model development

History of left-sided colon cancer (OR 1.65, 95%CI 1.03-2.66), ≥1 advanced adenoma at the index colonoscopy (OR 1.90, 95%CI 1.05-3.42), and ≥1 adenoma at the first surveillance colonoscopy (OR 2.06, 95%CI 1.29-3.27) were independently associated with an increased risk of metachronous colorectal neoplasms at 2nd surveillance colonoscopy (**Table 2**). In order to exclude a possible multicollinearity between age and stage of index cancer, we excluded from the statistical model one of these two variables at a time; we found that the association between aforesaid variables and outcome remained statistically significant. We found that the presence of ≥1 adenoma at index colonoscopy, differently from advanced adenoma, was not significantly associated with the outcome (52/112, 46.4%, and 119/309, 38.5% of patients with and without neoplasms at 2nd surveillance colonoscopy respectively; OR 1.25, 95%CI 0.79-1.98).

We defined a patient with a history of right-sided colon cancer, no advanced adenomas at index colonoscopy, and no adenomas at first surveillance colonoscopy as a "low-risk" patient. Excluding this patient from the 2nd surveillance colonoscopy, the diagnostic accuracy parameters of our model were as follows: 89.3% (95%CI,82-94.3%) and 78.2% (95%CI,65-88.2%) sensitivity, and 28.5% (95%CI,23.5-33.9%) and 33.8% (95%CI,26.2-42%) specificity, in the derivation and validation group respectively. Considering a 26.6% and 27.1% prevalence of neoplasms at 2nd surveillance colonoscopy in the derivation and validation group, we obtained 88% (95%CI,80-93.6%) and 80.6% (95%CI,68.6-89.6%) negative predictive value, and 31.2% (95%CI,26.1-36.5%) and 30.5% (95%CI,23-38.8%) positive predictive value, in the two cohorts respectively. Three out of 22 (13.6%) and 3 out of 20 (15%) advanced adenomas would be missed in the derivation and validation cohort, respectively. No cancer would be missed in the validation cohort.

DISCUSSION

In this study, we found that patients with prior colon cancer who underwent cleansing colonoscopy had an occurrence of pre-malignant metachronous lesions of 32.3% and 34.5% at the 1st surveillance colonoscopy, and of 26.6% and 27.1% at the 2nd surveillance colonoscopy, in the derivation and validation cohort respectively. Of note, the rate of metachronous CRCs was 2.4% and 2.9% at 1st surveillance colonoscopy and decreased to 0% and 1.4% at 2nd surveillance colonoscopy in the two groups. We identified the following risk factors for metachronous neoplasms at 2nd surveillance colonoscopy: (i) history of left-sided colon cancer, (ii) having ≥1 advanced adenoma at index colonoscopy, and (iii) having ≥1 adenoma at 1st surveillance colonoscopy. In an attempt of risk stratification, we provided a rule-out strategy to select patients who could safely skip the 2nd surveillance colonoscopy. Indeed, if "low-risk" patient would not undergo the 2nd colonoscopy, our model excluded a colorectal neoplasm with sensitivity and NPV both around 90% in the derivation cohort, with sensitivity and NPV both around 80% in the validation cohort. On the other hand, the model had low specificity and PPV. However, we were much more interested in finding a "rule-out" strategy with high sensitivity and negative predictive value in order to exclude from 2nd surveillance colonoscopy patients at low risk of metachronous neoplasms.

Current guidelines recommend performing a surveillance colonoscopy one year after surgery, in order to early detect anastomotic recurrence at a curable stage, as well as to identify pre-cancerous and cancerous metachronous lesion [3,15]. Several evidences support the role of endoscopic post-operative surveillance and have shown that performing at least one surveillance colonoscopy in the first five years after surgery significantly reduces mortality [5–7]. However, both a meta-analysis of randomized controlled trials (RCTs) and a recent RCT failed to show improved survival in patients undergoing more frequent colonoscopies [16,17]. Nevertheless, more recent series have shown that the actual risk of detecting metachronous cancer at subsequent examinations could be much lower [18]. Furthermore, a recent systematic review with meta-analysis on 27 endoscopy-based studies showed that most of metachronous CRCs were detected during the first 2-3 years after surgery for primary cancer, with a substantial decrease in the incidence after 36 months [19]. These findings were confirmed by our results, as the rate of metachronous CRCs decreased from around 2-3% at 1st surveillance colonoscopy to 0-1% at 2nd surveillance colonoscopy in the two cohorts, and can be at least partly explained by an increased detection rate of premalignant lesions at previous endoscopies, probably resulting from an increased awareness of the endoscopists, better bowel cleansing and better performing endoscopes. Indeed, better bowel cleansing has been associated with higher adenoma detection rate [20], which inversely correlates with CRC occurrence and mortality [21,22]. These findings have led the European Society of Gastrointestinal Endoscopy to draw recommendations on performing high-quality colonoscopy [23], which plays a crucial role also in the surveillance setting, probably much more than narrow endoscopic intervals.

Given the abovementioned considerations, and the costs associated with colon cancer endoscopic surveillance, it may seem reasonable to rationalize endoscopic surveillance by stratifying the risk of developing subsequent colorectal neoplasms, allowing the creation of customized surveillance programs. Data on the association between site of colon cancer and occurrence of metachronous CRC are conflicting [24], however this study confirmed our previous finding that patients with prior left colon cancer have an increased risk of adenomas in the residual colon [8]. This fact may have at least two explanations. First, right-sided colon cancer is more frequently associated to microsatellite instability, having been associated with better prognosis and reduction of recurrence risk [25,26]. Second, right colectomy implies the resection of the terminal ileum and the ileo-cecal valve, which may be related to an accelerated bowel transit [27], thus reducing the contact time of potential carcinogenic substances with the residual colon. On the other hand, advanced adenoma(s) at index colonoscopy as risk factor confirmed previous finding by Moon et al, who demonstrated in a cohort of 503 patients with prior surgery for CRC an increased risk of metachronous adenomas according to this feature [28].

Therefore, the strength of our model relies principally on four factors. First, variables in our model are consistent with the published literature. Second, data can be easily extracted from the index and first surveillance colonoscopy report. Third, the validation is remarkable as we applied a temporal approach which is regarded as the strongest method [12], and the validating cohort was nearly as large as half the derivation group. Fourth, we decided to include in the composite endpoint of our model not only advanced adenomas or cancer, but also adenomas, both for consistency and to better define the low-risk patient. Thus, our model seems appealing as it is not time-consuming and it could save a considerable amount of resources.

On the other hand, our study has some limitations. First, the retrospective design might have hampered our findings and we cannot exclude a selection bias, as the sample size is relatively small in contrast with the pathology volume of centers and the study duration of more than ten years. However, this can be partly explained by the fact that the patient had to undergo all of the three colonoscopies at the same center, and that we included only complete colonoscopies with bowel cleansing explicitly reported as adequate. Second, the temporal validation, although being the most robust method is based on data derived from the same centers which constituted the derivation cohort. Third, we had no information on the 3rd surveillance colonoscopy and therefore we could not assess the occurrence of metachronous neoplasms in “low-risk” patients.

In conclusion, we found that subjects with prior left-sided colon cancer or ≥1 advanced adenoma at index colonoscopy or ≥1 adenoma at 1st surveillance colonoscopy are significantly more likely to have neoplasms at 2nd surveillance colonoscopy. Subjects without such factors, i.e. subjects with history of right-sided colon cancer, no advanced adenoma at index colonoscopy, and no adenoma at 1st surveillance colonoscopy have a substantial lower risk and could safely skip the 2nd surveillance colonoscopy in view of cost-effectiveness. Nevertheless, a prospective, multicenter validation study is needed.

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TABLES

Table 1. Patients characteristics and findings at index, 1st and 2nd surveillance colonoscopy. Data are presented for derivation and validation cohort.

Patient characteristics	Derivation cohort (n=421)	Validation cohort (n=203)
n (%)		
Female gender	224 (53.2)	104 (51.2)
Age (years), mean (SD)	62.3 (9.2)	63.4 (11.3)
TNM stage		
Stage I	147 (34.9)	80 (39.4)
Stage II	147 (34.9)	71 (35.0)
Stage III	123 (29.2)	50 (24.6)
Stage IV	4 (1.0)	2 (1.0)
History of left-sided colon cancer	253 (60.1)	104 (51.2)
≥1 adenoma at index colonoscopy	171 (40.6)	70 (34.5)
≥1 advanced adenoma at index colonoscopy	61 (14.5)	35 (17.2)
Days between surgery and 1st surveillance colonoscopy, median (IQR)	365 (273-504)	388 (335-500)
≥1 adenoma at 1st surveillance colonoscopy	136 (32.3)	70 (34.5)
≥1 advanced adenoma at 1st surveillance colonoscopy	21 (5.0)	25 (12.3)
Days between surgery and 2nd surveillance colonoscopy, median (IQR)	960 (726-1386)	1088 (803-1444)
≥1 adenoma at 2nd surveillance colonoscopy	112 (26.6)	55 (27.1)
≥1 advanced adenoma at 2nd surveillance colonoscopy	22 (5.2)	20 (9.9)
≥1 cancer at 2nd surveillance colonoscopy	0 (0)	3 (1.4)

SD, Standard Deviation; IQR, InterQuartile Range.

Table 2. Characteristics of patients with and without metachronous neoplasms at 2nd surveillance colonoscopy in derivation cohort.

	Neoplasms at 2nd surveillance colonoscopy		Beta coefficient (95%CI)	OR (95%CI)
	Absent (n=309)	Present (n=112)		
Intercept	-	-	-1.52 (-3.17, 0.13)	0.22 (0.04-1.14)
Female gender	162 (52.4)	62 (55.4)	0.24 (-0.43, 0.48)	1.02 (0.65-1.61)
Mean age, years (SD)	62.2 (9.4)	62.7 (8.7)	0.01 (-0.02, 0.03)	1.00 (0.98-1.03)
TNM stage	-	-	-	-
Stage I	96 (31.1)	51 (45.5)	-	-
Stage II	114 (36.9)	33 (29.5)	-0.48 (-1.02, 0.05)	0.62 (0.36-1.05)
Stage III	96 (31.1)	27 (24.1)	-0.57 (-1.13, -0.01)	0.57 (0.32-1.00)
Stage IV	3 (1.0)	1 (0.9)	-0.29 (-2.63, 2.04)	0.75 (0.07-7.68)
History of left-sided colon cancer	175 (56.6)	78 (69.6)	0.50 (0.02, 0.97)	1.64 (1.02-2.64)
≥1 advanced adenoma at index colonoscopy	37 (12.0)	24 (21.4)	0.64 (0.05, 1.23)	1.90 (1.05-3.43)
≥1 adenoma at 1st surveillance colonoscopy	86 (27.8)	50 (44.6)	0.72 (0.26, 1.18)	2.06 (1.29-3.27)

OR, Odds Ratio; CI, Confidence Interval. Beta coefficient, OR, and 95% CI computed by a multivariable logistic regression model adjusted for all variables in the table.

Table 3. Sensitivity and Specificity for finding ≥1 neoplasm at 2nd surveillance colonoscopy, according to model-derived scenarios in the derivation and validation cohorts.

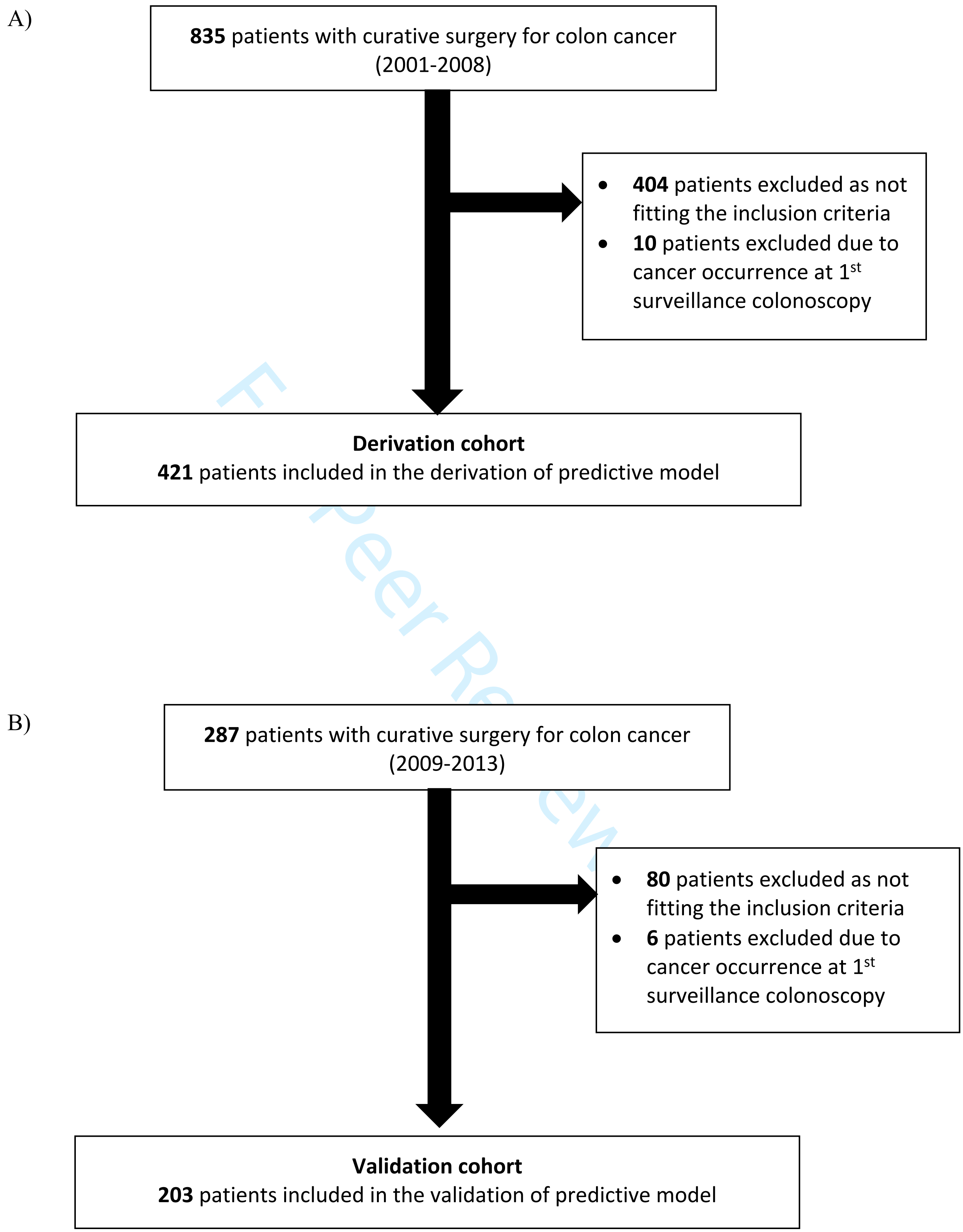
	TP	TN	FN	FP	Sensitivity, % (95%CI)	Specificity, % (95%CI)
Derivation Cohort						
Absence of risk factors	100	88	12	221	89.3 (82-94.3)	28.5 (23.5-33.9)
History of left-sided colon cancer	63	195	49	114	56.3 (46.6-65.6)	63.1 (57.5-68.5)
≥1 advanced adenoma at index colonoscopy	57	207	55	102	50.9 (41.3-60.5)	67 (61.4-72.2)
≥1 adenoma at 1st surveillance colonoscopy	43	238	69	71	38.4 (29.4-48.1)	77 (71.9-81.6)
Validation Cohort						
Absence of risk factors	43	50	12	98	78.2 (65-88.2)	33.8 (26.2-42)
History of left-sided colon cancer	31	85	24	63	56.4 (42.3-69.7)	57.4 (49-65.5)
≥1 advanced adenoma at index colonoscopy	29	94	26	54	52.7 (38.8-66.3)	63.5 (55.2-71.3)
≥1 adenoma at 1st surveillance colonoscopy	23	111	32	37	41.8 (28.7-55.9)	75 (67.2-81.7)

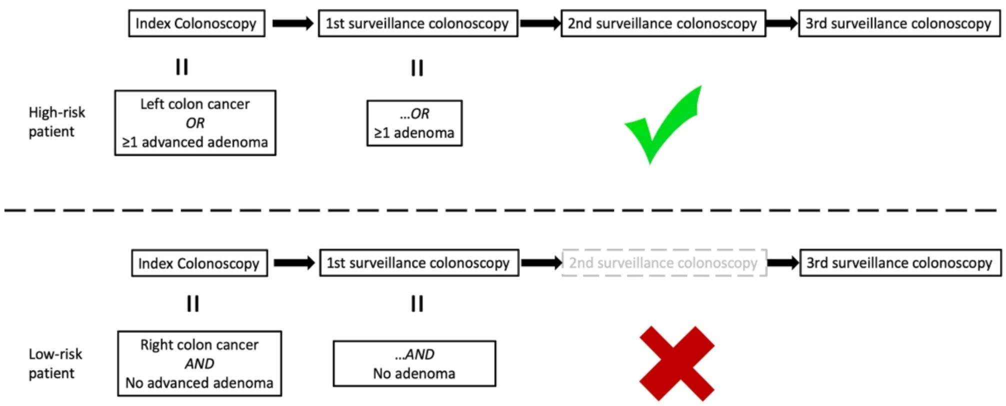
TP, True Positives; TN, True Negatives; FN, False Negatives; FP, False Positives. CI, confidence interval.

FIGURES

Figure 1. Study flowchart; A) derivation cohort; B) validation cohort.

Graphical figure. Profile of the patient at low risk for metachronous neoplasms at 2^{nd} surveillance colonoscopy, and performance of the predictive model based on such profile.


A)
835 patients with curative surgery for colon cancer (2001-2008)
404 patients excluded as not fitting the inclusion criteria
10 patients excluded due to cancer occurrence at 1st surveillance colonoscopy
Derivation cohort
421 patients included in the derivation of predictive model
B)
287 patients with curative surgery for colon cancer (2009-2013)
80 patients excluded as not fitting the inclusion criteria
6 patients excluded due to cancer occurrence at 1st surveillance colonoscopy
Validation cohort
203 patients included in the validation of predictive model


Index Colonoscopy
1st surveillance colonoscopy
2nd surveillance colonoscopy
3rd surveillance colonoscopy
=
=
High-risk patient
Left colon cancer
OR
≥1 advanced adenoma
...OR
≥1 adenoma
Index Colonoscopy
1st surveillance colonoscopy
2nd surveillance colonoscopy
3rd surveillance colonoscopy
=
=
Low-risk patient
Right colon cancer
AND
No advanced adenoma
..AND
No adenoma

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	4
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5,6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	6
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured.	6,7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	7
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6,7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6,7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6,7
	10c	V	For validation, describe how the predictions were calculated.	6,7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6,7
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6,7
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	6,7
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	8
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	8
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	8, table 1
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	9
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 2
	15b	D	Explain how to use the prediction model.	8,9
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	8,9
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	10,11
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	11,12
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	11,12, 13
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	7
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	NA