Published online: 2019-12-13

How to identify patients who are less likely to have metachronous neoplasms after a colon cancer: a predictive model

Authors

Leonardo Frazzoni[1], Liboria Laterza[2], Alessandro Mussetto[3], Rocco Maurizio Zagari[1], Cristina Trovato[4], Mario De Bellis[5], Silvia Paggi[6], Stefania Piccirelli[7], Luigi Ricciardiello[1], Paola Cesaro[7], Cristiano Spada[7], Giulia Dal Piaz[3], Marina La Marca[1], Fabio Fabbian[2], Laura Petrella[8], Veronica Smania[1], Pietro Marone[5], Fabiana Tatangelo[9], Franco Bazzoli[1], Franco Radaelli[6], Alessandro Repici[10], Cesare Hassan[11], Michele Scagliarini[8], Lorenzo Fuccio[1]

Institutions

1 Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, Bologna, Italy
2 Endoscopy Service, AUSL Reggio Emilia, Reggio Emilia, Italy
3 Division of Gastroenterology, S. Maria delle Croci Hospital, Ravenna, Italy
4 Division of Endoscopy, European Institute of Oncology, IRCCS, Milan, Italy
5 Gastroenterology and Endoscopy Unit, Department of Abdominal Oncology, Istituto Nazionale Tumori – IRCCS – Fondazione G. Pascale, Naples, Italy
6 Division of Digestive Endoscopy and Gastroenterology, Valduce Hospital, Como, Italy
7 Digestive Endoscopy Unit, Fondazione Poliambulanza, Brescia, Italy
8 Department of Statistics, University of Bologna, Bologna, Italy
9 Division of Pathology and Cytology, Istituto Nazionale Tumori – IRCSS – Fondazione Pascale, Naples, Italy
10 Digestive Endoscopy Unit, Division of Gastroenterology, Humanitas Clinical and Research Center, Rozzano, Italy
11 Endoscopy Unit, Nuovo Regina Margherita Hospital, Rome, Italy

submitted 23.5.2019
accepted after revision 8.10.2019

Bibliography
DOI https://doi.org/10.1055/a-1041-2945
Published online: 13.12.2019 | Endoscopy 2020; 52: 220–226
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

Corresponding author
Lorenzo Fuccio, MD, Gastroenterology Unit, DIMEC, S. Orsola-Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy
Fax: +39-051-2149112
lorenzo.fuccio3@unibo.it

Table 1s
Online content viewable at:
https://doi.org/10.1055/a-1041-2945

ABSTRACT

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

Methods This was a multicenter, retrospective study including patients who underwent surgery for colon cancer in 2001 – 2008 (derivation cohort) and 2009 – 2013 (validation cohort). A predictive model for neoplasm occurrence at second surveillance colonoscopy was developed and validated.

Results 421 and 203 patients were included in derivation and validation cohort, respectively. At second surveillance colonoscopy, 112 (26.6 %) and 55 (27.1 %) patients had metachronous neoplasms in derivation and validation groups; three cancers were detected in the latter. History of left-sided colon cancer (OR 1.64, 95 %CI 1.02 – 2.64), ≥ 1 advanced adenoma at index colonoscopy (OR 1.90, 95 %CI 1.05 – 3.43), and ≥ 1 adenoma at first surveillance colonoscopy (OR 2.06, 95 %CI 1.29 – 3.27) were independently predictive of metachronous colorectal neoplasms at second surveillance colonoscopy. For patients without such risk factors, diagnostic accuracy parameters were: 89.3 % (95 % CI 82.0 %-94.3 %) and 78.2 % (95 %CI 65.0 %-88.2 %) sensitivity, and 28.5 % (95 %CI 23.5 %-33.9 %) and 33.8 % (95 %CI 26.2 %-42.0 %) specificity in derivation and validation group, respectively. No cancer would be missed.

Conclusions Patients with prior left-sided colon cancer or ≥ 1 advanced adenoma at index colonoscopy or ≥ 1 adenoma at first surveillance colonoscopy had a significantly higher risk of neoplasms at second surveillance colonoscopy; patients without such factors had much lower risk and could safely skip the second surveillance colonoscopy. A prospective, multicenter validation study is needed.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

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 of 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; if results are negative, the interval to the next colonoscopy should be 3 years and if negative again, an interval of 5 years is proposed; subsequent colonoscopies should occur at 5-year intervals [3, 4]. However, current surveillance recommendations are mostly based on outdated studies [5 – 7], despite the fact that treatment modalities for colon cancer have evolved over time, and the data 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 a history of colonic resection for cancer, we found that patients with a prior left-sided colon cancer were at significantly increased risk of having metachronous colorectal adenomas at the second surveillance colonoscopy than patients with a history of right-sided colon cancer [8]. However, this study had several limitations as it did not consider additional potentially relevant information, such as the findings at the index colonoscopy (i. e. the examination performed at the cancer diagnosis) and at the first surveillance colonoscopy.

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

Methods

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

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 colonoscopies, conducted after the surgical intervention; iv) complete colonoscopy to the cecum or ileocolonic anastomosis, explicitly defining the quality of bowel cleansing as adequate; in detail, bowel cleansing was reported according to the Aronchick scale and the Boston Bowel Preparation Scale, and was judged as adequate when the Aronchick scale was “good” or “fair”, or the Boston score was ≥ 2 for each colonic segment; v) age ≥ 18 years at the time of the diagnosis of colon carcinoma. All participating centers adopted the same surveillance recommendations [9].

Patients had to undergo a perioperative cleansing colonoscopy, either at the time of diagnosis or performed within 6 months after the surgical resection. In cases where the cleansing colonoscopy was performed after the resection, this colonoscopy was not considered as the first surveillance colonoscopy.

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

The following data were extracted for each patient: sex, 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 second 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 the first surveillance colonoscopy were excluded from the analysis as they would restart their surveillance protocol after surgery for recurrent CRC. The TRIPOD checklist is available in **Table 1s** in the online-only supplementary material.

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 center.

Statistical analysis

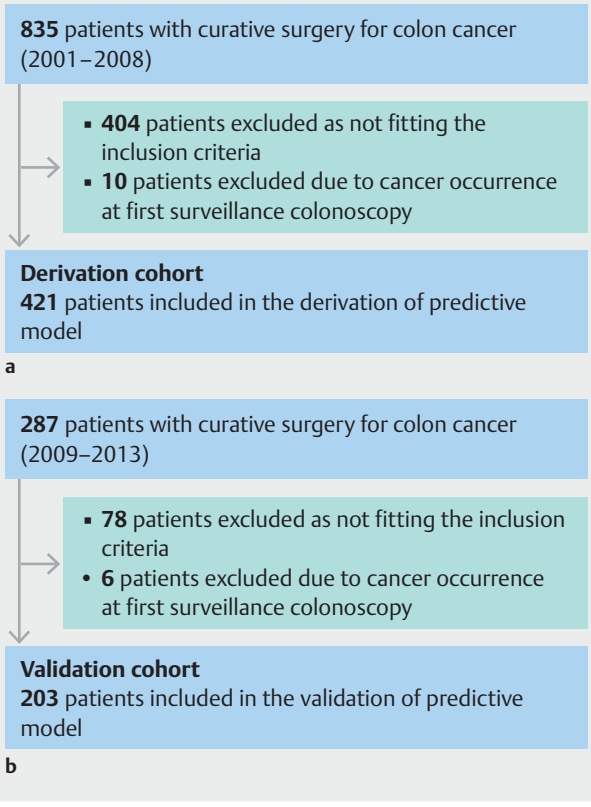
Results are presented as absolute frequency and percentage with 95 % confidence interval (CI) for categorical variables, and mean with standard deviation (SD) or median with interquartile range (IQR) for normally or non-normally distributed continuous variables, respectively. A multivariate logistic regression

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

analysis was performed in order to identify predictive factors of neoplasms at the second surveillance colonoscopy. Odds ratios (ORs) and 95 %CIs were estimated for endoscopic findings at the index and first surveillance colonoscopies, adjusted for age, sex, and stage of index cancer. A predictive model was subsequently developed. The diagnostic accuracy of the 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, Texas, USA).

Sample size

The sample size estimation was based on deriving a predictive model for metachronous neoplasm occurrence at the second surveillance colonoscopy. Estimating that a model based on logistic regression would increase the probability of finding ≥ 1 metachronous neoplasm from 22 % to 35 % (OR 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].



▶ **Fig. 1** Study flow chart. **a** Derivation cohort. **b** Validation cohort.

Results

Study population

Derivation cohort

A total of 431 patients with prior curative surgery for colon cancer between 2001 and 2008 were included (▶ **Fig. 1a**). A total of 10 patients (2.3 %) had cancer at the first surveillance colonoscopy and were excluded from the analysis, giving 421 patients in the derivation cohort.

The time interval between surgery and first surveillance colonoscopy was 365 days (IQR 273 – 504). A history of left-sided colon cancer was documented in 253 patients (60.1 %). Mean age was 62.3 years (SD 9.2), and 224 patients (53.2 %) were female. At the index and first surveillance colonoscopies, 171 (40.6 %) and 136 (32.3 %) patients had ≥ 1 adenoma, of whom 61 (35.7 %; 14.5 % of whole group) and 21 (15.4 %; 5.0 % of whole group) had ≥ 1 advanced adenoma, respectively. At the second surveillance colonoscopy, no CRCs were discovered, whereas ≥ 1 adenoma was found in 112 patients (26.6 %), of whom 22 patients (19.6 %; 5.2 % of whole cohort) had ≥ 1 advanced adenoma (▶ **Table 1**). The time interval between surgery and the second 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 (▶ **Fig. 1b**). Six patients (2.9 %) had cancer at the first surveillance colonoscopy and were excluded from the analysis, giving 203 patients in the validation cohort. The time interval between surgery and the first surveillance colonoscopy was 388 days (IQR 335 – 500). A history of left-sided colon cancer was reported in 104 patients (51.2 %). Mean age was 63.4 years (SD 11.3), and 104 patients (51.2 %) were female. At index and first surveillance colonoscopies, 70 (34.5 %) and 70 (34.5 %) patients had ≥ 1 adenoma, of whom 35 (50.0 %; 17.2 % of whole group) and 25 (35.7 %; 12.3 % of whole group) had ≥ 1 advanced adenoma, respectively. At the second surveillance colonoscopy, one metachronous colon cancer and two anastomotic recurrences were found (▶ **Table 1**). In addition, ≥ 1 adenoma was found in 55 patients (27.1 %), of whom 20 patients (36.3 %; 9.9 % of whole group) had ≥ 1 advanced adenoma. The time interval between surgery and the second surveillance colonoscopy was 1088 days (IQR 803 – 1444).

Predictive model development

A history of left-sided colon cancer (OR 1.64, 95 %CI 1.02 to 2.64), ≥ 1 advanced adenoma at the index colonoscopy (OR 1.90, 95 %CI 1.05 to 3.43), and ≥ 1 adenoma at the first surveillance colonoscopy (OR 2.06, 95 %CI 1.29 to 3.27) were independently associated with an increased risk of metachronous colorectal neoplasms at second 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

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

▶ **Table 1** Patient characteristics and findings at index, first, and second surveillance colonoscopies in the derivation and validation cohorts.

Patient characteristics	Derivation cohort (n = 421)	Validation cohort (n = 203)
Female sex, n (%)	224 (53.2)	104 (51.2)
Age, mean (SD), years	62.3 (9.2)	63.4 (11.3)
TNM stage, n (%)		
▪ 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, n (%)	253 (60.1)	104 (51.2)
Index colonoscopy		
▪ ≥ 1 adenoma at index colonoscopy, n (%)	171 (40.6)	70 (34.5)
▪ ≥ 1 advanced adenoma at index colonoscopy, n (%)	61 (14.5)	35 (17.2)
First surveillance colonoscopy		
▪ Interval between surgery and first surveillance colonoscopy, median (IQR), days	365 (273 – 504)	388 (335 – 500)
▪ ≥ 1 adenoma at first surveillance colonoscopy, n (%)	136 (32.3)	70 (34.5)
▪ ≥ 1 advanced adenoma at first surveillance colonoscopy, n (%)	21 (5.0)	25 (12.3)
Second surveillance colonoscopy		
▪ Interval between surgery and second surveillance colonoscopy, median (IQR), days	960 (726 – 1386)	1088 (803 – 1444)
▪ ≥ 1 neoplasm at second surveillance colonoscopy, n (%)	112 (26.6)	55 (27.1)
▪ ≥ 1 advanced adenoma at second surveillance colonoscopy, n (%)	22 (5.2)	20 (9.9)
▪ ≥ 1 cancer at second surveillance colonoscopy, n (%)	0 (0)	3 (1.5)

SD, standard deviation; IQR, interquartile range.

of ≥ 1 adenoma at the 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 second surveillance colonoscopy, respectively; OR 1.25, 95 %CI 0.79 to 1.98).

We defined a patient with a history of right-sided colon cancer, no advanced adenomas at the index colonoscopy, and no adenomas at the first surveillance colonoscopy as a "low-risk" patient. When we excluded this patient group from the second surveillance colonoscopy, the diagnostic accuracy parameters of our model were as follows: 89.3 % (95 %CI 82.0 % to 94.3 %) and 78.2 % (95 %CI 65.0 % to 88.2 %) sensitivity, and 28.5 % (95 %CI 23.5 % to 33.9 %) and 33.8 % (95 %CI 26.2 % to 42.0 %) specificity, in the derivation and validation groups, respectively (▶ **Table 3**). Considering a 26.6 % and 27.1 % prevalence of neoplasms at the second surveillance colonoscopy in the derivation and validation group, we obtained 88.0 % (95 %CI 80.0 % to 93.6 %) and 80.6 % (95 %CI 68.6 % to 89.6 %) NPV and 31.2 % (95 %CI 26.1 % to 36.5 %) and 30.5 % (95 %CI 23.0 % to 38.8 %) PPV, in the two cohorts, respectively. Three out of 22 (13.6 %) and 3 out of 20 (15.0 %) advanced adenomas would be missed in the derivation and validation cohorts, respectively, but 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 premalignant metachronous lesions of 32.3 % and 34.5 % at the first surveillance colonoscopy, and of 26.6 % and 27.1 % at the second surveillance colonoscopy, in the derivation and validation cohorts, respectively. Of note, the rate of metachronous CRCs was 2.4 % and 2.9 % at the first surveillance colonoscopy and decreased to 0 % and 1.5 % at the second surveillance colonoscopy in the two groups. We identified the following risk factors for metachronous neoplasms at the second surveillance colonoscopy: i) history of left-sided colon cancer, ii) having ≥ 1 advanced adenoma at the index colonoscopy, and iii) having ≥ 1 adenoma at the first surveillance colonoscopy. In an attempt at risk stratification, we provided a rule-out strategy to select patients who could safely skip the second surveillance colonoscopy. Indeed, if "low-risk" patients did not undergo the second colonoscopy, our model excluded a colorectal neoplasm with both sensitivity and NPV of about 90 % in the derivation cohort and about 80 % in the validation cohort. However, the model had low specificity and PPV. Nonetheless, we were much more interested in finding a "rule-out" strategy with high sensitivity

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

▶ **Table 2** Characteristics of patients with and without metachronous neoplasms at the second surveillance colonoscopy in the derivation cohort.

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

OR, odds ratio; CI, confidence interval; SD, standard deviation.
Beta coefficient, OR, and 95 %CI computed by a multivariable logistic regression model adjusted for all variables in the table.

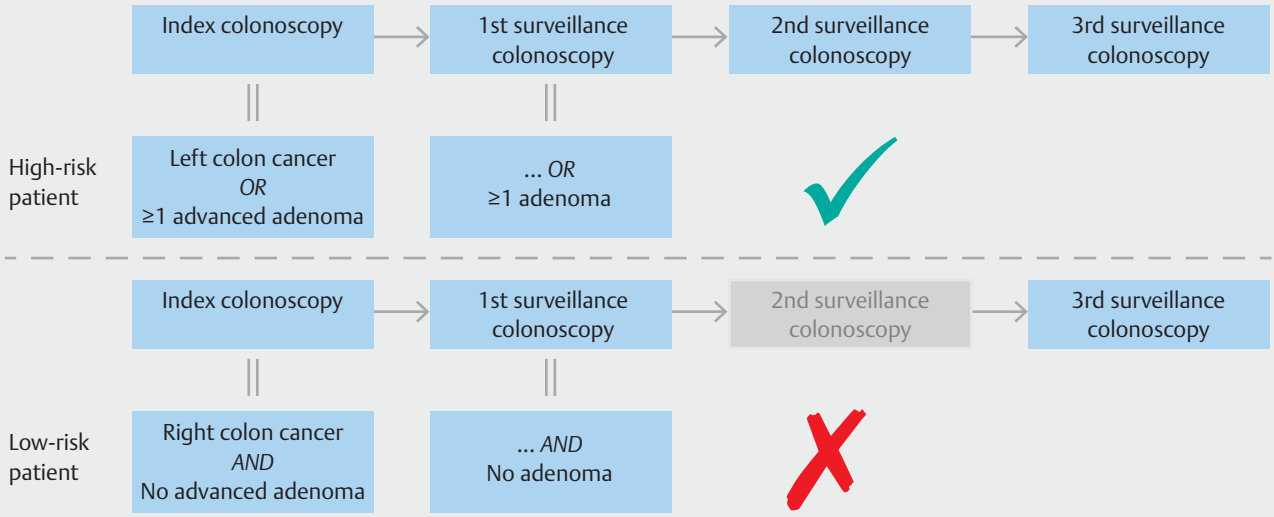
and NPV in order to exclude patients at low risk of metachronous neoplasms from undergoing a second surveillance colonoscopy (▶ **Fig. 2**).

Current guidelines recommend performing a surveillance colonoscopy 1 year after surgery in order to detect anastomotic recurrence early and at a curable stage, as well as to identify precancerous and cancerous metachronous lesions [3, 15]. Published evidence supports the role of endoscopic postoperative surveillance and has shown that performing at least one surveillance colonoscopy in the first 5 years after surgery significantly reduces mortality [5 – 7]. 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]. However, 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 of 27 endoscopy-based studies showed that most 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 about 2 % – 3 % at first surveillance colonoscopy to 0 % – 1 % at second surveillance colonoscopy in the two cohorts. These findings can be at least partly explained by an increased detection of premalignant lesions at previous colonoscopies, probably as a result of an increased awareness by the endoscopist, better bowel cleansing, and improved performance of endoscopes. Indeed, better bowel cleansing has been associated with a 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 recommend performing high-quality colonoscopy [23], which plays a crucial role in the surveillance setting, probably much more than shorter colonoscopy 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, the present study confirmed our previous finding that patients with prior left-sided 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 with 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 ileocecal valve, which may be related to an accelerated bowel transit [27], thus reducing the contact time of potential carcinogenic substances within the residual colon. Our finding that advanced adenoma(s) at the index colonoscopy was a risk factor confirmed previous findings by Moon et al., who demonstrated an increased risk of metachronous adenomas in a cohort of 503 patients with prior surgery for CRC [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 reports. Third, the validation is remarkable as we applied a temporal approach, which is regarded as the strongest method [12], and

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



▶ **Fig. 2** Profiles of patients at high and low risk of metachronous neoplasms at the second surveillance colonoscopy, according to the predictive model. A risk-stratified strategy of endoscopic surveillance is proposed.

▶ **Table 3** Sensitivity and specificity for finding ≥ 1 neoplasm at the second surveillance colonoscopy, according to model-derived scenarios in the derivation and validation cohorts.

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

CI, confidence interval.

the validating cohort was nearly as large as half the derivation group. Fourth, we decided to include in the composite end point 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.

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 to the pathology volume of the centers and the study duration of more than 10 years. However, this can be partly explained by the fact that patients 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 that constituted the derivation cohort. Third, we had no information on the third surveillance colonoscopy and therefore we could not assess the occurrence of metachronous neoplasms in "low-risk" patients.

In conclusion, we found that patients with prior left-sided colon cancer or ≥ 1 advanced adenoma at the index colonoscopy or ≥ 1 adenoma at the first surveillance colonoscopy were significantly more likely to have neoplasms at the second surveillance colonoscopy. Patients without such factors (i. e. pa-

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

tients with a history of right-sided colon cancer, no advanced adenoma at the index colonoscopy, and no adenoma at the first surveillance colonoscopy) had a substantially lower risk and could safely skip the second surveillance colonoscopy in view of cost-effectiveness. Nevertheless, a prospective, multicenter validation study is needed.

Competing interests

The authors declare that they have no conflict of interest.

References

[1] Arnold M, Sierra MS, Laversanne M et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017; 66: 683–691

[2] Kjeldsen BJ, Kronborg O, Fenger C et al. A prospective randomized study of follow-up after radical surgery for colorectal cancer. Br J Surg 1997; 84: 666–669

[3] Kahi CJ, Boland CR, Dominitz JA et al. Colonoscopy surveillance after colorectal cancer resection: recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2016; 150: 758–768.e11

[4] Hassan C, Wysocki P, Fuccio L et al. Endoscopic surveillance after surgical or endoscopic resection for colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Digestive Oncology (ESDO) Guideline. Endoscopy 2019; 51: 266–277

[5] Kjeldsen BJ, Kronborg O, Fenger C et al. The pattern of recurrent colorectal cancer in a prospective randomised study and the characteristics of diagnostic tests. Int J Colorectal Dis 1997; 12: 329–334

[6] Mäkelä JT, Laitinen SO, Kairaluoma MI. Five-year follow-up after radical surgery for colorectal cancer. Results of a prospective randomized trial. Arch Surg 1995; 130: 1062–1067

[7] Ohlsson B, Breland U, Ekberg H et al. Follow-up after curative surgery for colorectal carcinoma. Randomized comparison with no follow-up. Dis Colon Rectum 1995; 38: 619–626

[8] Fuccio L, Spada C, Frazzoni L et al. Higher adenoma recurrence rate after left- versus right-sided colectomy for colon cancer. Gastrointest Endosc 2015; 82: 337–343

[9] Rex DK, Kahi CJ, Levin B et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006; 130: 1865–1871

[10] Strum WB. Colorectal adenomas. N Engl J Med 2016; 374: 1065–1075

[11] Collins GS, Reitsma JB, Altman DG et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2015; 162: 55–63

[12] Moons KGM, Altman DG, Reitsma JB et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015; 162: W1–W73

[13] Demidenko E. Sample size determination for logistic regression revisited. Stat Med 2007; 26: 3385–3397

[14] Faul F, Erdfelder E, Lang AG et al. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007; 39: 175–191

[15] Hassan C, Wysocki PT, Fuccio L et al. Endoscopic surveillance after surgical or endoscopic resection for colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Digestive Oncology (ESDO) Guideline. Endoscopy 2019; 51: 266–277

[16] Tjandra JJ, Chan MKY. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum 2007; 50: 1783–1799

[17] Wang T, Cui Y, Huang W-S et al. The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective, randomized clinical study. Gastrointest Endosc 2009; 69: 609–615

[18] Cone MM, Beck DE, Hicks TE et al. Timing of colonoscopy after resection for colorectal cancer: are we looking too soon? Dis Colon Rectum 2013; 56: 1233–1236

[19] Fuccio L, Rex D, Ponchon T et al. New and recurrent colorectal cancers after resection: a systematic review and meta-analysis of endoscopic surveillance studies. Gastroenterology 2019; 156: 1309–1323.e3

[20] Radaelli F, Paggi S, Hassan C et al. Split-dose preparation for colonoscopy increases adenoma detection rate: a randomised controlled trial in an organised screening programme. Gut 2017; 66: 270–277

[21] Kaminski MF, Regula J, Kraszewska E et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010; 362: 1795–1803

[22] Corley DA, Jensen CD, Marks AR et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014; 370: 1298–1306

[23] Kaminski M, Thomas-Gibson S, Bugajski M et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. Endoscopy 2017; 49: 378–397

[24] Mulder SA, Kranse R, Damhuis RA et al. The incidence and risk factors of metachronous colorectal cancer: an indication for follow-up. Dis Colon Rectum 2012; 55: 522–531

[25] Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol 2004; 88: 261–266

[26] Moritani K, Hasegawa H, Okabayashi K et al. Difference in the recurrence rate between right- and left-sided colon cancer: a 17-year experience at a single institution. Surg Today 2014; 44: 1685–1691

[27] Gracie DJ, Kane JS, Mumtaz S et al. Prevalence of, and predictors of, bile acid malabsorption in outpatients with chronic diarrhea. Neurogastroenterol Motil 2012; 24: 983–e538

[28] Moon CM, Cheon JH, Choi EH et al. Advanced synchronous adenoma but not simple adenoma predicts the future development of metachronous neoplasia in patients with resected colorectal cancer. J Clin Gastroenterol 2010; 44: 495–501

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.