New and Recurrent Colorectal Cancers After Resection: a Systematic Review and Meta-analysis of Endoscopic Surveillance Studies

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Abbreviations used: CI, confidence intervals; CRC, Colorectal Cancer; NA, Not Available.

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ABSTRACT

Background & Aims: Outcomes of endoscopic surveillance following surgery for colorectal cancer (CRC) vary with the incidence and timing of CRC detection, at anastomoses or non-anastomoses in the colorectum. We performed a systematic review and meta-analysis to evaluate the incidence of CRCs identified during surveillance colonoscopies of patients who have already undergone surgery for this cancer.

Methods: We searched PubMed, EMBASE, SCOPUS, and the Cochrane Central Register of Clinical Trials through January 1, 2018 to identify studies investigating rates of CRCs at anastomoses or other locations in the colorectum after curative surgery for primary CRC. We collected data from published randomized controlled, prospective, and retrospective cohort studies. Data were analyzed by multivariate meta-analytic models.

Results: From 2373 citations, we selected 27 studies with data on 15,803 index CRCs for analysis (89% of patients with stage 1–3 CRC). Overall, 296 CRCs at non-anastomotic locations were reported over time periods of more than 16 years (cumulative incidence, 2.2% of CRCs; 95% CI, 1.8%–2.9%). The risk of CRC at a non-anastomotic location was significantly reduced more than 36 months after resection compared with before this timepoint (odds ratio for non-anastomotic CRCs at 36–48 months vs 6–12 months after surgery, 0.61; 95% CI, 0.37–0.98; P=.031); 53.7% of all non-anastomotic CRCs were detected within 36 months of surgery. One hundred fifty-eight CRCs were detected at anastomoses (cumulative incidence of 2.7%; 95% CI, 1.9%–3.9%). The risk of CRCs at anastomoses was significantly lower 24 months after resection than before (odds ratio for CRCs at anastomoses at 25–36 months after surgery vs 6–12 months, 0.56; 95% CI, 0.32–0.98; P=.036); 90.8% of all CRCs at anastomoses were detected within 36 months of surgery.

Conclusions: After surgery for CRC, the highest risk of CRCs at anastomoses and at other locations in the colorectum is highest during 36 months after surgery—risk decreases thereafter. Patients who have undergone CRC resection should be evaluated by colonoscopy more closely during this time period. Longer intervals may be considered thereafter.

KEY WORDS: colon cancer; recurrence; endoscopy; early detection

INTRODUCTION

Worldwide, over 1.8 million new colorectal cancer (CRC) cases are estimated to occur in 2018, ranking third in terms of incidence and accounting for about 1 in 10 of all cancer cases [1]. Despite a wide variation of its incidence by world region, a steady increase in incidence has been observed, in particular a generational change and a rise in transitioning countries. Indeed, CRC incidence may be considered a surrogate marker of socioeconomic development [1].

Patients with a history of CRC are at increased risk of developing metachronous colorectal lesions, therefore post-CRC surgery patients are generally recommended to adhere to colonoscopy-based surveillance protocols [2]. The main goals of surveillance colonoscopy are to diagnose cancers at anastomotic and non-anastomotic location at a curable stage, and to prevent the development of new cancer by detecting and removing precancerous lesions. Cancer at anastomotic location generally represents recurrent cancer while cancer at non-anastomotic location may represent, according to the timing of previous colonoscopy and site of detection, new onset cancer, missed or incompletely resected lesions [3]. Current guidelines recommend performing surveillance colonoscopy 1 year after surgery; the interval to the next colonoscopy should be 3 years and then 5 years; thereafter, colonoscopies should occur at 5-year intervals.[2]. This protocol was based on a systematic review of the literature performed by a panel of experts, however a formal systematic review with meta-analysis on this issue has never been performed.

Thus, aim of the present systematic review was to evaluate the incidence of cancer at anastomotic and non-anastomotic location diagnosed during surveillance colonoscopy in order to help decision-makers on the most appropriate intervals of colonoscopy-based surveillance in patients with a history of CRC.

METHODS

We followed the PRISMA guideline and checklist for reporting systematic reviews and meta-analyses[4].

Data Sources and Searches

We performed a comprehensive literature search by consulting PubMed, EMBASE, SCOPUS, and the Cochrane Central Register of Clinical Trials (up to Jan 1st, 2018) to identify full-text studies, published in English, investigating the rate of CRCs at anastomotic and non-anastomotic location occurring after curative surgery for primary CRC. ClinicalTrials.gov was assessed for ongoing or recently completed trials, and PROSPERO for ongoing or recently completed systematic reviews. Electronic searches were integrated by manual searches of references of included studies.

We used the following medical subject headings (MeSH) and keywords to include studies: ("colon"[MeSH Terms] OR "colon"[All Fields] OR "rectum"[MeSH Terms] OR "rectum"[All Fields] OR "colorectal"[All Fields]) AND ("General Surgery/surgery"[MeSH Terms] OR "resection"[All Fields]) OR "colectomy"[All Fields] AND ("Colonoscopy"[All Fields] OR "Colonoscopy"[Mesh] OR "Endoscopy"[Mesh]) AND ("Surveillance"[All Fields] OR "Follow up"[All Fields]) AND English[lang].

Study Selection

We ran a literature search to identify all relevant randomized controlled trials (RCTs), and prospective or retrospective cohort studies investigating the occurrence of CRC at anastomotic and/or non-anastomotic location after curative surgery, published since 1985. In order to be included in our search, studies had to use complete colonoscopy as the surveillance procedure, to specify the colonoscopy-based surveillance protocol and report the timing of diagnosis of cancer at

non-anastomotic (NA-CRC) or anastomotic (A-CRC) location. Studies conducted in specific setting, i.e. inflammatory bowel disease, and hereditary CRC syndromes (e.g. Lynch syndrome or Familial Adenomatous Polyposis syndromes) were excluded. Other exclusion criteria were review articles, abstracts, case reports, editorials, and corresponding letters not reporting original results.

Data Extraction and Quality Assessment

Three independent reviewers (LF, LFr, CH) evaluated the eligibility of the publications for selection, resolving any disagreement by consensus assessment. We registered the reasons for excluding studies. The authors were not blinded to the journal titles nor to the study authors or institutions.

The following data were extracted for each study: publication status, publication year, enrolment period, study design and location, number of centers involved, study population, patient characteristics (e.g. site of primary tumor, mean age and gender), follow-up period and protocol (i.e., according to US Multi-Society Task force on CRC recommendations[3], namely 1-, 3- and 5-year protocol or not following US recommendations), number, site, stage and timing of CRCs at anastomotic and non-anastomotic location found during surveillance. We used a modified Newcastle-Ottawa scale to assess the risk of bias in included studies [5].

Outcomes assessment

The primary outcomes of this study were rates and timing of CRCs at anastomotic and non-anastomotic location. Outcomes were assessed at progressive time-intervals of 12 months (i.e. time-point rates, ranging from 6-12 months to 180 months) after primary resection. For each included study, time-interval rates were calculated as the number of A/NA-CRCs occurred in a given time interval, divided by the total number of patients with CRC. All the analyses performed assumed no 'drop out', that is, that no participants were censored. Only very few studies provided exhaustive information about drop-out rates. For consistency, drop out was ignored in our analyses. Since

some studies did not report data on all time-intervals, the number of time-interval rates differed between studies. Hence, there were missing data on some of the 12-month time-intervals. For recurrence, we also performed a subgroup analysis between colon *vs.* rectal localization of the index tumor, for those studies providing this information.

To assess the robustness of our results (to the assumption that all patients included in the follow-up spanned the entire follow-up period), subgroup and sensitivity analyses were carried out (see **supplementary appendix** for details). We also assessed the cumulative proportion of all A- or NA-CRCs over times. The cumulative proportion of A- or NA-CRCs at a given time was computed as the number of A- or NA-CRCs observed at all time-intervals preceding that time, divided by the number of all A- or NA-CRCs discovered during the entire follow-up period.

Variables potentially influencing the occurrence of A- and/or NA-CRCs were also investigated. The *a priori* selected covariates were: demographic characteristics (i.e. mean age, male gender proportion), clinical features (i.e. primary CRC site, endoscopic surveillance protocol and timing) and study size. Secondary outcomes included the cumulative proportions of A- and NA-CRCs at different follow time intervals.

Data Synthesis and Analysis.

In our meta-analyses, each study provided outcome values for several time-intervals and these values were inherently dependent. Effectively, true outcomes within a study might be more similar to each other than between-studies (correlated true outcomes). Therefore, the assumption of statistical independence, which underlines classical meta-analytic strategies, was violated. In cases where an effect size is reported at each one of multiple pre-determined time points, a multivariate meta-analysis via linear (mixed-effects) models can be used to estimate overall effect sizes at each time, while taking account of any correlation between effect sizes, both within and between studies [6,7].

All analyses were conducted in R version 3.3.2 [8], with the package *metafor* [9]. The *rma.mv* function was used to fit the multivariate random effects model. In this model, the time was entered as a predictor of a second CRC and the study was included as a random factor to deal with non-independent samplings from a single study and to consider variation in findings among studies. In details, the model allowed each study to have a different effect at each time point. The model requires specifications of the covariance structure for the correlation between with-study effects. Therefore, we compared models where this correlation was accounted for in different alternatives, including 1) a random-effects model accounting for this correlation using the compound symmetry structure (i.e., correlations are assumed to be the same for each set of time points, regardless of the time lag between the time points); 2) a correlated random-effect model that accounts for within-study serial correlation between effects using the autoregressive structure (i.e., the dependence between effect sizes become stronger as the lag between them gets smaller); 3) a random-effect model assuming complete independence between random-effects and residuals. The latter is equivalent to meta-analyzing the data at each time separately (independent random-effect meta-analysis). The models were compared by likelihood-ratio tests and Akaike information criteria (AIC) (see **Supplementary Appendix for details**). Results from the best fitting model (i.e. AR = autoregressive structure) were reported here. Study-level covariates (e.g. year of publication, gender, study country) and interaction terms between variables and time were also included in the analyses as predictors or moderator of effects over time, to explain residual heterogeneity. These covariates were considered to have fixed-effects and, therefore, did not impact the specification of correlation.

The above-mentioned methodology was also applied to assess the cumulative proportion of patients with A- and/or NA-CRCs at successive time intervals of 12 months.

Meta-analyses can be subject to publication bias. In order to check the presence of publication bias in our dataset, we tested correlations between the observed outcomes and the study sample size. We tested this by including the total sample size of the study as a covariate in the

multivariate regression model. Further, we performed a trim-and-fill procedure to determine the number of missing studies based on a pooled effect that adjusts for bias by imputing studies that make the funnel plot more symmetric [10]. An estimate of the A-/NA-CRCs rate when including these potentially missing studies was reported. Since there are methodological difficulties in the use of trim-and-fill procedures in multivariate meta-analytic data, the trim-and-fill procedure was performed for each time-interval, separately.

RESULTS

Characteristics of the included studies

Our search identified 2,373 publications, of which 27 studies were included in the analysis for a total of 15,589 patients, and 15,803 index CRCs (Supplementary **Figure 1**) [11–37]. Baseline characteristics of the included studies are detailed in **Tables 1-3.** Overall, 14 (52%) studies were conducted in Europe, 7 (26%) in Asia, 4 (15%) in North America and 2 (7%) in Australia. The publication year ranged from 1986 to 2017; in detail, 12 (44%) studies were published before 2000, 5 (19%) between 2000 and 2005, and 10 (37%) after 2005. Seventeen (63%) articles were retrospective, and 25 (93%) studies were conducted at a single center. Five studies[19,27,29,35,37] followed the 1-3-5-year surveillance protocol. Twenty-one studies[11,12,14,16–18,20,22,23,25–27,29,31–37] performed clearing colonoscopy in the peri-operative time period. Three studies [21,36,37] clearly stated that "high-quality" colonoscopy, i.e. scope introduction up to the caecum or ileo-colonic anastomosis with adequate bowel preparation was carried out, whilst all the other studies did not provide any information on this issue.

Among included patients, mean age ranged from 54 to 71 years, whereas male gender proportion ranged from 46% to 69%. Seventeen studies for a total of 13,085 CRCs reported the stage of primary CRC, of which 3,016 (23%) were stage I, 4,805 (37%) stage II, 3,829 (29%) stage III, and 1,435 (11%) stage IV. Fifteen studies reported the colon location of primary CRCs, for a

total of 3,664 cases of which 2,401 (65.5%) were located in the colon and 1,266 (34.5%) in the rectum. The mean length of follow-up varied across the studies, ranging from 18 to 108 months.

CRC at Non-Anastomotic Location

Non-Anastomotic CRC rate at various time-intervals

Twenty-seven studies with 15,589 patients provided data on NA-CRCs occurrence. Overall, 296 NA-CRCs were reported during a follow-up period of up to >16 years, corresponding to an overall cumulative incidence of 2.2% (95% CI: 1.8-2.9%). Tumor stage was available for 206 NA-CRCs, of which 125 (61%) were stage I to II. Colon location was reported in 215 NA-CRCs, of which 95 (44%) were located proximally to the splenic flexure and 120 (56%) in the distal colon. Among the included studies, 202 estimates of NA-CRCs rate were reported in at least one of the specified time-intervals. Six studies reported data on NA-CRCs for all 16 time intervals [13,16,19,24,27,36].

The pattern of the results was the same across all the 3 investigated models (see details in the **Supplemental Appendix**): the odds of NA-CRCs at time points >36 months after resection were lower as compared with those at the first 36 months. Time interval rates from the best fitting model (AR structure) are displayed in **Figure 1**. In details, NA-CRCs rate was 0.74% (95% CI:0.50-1.09%) at 6-12 months after resection and it did not decrease (0.63% 95% CI:0.47-0.90%; OR: 0.81; 95% CI: 0.53-1.26; P=0.349) at 13-24 months and at 25-36 months (0.69%; 95% CI:0.49-1.01%; OR, 0.94; 95% CI:0.62-1.46; P=0.778). Time-points >36 months provided significantly different estimates. At 37-48 months, a significant decrease in the NA-CRCs rate (as compared with 6-12 months rate) was observed, corresponding to an estimated rate of 0.45% (95% CI: 0.29-0.70%; OR: 0.61; 95% CI: 0.37-0.98; P=0.031). The incidence of NA-CRCs remained very low in the remaining intervals of follow-up (as compared with 6-12 months), corresponding to

0.34% (95% CI:0.24-0.58%; OR: 0.48; 95% CI:0.29-0.81; P=0.005) at 49-60 months, to 0.29% (95% CI:0.15-0.56% OR: 0.41; 95% CI:0.19-0.84; P=0.016) at 85-96 months, and to 0.28% (95% CI:0.14-0.57%; OR: 0.38; 95% CI:0.18-0.81; P=0.011) at 109-120 months.

Patients with a diagnosis of stage IV cancer were generally not included in the studies, unless oncological curative resection of metastases was achieved. Only one study included a large group of Stage IV cases (25.6% of the entire study population) [36]. A sensitivity analysis excluding the study by le Clercq et al[36] was carried out and the main findings did not substantially change: NA-CRCs occurred in 0.82% (95% CI:0.55-1.23%) between 6 and 12 months, 0.61% (95% CI:0.41-0.91%) between 12 and 24 months and in 0.72% (95%CI:4.8-1.1%) between 25-36 months. Differences were not significant. Over the longer time-intervals, rate of NA-CRCs decreased to 0.51% (95%CI:0.32-0.81%) between 37 and 48 months (P=0.092) and to 0.41% (95%CI:0.26-0.66%) between 49 and 60 months (P=0.012).

Cumulative proportion of non-anastomotic CRCs on all non-anastomotic CRCs, at various time-intervals.

Among the included studies, 53.7% (95% CI:41.3-65.7%) of all discovered NA-CRCs occurred within 36 months after resection, 70.4% (95% CI:60.0-79.7%) within 60 months, and 89.0% (95% CI:82.1-93.5) within 120 months (**Figure 2**).

Predictors of CRC rate at non-anastomotic location

Overall, the only variable significantly associated with NA-CRCs rate was the study size, so that larger studies were significantly associated with lower NA-CRCs rates (OR: 0.96; 95% CI: 0.95-0.98; P<0.001) (see **Supplemental Table 1**).

CRC at Anastomotic Location

Anastomotic CRC rate at various time-intervals

Among 25 studies for a total of 6,048 patients in which time-point data on CRCs at anastomotic location were given, 158 A-CRCs were reported during a follow-up period of up to 16 years, corresponding to an overall incidence of 2.7% (95% CI: 1.9-3.9%). Of note, no A-CRC was reported for time intervals ≥ 60-72 months after surgical intervention.

On multivariate meta-analysis, the follow-up time interval was significantly associated with outcome (see **Figure 3**). The highest rate was at 6-12 months after resection, being 1.7% (95% CI: 1.04-2.8%) and it did not differ significantly at 13-24 months (1.23%; 95% CI: 0.74-2.1%; P=0.219; OR: 0.72; 95% CI: 0.44-1.24; P=0.219). Time points >24 months provided significantly lower estimates compared to 6-12 months: at 25-36 months, the rate was 0.93% (95% CI: 0.53-1.60%; P=0.036; OR: 0.56; 95% CI: 0.32-0.98; P=0.036) and further decreased to 0.30% (95% CI: 0.14-0.64; P=0.006; OR: 0.18; 95% CI: 0.08-0.39; P=0.001) at 37-48 months.

Cumulative proportion of anastomotic CRCs on all anastomotic CRCs, at various time-intervals

Among the included studies, 70.5% (95% CI:53.6-83.2%) of all discovered A-CRCs occurred within 24 months, 90.8% (95% CI:80.9-95.9%) within 36 months, 91.2% (95% CI: 80.8-96.0%) within 48 months and 94.5% (95% CI:86.6-97.9%) within 60 months (**Figure 4**).

Predictors of CRC at anastomotic location

Anastomotic CRC was significantly associated with the study size, so that larger studies yielded lower rate (OR, 0.98; 95% CI: 0.95-0.99; P=0.043). There was some evidence of an association between timing of the first colonoscopy and occurrence of anastomotic CRC (≥12 months vs. <12 months, OR, 0.42; 95% CI: 0.15-1.13), although not reaching significance (p=0.089). (see **Supplementary Table 2**)

Cancer at anastomotic location development according to cancer-site

We performed a subgroup analysis on the A-CRCs rates stratified according to the site of primary cancer (i.e., rectum *vs*. colon). Four studies[16,23,24,33] provided data and were analyzed. Among primary rectal cancer group, 27 A-CRCs out of 482 primary rectal cancer were diagnosed during follow-up, yielding a pooled cumulative rate of 5.46% [95%CI 2.3-12.41]. Among primary colon cancer group, 18 A-CRCs out of 921 primary colon cancers were identified, yielding a pooled cumulative rate of 1.95% [95%CI 0.82-4.58]. Thus, patients with a history of rectal cancer compared to patients with prior colon cancer had a two-fold higher risk of developing an A-CRC during surveillance [Relative Risk 2.66; 95%CI 1.31-5.41].

Risk of bias

Multivariate regression analysis indicated a significant negative association between the study sample size and occurrence of A-/NA-CRCs, suggesting that studies with limited sample sizes were more likely to report larger rates of A-/NA-CRCs. The negative correlation was not limited to a particular time-interval, thus possibly suggesting publication bias. We also evaluated publication bias by performing trim-and-fill procedure for each time-interval, separately.

The number of studies was too small to test publication bias for time-intervals >120 months. Therefore, 11 trim-and-fill procedures were performed, of which only one yielded a A-/NA-CRCs rate (at the 6-12 months) potentially biased result because 7 studies could be missing. The imputation and inclusion of these studies, however, yielded a A-/NA-CRCs estimate (0.86%; 95% CI:0.40-1.00) comparable with the multivariate estimate (0.74%; 95% CI:0.50-1.09%). Thus, although it is likely there are unpublished studies not yet included, the impact attributable to publication bias is potentially minimal for this set of studies.

According to the modified Newcastle-Ottawa scale for bias assessment, 17 out of 27 studies (63%) were judged at high risk of bias (see **Supplementary Table 3** for details).

DISCUSSION

After surgery for CRC, the highest risk of CRCs at anastomotic and non-anastomotic location was restricted to the early follow up period, with a decrease after 24-36 months from surgery and this time-dependent decrease was more evident for CRC at anastomotic than non-anastomotic location.

The clinical impact of the time-dependent incidence in the risk of NA-CRC is highly relevant because early diagnosis of NA-CRC is the main target of surveillance colonoscopy. According to our estimate, the absolute annual risk of NA-CRC is substantially lower than 1%, ranging between 0.63% and 0.74% in the first 3 years of follow up, further dropping to <0.5% after the 36 months. In addition, we excluded a peak of NA-CRC within the first year – i.e. 6-12 months – as the overall risk of NA-CRC appeared to be uniformly distributed in the first 36 months, the remaining being diluted in the next 13 years of follow up. This decrease of risk after 3 years from surgery is compatible with a missed lesion at pre-operative assessment rather than new-onset cancer due to an underlying high-risk status of the patient. In the latter case, indeed, a progressive increase of CRC risk at follow up should have been observed, similarly to that reported in long-lasting cohorts of ulcerative colitis or Lynch syndrome. Despite most of the included studies performed clearing colonoscopies at the CRC diagnosis, our findings confirm the need for a high-quality peri-operative colonoscopy as recommended by current guidelines [38,39], before applying longer surveillance intervals. The finding that over 60% of NA-CRC were detected in stage I/II further supports the value of endoscopic surveillance, especially in the early high-risk period.

In our review, we adopted the nomenclature of cancer at anastomotic and non-anastomotic location, that can reasonably be considered surrogates of recurrent and metachronous cancers, respectively. Cancers diagnosed during surveillance colonoscopy may also be named as post-colonoscopy colorectal cancers (PCCRC). The World Endoscopy Organization [3] recently proposed an algorithm for the identification of the most plausible PCCRC explanation, considering five

groups (i.e., likely incomplete resection of previously identified lesion; detected lesion, not resected, possible missed lesion, prior examination adequate, possible missed lesion, prior examination negative but inadequate and likely new CRC). Unfortunately, in our study available data did not allow to categorize cancer as above suggested. However, early (<36 months) cancer at non-anastomotic location should very likely belong to the category "possible missed or incompletely resected lesion".

The absolute annual risk of A-CRC appeared to be >1% in each of the initial two years of follow up, dramatically decreasing to <0.5% after such period and disappearing after 60 months. Of note, 70% of the overall risk of A-CRC appeared to be restricted in the first 24 months of follow up. As focused only on mere detection of intraluminal A-CRC, our analysis would justify the role of an early endoscopy to rule out such occurrence. However, the clinical relevance of endoscopic detection of CRC at anastomotic location may be limited. Indeed, the clinical impact of early detection may be reduced by the co-existence of extra-mural disease, such as nodal or distant metastases. Extra-luminal peri-anastomotic recurrences are more frequent than luminal recurrences [2,40,41] and usually detected by computed tomography (CT) or CT-colonography [42,43]. Once detected, patients are evaluated for further oncological treatments and generally quit colonoscopy surveillance. Unfortunately, extra-luminal cancer rates were not reported in studies included in our review, likely due to a poor reporting quality. We showed a 2-fold higher rate of A-CRCs for rectal *vs*. colon location of the index tumour, although such information was provided only by 4 out of 27 studies.

While our data are informative for decision-making and clinical guidelines, there are limitations in our analysis. First, we did not incorporate the drop-out rate in our analysis, because it was provided by very few studies. However, it is unlikely that patients with A-/NA-CRCs would have not adhered to the planned study visit, so that the drop-out-related bias is more likely to over- rather than under-estimate the long-term risk. In addition, as most of the risk in our pooled cohort was in the very early phase of the follow up, the possible effect of drop-out rate may be

marginalized, especially when considering the very long CRC-survival associated with early stages that represented the vast majority of our population. Finally, the robustness of our results to the assumption that all initial CRCs (ie, CRCs included in the follow-up program) spanned the entire follow-up period, was confirmed by sensitivity analyses carried out for the studies reporting information on the number of patients actually present at each follow-up time interval (ie, patients at risk) (see **supplementary appendix** for details). Secondly, most studies were initiated before the advent of high-quality colonoscopy, so that there may be an overestimation of the post-surgery CRC risk. In addition, information of main key-quality indicators of colonoscopy, such as caecal intubation and level of cleansing were not available for most of the studies. Indeed, only 3 out of 27 studies clearly specified that surveillance colonoscopy was high-quality colonoscopy or assessed the quality of colonoscopy, thus precluding any analysis. It is very likely that this is due to poor reporting, especially for the most recent series, while this could be an issue for the oldest series. Notably, the year of ending the enrollment (<2005 vs ≥2005) was not a predictor of developing CRCs at the metaregression analysis. Quality of colonoscopy is more than achieving the caecum or ileo-colonic anastomosis and adequate bowel preparation; however, more recent key-quality indicators, such as the importance of the adenoma detection rate and withdrawal time, the need for continuous re-training and internal audit to maintain high quality standard were not considered in studies included in our systematic review. Indeed, also in the few studies clearly stating that "high-quality" colonoscopy was performed a non-negligible rate of NA-CRCs was attributable to missed lesions. In the study by le Clercq et al [36], about 40% of NA-CRCs were due to missed lesions during surveillance. Nevertheless, in the study by Marques-Antunes et al [37], patients that underwent a high-quality baseline colonoscopy presented a significantly lower risk of having advanced adenomas at surveillance, thus underscoring the importance of quality of colonoscopy at baseline and surveillance investigation to reduce the incidence of CRCs. However, as already outlined, the decrease in the risk of NA-CRC after the third year from surgery is reassuring regarding the use of longer surveillance colonoscopy intervals after the early period. Third, the pooling of incidence data

at each specific time-point differed among the studies leading to multiple combined cohorts at different time-points. However, the temporal trends in both A/NA-CRCs were so clear as to indicate an internal robustness in our analysis. In addition, we did not find differences according to whether US recommendations on surveillance (i.e., 1-3-5-year protocol) were followed. Fourth, we limited our analysis of endoscopic surveillance to cancer detection, despite endoscopic surveillance may be effective also as preventive technique by removing precancerous lesions. However, there is a clear hierarchy in outcomes between cancer detection and prevention, so that the main goal of early post-surgery surveillance is represented by the detection of malignancies.

Finally, older studies may be more prone to poor reporting. The choice of beginning the literature search from 1985 may be questioned, however this allowed us to have consistent data and evaluate possible changes of cancer detection over time. Indeed, the analyses were based on 27 studies performed throughout a 30-year period. Notably, poor reporting was unfortunately a constant independently of the year of publication. Lack of information such as quality of colonoscopy, drop-out rates and incidence of extra-luminal recurrences strongly limited the quality of the available evidences. Despite most of the included studies were scored at high-risk of bias, this could have been overestimated due to poor reporting. Indeed, items with missing information were considered at substantial risk of bias.

Large, prospective, multicenter, international studies should be performed in order to verify the impact of high-quality peri-operative colonoscopy on the risk of A-/NA-CRCs and to identify subgroups of patients at higher risk, thus enabling tailored endoscopic surveillance.

In conclusion, the present systematic review further strengthens the current guidelines recommendations [2,42,43]. We showed a concentration of the post-surgery CRCs at surveillance colonoscopy in the very early phase of follow up, with a decrease thereafter. The present systematic review confirms the need for an as early as 1-year and 3-year surveillance colonoscopy. When considering the significant drop of the incidence after such period, longer surveillance intervals (i.e.

5-year) are reasonable. Challenge of the future is the assessment of the impact of high-quality colonoscopy on the early diagnosis and prevention of post-surgery CRCs.

Figure legend

Figure 1. Non-anastomotic CRCs rate plotted against the time intervals from <12 months to ≥180 months after the initial CRC resection.

Figure 2. Cumulative proportion of non-anastomotic CRCs on all non-anastomotic CRCs, at various time-intervals.

Figure 3. Anastomotic CRCs rates plotted against the time follow-up intervals from <12 months to ≥180 months after the initial CRC resection.

Figure 4. Cumulative proportion of anastomotic CRCs on all anastomotic CRCs, at various time-intervals.

Table legend

Table 1. Baseline characteristics of the included studies

Table 2. Characteristics of index colorectal cancer (CRC) cases

Table 3. Colorectal cancer (CRC) diagnosed during follow-up.

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Table 1 – Baseline characteristics of the included studies. RCT: randomized controlled trial; NA: Not Available;
***High quality colonoscopy means scope introduction up to the caecum or ileo-colonic anastomosis with adequate bowel preparation**

Reference	Enrolment period	Study Design	Study location	n centers	n CRC	n patients	Mean age (years)	Male gender (%)	Quality* of colonoscopy	Risk of bias
Weber et al, 1986 [11]	1978-1986	Retrospective	USA	1	79	75	71	NA	NA	High
Michael et al, 1988 [12]	1983-1988	Retrospective	UK	1	63	63	NA	NA	NA	High
Brady et al, 1990 [13]	NA	Prospective	USA	1	207	207	NA	NA	NA	High
Himal et al, 1991 [14]	1982-NA	Retrospective	Canada	1	112	112	NA	NA	NA	High
McFarland et al, 1991 [15]	1980-NA	Prospective	UK	1	74	74	66	50	NA	High
Granqvist et al, 1992 [16]	1981-1990	Retrospective	Sweden	1	396	390	64	47.4	NA	High
Patchett et al, 1993 [17]	1983-NA	Prospective	UK	1	132	132	63.5	59.1	NA	Intermediate
Chen et al, 1994 [18]	1972-1990	Prospective	Australia	1	231	231	NA	48.5	NA	Intermediate
Khoury et al, 1996 [19]	1984-1994	Retrospective	USA	1	389	389	65.8	53.2	NA	High
Leggett et al, 1997 [20]	1980-NA	Retrospective	Australia	1	433	433	NA	NA	NA	High
Barrier et al, 1998 [21]	1986-NA	Retrospective	France	1	179	175	66	55.4	High	Intermediate
Togashi et al, 1999 [22]	1992-1995	Retrospective	Japan	1	341	341	59.6	61.3	NA	Intermediate
Stigliano et al, 2000 [23]	1970-1988	Retrospective	Italy	1	322	322	NA	NA	NA	Intermediate
McFall et al, 2003 [24]	1990-2002	Retrospective	UK	1	226	226	67.7	46	NA	High
Skaife et al, 2003 [25]	NA	Prospective	Singapore	1	611	611	66.7	53.2	NA	High
Ntinas et al, 2004 [26]	2001-2004	Retrospective	Greece	1	41	41	69.5	65.9	NA	High
Lan et al, 2005 [27]	1981-2001	Retrospective	Taiwan	1	3846	3846	63.9	70.9	NA	Intermediate
Mathew et al, 2006 [28]	1998-2003	Retrospective	UK	1	105	105	67.8	58.1	NA	High
Hassan et al, 2006 [29]	1998-2004	Prospective	Italy	3	318	318	62	51.6	NA	High
Ballesté et al, 2007 [30]	2000-2001	Prospective	Spain	10	355	355	67	62.8	NA	High
Wang et al, 2009 (intensive surveillance) [31]	1995-2001	RCT -Prospective	China	1	165	165	54.6	53.5	NA	Low
Wang et al, 2009 (routine surveillance) [31]	1995-2001	RCT- Prospective	China	1	161	161	54.4	55.3	NA	Low
Hahn et al, 2012 [32]	2001-2009	Prospective	Korea	1	58	58	62.7	53.5	NA	High
Sakamoto et al, 2013 [33]	2004-2005	Retrospective	Japan	1	459	459	62	58.4	NA	Intermediate
Heo et al, 2014 [34]	2005-2010	Retrospective	Korea	1	70	70	63.2	52.9	NA	High
Battersby et al, 2014 [35]	1995-2012	Prospective	UK	1	538	538	70.8	56.3	NA	High
le Clercq et al, 2015 [36]	2001-2010	Retrospective	Netherlands	3	5357	5157	70	53.7	High	Low
Marques-Antunes et al, 2017 [37]	2008-2011	Retrospective	Portugal	1	535	535	65	62.2	High	Intermediate

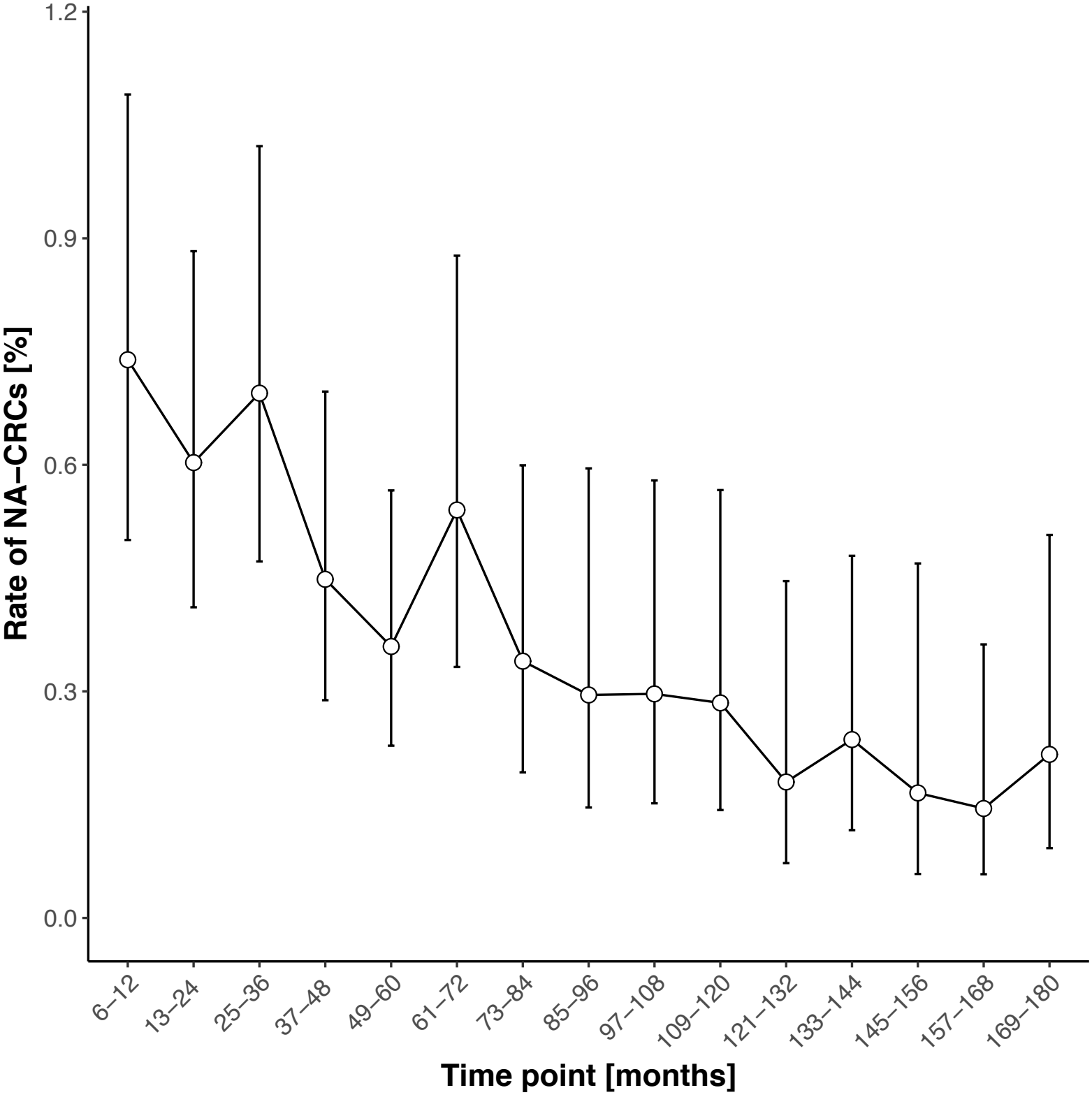
Table 2. Characteristics of index colorectal cancer (CRC) cases

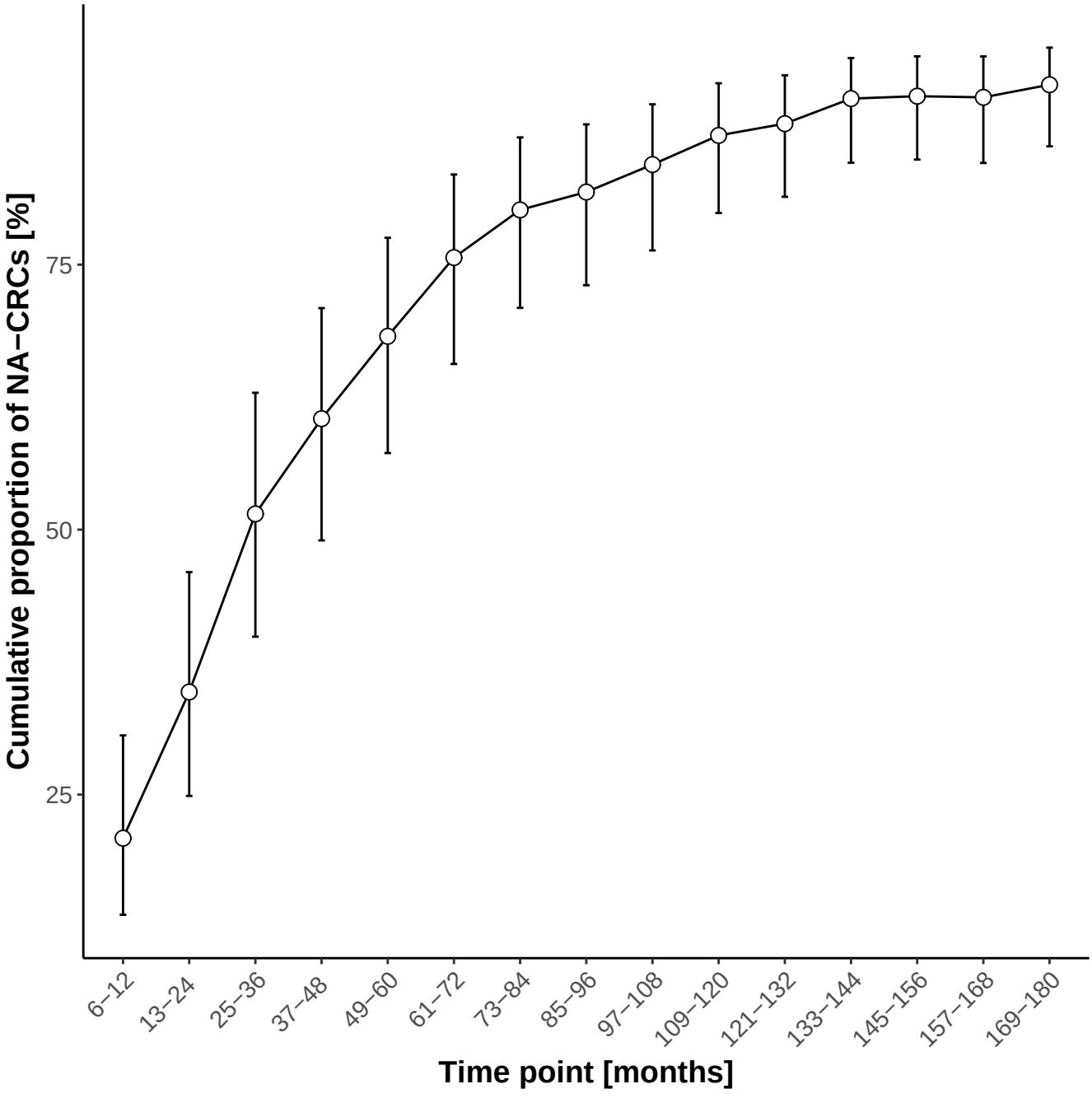
Reference	Number of patients	Number of CRC	Number of index CRC cases located in the colon	Number of index CRC cases located in the rectum	Number of patients with index CRC cases located in the colon	Number of patients with index CRC cases located in the rectum	Site of index Colon Cancer: proximal to splenic flexure (N)	Index CRC stage I	Index CRC stage II	Index CRC stage III	Index CRC stage IV
Weber et al, 1986 [11]	75	79	58	21	54	21	22	13	44	15	3
Michael et al, 1988 [12]	63	63	NA	NA	NA	NA	NA	NA	NA	NA	NA
Brady et al, 1990 [13]	207	207	207	0	207	0	NA	NA	NA	NA	NA
Himal et al, 1991 [14]	112	112	NA	NA	NA	NA	NA	NA	NA	NA	NA
McFarland et al, 1991 [15]	74	74	48	26	48	26	19	11	35	25	NA
Granqvist et al, 1992 [16]	390	396	302	94	296	94	176	59	187	108	36
Patchett et al, 1993 [17]	132	132	NA	NA	NA	NA	NA	23	72	37	NA
Chen et al, 1994 [18]	231	231	NA	NA	NA	NA	NA	NA	NA	NA	NA
Khoury et al, 1996 [19]	389	389	284	105	284	105	149	136	148	93	12
Leggett et al, 1997 [20]	433	433	NA	NA	NA	NA	NA	NA	NA	NA	NA
Barrier et al, 1998 [21]	175	179	134	45	130	45	54	13	111	55	NA
Togashi et al, 1999 [22]	341	341	190	151	190	151	63	NA	NA	NA	NA
Stigliano et al, 2000 [23]	322	322	182	140	182	140	38	67	189	66	NA
McFall et al, 2003 [24]	226	226	127	99	127	99	69	50	112	64	NA
Skaife et al, 2003 [25]	611	611	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ntinas et al, 2004 [26]	41	41	NA	NA	NA	NA	NA	1	18	23	7
Lan et al, 2005 [27]	3846	3846	NA	NA	1895	1951	NA	845	1609	1388	NA
Mathew et al, 2006 [28]	105	105	NA	NA	NA	NA	NA	19	54	26	NA
Hassan et al, 2006 [29]	318	318	NA	NA	NA	NA	NA	265	48	5	0
Ballesté et al, 2007 [30]	355	355	NA	NA	NA	NA	83	75	158	116	6
Wang et al, 2009 (intensive surveillance) [31]	165	165	88	77	88	77	NA	48	67	50	NA
Wang et al, 2009 (routine surveillance) [31]	161	161	83	78	83	78	NA	52	66	43	NA
Hahn et al, 2012 [32]	58	58	58	0	58	0	44				
Sakamoto et al, 2013 [33]	459	459	310	149	310	149	NA	NA	NA	174	0
Heo et al, 2014 [34]	70	70	35	35	35	35	17	NA	NA	NA	NA
Battersby et al, 2014 [35]	538	538	295	246	295	246	174	106	225	214	8
le Clercq et al, 2015 [36]	5157	5357	NA	NA	NA	NA	NA	1126	1482	1280	1340
Marques-Antunes et al, 2017 [37]	535	535	535	0	535	0	100	107	180	221	23

Table 3. Colorectal cancer (CRC) diagnosed during follow-up. CS, colonoscopy; NA, not available.

Reference	Follow-up protocol	Mean follow-up (months)	Clearing colonoscopy performed	Anastomotic and Non-Anastomotic CRCs	Non-Anastomotic CRCs	Anastomotic CRCs
Weber et al, 1986 [11]	CS preoperatively when possible and postoperatively at regular intervals (semiannually for the first 2 years and annually thereafter)	33.6	Yes	3	3	0
Michael et al, 1988 [12]	CS at 3, 9, 15 and 21 months after resection (not carried in all pts)	NA	Yes	2	2	0
Brady et al, 1990 [13]	CS annually or at 2-year intervals after the first 2 examinations, conducted for 2 to 8 years	NA	NA	15	9	6
Himal et al, 1991 [14]	CS every 3 months in the 1st year and every 6 months in the 2nd and 3rd year	NA	Yes	17	0	17
McFarland et al, 1991 [15]	CS yearly for first 5 years, then 2 yearly	51.6	NA	2	0	2
Granqvist et al, 1992 [16]	CS at 6 months or preoperatively, then two years later, and then every fourth year until the age of about 70 years	NA	Yes	26	12	14
Patchett et al, 1993 [17]	CS after operation and at 6, 12, 18, 30 and 48 months	66	Yes	8	2	6
Chen et al, 1994 [18]	CS at 1st and 3rd year post-operatively	67	NA	4	4	0
Khoury et al, 1996 [19]	Clearing CS peri-operatively, then first surveillance CS within the first 24 months postoperatively	NA	Yes	3	1	2
Leggett et al, 1997 [20]	CS at 6 months and at three-year intervals thereafter; if 2 or more polyps were found, CS was performed at intervals of 18 months	45	Yes	21	10	11
Barrier et al, 1998 [21]	CS at 12 months, 30 months, 54 months after operation	NA	Clearing CS performed in 61/175 patients	14	3	11
Togashi et al, 1999 [22]	Pre-operative CS and then CS at least twice during a period of ≥ 3 years after surgery.	72	Yes	22	22	0
Stigliano et al, 2000 [23]	Clean CS before surgery, then CS once yearly for the first 5 years and then every 2 years	105	Yes	27	5	22
McFall et al, 2003 [24]	The frequency of colonoscopic surveillance amongst those screened was not determined by a rigid protocol (many factors were considered to decide interval between repeat CS)	NA	NA	15	9	6
Skaife et al, 2003 [25]	Colonoscopy routinely scheduled annually for all patients until the colon was polyp-free, then three to five yearly thereafter	44	Yes	9	5	4
Ntinas et al, 2004 [26]	CS at 6 months, at 12 months then annually	NA	Yes	2	0	2
Lan et al, 2005 [27]	First CS at 6 months after surgery or 1 year; if negative, 2 or 3 years later; if negative, 5 years later; if a CS is positive, next is at 1 year	72	Yes	43	43	NA
Mathew et al, 2006 [28]	2 and 5-year scheduled CS	NA	NA	5	2	3
Hassan et al, 2006 [29]	CS at 1-year, 3-year and 5-year	NA	Yes	10	10	0
Balleste' et al, 2007 [30]	CS performed between the 1st and 2nd year after surgery	18	NA	14	7	7
Wang et al, 2009 (intensive surveillance) [31]	Colonoscopy every 3 months for the first year, every 6 months for the next 2 years and then annually for the next 2 years	74 months for 161 patients	Yes	13	3	10
Wang et al, 2009 (routine surveillance) [31]	Colonoscopy at 6, 30, and 60 months postoperatively (not necessary at 6 months if it had been performed preoperatively)	69 months for 158	Yes	18	6	12

		patients				
Hahn et al, 2012 [32]	CS annually	41	Yes	0	0	0
Sakamoto et al, 2013 [33]	Pre-operative CS and post-operative CS not schematically defined	60	Yes	9	6	3
Heo et al, 2014 [34]	CS performed at 6 months, then annually or biennially after the initial treatment	NA	Yes	1	1	0
Battersby et al, 2014 [35]	CS at 1-year, 3-year and 5-year	50	Yes	15	15	NA
le Clercq et al, 2015 [36]	Clearing CS pre-operatively or within 3 months post-operatively, followed by a CS at 3 years. Subsequent CS was at 6y when 1-2 adenomas were found, at 3y when 3 or more adenomas were found	NA	Yes	98	98	NA
Marques-Antunes et al, 2017 [37]	Not defined in the article. Directly asked to the Authors: CS at 1-year, 3-year and 5-year	62	Yes	38	18	20




Cumulative proportion of NA−CRCs [%]
25
50
75
6−12
13−24
25−36
37−48
49−60
61−72
73−84
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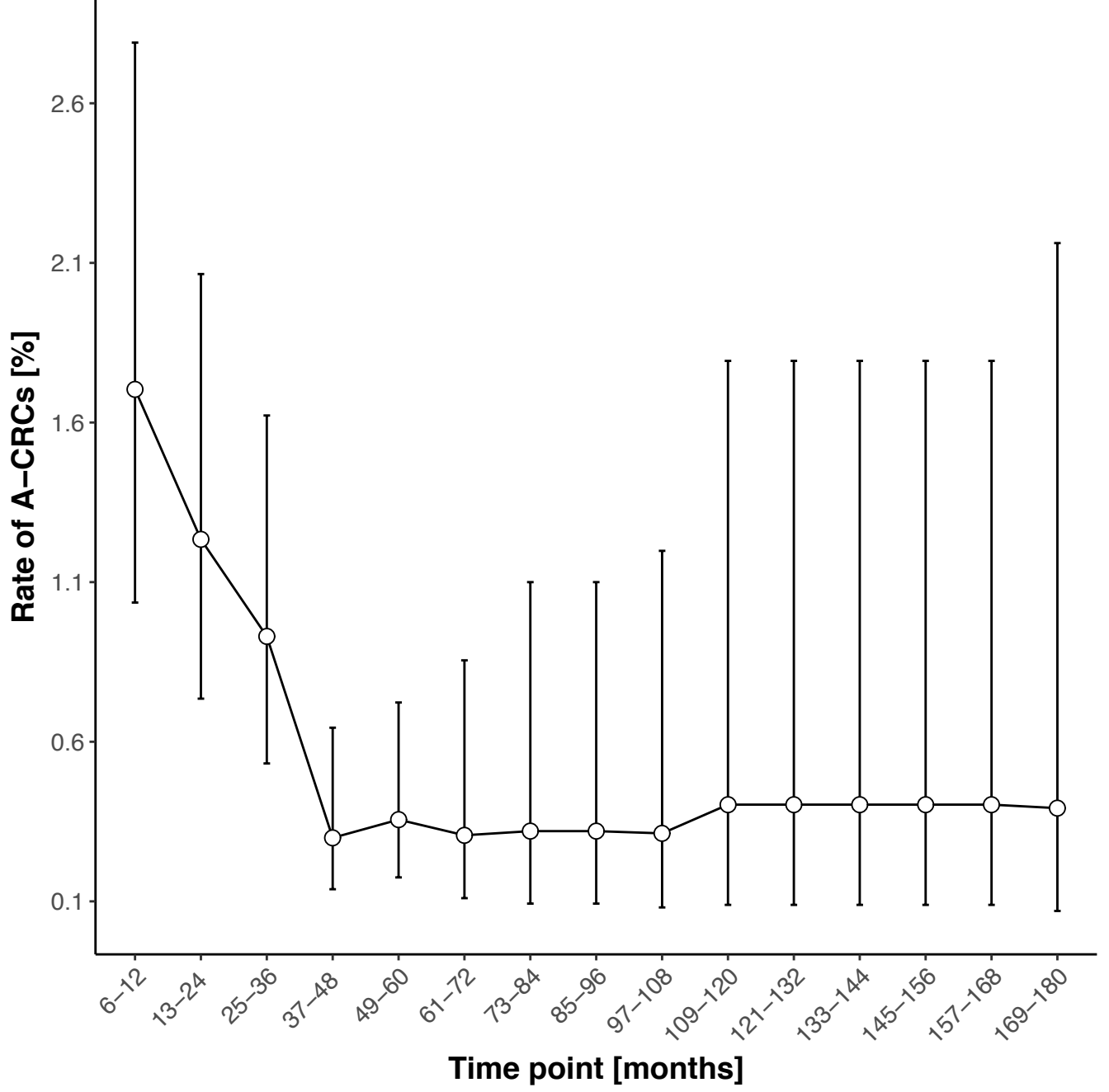
97−108
109−120
121−132
133−144
145−156
157−168
169−180
Time point [months]


Rate of A–CRCs [%]
2.6
2.1
1.6
1.1
0.6
0.1
6–12
13–24
25–36
37–48
49–60
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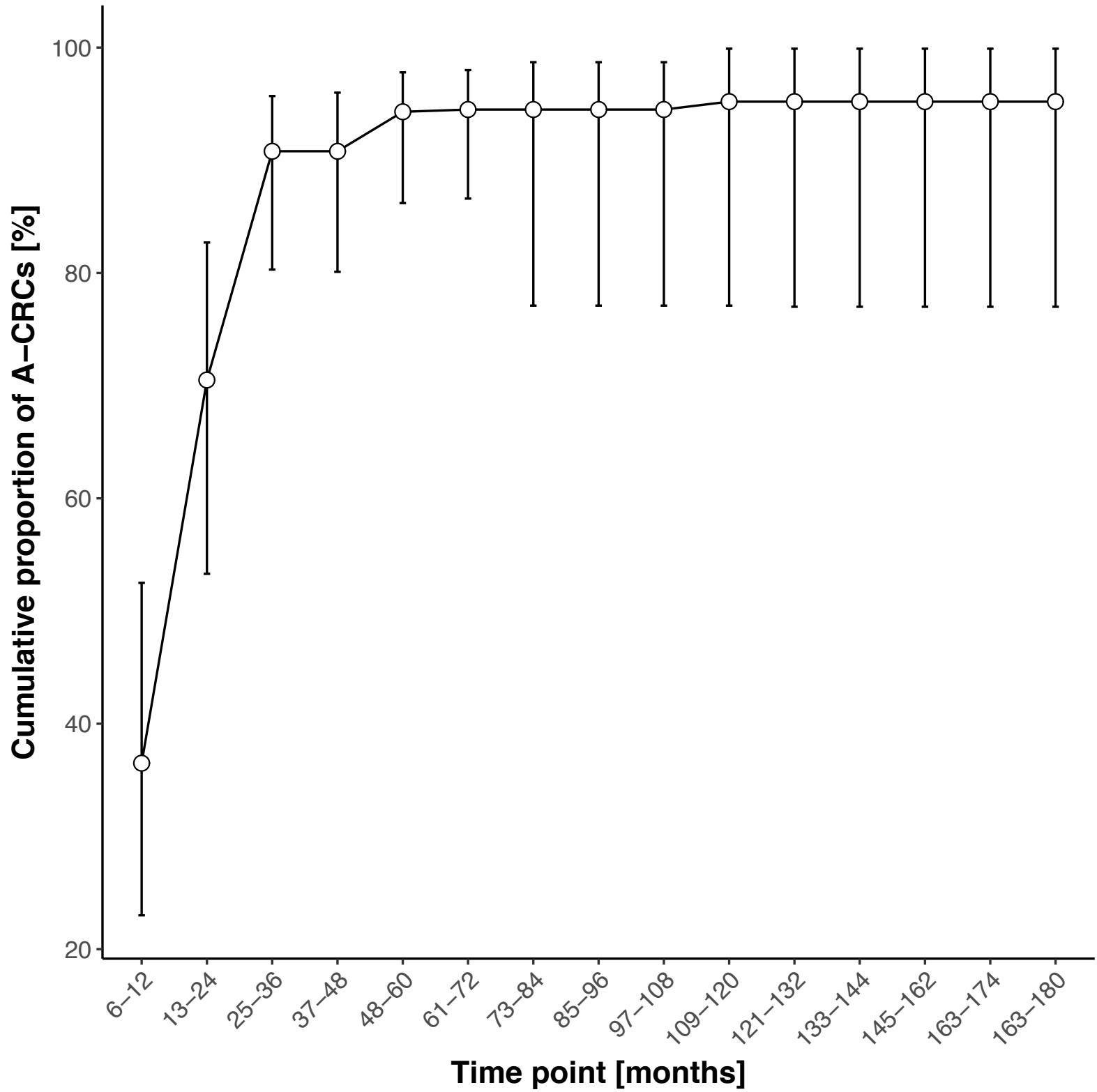
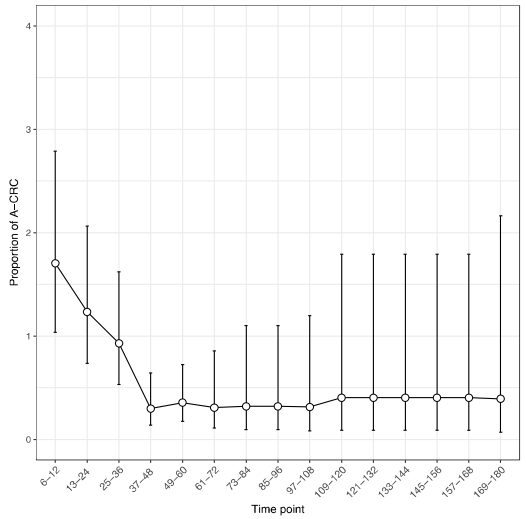
169–180
Time point [months]

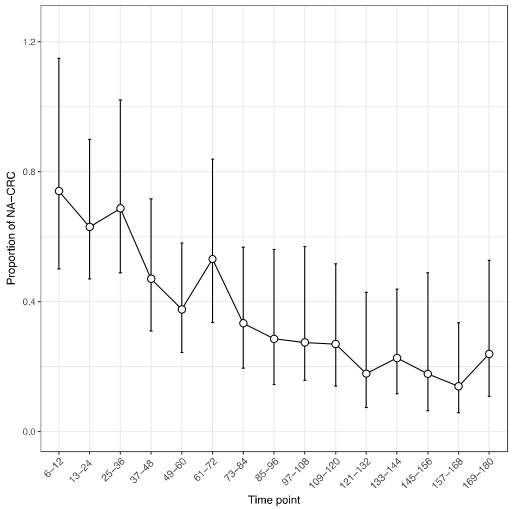


Highest risk of CRCs at anastomotic and non-anastomotic location in the first 24-36 months

After surgery for colorectal cancer (CRC), a significant decrease after 24-36 months of the incidence of cancer at anastomotic (A) and non-anastomotic (NA) location was detected.

The time-dependent decrease was more evident for cancer at anastomotic location.





Gastroenterology

SUPPLEMENTAL MATERIAL

Supplementary Appendix containing: Results for the separate univariate random effects meta-analysis (Independent random effects meta-analyses). Results from the multivariate random-effect meta-analysis. Table A1 - Meta-analysis results for the independent random-effects model and the models 1 and 2 from multivariate approach for the rate of NA-CRCs at different follow-up time points. The issue of missing information (dropouts/deaths).

Supplementary Figure 1. Study flow-chart.

Supplementary Table 1. Multivariate meta-analysis via random-effects regression model assessing predictors of occurrence of non-anastomotic CRC over time. The regression analysis was performed by adding study-level factors (such as gender) to the model involving the time as predictor of effects. Two-way interactions for all considered variables were not significant and therefore not included in the final model.

Supplementary Table 2. Multivariate meta-analysis via random-effects regression model assessing predictors of anastomotic CRCs over time. The regression analysis was performed by adding study-level factors (such as gender) to the model involving the time as predictor of effects. Two-way interactions for all considered variables were not significant and therefore not included in the final model.

Supplementary Table 3. Assessment of risk of bias for included studies according to modified Newcastle-Ottawa Scale. Green "*" denotes low risk of bias, red "-" indicates substantial risk of bias.

Supplementary Appendix

Results for the separate univariate random effects meta-analysis (Independent random effects meta-analyses)

We first ran separate univariate random effects meta-analyses for each time point of interest. The results in **Table A1** clearly shows that the odds of NA-CRC were significantly higher in the first 36 months after primary CRC resection. In details, the NA-CRC rate was 0.59 (0.36;0.97) at 6-12 months, which did not decreased significantly at 13-24 months (OR, 0.78; 95% CI0.42-1.61; P=0.251 and at 25-36 months (OR, 0.89; 95% CI:0.54-1.98; P=0.571). Time points >36 months provided significantly different estimates. At 37-48 months a significant decrease in NA-CRC rate (as compared with 6-12 months) was observed (OR, 0.58; 95% CI:0.26-0.96;P=0.026). 9%). This was consistent across longitudinal time points >36 months.

Results from the multivariate random-effect meta-analysis

Table A1 shows the results of applying the multivariate random-effects meta-analysis mixed model to the data using two different models:

1. **Random study effects, model 1 - "CS" compound symmetry structure;** This model accounts for dependence between outcomes by assigning a random intercept effect that is common to all longitudinal effect sizes from a given study while assuming zero within-study serial correlations between longitudinal effect sizes. By including a random study effect, we automatically induce a correlation between any two effect sizes within a study. These correlations are assumed to be the same for each set of time points, regardless of the time lag between the time points. This covariance structure is also known as compound symmetry. However, this model allows only one random effect for all the longitudinal effect sizes from each study and therefore ignores the serial correlation between effect sizes for instance, effect sizes closer together tend to be more strongly correlated than those measured far apart due to factors such as characteristics of patients at longer follow-up.

2. **Correlated random study effects, model 2- for a "AR" structure.** This is an extension of the independent random time effects model where the dependence between effect sizes is accounted for through the dependence between random time effects. This model imposes heteroscedastic AR covariance structure for the random time effects while assuming zero within-study serial correlations between longitudinal effect sizes. Therefore, the dependence between effect sizes become stronger as the lag between them gets smaller. This is plausible in longitudinal studies where loss-to-follow up increases with time such that effect sizes measured far apart have less dependence than those closer to one another.

The results of applying the multivariate random-effects model to the data using models 1 and 2 are shown in **Table A1**. Inspection of the estimates from all the three models show slight differences between the models. It's also clear that the pattern of the results was the same across all the 3 models: the odds of NA-CRC at time points >36 months after resection were lower as compared with those at the first 36 months. The model fit as shown by the values of Akaike Information Criterion (AIC), where smaller values indicate better fit, show that models 1 and 2 had better fit than the independence model. The model that performed best was the AR model using the heteroscedastic autoregressive structure. Therefore, in the manuscript we reported results from this model.

Table A1 - Meta-analysis results for the independent random-effects model and the models 1 and 2 from multivariate approach for the rate of NA-CRCs at different follow-up time points.

	Indep random effects			Random effects Model 1 - "CS"			Random effects Model 2 - "AR"		
Time	Rate [95% CI]	ORs [95% CI]	P	Rate [95% CI]	ORs [95% CI]	P	Rate [95% CI]	ORs [95% CI]	P
6-12	0.59 (0.36;0.97)	-	-	0.79 (0.55;1.15)	-	-	0.74 (0.50;1.09)	-	-
13-24	0.49 (0.32;0.77)	0.83 (0.42;1.61)	0.575	0.62 (0.43;0.9)	0.78 (0.51;1.19)	0.251	0.63 (0.47;0.90)	0.81 (0.53;1.25)	0.349
25-36	0.61 (0.4;0.93)	1.03 (0.54;1.96)	0.933	0.70 (0.48;1.02)	0.89 (0.58;1.35)	0.571	0.69 (0.49;1.01)	0.94 (0.62;1.46)	0.778
37-48	0.3 (0.2;0.46)	0.50 (0.26;0.96)	0.038	0.47 (0.3;0.71)	0.58 (0.36;0.94)	0.026	0.45 (0.29;0.7)	0.61 (0.37;0.98)	0.031
49-60	0.26 (0.17;0.38)	0.43 (0.23;0.81)	0.008	0.37 (0.24;0.58)	0.47 (0.29;0.76)	0.002	0.34 (0.24;0.58)	0.48 (0.29;0.81)	0.005
61-72	0.35 (0.23;0.55)	0.60 (0.31;1.15)	0.122	0.53 (0.33;0.84)	0.66 (0.4;1.1)	0.109	0.54 (0.33;0.88)	0.73 (0.42;1.26)	0.256
73-84	0.17 (0.11;0.27)	0.29 (0.15;0.56)	<0.001	0.33 (0.19;0.57)	0.42 (0.23;0.74)	0.003	0.34 (0.19;0.6)	0.46 (0.25;0.85)	0.014
85-96	0.24 (0.1;0.57)	0.40 (0.15;1.1)	0.076	0.29 (0.14;0.56)	0.36 (0.18;0.72)	0.004	0.29 (0.15;0.56)	0.41 (0.19;0.84)	0.016
97-108	0.21 (0.09;0.52)	0.35 (0.13;0.99)	0.049	0.3 (0.16;0.57)	0.37 (0.19;0.74)	0.005	0.3 (0.15;0.58)	0.4 (0.19;0.83)	0.013
109-120	0.21 (0.08;0.53)	0.35 (0.12;1.01)	0.053	0.27 (0.14;0.52)	0.34 (0.17;0.68)	0.002	0.28 (0.14;0.57)	0.38 (0.18;0.81)	0.011
121-132	0.13 (0.05;0.34)	0.22 (0.08;0.64)	0.005	0.18 (0.07;0.43)	0.22 (0.09;0.55)	0.001	0.18 (0.07;0.45)	0.24 (0.09;0.63)	0.003

133-144	0.14 (0.07;0.29)	0.24 (0.1;0.57)	0.001	0.23 (0.12;0.44)	0.28 (0.14;0.57)	<0.001	0.24 (0.12;0.48)	0.32 (0.15;0.68)	0.003
145-156	0.15 (0.06;0.41)	0.26 (0.09;0.78)	0.016	0.18 (0.06;0.49)	0.22 (0.08;0.63)	0.005	0.17 (0.06;0.47)	0.22 (0.08;0.66)	0.007
157-168	0.1 (0.04;0.22)	0.16 (0.06;0.42)	<0.001	0.14 (0.06;0.34)	0.17 (0.07;0.43)	<0.001	0.14 (0.06;0.36)	0.19 (0.07;0.51)	0.001
169-180	0.15 (0.06;0.39)	0.26 (0.09;0.74)	0.012	0.24 (0.11;0.53)	0.3 (0.13;0.68)	0.004	0.22 (0.09;0.51)	0.29 (0.12;0.72)	0.007
AIC	**597.76**			**531.13**			**529.93**		
l ogLik	**-266.8818**			**-247.5686**			**-246.9698**		
Indep = Independence									
CS = Compound symmetry									
AR = autoregressive structure									
AIC = Akaike information criterion (AIC)									
LogLik= log-likelihood									

The issue of missing information (dropouts/deaths).

As already discussed in the manuscript, the majority of the included studies provided incomplete information because of missing data due to dropouts and/or deaths. A few studies provided information about patients who were actually present at each time interval, but they did not distinguish between censoring by dropout and deaths. Therefore, the two patterns of deaths vs. dropouts could not be separated. To assess the robustness of our results to the assumption that all initial CRCs (i.e. CRCs included in the follow-up program) spanned the entire follow-up period, sensitivity analyses were carried out for the studies (15 trials of 8911 patients) reporting information on the number of patients being alive and being not censored (i.e., patients at risk) at each follow-up time interval.

In **Figure A,** the mean and 95% CIs of the proportion of patients being alive and being not censored per time-point are presented. Within 48 months, the means proportions remained rather constant, and they were very high (range, 99%-96%). There was a decrease in the observed means for follow-up time >48 months: at 49-60 months, the mean proportion of patients at risk was 91.0% and decreased not significantly to 90% at 97-108 months. Concerning statistical analyses on the level of time-points, two approaches for dealing with missing data were used: 1. omitting all studies with missing information and analyzing them as a separate group; 2. using an imputation method for missing information that retain all the data.

Approach 1- Restricting the analysis to the subgroup of studies reporting the number of patients at risk, we found that 1) NA-CRCs occurred in 0.84% (95% CI:0.48-1.50%) between 6 and 12 months, in 0.80% (95% CI:0.44-1.44%) between 13 and 24 months and in 1.00% (95% CI:0.57-1.23%) between 25 and 36 months. Differences in time points were not statistically significant. Over the longer times, rate of NA-CRC decreased (significantly) to 0.50% (95% CI:0.25-1.00%; P=0.045) between 37 and 48 months and to 0.47% (95% CI:0.20-0.68%; P=0.007) between 73 and 84 months. Note, the results from this sub-analysis are consistent with those from the simplest model ignoring dropout/deaths (Table A1).

Approach 2 - We assumed that the studies reporting information on the number of patient at risk at different time points were similar to those with missing information. Then, in the complete dataset, denominators with missing information were adjusted based on the expected distribution of dropout/death rate (shown in **Figure A**). In **table A2**, the model assuming dropout/death is presented together with the simplest model ignoring dropout/death. The results from the model assuming dropout/deaths were statistically comparable to those from the simplest model where dropout (death and censoring) was not taken into account. The pattern of the two models was also the same: the odds of NA-CRCs at time >36 months were lower than were those within 36 months: 37-48 months vs. 6-12 months, ORs, 0.62; 95% CI:0.52-1.13; P=0.050; 48-60 months vs. 6-12 months, OR, 0.40; 95% CI:0.25 0.62; P=0.011). Therefore, we think that the simplest model assuming no dropout/deaths satisfies all criteria for responding to the study questions.

Figure A - Means and 95% CIs of the proportion of patients at risk for different follow-up times.

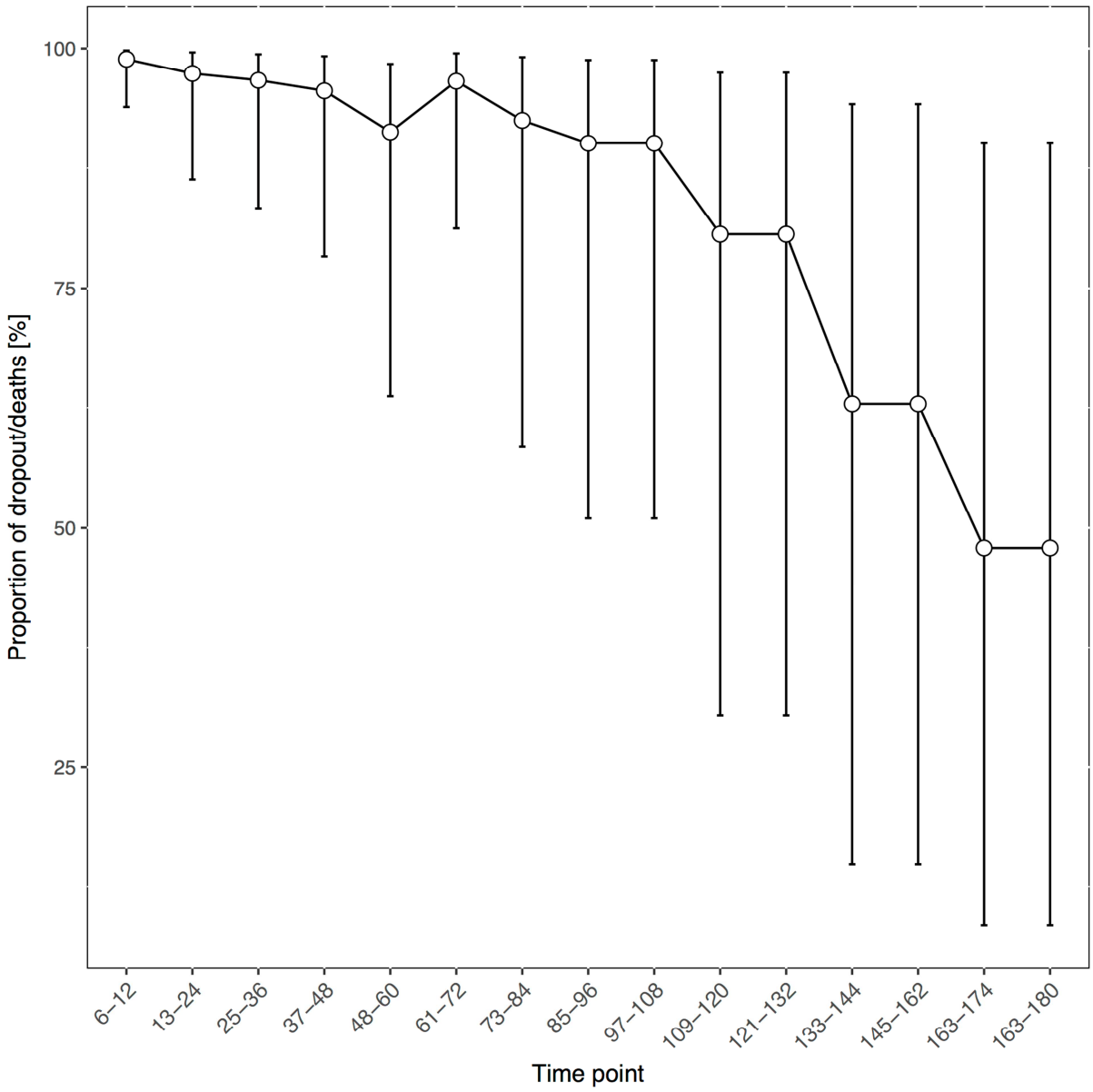
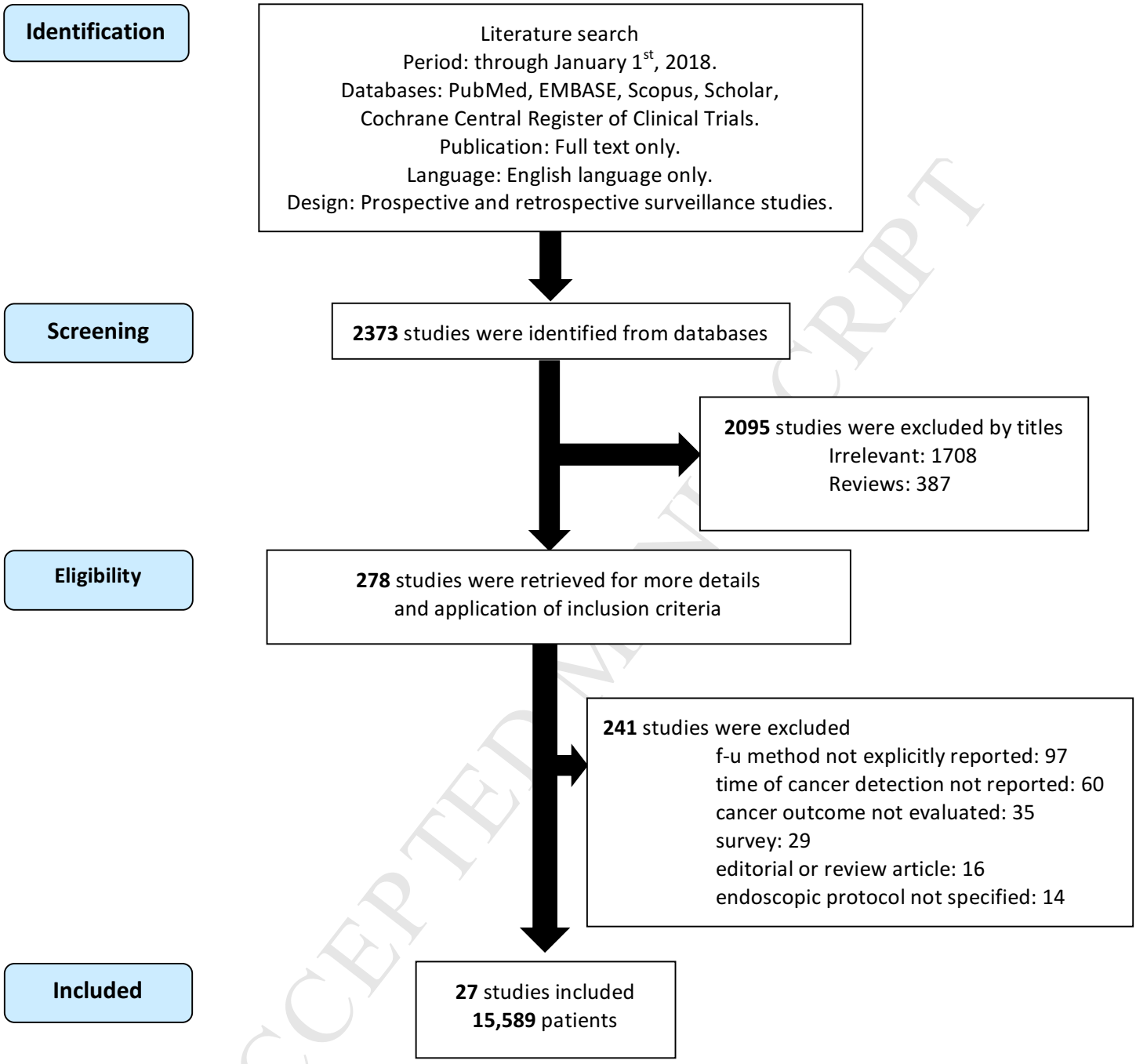


Table A2 - Estimates of NA-CRCs times starting from the model for the hypothetical cohort without dropout/deaths. Dropout/death rates for all times points were extracted from the subgroup of the studies reporting information on the patients who were complaints at follow-up times .

Time	Model assuming no dropout/deaths	% of patients at risk	Dropout/Death Rate	Model assuming dropout/deaths
6-12	0.74 (0.51;1.10)	0.989	0.011	0.76 (0.51-1.11)
13-24	0.63 (0.47;0.90)	0.974	0.026	0.62 (0.43-0.91)
25-36	0.69 (0.49;1.01)	0.967	0.033	0.72 (0.49-1.06)
37-48	0.45 (0.29;0.70)	0.956	0.044	0.47 (0.30-0.73)
48-60	0.34 (0.24;0.58)	0.913	0.087	0.40 (0.25-0.62)
61-72	0.54 (0.33;0.88)	0.966	0.034	0.57 (0.35-0.92)
73-84	0.34 (0.19;0.6)	0.925	0.075	0.37 (0.21-0.65)
85-96	0.3 (0.15;0.6)	0.901	0.099	0.33 (0.21-0.66)
97-108	0.3 (0.15;0.58)	0.901	0.099	0.33 (0.17-0.67)
109-120	0.28 (0.14;0.57)	0.806	0.194	0.35 (0.18-0.70)
121-132	0.18 (0.07;0.45)	0.806	0.194	0.23 (0.09-0.57)
133-144	0.24 (0.12;0.48)	0.629	0.371	0.38 (0.19-0.76)
145-162	0.17 (0.06;0.47)	0.629	0.371	0.27 (0.10-0.77)
163-174	0.14 (0.06;0.36)	0.479	0.521	0.29 (0.12-0.72)



Supplementary Table 1. Multivariate meta-analysis via random-effects regression model assessing predictors of occurrence of non-anastomotic CRC over time. The regression analysis was performed by adding study-level factors (such as gender) to the model involving the time as predictor of effects. Two-way interactions for all considered variables were not significant and therefore not included in the final model.

Variable	ORs [95% CI]	P value
Time interval (months)		
6-12	-	-
13-24	0.81 (0.53;1.26)	0.349
25-36	0.94 (0.62;1.46)	0.778
37-48	0.61 (0.37;0.98)	0.031
49-60	0.48 (0.29;0.81)	0.005
61-72	0.73 (0.42;1.26)	0.256
73-84	0.46 (0.25;0.85)	0.014
85-96	0.4 (0.19;0.84)	0.016
97-108	0.4 (0.19;0.83)	0.013
109-120	0.38 (0.18;0.81)	0.011
121-132	0.24 (0.09;0.63)	0.003
133-144	0.32 (0.15;0.68)	0.003
145-156	0.22 (0.08;0.66)	0.007
157-168	0.19 (0.07;0.51)	0.001
169-180	0.29 (0.12;0.72)	0.007
Mean patient age (as a continuous variable)	0.95 (0.88-1.03)	0.205
Gender (M > 50% *vs.* M < 50%)	1.01 (0.44-2.34)	0.977
Primary CRC site (colon *vs.* rectum)	0.98 (0.17-5.71)	0.985
1-3-5-year endoscopic surveillance protocol implementation	0.72 (0.41-1.28)	0.267
Date of enrollment ending (≥ 2005 *vs.* < 2005)	1.56 (0.61-3.97)	0.356
Study size	0.96 (0.95-0.98)	<0.001

Supplementary Table 2. Multivariate meta-analysis via random-effects regression model assessing predictors of anastomotic CRCs over time. The regression analysis was performed by adding study-level factors (such as gender) to the model involving the time as predictor of effects. Two-way interactions for all considered variables were not significant and therefore not included in the final model.

Variable	ORs [95% CI]	P value
Time interval (months)		
6-12	-	-
13-24	0.72 (0.44-1.24)	0.219
25-36	0.56 (0.32-0.98)	0.036
37-48	0.18 (0.08-0.39)	0.001
49-60	0.21 (0.18;0.38)	<0.001
61-72	0.18 (0.09-0.41)	<0.001
73-84	0.19 (0.06-0.51)	0.001
85-96	0.19 (0.09-0.65)	0.001
97-108	0.18 (0.05-0.71)	0.012
109-120	0.23 (0.05;1.01)	0.048
121-132	0.23 (0.05;1.01)	0.048
133-144	0.23 (0.05;1.01)	0.048
145-156	0.23 (0.05;1.01)	0.048
157-168	0.23 (0.05;1.01)	0.048
169-180	0.23 (0.05;1.23)	0.090
Timing of the 1st surveillance colonoscopy (≥12 months *vs.* <12 months)	0.42 (0.15-1.13)	0.089
Mean patient age	0.99 (0.85-1.16)	0.929
Gender (M > 50% *vs.* M < 50%)	1.86 (0.41-8.57)	0.424
Primary CRC site (colon *vs.* rectum)	0.99 (0.99-1.01)	0.198
1-3-5 years endoscopic surveillance protocol implementation	0.42 (0.15-1.13)	0.182
Date of enrollment ending (≥ 2005 *vs.* < 2005)	1.11(0.30-4.13)	0.871
Study size	0.98 (0.95-0.99)	0.043

Supplementary table 3. Assessment of risk of bias for included studies according to modified Newcastle-Ottawa Scale. Green "*" denotes low risk of bias, red "-" indicates substantial risk of bias. Those studies in which the mean follow-up length was reported and it was at least 60 months after resection (i.e., thus allowing two surveillance colonoscopies to be performed), were considered at low-risk of bias.

Reference	Representativeness of the CRC cohort	Assessment of outcome	Follow-up length	Follow-up adequacy	Total	Risk of Bias
Weber et al, 1986 [11]	*	*	-	-	2	High
Michael et al, 1988 [12]	*	*	-	-	2	High
Brady et al, 1990 [13]	*	*	-	-	2	High
Himal et al, 1991 [14]	*	*	-	-	2	High
McFarland et al, 1991 [15]	*	*	-	-	2	High
Granqvist et al, 1992 [16]	*	-	-	-	1	High
Patchett et al, 1993 [17]	*	*	*	-	3	Intermediate
Chen et al, 1994 [18]	*	*	*	-	3	Intermediate
Khoury et al, 1996 [19]	*	*	-	-	2	High
Leggett et al, 1997 [20]	*	*	-	-	2	High
Barrier et al, 1998 [21]	*	*	-	*	3	Intermediate
Togashi et al, 1999 [22]	*	*	*	-	3	Intermediate
Stigliano et al, 2000 [23]	*	*	*	-	3	Intermediate
McFall et al, 2003 [24]	*	*	-	-	2	High
Skaife et al, 2003 [25]	*	*	-	-	2	High
Ntinas et al, 2004 [26]	*	*	-	-	2	High
Lan et al, 2005 [27]	*	*	*	-	3	Intermediate
Mathew et al, 2006 [28]	*	*	-	-	2	High
Hassan et al, 2006 [29]	*	*	-	-	2	High
Balleste' et al, 2007 [30]	*	*	-	-	2	High
Wang et al, 2009 (intensive surveillance) [31]	*	*	*	*	4	Low
Wang et al, 2009 (routine surveillance) [31]	*	*	*	*	4	Low
Hahn et al, 2012 [32]	*	*	-	-	2	High
Sakamoto et al, 2013 [33]	*	*	*	-	3	Intermediate
Heo et al, 2014 [34]	*	*	-	-	2	High
Battersby et al, 2014 [35]	*	*	-	-	2	High
le Clercq et al, 2015 [36]	*	*	*	*	4	Low
Marques-Antunes et al, 2017 [37]	*	*	*	-	3	Intermediate