Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis

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Background: A wide variety of follow-up strategies are used for patients with colorectal cancer (CRC) after curative surgery. The aim of this study is to review the evidence of the impact of different follow-up strategies in patients with non-metastatic CRC after curative surgery, in relation to overall survival and other outcomes.

Patients and methods: A systematic search of PubMed, EMBASE, SCOPUS and ISI Web of Knowledge up to June 2014 was carried out. Eligible studies were all randomized clinical trials comparing the effectiveness of different follow-up strategies after curative resection in nonmetastatic CRC.

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Results: Eleven studies with n = 4055 participants were included in a meta-analysis. A significant improvement in overall survival was observed in patients with more intensive follow-up strategies [hazard ratio = 0.75; 95% confidence interval (CI) 0.66–0.86]. A higher probability of detection of asymptomatic recurrences [relative risk (RR) = 2.59; 95% CI 1.66–4.06], curative surgery attempted at recurrences (RR = 1.98; 95% CI 1.51–2.60), survival after recurrences (RR = 2.13; 95% CI 1.24–3.69), and a shorter time in detecting recurrences (mean difference = −5.23 months; 95% CI −9.58 to −0.88) was observed in the intervention group. There were no significant differences in the total tumor recurrences, nor in the mortality related to disease.

Conclusion: Intensive follow-up strategies improve overall survival, increase the detection of asymptomatic recurrences and curative surgery attempted at recurrence, and are associated with a shorter time in detecting recurrences. This more intensive follow-up could not be associated with an improvement in cancer-specific survival nor with an increased detection of total tumor recurrences. Follow-up with serum carcinoembryonic antigen and colonoscopies are related to an increase in overall survival.

Key words: colorectal neoplasms, surveillance, curative surgery, meta-analysis

introduction

Colorectal cancer (CRC) is one of the most common cancers in the world. As the Globocan database shows, the worldwide incidence of CRC is 17.2 per 100 000 person-year and the worldwide age-standardized mortality is 8.4 per 100 000 person-year [1]. CRC is the third most incident cancer in men and the second most incident in women.

Once the CRC is detected, curative surgery is the treatment of choice for nonmetastatic CRC. Despite the fact that patients are considered to be free from the illness and cured after curative surgery and adjuvant treatment (chemotherapy and/or radiation therapy), ∼30% of these patients who present with stage II or III disease will have a disease recurrence [2]. The most frequent locations of recurrence are the liver, lungs, and locoregional structures [3]. A smaller percentage (7.7%) of these patients will have a metachronous CRC [3]. About 90% of these recurrences are presented in the first 5 years after curative surgery, and most of them are detected within the first 3 years after surgery [2–4].

Over the last few decades, there has been a significant variability in the follow-up strategies used after the curative resection of CRC by physicians [5–7] and the guidelines from major societies [8–12]. There are also considerable differences in the costs of the follow-up strategies in the different guides and major health societies, ranging from hundreds to several thousands of dollars per patient [13, 14].

The purpose of intensive postoperative surveillance programs is to detect asymptomatic recurrences, with the premise that an important rate of these recurrences will be potentially eligible for curative resection [15], improving the survival of these patients.

Two [16, 17] of the 11 [16–26] randomized clinical trials carried out to date support a modest yet significant benefit related to global mortality. However, six previous meta-analyses [4, 27–31] support a modest yet significant benefit related to global mortality. Out of these previous meta-analyses, the study by Tjandra and Chan [30] included the largest number of clinical trials [8].

Our meta-analysis includes 11 clinical trials that have been carried out to date with the aim of evaluating the impact of intensive monitoring strategies in patients with CRC undergoing curative surgery, in terms of: overall survival, mortality related to disease, total tumor recurrences, asymptomatic recurrences, curative surgery attempted at recurrence, time to detection of recurrences and survival after recurrences. The aim was also to evaluate the diagnostic tests used in monitoring patients that may have associations with improved mortality.

materials and methods

criteria for considering studies for this review

the following inclusion criteria were selected

- types of studies: Randomized and controlled clinical trials comparing the effectiveness of different follow-up strategies (intensive versus less intensive follow-up, intensive follow-up versus no follow-up and follow-up in different health care settings).

- participants: Patients of any age diagnosed with nonmetastatic CRC who have been declared free of the disease once the curative surgery and treatment of tumor have been finished.

- interventions: Intensive follow-up strategies are compared with less intensive follow-up strategies. Each follow-up strategy was defined in each study according to the frequency of monitoring and diagnostic tests (colonoscopies, proctoscopic explorations, clinical examination, serum carcinoembryonic antigen (CEA) levels, imaging tests and liver function tests).

If there was any doubt about the inclusion of any of the studies, the issue was discussed between several reviewers, who would reach the final decision.

data sources and searches

types of outcome measures

Data on the following outcome measures were studied: (i) overall survival (according to follow-up strategies, and diagnostic tests), (ii) cancer-specific survival, (iii) total tumor recurrences, (iv) asymptomatic recurrences, (v) curative surgery attempted at recurrence, (vi) time to detection of recurrence, (vii) survival after recurrence.

quality assessment for individual studies

The quality of the trials included in the study was evaluated according to the following criteria: (i) The clear classification and initial comparison of both groups, (ii) explicit and defined diagnostic criteria, (iii) compliance with follow-up by patients, (iv) analysis by intention to treat, (v) compliance with the inclusion/exclusion criteria, (vi) clear and precise definition of outcome variables.

Figure 1 explains the search process and the steps that were involved in the selection of studies that were finally identified in the systematic review and included in the meta-analysis.

data extraction

From each study, two researchers independently extracted the following information: authors and country where the study was conducted, date of publication, characteristics of the study population, study design, description of interventions used or exposures evaluated, statistical analysis, results of studies with raw and adjusted confidence intervals (CIs), potential biases and noteworthy limitations of aspects of the study.

statistical analysis

To take into account heterogeneity between the studies, the random-effects model described by DerSimonian and Laird was used to calculate summary statistics and their 95% CIs [32].

Based on the number of outcomes in each of the branches of the study, odd ratios (ORs) and relative risks (RRs) could be extracted from each of the included studies, together with their standard errors or 95% CIs. However, the ORs and RRs only measure the number of events and do not take into account when they occur, which means that they are suitable for measuring dichotomous outcomes, but less appropriate for analyzing time-to-event outcomes. In contrast, time-to-event outcomes are most appropriately analyzed using hazard ratios (HRs) [33], which take into account the number and timing of events. To take this into account, we proposed to use HRs as summary statistics whenever possible. In the absence of individual patient data, different methods are available to obtain HRs and associated statistics by carefully manipulating the published data. Therefore, if they were not directly available, both the log HR and its variance were obtained for each of the included studies from the number of observed events in each branch and the log-rank or Cox-regression P value [33–35].

Therefore, HR was used as the summary statistic to evaluate the impact of an intensive follow-up strategy on overall survival. For the remaining qualitative outcomes, RR was selected as the most appropriate summary statistic, since the included trials did not report the necessary statistical information to estimate HRs. Finally, in analyzing the impact on time-to-recurrence detection, the results were expressed as the weighted mean difference and its 95% CI.

Figure 1. Flow diagram of the systematic search of literature on follow-up strategies in colorectal cancer.
Meta-analysis results were presented on a Forest plot graph. To explore heterogeneity between the studies, the DerSimonian-Laird’s Q heterogeneity test, Galbraith and L’Abbé plots were used. A sensitivity analysis was also conducted to investigate the influences of single studies on the overall risk estimate by omitting one study in each turn. Publication bias was assessed using funnel plots and Begg’s adjusted rank correlation [36, 37] with P values <0.10 considered to indicate potential publication bias.

Separate analyses were carried out for studies comparing intensive versus minimalist follow-up strategies and for studies comparing an intensive follow-up strategy with no follow-up. Subgroup analyses were also carried out in order to evaluate whether there was any improvement in the outcomes by using different diagnostic tests during follow-up in different trials, based on a priori hypothesis for the early detection of recurrent disease using different investigation strategies: computerized tomography and/or serum CEA level to detect extramural recurrent disease, ultrasonography to detect liver metastasis, chest radiograph to detect lung metastasis and colonoscopy to detect intramural disease. However, a subgroup analysis with stratification by patients’ age, tumor staging or site was not attempted, as raw data were not available.

The analysis and reporting were carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [38].

All statistical analyses were carried out using the R software program (version 2.15.1), using the meta-package. A two-tailed P value <0.05 was considered to be significant.

### results

#### description of studies

Having carried out the systematic review, 11 studies were included in this meta-analysis. All of the studies met the inclusion and exclusion criteria. Table 1 shows the sample size for each trial, and the result of the different outcomes studied: overall survival (according to follow-up strategies, and diagnostic tests), cancer-specific survival, total recurrences, asymptomatic recurrences, curative surgery attempted at recurrence, time to detection of recurrence and survival recurrences.

In the 11 studies, 4055 patients (2330 men and 1725 women) underwent curative surgery for CRC. These patients were randomized in intensive follow-up groups, less intensive follow-up groups or groups without any follow-up. Nine of the studies provided information on the location of the tumor (colon or rectum). According to this information, 67% of the patients had primary colon cancer, and 33% had primary rectum cancer.

#### intervention and follow-up strategies of the studies included

The follow-up strategies and types of interventions are shown in Table 2.

The frequency of the follow-up visits and the examinations that were carried out at each visit were different in each study (Table 2). There was considerable variation in the follow-up strategies employed in the included clinical trials.

In nine studies (n = 3611 patients), patients who had undergone intensive follow-up were compared with another group of patients who had undergone less intensive follow-up. Two studies compared patients undergoing intensive follow-up with another group of patients without any follow-up [16, 18] (n = 444 patients). There is even variability in the type of professionals who carried out the follow-up. In the study by Wattchow et al. [24], the patients have been classified into two groups: the intervention group, in which the patients were monitored by the surgeons who carried out more colonoscopies and ultrasound scans on these patients, and the control group, in which the patients were monitored by the primary care doctors who carried out less colonoscopies and ultrasound scans. The follow-up time for the patients was around 5 years, with the exception of two studies, by Watchow et al. [24] and Grossmann et al. [22] which have follow-up times of around 24 and 14 months, respectively.

The frequency of the follow-ups varies in the intervention group and in the control group. Some studies in the intervention group carry out follow-ups every 3 months [23] during the first 5 years, while others do so every 4 months or more after the second year [22]. The majority of the studies carried out a follow-up every 3 months in the first 2 years, and then every 6 months up to 5 years.

In the control group, there is also variability in the frequency of the surveillance. There are studies that carry out follow-ups at highly separated intervals of 60, 120 and 180 months [20] while others carry out follow-ups more frequently, every 3 months up to a total of 5 years [23]. Some also carry out follow-ups with the same frequency as the intervention group, although without carrying out certain diagnostic tests in each visit [16, 21, 22, 25, 26].

The tests used in the follow-up procedures in the studies included were: combination of laboratory tests (CEA level, liver function tests, complete blood counts, fecal occult blood tests), diagnostic imaging [chest X-ray, liver ultrasound, computed tomography (CT) scan imaging] and colonoscopy.

#### overall survival

Ten trials reported the data needed to calculate the HR associated with the effect of follow-up regimen on overall survival. They included a total of 1511 patients undergoing an intensive follow-up, with 390 all-cause deaths (25.8% mortality), and 1559 patients in the group of less intensive/minimal follow-up, with 455 all-cause deaths (29.2% mortality). All of these studies resulted in a protective effect of an intensive surveillance over mortality, but a significant effect was only detected in Pietra et al. [17] (1998) (HR = 0.6; 95% CI 0.3–0.9) and Secco et al. [16] (HR = 0.6; 95% CI 0.4–0.8).

The meta-analysis results showed that the overall survival rate improved significantly for patients having a more intensive follow-up (HR = 0.7; 95% CI 0.7–0.9).

The same effect was observed in the subgroup analysis, when the trials comparing an intensive versus nonintensive follow-up or intensive surveillance versus less-intensive surveillance were analyzed independently.

In comparison with no follow-up, an intensive strategy was significantly associated with reduced mortality (HR = 0.6; 95% CI 0.4–0.8). Intensive follow-up regimens were also significantly associated with reduced mortality, when compared with less-intensive strategies (HR = 0.8; 95% CI 0.7–0.9) (Figure 2A).

Although little heterogeneity was observed among the studies, a sensitivity analysis was carried out, without any variation in
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control</th>
<th>N by group</th>
<th>Overall survival RR</th>
<th>Cancer-specific survival RR</th>
<th>Total recurrences</th>
<th>Asymptomatic recurrence RR</th>
<th>Curative surgery attempted at recurrence OR</th>
<th>Time to recurrence Mean (months)</th>
<th>Survival after recurrences Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primrose [26]</td>
<td>Intervention (n = 302)</td>
<td>Control (n = 301)</td>
<td>n = 603</td>
<td>RR = 1</td>
<td>RR = 0.95</td>
<td>RR = 1.29</td>
<td>OR: 3.10</td>
<td>CI 0.65–1.55</td>
<td>CI 0.77–1.66</td>
<td>CI 1.27–7.57</td>
</tr>
<tr>
<td>Ting Wang [25]</td>
<td>Intervention (n = 165)</td>
<td>Control (n = 161)</td>
<td>n = 326</td>
<td>RR = 0.82</td>
<td>RR = 0.90</td>
<td>RR = 1.4</td>
<td>CI 0.58–1.16</td>
<td>CI 0.72–1.11</td>
<td>CI 0.36–1.39</td>
<td>CI 0.54–3.57</td>
</tr>
<tr>
<td>Wachtchow [24]</td>
<td>Intervention (n = 106)</td>
<td>Control (n = 97)</td>
<td>n = 203</td>
<td>RR = 1.26</td>
<td>CI 0.53–2.10</td>
<td>RR = 1.10</td>
<td>OR = 2.58</td>
<td>CI 0.71–1.60</td>
<td>CI 1.04–7.87</td>
<td>IG: 22</td>
</tr>
<tr>
<td>Rodriguez [23]</td>
<td>Intervention (n = 127)</td>
<td>Control (n = 132)</td>
<td>n = 259</td>
<td>OR = 0.87</td>
<td>CI 0.49–1.54</td>
<td>RR = 0.88</td>
<td>CI 0.44–0.95</td>
<td>CI 0.66–1.17</td>
<td>CI 1.62–29.74</td>
<td>CI 0.73–1.18</td>
</tr>
<tr>
<td>Grossmann [22]</td>
<td>Intervention (n = 489)</td>
<td>Control (n = 496)</td>
<td>n = 985</td>
<td>RR = 1.35</td>
<td>CI 0.81–2.26</td>
<td>RR = 1.20</td>
<td>RR = 1.19</td>
<td>CI 0.63–2.31</td>
<td>CI 0.87–1.62</td>
<td>CG: 10</td>
</tr>
<tr>
<td>Secco [16]</td>
<td>Intervention (n = 145)</td>
<td>Control (n = 192)</td>
<td>n = 337</td>
<td>RR = 0.71</td>
<td>CI 0.56–0.91</td>
<td>RR = 0.92</td>
<td>RR = 2.45</td>
<td>CI 0.76–1.12</td>
<td>CI 1.58–3.79</td>
<td>CI 1.15–4.94</td>
</tr>
<tr>
<td>Schoemaker [21]</td>
<td>Intervention (n = 167)</td>
<td>Control (n = 158)</td>
<td>n = 325</td>
<td>RR = 0.74</td>
<td>CI 0.53–1.03</td>
<td>RR = 0.85</td>
<td>RR = 1.42</td>
<td>CI 0.64–1.14</td>
<td>CI 1.89–34.25</td>
<td>CI 0.41–4.92</td>
</tr>
<tr>
<td>Pietra [17]</td>
<td>Intervention (n = 104)</td>
<td>Control (n = 103)</td>
<td>n = 207</td>
<td>RR = 0.64</td>
<td>CI 0.44–0.95</td>
<td>RR = 0.88</td>
<td>RR = 6.93</td>
<td>CI 0.66–1.17</td>
<td>CI 1.62–29.74</td>
<td>CI 3.12–66.93</td>
</tr>
<tr>
<td>Kjeldsen [3, 20]</td>
<td>Intervention (n = 290)</td>
<td>Control (n = 307)</td>
<td>n = 597</td>
<td>RR = 0.93</td>
<td>CI 0.73–1.18</td>
<td>RR = 0.99</td>
<td>RR = 1.01</td>
<td>CI 0.77–1.32</td>
<td>CI 1.91–7.02</td>
<td>CI 1.21–8.27</td>
</tr>
<tr>
<td>Ohlsson [18]</td>
<td>Intervention (n = 53)</td>
<td>Control (n = 54)</td>
<td>n = 107</td>
<td>RR = 0.69</td>
<td>CI 0.41–1.19</td>
<td>RR = 0.64</td>
<td>RR = 3.06</td>
<td>CI 0.56–1.66</td>
<td>CI 0.88–10.67</td>
<td>CI 0.19–27.58</td>
</tr>
<tr>
<td>Makela [19]</td>
<td>Intervention (n = 52)</td>
<td>Control (n = 54)</td>
<td>n = 106</td>
<td>RR = 0.88</td>
<td>CI 0.59–1.33</td>
<td>RR = 1.09</td>
<td>RR = 1.29</td>
<td>CI 0.69–1.73</td>
<td>CI 0.68–2.39</td>
<td>CI 0.36–8.55</td>
</tr>
</tbody>
</table>

RR, relative risk; OR, odds ratio; CI, confidence interval; IG, intervention group; CG, control group; SD, standard deviation.
Table 2. Description of interventions and follow-up strategies of the studies included

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primrose [26]</td>
<td>Intervention group: - CEA follow-up: measurement of blood CEA every 3 months for 2 years, then every 6 months for 3 years, with a single chest, abdomen, and pelvis CT scan at 12–18 months if requested at study entry by hospital clinician (n = 300). - CT follow-up: CT of the chest, abdomen, and pelvis every 6 months for 2 years, then annually for 3 years (n = 299). - CEA and CT follow-up: both blood CEA measurement and CT imaging as above (n = 302).</td>
<td>Minimum follow-up: no scheduled follow-up except a single CT scan of the chest, abdomen, and pelvis at 12–18 months if requested at study entry by the hospital clinician (n = 301).</td>
</tr>
<tr>
<td>Ting Wang [25]</td>
<td>Intervention group: - A visit every 3 months the first year. Every 6 months the next 2 years. And then annually. - At each visit: medical exams, medical history, CEA, chest X-ray, CT and liver ECO. - Colonoscopy every visit. - Additional tests if the patient has symptoms suggestive of recurrence were carried out.</td>
<td>Control group: - At each visit: medical exams, medical history, CEA, chest X-ray, CT and liver ECO. - Colonoscopy at months 6, 30, 60. - Additional tests will be carried out if the patient has symptoms suggestive of recurrence.</td>
</tr>
<tr>
<td>Watchow [24]</td>
<td>Intervention group: - Follow by surgeons: more ultrasound, colonoscopy and sigmoidoscopy.</td>
<td>Control group: Follow-up by general practitioners: more fecal occult blood. CEA, CT, Rx, endoscopy: the same in both groups.</td>
</tr>
<tr>
<td>Rodriguez [23]</td>
<td>Intervention group: Examination, bloods (including CEA) at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60 months. US/CT at 6, 12, 18, 24, 30, 36, 42, 48, 56 months, CXR and colonoscopy at 12, 24, 36, 48, 56 months.</td>
<td>Control group: History, examination, bloods (including CEA) at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60 months.</td>
</tr>
<tr>
<td>Grossmann [22]</td>
<td>Intervention group: - Clinical testing: Every 4 months in the first 2 years and every 6 months in the next 3 years. - Analysis (CEA, liver function, blood counts): Every 6 months for the first 2 years and every 6 months in the next 3 years. - Chest X-ray: Annually until 5 years. - Colonoscopy: Annually until 5 years.</td>
<td>Control group: - Clinical testing: As in the intervention group. - Analysis (CEA, liver function, blood counts): Same as in the control group. - No CT, no abdominal US and no X-ray. - Colonoscopy: The first and third years.</td>
</tr>
<tr>
<td>Secco [16]</td>
<td>Intervention group: High risk of recurrence: - Clinical testing and CEA every 3 months in the first 2 years, every 4 months in the third year, and every 6 months in the fourth and fifth years. - Abdominal and pelvic ECO every 6 months in the first 3 years and each year in the fourth and fifth years. - Rx and thoracic rectosigmoidoscopy annually in the first 5 years. Low risk of recurrence: - Clinical testing and CEA every 6 months the first 2 years, and annually through 5 years. - ECO abdomen and pelvis every 6 months in the first 2 years then annually. - Rectosigmoidoscopy in patients with rectal cancer annually in the first 2 years and every 2 years thereafter. - Rx annually after the end of the track. - No blood counts and liver function tests.</td>
<td>Control group: - Common and inexpensive tests. - More sophisticated tests for suspected recurrence. - Not specified.</td>
</tr>
</tbody>
</table>
the pooled result after excluding each of the analyzed trials (Figure 2B). Moreover, the result of the Egger test for publication bias was not significant ($P = 0.446$), and no funnel plot asymmetry was observed, indicating no evidence of publication bias.

**cancer-specific survival**

Only five randomized clinical trials ($N = 2618$ patients) provided data about CRC-specific mortality. No significant differences in any of these studies were found in cancer-related survival according to the surveillance strategy. Except for the study by Grossmann et al. [22], the remaining three trials found a lower risk of death in the intensive follow-up group, although it was not statistically significant. Similarly, the results from the meta-analysis failed to detect any significant effect of the follow-up protocol on cancer-specific survival ($RR = 0.9; 95\% CI 0.7–1.1$) (Figure 2C).

**recurrences**

Ten of the 11 included studies provided data on the recurrence detection rate, and 7 on asymptomatic recurrences. None of these studies found a significant effect of the follow-up regimen on the probability of recurrences detection. The pooled RR of recurrence detection associated with an intensive follow-up was 0.98 (95% CI 0.9–1.1), showing that the recurrence rate is not related to the type of surveillance. Analogous results were obtained in the subgroup analysis, comparing an intensive follow-up with no follow-up (RR = 0.9; 95% CI 0.8–1.1) or with a less-intensive follow-up (RR = 1.0; 95% CI 0.9–1.1) (Figure 3A).
Figure 2. Overall survival rate and cancer-related mortality in relation to different follow-up strategies (intensive follow-up versus minimalist follow-up or no follow-up) for patients treated for nonmetastatic colorectal cancer. A: Overall survival rate after curative resection of colorectal cancer. B: Sensitivity analysis for overall survival rate. C: Cancer-specific survival.
On the contrary, when asymptomatic recurrences were analyzed, a higher detection rate of asymptomatic recurrences was observed in patients with a more intensive follow-up (RR = 2.6; 95% CI 1.7–4.1) (Figure 3B).

curative surgery attempted at recurrences

The reoperation rate with curative intention for recurrent disease was reported in nine trials. All these studies found a higher percentage of resectable recurrences in patients with a more intensive follow-up than in patients with less-intensive/minimal follow-up, with RRs ranging from 1.4 to 9.6. An overall significant effect was found, with a more intensive surveillance associated with a higher probability of curative reoperations (RR = 2.0; 95% CI 1.5–2.6), both when comparing with less-intensive follow-ups (RR = 2.1; 95% CI 1.4–3.0) or no follow-up (RR = 1.9; 95% CI 1.1–3.3) (Figure 4A).

survival after recurrences

A total sample size of n = 1957 patients were included in the six trials assessing mortality after recurrence diagnosis. Of these, 59 were alive after the follow-up (42 in the group of more intensive surveillance versus 17 in the group of less-intensive/minimal follow-up). Except for the study of Makela et al. [19], the remaining trials found a higher post-recurrence survival.

An overall significant effect was found, with more intensive surveillance associated with a higher probability of survival after the detection of recurrences (RR = 2.1; 95% CI 1.2–3.7) (Figure 4B).
Figure 4. Curative reoperation rate, mortality after recurrence and time to recurrence in relation to different follow-up strategies (intensive follow-up versus minimal follow-up or no follow-up) for patients treated for nonmetastatic colorectal cancer. A: Curative reoperation rate of patients for recurrent disease that developed after curative resection of colorectal cancer. B: Survival after recurrence detection. C: Time to detection of recurrences.
time to detection of recurrences

Ten of the 11 studies contained data on time to recurrence detection. For the studies comparing intensive follow-up strategies with less intensive strategies, all of the studies except for the study by Rodriguez et al. [23] found a significantly shorter interval for patients with intensive follow-up surveillance, with differences of between 5 and 13 months. Both of the trials comparing intensive versus no follow-up found concurrent differences.

A pooled analysis of all of the studies on time to recurrence detection revealed that more intensive surveillance resulted in earlier recurrence detection, with a mean difference of −5.2 months (95% CI −9.6 to 0.9) (Figure 4C).

overall survival in relation to different diagnostic tests

Table 3 shows the effects of the different diagnostic tests that were analyzed individually on overall survival, where it can be seen that colonoscopies, imaging tests, determining the CEA, and medical visits have a protective effect on mortality.

discussion

The results of this meta-analysis indicate an improvement in the overall survival of patients who have undergone more intensive follow-up after curative surgery for CRC.

Out of the studies included in the meta-analysis, only two individual studies [16, 17] described a significant improvement in the overall survival of the patients who underwent more intensive follow-up. Some of these studies [16–19, 24] do not make any mention of the statistical power required to detect significant differences in the survival rate associated with more intensive follow-up.

Taking into account the fact that the overall mortality in the intervention group (with the most intensive follow-up) is 25.8%, and that the overall mortality in the control group (with less intensive follow-up or no follow-up) is 29.1%, the result is a number needed to treat (NNT) of 30 patients (95% CI 16–458), which means that it is necessary to carry out an intensive follow-up of 30 patients who have previously undergone curative surgery for colorectal surgery to avoid one death. It was not possible to detect significant differences with regard to the mortality related to disease. This outcome was only evaluated in five of the clinical trials included in the meta-analysis, and although the difference was not significant, it was possible to identify a protective effect on the cancer-specific survival rate.

With regard to the total recurrences, there were no significant differences between both groups after curative surgery. However, the time to detection of recurrences was shorter in the patients who had undergone more intensive follow-up, which may explain the higher probability observed in this meta-analysis of detecting asymptomatic recurrences in these patients. A higher probability of carrying out curative surgery attempted at recurrences was also observed in the patients undergoing more intensive follow-up. This could explain the improved overall survival rate seen in the patients in the experimental group. In the patients subjected to intensive follow-up, a higher probability of survival after recurrences is seen, with a significant association, RR = 2.1 (95% CI 1.2–3.7).

The carrying out of colonoscopies has a protective effect on the mortality of the patients, although carrying out colonoscopies more frequently does not seem to be associated with improvements in the overall survival rate, although the results are close to statistical significance. In the only study that evaluated carrying out colonoscopies more frequently [25], a trend toward reduced mortality was found, but which was not significant.
Imaging tests, CEA and clinic visits are associated with improved overall survival among the patients who undergo more intensive follow-up. It is reasonable to consider that both colonoscopies and liver ultrasonography and CT make it possible to detect recurrences earlier, and therefore operate on the patient at an earlier stage. The combined effect of the different endoscopic, analytical and imaging tests is the subject of this meta-analysis and, for this reason, certain findings such as the one associated with thorax X-rays are secondary to the fact that other diagnostic tests are carried out simultaneously with these patients. In this study, based on the information available from the randomized clinical trials that have been published, no data are available that make it possible to determine the effect associated with carrying out each test separately.

Like all meta-analyses, this study has as a limitation the heterogeneity of the studies it includes. There are differences in the populations of these studies, such as the TNM staging or degree of tumor invasion. For example some studies excluded patients with Dukes’ grade A [17, 23].

There is also variability in terms of the follow-up strategies. The intensity of the follow-up in the experimental group from the study by Ohlsson et al. [18] was similar to the intensity of the follow-up in control groups from other studies included in the review [17, 19, 21].

In the majority of the trials, the randomization method is not described in detail. Six of the studies [20–23, 25, 26] stratified the patients according to the main prognostic factors, such as the tumor stage and location. Due to the characteristics of the clinical trials, all the studies were open and not blinded studies.

Although two of the studies [22, 24] used a short follow-up time with the patients, excluding these studies from the meta-analysis did not affect the results obtained on including them, as shown in Figure 2B.

This study contributed the following information in addition to what we already know: the last meta-analysis on this subject carried out in 2007 included eight randomized clinical trials [30]. This study includes 11 randomized clinical trials. The previous meta-analyses used the OR or RR for studying overall survival as a measure of association while, in this study, we have used and calculated the HR, as we have taken the follow-up time into account. This study provides data on the survival of patients once recurrences are detected, something that was not included in any of the previous meta-analyses.

Our meta-analysis has made it possible to improve the precision of the outcomes studied in comparison to previous meta-analyses in terms of overall survival. All of the previous meta-analyses detected an improvement in the overall survival, but with less precision in terms of the CIs.

None of the previous meta-analyses were able to detect significant differences in the total recurrences between both groups of patients. The same is true for our study. In the case of asymptomatic recurrences, our study is in line with two meta-analyses that evaluated asymptomatic recurrences [4, 30] and detected a greater possibility of detecting asymptomatic recurrences in the intensive follow-up.

Three of the previous meta-analyses [29, 30] found a higher probability of curative surgery in patients with intensive follow-up, and our study shows the same effect. Earlier detection was also observed for recurrences in patients subjected to more intensive follow-up, coinciding with two previous meta-analyses that evaluated this outcome.

As previously mentioned, none of the previous meta-analyses evaluated the survival rate of the patients once recurrences were detected. This study detected an improvement in survival after recurrence in the most intensive follow-up, with a significant association (RR = 2.1; 95% CI 1.2–3.7).

This meta-analysis has found that more intensive follow-up with patients who have been operated for CRC and declared to be free from the illness significantly improves the overall survival rate, increases the probability of detecting asymptomatic recurrences and curative surgery attempted at recurrences, and is associated with a shorter recurrence detection time. More intensive follow-up of patients operated for CRC are not associated with a greater detection of total recurrences, or a decrease in mortality related to disease, even though there is a trend toward a protective effect. Undertaking follow-up with CEA and colonoscopy is associated with an improved overall survival. The variability of the studies regarding the follow-up strategies only lets us affirm that the intensive follow-up strategies have a benefit effect in relation with the outcomes in nonmetastatic CRC patients after curative surgery.

disclosure

The authors have declared no conflicts of interest.

references


