

Do the benefits outweigh the side effects of colorectal cancer surveillance? A systematic review

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Abstract

Most patients treated with curative intent for colorectal cancer (CRC) are included in a follow-up program involving periodic evaluations. The survival benefits of a follow-up program are well delineated, and previous meta-analyses have suggested an overall survival improvement of 5%-10% by intensive follow-up. However, in a recent randomized trial, there was no survival benefit when a minimal vs an intensive follow-up program was compared. Less is known about the potential side effects of follow-up. Well-known side effects of preventive programs are those of somatic complications caused by testing, negative psychological conse-

quences of follow-up itself, and the downstream impact of false positive or false negative tests. Accordingly, the potential survival benefits of CRC follow-up must be weighed against these potential negatives. The present review compares the benefits and side effects of CRC follow-up, and we propose future areas for research.

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Key words: Colorectal cancer; Follow-up; Surveillance; False positive; Cancer survivorship

Core tip: Most western countries have a national follow-up program for colorectal cancer (CRC) survivors. The reported reduction in absolute mortality from intensive follow-up is 5%-10%, though recent data from the follow-up after colorectal surgery randomized trial call this effect into question. There exists limited evidence of improved quality of life (QoL) due to participation in a follow-up program, and the impact of false positive tests on QoL might be considerable. Several national experts advocate for low-cost, low-intensity CRC follow-up programs.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the western world, and surgery is the only curative treatment. Approximately one-third of those surgically resected will experience recurrent disease with an expected survival of less than two years^[1]. Patients treated with curative intent are usually included in some form of

Table 1 Benefits and side effects of colorectal cancer surveillance

Benefits	Harms
Reassurance of surveillance	Impact of false positive tests
For the CRC survivor	Over diagnoses
For spouses and family	Complications related to the screening tests
Improved survival	Labeled as sick or at high risk
Control of treatment effects	False assurance of disease free status
Is the societal harm-to benefit ratio acceptable?	

CRC: Colorectal cancer.

preventive follow-up program involving periodic evaluations. Reviews comparing various follow-up programs have suggested that more intensive follow-up strategies tend to increase the five-year survival rate by 5%-10%^[2,3].

Most national follow-up programs recommend intensive follow-up. However, there exist controversies on how to define an “intensive” follow-up program. This is mirrored in the fact that two identical national follow-up programs do not exist. In general, an intensive follow-up program consists of regular testing (usually every 3 mo the first two years) and consultations, whereas a low intensive follow up program is defined as no regular testing and consultations. In addition, most national follow-up programs make a distinction between rectal cancer and colon cancer surveillance, which is reflected in the difference of recommended radiological test modalities.

However, all preventive programs have the potential to harm patients^[4-6]. The potential survival benefits of a follow-up program for CRC cancer patients have been well described, but much less is known about the potential negative effects accruing to patients and their families^[2,3]. Patients surgically treated for CRC have to decide in partnership with the treating surgeon or family physician, whether they should participate in a CRC follow-up program. In making this personal decision, it is important to know not only the magnitude of potential benefits, but also the magnitude and likelihood of the potential adverse and unintended effects^[5].

Firstly the survival benefits of intensive CRC follow-up must be delineated. In general, the benefits of preventive programs can be described as: (1) relative reduction of mortality rate; (2) absolute reduction of mortality; (3) the number of patients needed to prevent one adverse event; (4) evaluation of treatment effect; (5) reassurance by follow-up leading to improved quality of life (QoL); and (6) detection of other diseases^[4]. In this paper we will further elaborate these terms.

Secondly, the side effects of CRC follow-up must be compared to the survival benefits. Well-known side effects of preventive programs are (1) over-diagnosis; (2) somatic complications caused by testing; (3) negative psychological consequences of follow-up; and (4) impact of a false positive (leading the patient to believe that he or she has recurrent disease) or false negative (leading to a potential diagnostic delay) tests.

Thirdly, the net benefits of follow-up must be con-

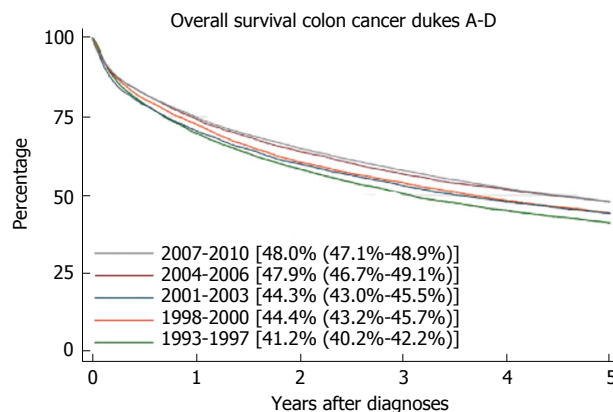


Figure 1 Overall survival of colon cancer dukes A-D. Eighty percent of the recurrences occur within the 3 first years after initial treatment, which is used as an argument to perform intensive surveillance the first 3 years. After 5 years, the survival curve is steady with few deaths caused by colon cancer. Courtesy of the Norwegian Cancer Registry (<http://www.krefregisteret.no/en/>).

sidered in light of the associated economic costs. The United Kingdom’s National Institute for Health and Clinical Excellence (<http://www.nice.org.uk>) has proposed a societal willingness-to-pay of £40000 per life year gained, but this upper limit is controversial. In the case of CRC follow-up, it means that the long-term benefits of a follow-up program (*i.e.*, the attempted curative resection of recurrent disease and resulting gains in survival) have to be balanced against society’s willingness to pay for such a service. To our knowledge, a systematic comparison of the benefits *vs* side effects of CRC follow-up has not been performed. Thus, the objective of this paper is to summarize the existing evidence regarding the benefits and side effects of CRC follow-up. An overview of the potential benefits and harms of CRC follow-up is provided in Table 1.

RESEARCH

We performed a systematic PubMed search with the medical subject heading (MeSH) keywords “colorectal” in combination with the keywords “follow-up”, “surveillance”, “cancer recurrence”; “risk benefit assessment” and “false positive reactions”. Inclusion of papers was decided by discussion among authors. All reference lists of included publications were searched for relevant publications. Finally we identified relevant publications from the author’s personal databases. This resulted in 60 publications included in the review.

Benefits of colorectal follow-up

Benefit: Improved survival: The recurrence rate in CRC has been reported to be 30%-40% within 5 years (Figure 1)^[1]. This means that all follow-up programs must focus on the early detection of recurrent cancers, aiming to offer curative metastases surgery to as many patients as possible.

Two contemporary meta-analyses revealed that intensive and less intensive follow-up led to detection of

a similar number of recurrences but that detection occurred between 5.91 mo (95%CI: 3.09-8.74) and 6.75 mo (95%CI: 2.44-11.06) earlier with intensive follow-up. Both analyses also found that curative reoperation for metastasis was significantly more likely in those subjects who were followed up intensively (Tjandra *et al*²¹: OR = 2.41, 95%CI: 1.63, 3.54. Jeffery *et al*³¹: OR = 2.81, 95%CI: 1.65-4.79). The survival benefits of intensive CRC follow-up has been reported to be a 5%-10% reduction in the total cohort mortality rate. The increased overall survival, earlier detection of recurrence, and higher reoperation rates observed provide only circumstantial evidence that intensive follow-up extends life by making cure of recurrent disease more likely. Neither meta-analyses found that cancer specific survival was improved by intensive follow-up.

However, there exists limited data regarding the relative reduction in mortality or number of patients who must be followed intensively in order to save one life from recurrent cancer death. Factors other than intensive follow-up have been postulated to contribute to the mortality reduction associated with CRC follow-up. Some combination of increased psychological well-being, improved health behavior, and improved treatment of coincidental disease may contribute to the mortality benefit. This issue represents an important direction for future studies¹⁷.

Recently, the results from the follow-up after colorectal surgery (FACS) trial were reported^{18,91}. The factorial randomized trial design, with independent allocation to the carcinoembryonic antigen (CEA) and computed tomography (CT) interventions, meant that patients received 1 of 4 types of follow-up: (1) CEA follow-up: measurement of blood CEA every 3 mo for 2 years, then every 6 mo for 3 years, with a single chest, abdomen, and pelvis CT scan at 12 to 18 mo if requested at study entry by hospital clinician; (2) CT follow-up: CT of the chest, abdomen, and pelvis every 6 mo for 2 years, then annually for 3 years; (3) CEA and CT follow-up: both blood CEA measurement and CT imaging as above; and (4) Minimum follow-up: no scheduled follow-up except a single CT scan of the chest, abdomen, and pelvis at 12 to 18 mo if requested at study entry by the hospital clinician.

Interestingly, there were no differences seen in overall or cancer-specific mortality between any of the intensive arms and the minimum follow-up group. Most patients with recurrence suffered from incurable disease. In fact, only 71 (5.9%) of 1202 patients followed were suitable for potentially curative treatment. Significantly more patients were treated with curative intent in the intensive follow up groups compared to minimalist follow-up, but there were no difference in the number of total deaths in the two groups. These data argue against very intensive follow-up schedules.

In conclusion, although two meta-analyses have reported a 5%-10% reduction in overall mortality among patients undergoing intensive follow-up, the existing

evidence of any benefit in terms of cancer-specific survival is limited. The results from the FACS trial did not show any compelling evidence of a significant survival benefit of CRC follow-up. Hopefully, the final results of the ongoing COLOFOL trial will help answer the debate regarding which follow program enables the highest survival¹¹⁰. A summary of randomized controlled trials and their potential survival benefit is provided in Table 2.

Benefit: Control of treatment effects: There exist several international controversies around treatment (drains *vs* no drains, laparoscopic technique *vs* open technique among others) and follow-up of patients with CRC^{111,12}. There are for instance no similarly designed follow-up program at an international level¹¹³⁻¹⁶. It is therefore imperative for improved CRC treatment quality that the effects of radio-chemotherapy, surgical technique and postoperative follow-up are continuously evaluated, and a structured follow-up program might be a way to perform such a quality control^{117,18}.

Benefit: Reassurance of follow-up: There is no existing evidence that participation in a follow-up program leads to increased personal well-being. Some researchers have investigated the psychological effects of CRC follow-up¹¹⁹⁻²². None of the resulting studies have found improvement in the patient QoL with follow-up.

Harms of CRC follow-up

Harm: False positive tests: Table 3 summarizes the false positive rates of the most commonly used CRC follow-up tests. As an illustration, consider a patient followed according to the most recent United States follow-up recommendations from the National Comprehensive Cancer Network¹¹⁶. Based on the most optimistic estimates in Table 3 the annual probability of at least one false positive test for a patient with no actual recurrence would be 41% in each of years one and two, and 28% in each of years three, four, and five. Over the entire five-year period, the probability of at least one false positive would be 87%.

Given their high likelihood, it is important to consider the possible consequences of false positive follow-up tests. Primarily, these can come in the form of economic costs and psychological impact. None of the prospective studies or economic models focusing on CRC recurrence have reported the economic costs of false positive follow-up tests, but quantifying these costs could provide important perspective.

While no studies appear to have specifically addressed the psychological or quality-of-life impact of false positive follow-up tests in colorectal or other types of cancer, a small number of investigators have examined the quality-of-life impact of false positive cancer screening tests. In general, these studies have shown increased anxiety following false positive screening results for as long as 18^[23] to 24^[24] mo after the false positive result^{123,25,26}. This data comes from populations who have not previously

Table 2 Comparison of randomized trials assessing follow-up after colorectal cancer curative surgery *n* (%)

Trial	Cancer stage included	Enrolled (<i>n</i>)	Recurrences	Time to cancer detection (mo)	Metastases surgeries (<i>n</i>)	Overall 5-yr survival	Disease free 5-yr survival	Survival after met surgery
Ohlsson 1995								
Total	Dukes A, B, C	107	35 (33)					
Intensive		53	17 (32)	20 (median)	5	75	78	29% 5 yr
Control		54	18 (33)	24 (median)	3	67	71	22% 5 yr
Makela 1995								
Total	Dukes A, B, C	106	43 (41)		8	58		Overall 3 pts mean 26 mo survival
Intensive		52	22 (42)	10 (mean)	5	59		
Control		54	21 (39)	15 (mean)	3	54		
Pietra 1998								
Total	Dukes B, C	207	82 (39)					Overall 8 pts mean 29 mo survival
Intensive		104	41 (39)	10.3 (mean)	21	73	68	
Control		103	41 (40)	20.2 (mean)	6	58	53	
Rodriguez-Moranta 2006								
Total	TNM II and III	259	69 (26)					NA
Intensive		127	35 (27)	39 (mean)	18	75	NA	
Control		132	34 (26)	38 (mean)	10	73		
Secco 2001								
Risk adapted intensive	Low risk vs high risk	108	74 (68)	Total	31	48	NA	NA
Risk adapted low intensive		84	27 (32)	13.5 (mean)		82		
Minimal follow-up: High risk		84	58 (69)		13	35		
Minimal follow-up: Low risk		61	25 (40)			60		

NA: Not available.

Table 3 Probability of false positive test results (1-specificity) for commonly used colorectal cancer follow-up tests

Test	False positive rate (1-specificity)	Ref.
Serum CEA	10%	[54]
CT-hepatic metastases	5%-28% ¹	[55-58]
CT-other abdominal metastases	2%	[58]
Contrast enhanced ultrasound-liver	4%-33% ²	[56,57,59]
Ultrasound-liver	50%	[59]
CT-lungs	4%	[58]
Colonoscopy	0%	[32]

¹Based on specificity estimates from individual studies of 89%^[55] (*n* = 24), 95%^[58] (*n* = 115), 72%^[56] (*n* = 87), and 91%^[57] (*n* = 100); ²Based on specificity estimates from individual studies of 96%^[60] (*n* = 68), 96%^[57] (*n* = 99), and 67%^[59] (*n* = 56) subjects. The last was the only to employ intraoperative confirmation of hepatic metastases. The annual probability of at least one false positive test for a patient with no actual recurrence would be 41% in each of year one and two, and 28% in each of year three, four, and five. Over the entire five-year period, the probability of at least one false positive would be 87%. CT: Computed tomography; CEA: Carcinoembryonic antigen.

been diagnosed with and treated for cancer, so the results are difficult to extrapolate to CRC survivors.

Harm: Somatic complications caused by tests: Aside from any unlikely negative sequelae of CT radiation exposure, colonoscopy related colonic perforation and post-procedure bleeding represent the most likely serious complications arising from CRC follow-up. Endoscopic follow-up is endorsed in most comprehensive follow-up recommendations^[16,27-31] primarily as a means to detect

metachronous CRC's (normally representing between 1.6% and 7.4% of CRC recurrences) or adenomas with advanced features^[2,32,33]. The relatively invasive procedure has sensitivity of 95% and specificity of 100% for detecting high-risk polyps or tumours, however the major complication rate has been reported as 0.2%-1.2%^[34-36].

To date, no trial has reported increased survival associated with colonoscopy follow-up after CRC resection. Because of the unproven benefit and non-trivial risk, some have argued against routine endoscopic follow-up after curative CRC resection^[37-39]. Further study is needed to explore whether CT Colonography may eventually provide a better balance of risks and benefits^[38].

Harm: QoL implications: There is limited evidence showing that enrolment in a follow-up program improves QoL among CRC survivors. In fact, available data from breast follow-up trails could be used to support the opposite viewpoint: such follow-up programs and tests might negatively influence QoL^[40-42]. It is often claimed-and some evidence corroborates^[22]-that follow-up tests can be reassuring for patients, and this may be true if all of the tests are completely normal every time. However, equivocal test results such as a slightly elevated CEA level, or questionable shadows on CT are quite common, and they commonly spur additional testing. This period between initial suggestive test result and subsequent conclusive work-up can be a stressful one for patients^[21].

Some researchers have investigated the psychological effects of CRC follow-up^[19,22]. None of the resulting studies have found improvement in the patient QoL with

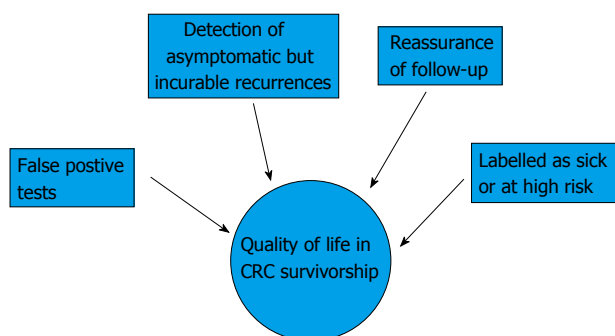


Figure 2 Factors influencing quality of life among colorectal cancer survivors enrolled in a follow-up program. CRC: Colorectal cancer.

follow-up. In a recent published randomized trial comparing general practitioner *vs* surgeon-organized follow-up, there were no differences between the two groups in QoL measured by ERTOC-QLQ C30 and EQ-5D^[21]. In fact, both groups had similar QoL levels as the general United Kingdom population at baseline (1 mo postoperatively). Results from a similar 2006 trial by Wattchow *et al*^[19] told a similar story. There, study patients remained in the normal range for depression and anxiety with no difference between the two groups at either 12 or 24 mo^[19,20]. In recent meta-analyses, it has been shown that anxiety rather than depression was a major problem among long-term cancer survivors. It is however unknown what impact an organized cancer follow-up program has on anxiety^[43]. It has been shown that 46 percent of patients reported physiological distress while awaiting the results of a potential cancer diagnosis^[44]. This and other trials suggest that tests recommended by a cancer screening or preventive program cause harm in terms of physiological distress^[44-46].

The only survey showing a slight improvement in QoL among CRC survivors with intensive follow-up was published in 1997^[47]. This survey included 350 Danish participants who reported a small but significant increase in QoL associated with more frequent follow-up, as measured by the Nottingham Health Profile.

In conclusion, there exists very limited evidence that CRC follow-up improves QoL among CRC survivors. Further research is needed, in particular, to address the impact of a false positive follow-up test on QoL among CRC survivors. From breast cancer follow-up trials, there is compelling evidence that postoperative follow-up does not improve QoL and that follow-up testing might cause physiological distress^[48]. Factors that may impact QoL in a positive or negative way among colon cancer survivors enrolled in a follow-up program are shown in Figure 2.

DIRECTION OF FUTURE RESEARCH

According to the World Health Organisation, the success of preventive programs depends on three fundamental principles (www.who.int/cancer/detection/variouscancer/en/): The target disease should be a common form

of cancer, with high associated morbidity or mortality; Effective treatment, capable of reducing morbidity and mortality, should be available; Test procedures should be acceptable, safe, and relatively inexpensive.

In CRC follow-up these principles are fulfilled: (1) CRC is the third most common cancer disease, and the risk of recurrence is as high as 30 to 40 percent; (2) if successful, metastasectomy can be curative (*i.e.*, R0 resections); and (3) the tests in most programs are acceptable, relatively safe and relatively inexpensive. However, as discussed, there are several potential side effects of CRC follow-up; future research much be directed at further exploring these harms and weighing them against the expected survival benefit. Recently, a survey published in British Medical Journal found that the harms of screening and preventive programs were poorly reported^[49]. Healthcare decision makers, surgeons, and patients therefore cannot make informed choices.

Personalized medicine is defined as a medical model that proposes the customization of healthcare, with medical decisions, practices and tests being tailored to the individual patient. To our knowledge there exist no individual risk stratification in the different national colorectal follow-up guidelines, and this is an area of future research.

Firstly we believe that genetic testing and biological determinants of tumor recurrence will gain increasingly importance^[50,51]. The individualization of cancer care requires a deep understanding of tumor biology and the identification of tumor subsets that offer targets for tumor specific treatment. Of specific interest for CRC follow-up programs, are the promising results of the 12-gene recurrence score (RS), which is a quantitative assay integrating stromal response and cell cycle gene expression. It is shown that the 12-gene RS predicts recurrence in stage II colon cancer. This tool appears promising as a means to inform decision making around adjuvant chemotherapy following resection of stage II colon cancer. The use of the tool in planning post-treatment follow-up does not appear to have been explored, however^[52].

Secondly, test intensity, test modality and the risk of false positive events has to be discussed in details with the patient. As shown in Table 3, the probability of at least one false positive event during a five-year follow-up program might be as high as 87%. High-test intensity programs should be offered to patients with a high probability of recurrent cancers, but this must be weighed against the patient's preferences of experiencing a false positive test.

Finally, research must be aimed to identify the optimal combination of test, blood samples and clinical examinations that creates the highest possible overall follow-up sensitivity and specificity.

CONCLUSION

Any survival benefit (or lack of benefit) of the CRC fol-

low-up must be considered along with the views of the patients to ensure that follow-up programs are accessible and acceptable, and that they address all patient needs and concerns. However, the problem of postoperative cancer follow-up is that a vast majority of patients must undergo a large number of tests without any benefit, or even with some harm, to identify a small number of patients with curable recurrence. Patients with asymptomatic but incurable disease (10%-20% of all recurrences) likely represent the group with the most potential to be harmed by follow-up^[21,53].

In conclusion, little is known about the potential harms of CRC follow-up, especially when it comes to the impact of false positive tests. Tailored follow-up programs based on the individual's risk of cancer recurrence and likely metastatic spread pattern must be developed. Further research is needed to settle these controversies, and new methods of decision-analytic modeling in combination with the emerging data from COLOFOL must be applied^[9,10].

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