

Intensive or not surveillance of patients with colorectal cancer after curative resection

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Abstract

It is common practice to follow patients with colorectal cancer for some years after resection and/or adjuvant treatment. Data are lacking about how often patients should be seen, what tests should be performed, and what surveillance strategy has a significant impact on patient outcome. Seven randomized trials have addressed this issue, but none had sufficient statistical power. Four published meta-analyses have established that overall survival is significantly improved for patients in the more intensive programs of follow-up. This improvement amounts to a risk difference of 7% (95% CI: 3%-12%, $P = 0.002$) in 5-year survival. This should be partly attributable to more frequent reoperation for cure of asymptomatic recurrence, or more intense follow-up, as well other factors, such increased psychosocial support and well-being, diet and lifestyle optimization, and/or improved treatment of coincidental diseases. A large-scale multicenter European study [Gruppo Italiano di Lavoro per la Diagnosi Anticipata (GILDA)] is underway to answer the question of what constitutes optimal surveillance for patients after primary therapy, based on an adequately powered study.

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Key words: Colorectal cancer; Follow-up; Meta-analysis; Recurrence; Salvage surgery

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies and the second leading cause of death related to cancer^[1]. Although about two-thirds of patients undergo radical surgery, up to 30%-50% of them will develop tumor relapse and die of their disease^[2]. This provided a rationale for trying to diagnose recurrence early, while resection is still feasible.

Although there is general agreement about the usefulness of postoperative patient follow-up, no consensus has been reached and there have been no clinical trials to demonstrate effectiveness. Thus, in a survey of members of the American Society of Colon and Rectal Surgeons, it was found that 31% of surgeons request computed tomography (CT) at least once during the first postoperative year after colon cancer surgery, while 53% do not employ CT at all. Similarly, 5% monitor carcinoembryonic antigen (CEA) levels monthly during the first postoperative year, while 4% never check CEA levels^[3]. This poses an important problem because there are many patients at risk and the costs of diagnosis (and treatment, if needed) are high.

OPEN QUESTIONS

An optimal level of follow-up would maximize patient welfare at the least cost. Patients are harmed if a strategy is too intensive, because they are unnecessarily exposed to radiation, and undergo uncomfortable endoscopy and blood tests. If high-intensity surveillance testing provides no improvement in duration or quality of life (QoL), society is also harmed by the waste of resources. If the strategy is not intensive enough, patients who relapse and are potential candidates for effective salvage treatment may die needlessly. Society is also harmed in this case because the costs to treat incurable CRC are high, patients are unable to work, their QoL decreases, and their children grow up without a parent^[4]. How good is the evidence for choosing which follow-up examinations to order?

Early detection of CRC recurrence is seldom useful. In this context, intensive testing leads to anxiety and financial burden, and seldom changes disease outcomes. On the contrary, to wait for signs or symptoms, rather than detecting early disease manifestations is defensible, albeit somewhat paternalistic. Physical examination virtually never discerns early hepatic, lung, or anastomotic recurrence, and CEA is only elevated in 60% of patients with recurrence. Thus, waiting for signs and symptoms seems contrary to the instinct that early detection and prompt disease management is best^[5].

WHAT IS KNOWN ON THIS TOPIC?

In an attempt to rationalize care, the concept of the randomized trial was introduced in the mid-twentieth century. However, very few of these studies have dealt with follow-up of patients with CRC, and no consensus has been reached with respect to the most effective strategy. Indeed, follow-up schedules are highly heterogeneous with regard to procedures (clinical history, physical examination, CEA monitoring, imaging techniques, and colonoscopy) and the frequency with which they are carried out.

Seven randomized controlled trials have addressed this issue, but none had sufficient statistical power^[6-12]. Thus, four meta-analyses have been published to evaluate the impact of various intensities and strategies on the outcome of patients after curative surgery for CRC^[13-16].

Overall survival is significantly improved for patients in the more intensive programs of follow-up. This improvement amounts to a risk difference of 7% (95% CI: 3%-12%, $P = 0.002$) in 5-year survival^[15]. The incidence of asymptomatic recurrence is significantly more common in patients in the more intensive follow-up program. This may explain the more frequent reoperation for recurrence in that group of patients.

The analysis of Renehan *et al*^[13] has found a larger impact on survival in trials using abdominal CT and frequent CEA determinations. The study by Jeffery *et al*^[14] had similar findings. The patients undergoing more intense follow-up have improved survival, earlier diagnosis of recurrence, and more frequent curative resection, as a result of undergoing more tests, especially liver imaging.

However, it is not clear to date which tests or frequency of visits is optimal. Also noted in these overviews are the paucity of data on complications and QoL.

One trial noted two perforations and two episodes of bleeding after polypectomy in 731 colonoscopies: a complication rate of 0.55%^[9]. This complication rate is comparable to that of other colonoscopy studies^[17].

The QoL and attitude of patients participating in follow-up programs have been investigated by Stiggelbout *et al*^[18]. Their results have indicated that regular contact with a physician reassures patients, and that visits and tests cause only slight anticipatory anxiety and other minor inconveniences^[18].

Kjeldsen *et al*^[6] have confirmed these findings in a subgroup of patients participating in a randomized trial that compared minimal to regular follow-up, and which demonstrated similar survival for both follow-up regimens. Patients were mailed the questionnaire to complete at home. Ninety-one percent returned the completed questionnaires. QoL measures and attitudes were almost the same for patients in the minimal and intensive follow-up programs, which indicated that the extra tests or inconveniences were balanced by the more frequent reassurance of health.

Other authors have postulated that improved survival with intensive follow-up is not only due to salvage surgery offering a second chance of cure, but that an additional 4%-11% gain in survival may be attributable to other factors^[19]. The following may be relevant: (1) increased psychosocial support and well-being; (2) cancer survivors tend to optimize their diet and lifestyle, although it is unclear whether these adjustments are self motivated, or a direct consequence of health-care interventions; and (3) improved treatment of coincidental disease.

CONCLUSION

Many doubts about follow-up of CRC patients must be clarified and further well-designed studies with a sufficient number of patients must be carried out. The generation of high-quality evidence for the practice of cancer patient follow-up is an important priority for the medical community, although trials are expensive to mount and take a long time to complete. In this context, two trials of high- vs low-intensity follow-up for breast cancer have been carried out, which indicates that such trials are feasible^[19]. Both employed a randomized two-arm design with a sample size of about 1500 patients. The same is likely to be necessary for trials of CRC patient follow-up; one such trial by Gruppo Italiano di Lavoro per la Diagnosi Anticipata (GILDA) completed patient recruitment in September 2006, and the results should be published during 2010. Major objectives of this study are: overall survival, better timing profile of diagnosis of recurrence, QoL, and program costs. It is hypothesized that the results of high- and low-intensity strategies will be equivalent, and it will answer the question of what constitutes optimal surveillance for patients after primary therapy, based on an adequately powered study.

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