

CHAPTER 17 FOLLOW UP AFTER CURATIVE RESECTION FOR COLORECTAL CANCER

17.1 Rationale for follow up

17.1.1 Detection of second primary tumours

Following curative surgery for Colorectal Cancer, patients have an increased incidence of metachronous primary Colorectal Cancers and adenomatous polyps.¹ In one series, the rates of development of new primary cancers and adenomas at four years were 7.7% and 62%, respectively.²

Colonoscopic surveillance and the removal of any adenomas may reduce the incidence of subsequent primary bowel cancer.

17.1.2 Early detection of recurrence

About one in three patients who have curative surgery for Colorectal Cancer will die as a result of recurrent disease.³ Follow up is performed to improve on this outcome by detecting recurrence at an earlier and potentially curable stage. In general, this will mean detecting recurrence in an asymptomatic person with resectable suture-line recurrence, or resectable liver and lung metastases. There is evidence of benefit in terms of cure by further surgery for about 1% of such patients.⁴

Proponents of intensive follow up argue that this approach could lead to earlier detection of recurrent and/or metachronous disease, and by improving resectability rates, may improve survival time.

Five single-institution, prospective randomised clinical trials of follow up have compared an intensive follow-up strategy with a less intense strategy.⁵⁻⁹ All considered overall survival as the main outcome measure. Two of the studies used additional tests in the intensive surveillance arm,^{7,8} two looked at the surveillance interval,^{5,9} and one looked at both.⁶ Although one study⁹ found a survival benefit associated with more frequent follow up, the majority of the trials seemed to indicate no survival advantage for intensive follow up — including the one Australian trial.⁸ All these studies, however, may be criticised on the basis that they lacked significant statistical power.

Meta-analyses overcome the problems associated with individual studies with regard to sample size and statistical power. However, there are problems with combining dissimilar follow up programs. Four meta-analyses¹⁰⁻¹³ have been performed to look at the relationship between intensive follow up and survival after curative resection for Colorectal Cancer. One meta-analysis was based entirely on non-randomised data,¹⁰ and another combined randomised trials with cohort studies.¹¹

Two of the studies, however,^{12,13} only reviewed published randomised studies.⁵⁻⁹ They independently reported their results. Both showed a significant improvement in all causes of mortality in patients followed intensively, compared with less follow up (combined risk ratio 0.81, 95% CI 0.70 to 0.94, $p = 0.007$).¹² No study directly compared specific tests, but in four trials, computed tomography (CT) and frequent carcinoembryonic antigen (CEA) measurements (modalities aimed at detecting extramural disease) were limited to the intensive arms. These four trials, adopting a targeted approach to detecting extraluminal recurrence, showed the greatest effect on mortality (combined risk ratio 0.73, 0.6–0.89, $p = 0.002$). Little effect was seen in the trial aimed at detecting intramural disease recurrence by intensive colonoscopy surveillance (risk ratio 0.93 0.73–1.18 $p = 0.88$).¹²

Perhaps this could be improved by a search for occult disease as suggested by Oberg.¹⁴

Although there was no difference in the rates of recurrence between intensive and control follow up (32% and 33% respectively), recurrences were detected 8.5 months earlier in the intensive group, (95% CI 7.6–9.4 months).

Rates of intraluminal recurrence and detection of metachronous cancers were low (3.2% and 1.3% respectively) in both groups, with no difference in the rates between the two.

The Cochrane review¹³ of the same five studies⁵⁻⁹ found that intensive follow up improves survival, although the studies lacked capacity to infer best follow-up methods or estimate potential harms or cost of intensifying follow up for these patients or adapt a cost-effectiveness approach. Further such trials are necessary.

A more recently published prospective randomised study¹⁵ — aimed at evaluating the diagnostic efficacy and costs of follow up tailored to risk of recurrence, compared with minimal surveillance — appears to support the above. It showed that risk-adapted follow up significantly improved the targeting of curative re-operation and overall survival of patients independently of the risk of recurrence.

17.1.3 Audit

Follow up provides information on clinical outcomes for clinicians to evaluate their practice against professional standards.¹⁶ It is essential for participation in clinical trials.¹⁷ Follow up is also required in order to produce national outcomes data to assess the impact of new guidelines and the introduction of alternative therapies.

17.1.4 Patient preference

Little data exists on the effect of follow up on quality of life, but it has been suggested that follow up may provide reassurance or conversely, cause anxiety. One study¹⁸ trying to address this issue interviewed Colorectal Cancer patients at different times related to their follow up visit, and found that the timing of the interviews had no effect on the patients' quality of life. They also found patients indicated a strong preference to be followed up. Another study¹⁹ found insignificant differences in quality of life based on intensity of follow up; patients who were followed more intensely also had greater confidence in the utility of follow up.

What are the recommendations for follow up?

Guideline — Follow up	Level of evidence	Practice recommendation	Refs
Intensive follow up for Colorectal Cancer should be considered for patients who have had potentially curable disease, although optimal investigation and pathways are yet to be firmly established.	I	Recommend	12, 13

17.2 Which patients should be followed up?

As there are no reliable indicators of an individual's risk of synchronous or metachronous lesions, nor of treatable recurrence, all patients who have undergone curative surgery and are fit for further intervention if disease is detected should be offered follow up.

Those who are unfit for further surgery or who have advanced disease require appropriate follow up directed at psychological support and symptom relief.

17.3 Who should perform the follow up?

The requirement for audit and sigmoidoscopy confirms the current practice of the operating surgeon or associated gastroenterologist performing the follow up, together with the general practitioner.

There is no evidence that intensive (hospital-based) follow up is associated with a survival advantage over general-practitioner-based care. Further studies are needed to determine whether community-based follow up can be adequately performed without decreasing patient survival, and to define the optimal balance between the general practitioner and the specialist in follow up.

17.3.1 Investigations

Colonoscopy

Colonoscopy is the most appropriate investigation for detection of synchronous, recurrent or metachronous cancers and polyps. However, it is not common to find intraluminal recurrences and metachronous cancers irrespective of the intensity of follow up, and intensive follow up with colonoscopy aiming to detect intraluminal recurrences is probably not justified.

A number of studies have clearly shown that colonoscopy should be performed at the time of diagnosis of the primary lesion in order to exclude synchronous lesions.^{20,21} Ideally, the colonoscopy that visualises the entire colon should be performed before the surgery for the primary lesion.

However, if this is not achievable for technical or other reasons (such as an obstructing left-sided cancer), then colonoscopy should be performed in the postoperative period. It is recommended that the procedure should be performed within three to six months of the surgery.²²

Studies have shown that metachronous cancers are unlikely to be detected earlier than three years following surgery for colorectal malignancy, and are most likely to be detected five years after the initial operation.^{23,24} Consequently, it is recommended that colonoscopy be performed three to five years after the initial operation.⁸

Sigmoidoscopy

Sigmoidoscopy may be useful as an adjunct to rectal digital examination for patients who have had an anterior resection in order to detect early suture-line recurrence.

Serum CEA levels

Serum CEA levels have been used to alert the presence of recurrent or metastatic cancer. In one meta-analysis of nonrandomised studies,¹⁸ some of which used historical controls, it was postulated that a rise in CEA is associated with improved survival as it allowed 'pick up' of resectable hepatic metastases. A more recent meta-analysis of randomised controlled trials looking at follow up showed a reduction in mortality with intensive follow up, including frequent measurement of CEA.¹² It is recognised as the marker of choice and its selective use is appropriate, as outlined in the American Society of Clinical Oncology protocols, for the use of tumour markers in breast and Colorectal Cancer.^{25,26} A large number of tumour markers in addition to CEA are currently undergoing evaluation. Although many have shown prognostic importance, none have been evaluated extensively enough in the context of follow up to be recommended for routine clinical use.²⁷

The use of regular CEA measurement and CT scans in follow-up protocols is supported by the current available literature. CEA testing is usually arranged 3–6 monthly in conjunction with the patient's clinical review.

CT scan of the liver

CT scan of the liver has been shown to be effective in the early detection of liver metastases, and may define a small group where hepatic resection is indicated (see Chapter 22). Meta-analysis of randomised controlled trials of follow up protocols has shown intensive follow-up protocols aimed at detection of extramural disease using computed tomography to be associated with reduced overall mortality.¹²

Ultrasonographic screening

Ultrasonographic screening for liver metastases has not been investigated in prospective randomised trials. However, the sensitivity and specificity of this investigation are no better than CT scanning, but it does not involve radiation exposure.

Chest x-ray

Chest x-ray (CXR) is a sensitive investigation for detecting lung metastases. Three prospective randomised trials⁶⁻⁸ that included colon and rectal cancer have suggested that resectable disease can be identified in 1.8–12% of patients through the use of CXR.²⁷ No study, however has compared differences in survival based on the use of CXR and at present, there is insufficient data to recommend or not recommend the routine use of CXR in follow up of Colorectal Cancer. Further studies are needed to define the role of CXR in this regard.²⁷

FOBT

Although FOBT is potentially capable of identifying both local recurrences (if an intraluminal component exists) and metachronous disease, the role of FOBT remains contentious.

PET and monoclonal antibody scans

Although both these investigations have been extensively studied in terms of their role in follow up of other abnormal tests, there is no data currently available that addresses the role of positron emission tomography or monoclonal antibodies scans as first-line investigations in the follow up of colorectal patients.²⁷

The Adelaide study⁸ showed clearly that a regular, planned clinical review, along with routine haematological and faecal tests, was effective in detecting both resectable and non-resectable recurrences and metastases.

Whatever the choice and frequency of investigations performed, symptoms are the first sign of recurrence for many patients with Colorectal Cancer. Even within carefully performed trials, 16–66% of patients were symptomatic at the time of the diagnosis of their disease recurrence.²⁷ A person developing clinical symptoms of disease requires full investigation.

17.4 Cost effectiveness of follow up

Cost-effectiveness of follow up has been less well studied for Colorectal Cancer than other diseases. However, a recently published United Kingdom study has addressed this issue by analysing the cost-effectiveness of intensive follow up compared with conventional follow up in patients with Colorectal Cancer.²⁸ The study looked at incremental cost-effectiveness, recognising differences in follow-up strategies, based on effectiveness data from a meta-analysis of five randomised trials,⁵⁻⁹ and then at the four trials designed for early detection of extramural recurrence⁶⁻⁹ — so-called targeted surveillance. For the five trials, the adjusted net (extra) cost for each patient was £2479 (€3550; \$A4288), and for each life year gained, it was £3402, substantially lower than the current threshold of NHS cost acceptability (£30,000).²⁸ Based on United Kingdom 2002 costings, the authors concluded that intensive follow up was economically justifiable (refer 22.8).

While this study justifies current costs of intensive follow up, there is need to evaluate the efficiency of specific surveillance tools that form the basis for economic evaluations in trials.²⁸

17.5 Suggested schedule

There should be an early post-discharge review, followed by a review three to six monthly for two years, and six-monthly to yearly thereafter.¹⁸ These intervals are still being discussed as a result of the Cochrane Review,¹³ further trials will be necessary to establish optimal protocols.

The review should consist of history and examination, including digital examination of the rectum, and sigmoidoscopy in patients who had an anterior resection of the rectum.

Regular CEA measurement and CT should be considered in follow-up protocols as they may provide useful clinical information.

Colonoscopy should be performed three to five years after the initial operation in order to detect any metachronous tumour, and repeated at three to five-yearly intervals thereafter.

The role of FOBT remains contentious. The optimal schedule, including duration, is not yet clear.

Future studies should focus on the cost-effectiveness and efficiency of investigations employed.²⁹

17.6 Summary

The debate regarding the rigour and intensity of follow-up investigations is complex. The benefits from follow up include:

- the provision of audit and survival data
- patient support
- the ability to remove metachronous polyps and to detect early metachronous cancers
- the detection of potentially curable recurrent disease.

Current literature, based on meta-analyses of randomised controlled trials,^{12,13} supports small but significant survival advantages for patients who are followed up intensively after curative resection of Colorectal Cancer. Although the costs and complications of follow-up investigations can be considerable, the cost may be economically justified.²⁸

Further large-scale trials are recommended to determine cost in the Australian setting, the impact of follow up on quality of life, exactly which tests should be used, and the timing of these tests, and to compare specialist follow up with general practitioner follow up.

The Followup after Colorectal Surgery (FACS) study is in progress in the United Kingdom and is designed to answer these questions.³⁰

These recommendations are for asymptomatic patients. All patients who develop symptoms should be investigated rigorously.

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