

TOPIC HIGHLIGHT

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Surveillance of patients following surgery with curative intent for colorectal cancer

Steven Gan, Katherine Wilson, Paul Hollington

Steven Gan, Department of Surgery, St George Hospital, Gray Street, Kogarah, NSW 2217, Australia

Katherine Wilson, Paul Hollington, Department of Surgery, Flinders Medical Centre, Flinders Drive, Bedford Park 5042, Adelaide, Australia

Correspondence to: Steven Gan, MBBS, FRACS, Department of Surgery, St George Hospital, Gray Street, Kogarah, NSW 2217, Australia. syogan@hotmail.com

Telephone: +61-2-91131111 Fax: +61-2-91131111

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Abstract

Surveillance after resection of colorectal cancer with curative intent is an important component of post-operative care. Clinical review, imaging, colonoscopy, and cost to the community are among significant issues to consider in planning a surveillance regime. This review aims to identify the available evidence for the use of surveillance and its individual components. The literature pertaining to follow-up of patients following potentially curative surgery for colorectal cancer was reviewed in order to formulate a summary of the wide range of clinical practice. There is evidence of improved survival of patients undergoing more intense follow-up compared with those having minimal surveillance, with an estimated overall 5-year gain of up to 10%. The efficacy of individual components of follow-up regimes remains unclear, but an overall package of 'intensive' follow-up including clinical review, liver imaging, and colonoscopy appears to be of benefit. It is cost-effective and can be specialist or community-based.

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Key words: Colorectal cancer; Colorectal carcinoma; Follow-up; Surveillance; Post-operative review; Post-operative imaging; Post-operative colonoscopy; Surveillance cost benefit

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INTRODUCTION

Colorectal cancer is a common malignancy in the
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developed world with a lifetime risk of 1 in 20^[1-3]. Around 20% of patients with colorectal cancer will have evidence of metastatic disease at presentation, and one third of patients undergoing surgical management with curative intent will subsequently relapse, resulting in significant morbidity, and the majority of these die of their disease^[1,4-13]. Relapse most often presents within 3 years, but rarely can occur up to 10 years after resection of primary disease^[14-20]. The most common sites of recurrence are the liver, the lungs, and the original site of resection^[4,7,14,16,21,22].

The primary aim of surveillance in patients with colorectal cancer treated by curative intent surgery is to detect locoregional recurrence, metastases, or metachronous primary disease at an early asymptomatic stage. Detecting recurrent disease is only useful if early treatment leads to an improved prognosis. Although the majority of relapsing patients are incurable, around one third of patients with isolated distant or locoregional recurrence are alive at 5 years after treatment, and long-term survival is possible^[21,23-33]. Rates of resection for isolated or limited disease recurrence have increased, and approximately 20% of patients with hepatic relapse are currently considered for surgery^[24,32,34]. Some additional patients may also have resectable disease after downstaging with chemotherapy^[35]. Long-term survival is also not uncommon after resection of pulmonary metastases, even after previous resection of recurrent hepatic disease^[36]. There is evidence that high risk (Stage II or III) patients with imaging-detected recurrence have better survival than those who relapse and present with symptoms, even after taking lead-time bias into account, most likely due to amenability to resection^[37]. Survivors of colorectal cancer are at increased risk of developing new primary tumours^[38-40], and surveillance results in metachronous primary cancers being diagnosed at earlier stages than index tumours, with high rates of potentially curative resection^[41].

Most relapse detected by surveillance is not curable. Length of survival of patients who develop widespread or inoperable relapse has steadily improved with current palliative chemotherapy regimes achieving median survival approaching 2 years, compared to 5 mo for best supportive care^[34,42-51]. There is also evidence that these patients have a stable or improved quality of life, despite side effects during chemotherapy^[52,53]. Palliative chemotherapy has been shown to prolong survival and the time to disease progression in asymptomatic patients, as well as duration of the asymptomatic period^[54]. Older patients with good performance status also tolerate palliative chemotherapy, with similar survival benefits to those aged less than

70^[55,56]. Radiotherapy, with or without chemotherapy, can be useful for symptom control of inoperable rectal tumour recurrence, although 5-year survival rates are very low^[24,57,58]. Chemoradiotherapy may also increase resectability of locally advanced pelvic recurrence in patients who have not previously been irradiated^[59].

Additional potential advantages of follow-up include the provision of psychological support, identification and treatment of complications, as well as quality control, teaching, research, or audit. From a patient's perspective, most view follow-up in a positive light even if it would not lead to earlier detection of recurrence^[60].

Follow-up practices and guidelines vary widely after potentially curative surgery^[61]. A number of randomized trials have failed to demonstrate survival advantage of intensive surveillance, but recent meta-analyses of the data have suggested a survival advantage of more intense follow-up^[62-64]. This review examines evidence for surveillance strategies and guidelines published in the current literature.

META-ANALYSES

Some authors have questioned the need for intensive follow-up, or even any surveillance, after surgery for colorectal cancer^[65-67]. Major debate occurs amongst those advocating surveillance, in relation to how intensive it should be, stemming from conflicting results of numerous studies, many of which are non-randomized^[62,68]. Initial meta-analyses suggested a survival benefit for patients kept under surveillance, but these included non-randomized publications, or a mix of cohort studies with randomized studies^[12,69].

A number of randomized trials comparing more with less intensive follow-up have failed to demonstrate a survival advantage, although they lacked statistical power to detect a difference^[70-72]. Another randomized study did reveal earlier detection of recurrent disease in the group kept under more intense surveillance, with a higher proportion undergoing resection with curative intent compared to relapse in those with less intense surveillance, but this did not translate into improved survival^[73]. Subsequent trials have shown improved survival at 5 years, most likely due to increased numbers of potentially curative re-resections in those followed more intensely^[15,74].

Three meta-analyses of reported randomized trials have been performed in an attempt to overcome the deficiency in patient numbers, and have demonstrated improved survival of patients undergoing more intense follow-up compared with those having minimal or no follow-up, with an estimated overall 5-year survival gain of 7%-10%^[62-64]. This improvement in overall survival has been attributed to earlier detection of recurrent disease in those followed more intensively, as well as a higher rate of detection of isolated locoregional recurrence in the same patients^[64]. The overall incidence of disease recurrence was similar for both groups. Re-operation rates were higher in the more intensive arm, but it has been argued that the number potentially curable salvage operations for recurrence remains low and does not account for all of the survival gain seen in these trials^[75]. In addition, cure attributable to

detection of resectable liver metastases is more likely than for resectable locally recurrent disease (8.5% *vs* 2.4%)^[7]. Other mechanisms contributing to a survival advantage of surveillance in these patients may include management of co-morbidity, promotion of beneficial dietary and lifestyle factors, and increased psychosocial supports^[75].

Although pooled data is suggestive of a survival advantage for intense surveillance after potentially curative colorectal cancer resection, marked heterogeneity exists between the intervention and control groups of the randomized studies included in the meta-analyses. Surveillance protocols in the intensive follow-up arm of 3 of the studies were similar to the control follow-up arm of another 2 studies, with a sixth study adopting 2 risk-stratified follow-up programs within the 'intensive' arm^[15,70-74]. Contributions of surveillance intervals, duration, or tests utilized towards a survival advantage, are not able to be extrapolated. Sub-group analysis suggests, however, that utilization of liver imaging may improve survival^[62]. It is difficult to draw conclusions about the use of carcinoembryonic antigen (CEA) testing from the pooled data, as it was used in conjunction with liver imaging in all but one study, and other studies also utilized CEA testing in the control arm, albeit at reduced frequency in one. Rates of detection of anastomotic recurrence and metachronous primary disease were equal in both surveillance regimes^[64]. Two additional randomized studies have been designed with adequate power to detect a difference between surveillance strategies^[63,76].

CLINICAL REVIEW

There is significant variation in clinical review patterns of patients post-operatively, in terms of frequency, duration, investigations utilized, as well as the specific clinician involved. Small sample populations of follow-up trials have resulted in a lack of definitive recommendations, and the value of routine consultation and physical examination has not been addressed. Rigid proctosigmoidoscopy following rectal cancer excision has been advocated by some organisational guidelines, but there is no evidence to support its use. Two randomized studies have included proctoscopy in follow-up, but very few locoregional recurrences were detected using this method^[71,72]. Some patients undergoing surveillance develop symptoms and re-present during the interval between clinical reviews, while others developing symptoms delay presentation until the next visit is scheduled, making interpretation of schedules difficult^[12].

RADIOLOGICAL IMAGING

Chest x-ray

Studies evaluating plain chest x-ray as a routine imaging modality for detecting recurrent colon cancer show a very modest, less than 5%, identification of asymptomatic disease^[77]. This may be slightly better if used in the context of rectal cancer which has a higher risk of lung metastases, with trials showing between a 2%-12% utility^[70-72]. There is, however, no evidence to show a survival benefit from the

Table 1 Recommendations of the Australian Cancer Network (ACN)^[79], Association of Coloproctology of Great Britain & Ireland (ACPGBI)^[79] and the American Society of Colon and Rectal Surgeons (ASCRS)^[80] for post-operative follow-up

	ACN	ACPGBI	ASCRS
Clinical review	3-6 monthly for 2 yr, then 6-12 monthly thereafter No end time	No recommendation for frequency No end time	3 times per year Minimum of 2 years
Laboratory tests	CEA 3-6 monthly No recommendation for LFT or FBC	No recommendation for CEA, LFT, or FBC	CEA recommended LFT & FBC not recommended
Imaging	CT liver (no recommendation for timing)	Liver imaging within 2 yr of resection if asymptomatic	Not recommended
Colonoscopy	Completion colonoscopy within 3-6 mo if not done pre-operatively 3-5 yearly No end time	Completion colonoscopy within 6 mo if not done pre-operatively 3-5 yearly No end time	Completion colonoscopy within 6 mo if not done pre-operatively 3 yearly No end time
Faecal occult blood tests	No recommendation	No recommendation	No recommendation

use of routine chest x-ray in follow-up regimes. Despite this, some guidelines consider it appropriate to include chest x-ray as part of any follow-up strategy^[62,78].

Liver imaging

The liver is the most common site of distant recurrence and yet the data available is inconclusive as to the timing and frequency of imaging. The evidence at hand allows interpretation to both support and refute the appropriateness of routine liver imaging and this is shown in the follow-up guidelines of the ACPGBI^[79] which recommends routine imaging in contrast to the ASCRS^[80] which recommends against this policy, with both groups citing the same reference^[70] (Table 1). A survival benefit has been demonstrated by the three meta-analyses however, where some form of liver imaging was confined to the 'high intensity' follow-up arms by most of the included trials^[62-64]. It is difficult to dissect out the influence of imaging from the other components of the individual protocols, such as CEA testing.

Others

Newer imaging modalities emerging include the use of monoclonal antibodies and positron emission tomography, but as yet there is no evidence that either of these provide any advantage over existing surveillance options^[80-82].

LABORATORY TESTS

CEA

CEA is not a reliable population screening tool for the initial detection of colorectal cancer. There have been numerous studies examining its use in surveillance of patients after resection for colorectal cancer, as it is well recognised that CEA titres are frequently elevated at the time of diagnosis of recurrent disease^[37,77,83-85]. Although detection of recurrent disease by this method is more common in patients with pre-operative elevation of CEA^[83], Zeng *et al*^[84] demonstrated subsequent elevation in 44% of high risk patients who had a normal CEA result pre-operatively. False positive rates of CEA elevation of 7%-16% have been reported, and false negative rates of around 40%^[83,86]. A rise in CEA titre is seen more commonly in metastases to the liver (up to 80%

of patients) than in locoregional or non-hepatic distant recurrence^[29,83,86].

Several studies have shown that CEA rise is often the first sign of recurrence^[71,83,85,86]. A positive CEA result has been shown to occur from 1.5-6 mo before recurrence is detected by other measures^[83,85]. This lead time between CEA elevation and diagnosis has led to the hypothesis that earlier detection may allow for re-resection with curative intent, and therefore, increased long-term survival. A number of individual studies have, however, shown that there is no significant survival advantage in patients whose surveillance involves CEA monitoring^[29,71,83,87]. Meta-analysis of randomized trials has demonstrated a reduction in mortality with intensive follow-up comprising combined liver imaging and regular CEA monitoring, although there were considerable differences in the CEA testing protocols included^[64]. CEA measurement has also not been standardized, resulting in publication of figures ranging from 40% to 89% of patients in whom CEA elevation was the first indicator of recurrent disease^[88,89].

There have been few studies to consider the cost-effectiveness of CEA surveillance. Kievit *et al*^[87] felt that the cost of CEA monitoring was not supported by an increase in quality-adjusted life expectancy, and that given the high cost of following up all patients with positive test results (true and false positives), CEA was not cost-effective enough to be used routinely in follow-up.

Others

A large meta-analysis by Kievit has shown that liver function tests (LFT) are not useful in the detection of liver metastases, as false positive results occur 15-70 times more frequently than true-positive results^[7]. In patients with recurrent cancer, at the time of diagnosis CEA was elevated more often than any individual LFT or a panel of combined LFTs. When CEA and LFTs are combined in surveillance, in comparison to CEA alone, the addition of LFTs did not result in a significant difference in the detection of recurrent cancer^[90].

There is no evidence of the usefulness of full blood counts (FBC), other tumour markers such as Ca19.9, or liver function tests in surveillance, and as such, none of these tests are currently recommended in the published guidelines^[91,92].

COLONOSCOPY

It is universally agreed that complete visualisation of the colon is recommended before curative resection to identify synchronous lesions. There may be situations which preclude this such as an obstructing lesion, or for technical reasons a complete intubation to the caecum/terminal ileum is not possible, then double-contrast enema or computed tomography pre-operatively, with completion colonoscopy within 3-6 mo after resection is acceptable^[79,80,93].

Patients of all stages having curative resection are considered appropriate for colonoscopic surveillance, unless other mitigating circumstances such as advanced age or co-morbidities apply^[41]. The aim is to identify either recurrent disease or metachronous primary lesions. There is, however, no evidence of a survival benefit in the detection of intraluminal recurrent disease. The randomized controlled trial by Shoemaker *et al*^[70] and the Cochrane meta-analyses by Jeffrey *et al*^[63] did not show any benefit of more intensive review which included colonoscopy. The hypothesis is that the infrequency with which local recurrence occurs in colon cancer, at between 2% to 4%, and the fact that this usually occurs in the presence of widespread unresectable recurrent disease, together lead to no perceivable survival benefit^[64]. There is some suggestion that the higher recurrence rates of rectal cancer may confer greater benefit^[41], but with the now prevalent use of the technique of total mesorectal excision, and neo-adjuvant chemoradiotherapy, this may change.

The first post-operative examination is recommended after 1 year, and this is based on historical data, which shows that there is a high incidence of metachronous primary cancers in the 2 years following curative resection^[94]. Subsequent studies are recommended at three to five yearly intervals, unless intervening events occur, such as the identification of polyps. In formulating their guidelines, the American Cancer Society^[41] performed a meta-analysis and reported a rate of 157 colonoscopies per metachronous primary cancer detected, with an incidence of 0.7% within the first two years after curative resection. The tumours were identified at an early stage, with a large proportion (65%) being Dukes' A or B, 56% asymptomatic, and 87% subsequently operated on for cure.

COST OF SURVEILLANCE

There are no randomised controlled trials of cost analysis. There are, however, a large number of studies evaluating the cost and cost-effectiveness of a variety of surveillance regimes. It is clear that post-op follow-up entails a significant cost, calculated in an Italian study by Audisio *et al*^[95] at \$136 779 (\$US) per patient cured, whilst Ketteniss *et al*^[96] measured the cost per life-year gained at 28 258 DM. Despite this, the general consensus of these and other studies is that follow-up is justified. Worthington *et al*^[97] cites the cost analysis of the Norwegian Gastrointestinal Cancer Group by Norum *et al*^[98], which calculated a value per quality adjusted life year (QALY) equivalent to

AUS\$28 690, and makes the point that this is less expensive than the cost of lung transplantation AUS\$275 000/QALY, and comparable to aortic aneurysm repair AUS\$27 192/QALY, carotid endarterectomy AUS\$12 500, and lumbar discectomy AUS\$52 967/QALY.

WHO SHOULD UNDERTAKE FOLLOW-UP?

Debate exists in relation to who should undertake follow-up^[61]. Options include specialist surgeons, oncologists, general practitioners, and colorectal nurse practitioners. Traditionally most patients having had potentially curative resection are kept under surveillance by their surgeon, often long term, and with considerable variability in specific tests and intervals utilized^[99-104]. It has been argued that patient support is the most useful aspect of follow-up, and that this is best offered by primary care physicians or specialist nurses, rather than surgeons^[7]. There is evidence that patients with follow-up led by either surgeons or general practitioners experience similar outcomes, in terms of rates of recurrence, time to recurrence detection, and survival^[105]. Patient satisfaction is also high in patients kept under surveillance by general practitioners or surgeons, and no difference in quality of life is seen between the two^[106]. Mental wellbeing has, however, been reported to be high in survivors of colorectal cancer, and there is evidence that any form of surveillance has little impact in terms of psychological benefit^[107-109].

CONCLUSION

There is evidence of a survival advantage of surveillance following surgery with curative intent for colorectal cancer. The efficacy of individual components of follow-up regimes remains unclear, due to the size and heterogeneity of published studies, resulting in a wide variation in current practice, but an overall package of 'intensive' follow-up appears to be of benefit. Community-based follow-up has been shown to be as effective as that undertaken by specialists. Intensive surveillance is felt to be cost-effective, with higher up front costs being acceptable^[110].

Mechanisms of improved survival are not clear, and appear to be multifactorial. Earlier detection of locoregional disease recurrence may only make a minor contribution, and the impact of potentially curative resection of liver metastases is likely to be more significant, although health promotion and management of co-morbidity may also contribute. A role for psychological benefit is less clear, and it appears that patients with colorectal cancer have a high baseline of mental wellbeing.

There also appears to be an advantage in the detection of non-curable recurrence. Asymptomatic patients, including the elderly, benefit from early palliative chemotherapy, and pelvic recurrence may be downstaged to resectable disease using radiotherapy.

The duration and schedule of surveillance, as well as which tests are utilized, cannot be determined from the current literature. Guidelines produced by major health organizations vary as illustrated in Table 1. There is evidence; however, that colonoscopy is a beneficial investigation. Although metachronous primary disease is

not detected more frequently with intense surveillance, it is relatively common and detected at an early stage by colonoscopy, resulting in high rates of curative resection^[39,41]. Metachronous primary disease is often detected within 2 years of the preceding tumour, and may be due to alternative pathways of colorectal cancer development which demonstrate accelerated carcinogenesis in a proportion of this higher risk population^[111]. There is also evidence from the meta-analyses that liver imaging is one of the important surveillance tools^[62-64], particularly as resectable liver metastases are likely to have major influence on survival in relapsing disease. Current adjuvant chemotherapy regimes can result in reduced short-term recurrence rates^[112]. It may be that they are prolonging the time to presentation of disease recurrence beyond 4 or 5 years however, and follow-up durations may need to be longer for Stage III disease.

Longer or more intensive follow-up schedules may themselves result in reduced patient compliance, another important aspect of care has not been well documented, and the threshold of adherence that is required for it to be beneficial has not been established.

Large randomized clinical trials will be needed to determine optimal evidence-based surveillance strategies. Two are in progress, namely the UK-based FACS Trial^[113] cited by Jeffery *et al*^[63] and the GILDA Trial^[76]. Until concrete evidence is available, a surveillance regime based on risk-stratified regular clinical review, with some form of liver imaging, as well as colonoscopy, is recommended.

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