ABC of colorectal cancer
Effectiveness of follow up

Colin McArdle

Population based studies show that for rectal cancer the incidence of local recurrence after apparently curative resection is about 20%. Local recurrence after surgery for colon cancer is less common. The liver is the commonest site of distant spread, followed by the lungs; brain and bone metastases are relatively rare. Most recurrences are within 24 months of surgery.

Symptomatic recurrence of colorectal cancer is seldom amenable to curative surgery

Aim of follow up

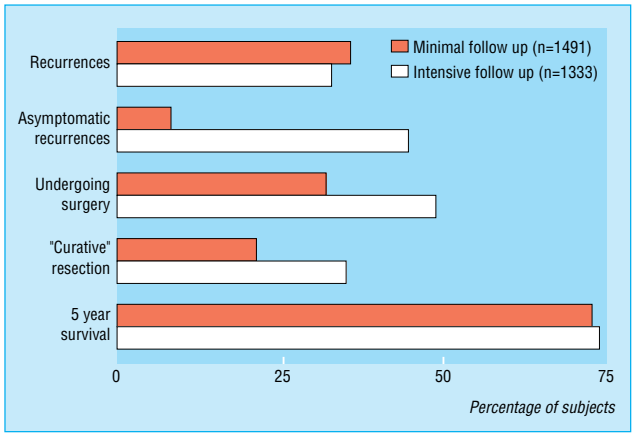
Traditionally surgeons have reviewed their patients at regular intervals after apparently curative resection. Recent surveys, however, have highlighted the lack of consensus among surgeons about the optimal modality and intensity of follow up; surveillance strategies range from a single postoperative visit to lifelong surveillance. Enthusiasts believe that intensive follow up and early intervention will lead to a reduction in the number of deaths from colorectal cancer; others point to the fact that the value of follow up is unproved. With so many tests available and no consensus on their value, it is not surprising that individual clinicians have tended to devise their own protocols.

Aims of follow up

- Early detection and treatment of recurrent disease
- Detection of a second, or metachronous, tumour in the large bowel
- Provision of psychological support and advice
- Facilitation of audit

Results of meta-analysis

A meta-analysis in the mid-1990s did little to clarify the situation. The researchers evaluated the results of seven non-randomised studies (covering over 3000 subjects in total) that compared intensive follow up with minimal or no follow up. Clearly several potential biases could and did exist. In the intensive group, investigations included clinical examination, faecal occult blood testing, liver function tests, measurement of the carcinoembryonic antigen, sigmoidoscopy, and either colonoscopy or barium enema examination. Liver ultrasonography was performed in only three studies and even then infrequently. In the intensive group more asymptomatic recurrences were detected, more patients underwent "second look" laparotomy, and more patients had a second potentially curative resection; more metachronous tumours were also detected and resected. However, although there were fewer deaths in the group receiving intensive follow up, this difference did not reach significance.



Results of meta-analysis of seven non-randomised trials that compared intensive with minimal or no follow up (Bruinvels et al, 1994)

Results of randomised clinical trials

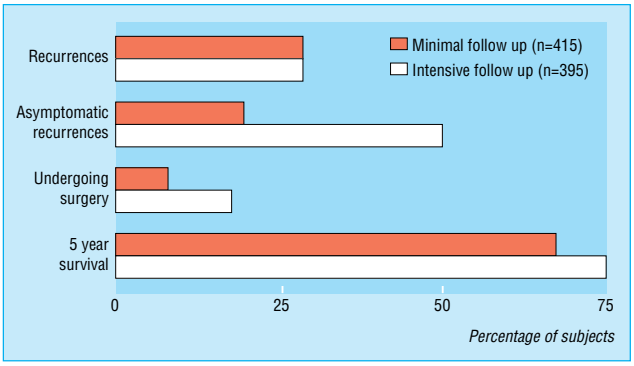
Since the meta-analysis, four randomised trials of intensive follow up have been reported. Ohlsson and his colleagues randomised 107 patients to no follow up or to intensive follow up, similar to that described above. No liver imaging was performed routinely. No differences were found in recurrence rates or in overall or cancer specific mortality.

Mákelá and his associates compared conventional with intensive follow up in 106 patients. In the intensive group flexible sigmoidoscopy was performed every three months, ultrasonography every six months, and colonoscopy and abdominal computed tomography at yearly intervals. Recurrences were detected at an earlier stage (median 10 months *v* 15 months) in the intensive group. Despite this, no difference in survival was found between the two groups.

The results of the four randomised controlled trials of intensive follow up should be interpreted with caution. Despite consistently fewer deaths in the intensive group in each study, the numbers in each were small, and no study had sufficient power to detect a survival advantage

Kjeldsen and his colleagues randomised almost 600 patients to either six monthly follow up or to follow up visits at five and 10 years only. Investigations included chest *x* ray and colonoscopy; no routine liver imaging was performed. Recurrence rates were similar (26%) in both groups, but the recurrences in the intensive group were detected on average nine months earlier, often at an asymptomatic stage. More patients with local recurrence underwent repeat surgery with curative intent. No difference existed, however, in overall survival (68% *v* 70%) or cancer related survival.

More recently, Schoemaker and his colleagues evaluated the addition of annual chest radiography, colonoscopy, and computed tomography of the liver to a standard follow up based on clinical examination, faecal occult blood testing, liver function tests, and measurement of the carcinoembryonic antigen, with further investigations as clinically indicated. At five years, fewer patients in the intensive group had died, but the result was not significant. At the cost of 505 additional investigations, annual colonoscopy failed to detect any asymptomatic local recurrences; only one asymptomatic metachronous colon tumour was detected. Six hundred and eight additional liver computed tomograms detected only one asymptomatic patient with liver metastases who might have benefited from liver resection.



Combined results of three randomised trials of intensive follow up

Results of intensive follow up*

Follow up	Colonoscopy	Chest *x* ray	Liver CT
Standard (n = 158)	72	17	66
Intensive (n = 167)	577	650	674
No of extra investigations	505	633	608
No of asymptomatic recurrences resulting from extra investigations	0	0	10
No of cures resulting from extra investigations	0	1	1

CT = computed tomography.
*Data from Schoemaker et al, 1998 (see Further reading box).

Carcinoembryonic antigen

Carcinoembryonic antigen concentrations have also been used to predict recurrence. About three quarters of patients with recurrent colorectal cancer have a raised carcinoembryonic antigen concentration before developing symptoms.

An alternative approach therefore would be to monitor this concentration regularly during follow up and, in those patients showing a rising concentration, undertake second look laparotomy. However, although early non-randomised studies suggested that surgery that was prompted by this method resulted in more potentially curative repeat operations for recurrence, more recent studies have failed to show a survival advantage.

Moertel analysed outcome in patients included in trials of adjuvant therapy, according to whether the patient underwent carcinoembryonic antigen testing. Of 1017 patients whose concentrations were monitored, 417 (41%) developed recurrence. A comparison of those patients whose follow up included measurements of carcinoembryonic antigen with those whose follow up did not, failed to show any difference in disease-free survival. Among 29 laparotomies performed solely on the basis of a raised concentration of carcinoembryonic antigen, only one patient remained alive and disease-free after one year.

In the randomised study by Northover and his colleagues, 1447 patients undergoing potentially curative surgery were randomised to an intervention group or a control group. Carcinoembryonic antigen was measured in all patients at frequent intervals. In the intervention group, a rising antigen concentration prompted further investigation, including second look laparotomy, if appropriate.

Preliminary analysis showed no difference in survival between the two groups. The failure to show a survival advantage in the intervention group may be due to the fact that a rising antigen concentration is a relatively poor predictor of local recurrence; furthermore, even in patients with liver metastases a rising concentration is a relatively late phenomenon.

Carcinoembryonic antigen concentrations have been used to predict recurrence of colorectal cancer, but recent evidence does not support this approach

Results of "second look" surgery according to measurement of carcinoembryonic antigen (CEA)*

CEA concentration	No of patients	No (%) of "curative" resections	% of patients free of recurrence at 1 year
Raised	345	47 (14)	2.9
Normal	672	38 (6)	1.9
Not measured	200	23 (12)	2.0

*Data from Moertel et al, 1993.

Cost effectiveness

Concern is also increasing about the cost of follow up. A review of the published literature suggests a 28-fold difference in costs between the least intensive and most intensive, published, five year follow up protocols.

Costs of follow up, suggested by recent study from Italy

- £2530 per patient over five years
- £9050 per recurrence detected
- £39 890 for each case undergoing further surgery
- £91 190 for each "cured" patient

Wrong target?

Clearly, follow up as currently practised is ineffective. Why, therefore, should we continue to follow patients up after apparently curative resection for colorectal cancer? There are several reasons. Firstly, we should do so to provide psychological support and advice; many patients welcome the reassurance that regular check up provides. Secondly, routine follow up facilitates audit of outcome measures after surgery, ensures quality control and facilitates evaluation of trials of new treatments and strategies.

There may, however, be a more fundamental reason that current follow up practices are ineffective. On theoretical grounds, attempts to identify potentially resectable local recurrences or metachronous tumours were never likely to have a significant impact on survival. Isolated resectable anastomotic recurrences are uncommon. Most local recurrences arise from residual disease left at the time of surgery and therefore, by definition, are unlikely to be amenable to further curative surgery. Metachronous tumours, although potentially amenable to surgery, are relatively uncommon.

Contrast enhanced computed tomogram (arterial phase) showing solitary liver metastasis

Wrong intervention?

In contrast, liver metastases are much more common. Furthermore, these metastases are confined to the liver in about a quarter of patients.

Perhaps, therefore, the emphasis should shift towards the early detection of liver metastases. It is worth noting that in contemporary studies of liver resection, mortality is less than 5% and about 35% of patients survive five years. These figures are better than the results obtained after primary surgery for many types of gastrointestinal cancer. Furthermore recent studies have shown that patients with disseminated disease who receive systemic chemotherapy at an asymptomatic stage have higher response rates, better quality of life, and improved survival compared with those in whom the administration of chemotherapy is delayed until symptoms appear. Therefore if liver metastases were diagnosed in more patients at a point at which they were amenable to resection or chemotherapy, more long term survivors might be anticipated.

To date only two randomised studies have included liver imaging. In both these studies the numbers were small and liver imaging was infrequent. In neither study was a survival advantage noted. However, intensive liver imaging for the first three years after surgery may be more effective: at the Royal Infirmary in Glasgow more than 80% of patients who developed liver metastases as the initial site of recurrence were detected at an asymptomatic stage.

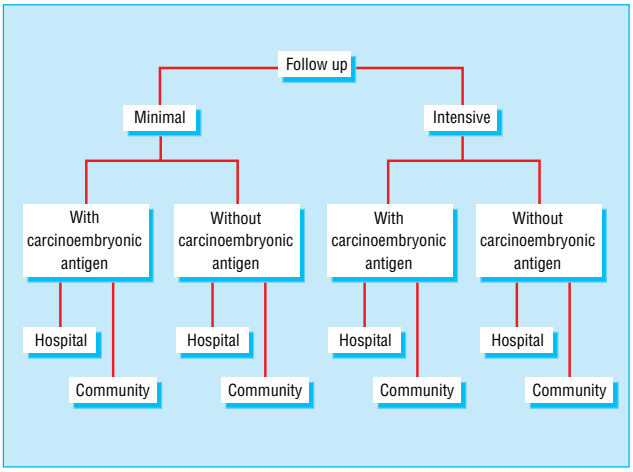
Comparison of results of trial of early versus delayed chemotherapy in patients with advanced colorectal cancer

Treatment group	No of patients	Median symptom-free survival (months)	Median survival (months)	Survival at 1 year (%)
Early	92	10	14	55
Delayed	91	2	9	38

Early chemotherapy was given when patients were asymptomatic; delayed chemotherapy was given when patients were symptomatic.
Data from the Nordic Gastrointestinal Tumor Group, 1992.

Hospital or community coordination of follow up?

Most patients with colorectal cancer are followed up in hospital. Yet overwhelming evidence from previous studies shows that few curable recurrences are detected at routine follow up based on history, physical examination, and routine blood tests. Few patients are followed up by their general practitioners, although



Suggested study outline to test three follow up strategies: intensive *v* minimalist; role of carcinoembryonic antigen; and general practitioner (community) coordinated *v* hospital coordinated

good evidence exists that, in other tumours at least, such follow up is as effective (or ineffective) as hospital follow up. Furthermore, provided that general practitioners have access to a "fast track" referral system for patients in whom they suspected recurrent disease, follow up coordinated by general practitioners might offer several advantages. It might be more acceptable to and convenient for patients and might reduce costs.

Perhaps it is time to reassess follow up. Formal studies to assess the value of these strategies might include:

- A comparison of the value of intensive versus minimalist follow up
- A re-evaluation of the role of carcinoembryonic antigen
- A comparison of the effectiveness of follow up that is coordinated by general practitioners rather than by hospitals.

Conclusion

Current methods of follow up, aimed at the early detection and treatment of local recurrence or metachronous tumours, have yet to be shown to be cost effective.

As liver metastases are common, a protocol that includes regular liver imaging to detect potentially resectable lesions may prove more effective. Further studies are needed to assess the value of this approach in patients undergoing apparently curative resection for colorectal cancer.

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Further reading

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The ABC of colorectal cancer is edited by D J Kerr, professor at the Institute for Cancer Studies, University of Birmingham; Annie Young, research fellow at the School of Health Sciences, University of Birmingham; and F D Richard Hobbs, professor in the department of primary care and general practice, University of Birmingham. The series will be published as a book by the end of 2000.

A memorable patient

A plastic plug resurfaces

In 1984 an 8 year old boy was rushed into our general practice from school with a sudden onset of a violent cough. His teacher had noticed him chewing his ballpoint pen immediately before the coughing spasm. He denied that he had inhaled a piece of the pen. His distress was so marked that she called an ambulance. I initially treated him with nebulised salbutamol which partly relieved his cough. He had no history of asthma and I was perplexed at what had caused this coughing spasm.When he had calmed down considerably I asked if he had inhaled a part of his pen. He said that he had had the plastic plug from the end of the barrel of a biro in his mouth when it suddenly disappeared. I then arranged transfer to a tertiary paediatric hospital for definitive management of a presumed aspirated foreign body.

Aspiration of a foreign body into the lungs is a relatively common occurrence in childhood. The age of peak incidence is less than 3 years and the diagnosis is made more difficult as the "actual event of aspiration is frequently not witnessed."[1] My patient was older at 8 years but similarly had an indefinite history.

His symptoms had resolved in the several hours it took to reach the capital city referral centre. He was investigated with inspiratory and expiratory chest *x* ray examinations, bronchoscopy, and a lung scan. In 1984 these were the only investigations available. No evidence of an aspirated foreign body was found and he remained symptom free. He was discharged home with a diagnosis of no foreign body in his lungs.

Difficulties in diagnosis still persist despite improvements in imaging techniques and flow charts to guide diagnosis.[2] Serious consequences occur with either acute respiratory distress or complications as a consequence of delayed diagnosis. Extraction becomes more difficult with delays in diagnosis. In one series of 94 cases, 30% of admissions for definite treatment occurred three days or more after aspiration and one death resulted.[3]

I next saw him one month later with a few days of mild cough. Examination showed no chest signs. Four months later he represented with intermittent cough. Repeat inspiratory and expiratory chest *x* ray examinations were again normal. At this time I prescribed oral theophylline.

Twenty one months later he presented to one of my partners with upper respiratory tract symptoms. He was noted to be wheezy. A viral infection was diagnosed and a salbutamol metered dose inhaler was prescribed.

More than three years after the initial event he fell into a lake while canoeing. He aspirated some water and another coughing spasm started. The following day he expectorated the plastic plug. Three years and three months had passed since the initial presumed aspiration event and he was now aged 12. He and his mother came to my surgery the next day to show me the plastic plug (approximately 5 mm × 5 mm).

General practice provides an opportunity to follow patients for prolonged periods of time. Despite minor symptoms this child remained in good health with an unrecognised pulmonary foreign body for over three years. Subsequently another event precipitated a coughing spasm. I presumed the growth in diameter of his bronchi enabled this violent coughing spasm to dislodge the plastic plug.

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3 Steen KH, Zimmermann T. Tracheobronchial aspiration of foreign bodies in children: a study of 94 cases. *Laryngoscope* 1990;100:525-30.