Colorectal cancer surveillance post-surgery

Andy Huang, Kirsten S Hindle, George Tsavellas

Current surveillance methods for detecting recurrence after apparently curative colorectal cancer resection are insensitive and have not been shown to significantly improve survival. New surveillance methods based on molecular, flow cytometric and immunohistochemical detection of small numbers of tumour cells may prove more sensitive in detecting early recurrent cancer and may improve outcome.

In the UK, the annual incidence of colorectal cancer (CRC) is 30 000 cases, accounting for approximately 20 000 deaths per year. Potentially curative resection is possible in only 70–80% of cases at presentation, but despite adjuvant and neoadjuvant treatments, almost half of these patients will develop a recurrence, most commonly in the liver.

The aims of surveillance after curative CRC resection are the early detection, identification and treatment of metachronous tumours or of metastases in order to prolong survival in those who have curable disease and to provide support in those who have not (Allen-Mersh et al, 1994). However, there is little evidence to suggest that any particular method for monitoring patients after curative CRC resection is most effective in achieving these aims (Expert Advisory Group, 1996). Furthermore, intensive postoperative surveillance may only confer a small survival benefit because of the late detection of recurrences by insensitive methods (Tornqvist et al, 1982). Any further improvement in surveillance is likely to involve the development of sensitive, specific tests for earlier detection of recurrent disease in CRC to enable treatment before the cancer is incurable.

PRESENT METHODS OF CRC FOLLOW-UP

Clinical examination and liver enzyme tests do not detect most recurrences or metastases until disease is advanced and therefore unlikely to be curable (Bohm et al, 1993). A persistently elevated serum level of carcinoembryonic antigen (CEA) after CRC resection is associated with residual disease but only 50% of patients have raised levels preoperatively. Nevertheless, a postoperative increase in the serum level of CEA after apparently curative resection of CRC is often associated with recurrent disease. However, there is no evidence that the 'lead time' provided by CEA monitoring confers any survival benefit (Moertel et al, 1993).

Although postoperative colonoscopy may detect asymptomatic metachronous tumours, this surveillance method can benefit at most fewer than 5% of patients and cannot detect extraluminal disease, which accounts for over 90% of recurrences. Furthermore, there is no evidence that colonoscopic follow-up has a significant impact on survival following surgery for CRC.

Hepatic ultrasonography or computed tomography are often used for postoperative surveillance in conjunction with the above methods. The sensitivity of both these modalities is greater than 90% for hepatic metastases over 1 cm diameter, but resection of the latter is likely to be curative in less than 10% of such patients (Scheele and Altendorf-Hofmann, 1999). Despite this, the main reason at present for follow-up after CRC resection is to detect those patients who have a potentially curative hepatic recurrence.

FUTURE METHODS OF CRC FOLLOW-UP

Over the last decade, new technologies have emerged that allow the detection of small numbers of tumour cells in the blood, bone marrow or stools of patients with malignant disease. The polymerase chain reaction (PCR) is a molecular biological technique that amplifies specific DNA sequences present in cells in these samples. DNA is separated into single strands by heat and oligonucleotides of a known sequence (primers) are used to flank the specific DNA sequence under investigation. Excess single nucleotides and a polymerase enzyme then create a double-stranded copy of the target DNA. This process is then repeated up to 60 times, resulting in the exponential accumulation of the specific DNA fragment. The products of these reactions are

Mr Andy Huang and **Mr George Tsavellas** are Surgical Research Fellows in the Department of Academic Surgery, Chelsea & Westminster Hospital, London SW10 9NH, and **Miss Kirsten S Hindle** is Specialist Registrar in General Surgery in the Department of Surgery, John Radcliffe Hospital, Oxford

Correspondence to: Mr A Huang

separated by gel electrophoresis, visualized under ultraviolet light and compared with a positive control to determine whether DNA amplification has occurred. PCR permits the recognition of tumour-specific DNA mutations present in malignant cells and allows the detection of a single tumour cell among 10 million normal cells. Mutations of the K-ras oncogene or p53 tumour suppressor gene are present in 38% (Andreyev et al, 1998) and 70% (Nigro et al, 1989) of colorectal neoplasms respectively. As colonocytes are continuously exfoliated into the faecal stream, minute amounts of DNA present in the stools of CRC patients may provide a useful source of highly specific and well-characterized markers for the early detection of metachronous lesions and anastomotic recurrences. At present, this molecular approach is being assessed as a screening tool in preliminary trials (Ahlquist, 2000).

The use of molecular assays is not restricted to the examination of stools. Several clinical studies have used PCR-based methods to detect circulating CEA or cytokeratin messenger RNA as markers of tumour cells in the blood (Hardingham et al, 2000; Taniguchi et al, 2000). Following tumour resection, cancer cells either disappear or may persist in the circulation in the presence of residual disease (Castells et al, 1998). Similarly, reappearance of circulating cancer cells after a period of absence might herald a recurrence when tumour burden might still be low enough to allow effective treatment. However, at present the clinical significance of such findings is unclear and the results of clinical trials are awaited.

The results from studies using other detection modalities lend support to this approach. The preoperative presence of bone marrow micrometastases, as detected by immunocytochemistry, has been shown to be an independent predictor of disease-free survival in CRC (Lindemann et al, 1992). Flow cytometric studies have suggested that tumour cells persisting in the bone marrow 6 months after primary CRC resection significantly predicts development of clinically detectable metastases (O'Sullivan et al, 1997). Such techniques could be applied to the detection of new micrometastatic disease arising from early tumour recurrence. Immunocytochemistry combined with computerized image analysis offers the prospect of highly accurate postoperative immunocytochemical bone marrow surveillance.

CONCLUSION

It is clear that present methods for postoperative surveillance after CRC surgery are inadequate. The ability to accurately detect small numbers of tumour cells in the blood, bone marrow or stools of patients who have undergone apparently curative CRC resection may enable clinicians to target investigations and treat those patients most at risk of recurrence. Such an approach could herald a new era of highly sensitive and specific postoperative surveillance. However, before this is feasible, long-term randomized studies will be required to determine whether earlier detection and the treatment of recurrent micrometastatic disease does indeed confer survival benefits. **HM**

Conflict of interest: none.

Ahlquist DA (2000) Molecular stool screening for colorectal cancer. *Br Med J* **321:** 254–5

Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J (1994) Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. *Lancet* **344:** 1255–60

Andreyev HJ, Norman AR, Cunningham D, Oates JR, Clarke PA (1998) Kirsten ras mutations in patients with colorectal cancer: the multicenter 'RASCAL' study. *J Natl Cancer Inst* **90:** 675–84

Bohm B, Schwenk W, Hucke HP, Stock W (1993) Does methodic long-term follow-up affect survival after curative resection of colorectal carcinoma? *Dis Colon Rectum* **36:** 280–6

Castells A, Boix L, Bessa X, Gargallo L, Pique JM (1998) Detection of colonic cells in peripheral blood of colorectal cancer patients by means of reverse transcriptase and polymerase chain reaction. *Br J Cancer* **78:** 1368–72

Expert Advisory Group (1996) *Guidelines for the Management of Colorectal Cancer.* The Royal College of Surgeons of England, London

Hardingham JE, Hewett PJ, Sage RE et al (2000) Molecular detection of blood-borne epithelial cells in colorectal cancer patients and in patients with benign bowel disease. *Int J Cancer* **89:** 8–13

Lindemann F, Schlimok G, Dirschedl P, Witte J, Riethmuller G (1992) Prognostic significance of micrometastatic tumour cells in bone marrow of colorectal cancer patients. *Lancet* **340:** 685–9

Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen C (1993) An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. *JAMA* **270:** 943–7

Nigro JM, Baker SJ, Preisinger AC et al (1989) Mutations in the p53 gene occur in diverse human tumour types. *Nature* **342:** 705–8

O'Sullivan GC, Collins JK, Kelly J, Morgan J, Madden M, Shanahan F (1997) Micrometastases: marker of metastatic potential or evidence of residual disease? *Gut* **40:** 512–5

Scheele J, Altendorf-Hofmann A (1999) Resection of colorectal liver metastases. *Langenbecks Arch Surg* **384:** 313–27

Taniguchi T, Makino M, Suzuki K, Kaibara N (2000) Prognostic significance of reverse transcriptase-polymerase chain reaction measurement of carcinoembryonic antigen mRNA levels in tumor drainage blood and peripheral blood of patients with colorectal carcinoma. *Cancer* **89:** 970–6

Tornqvist A, Ekelund G, Leandoer L (1982) The value of intensive follow-up after curative resection for colorectal carcinoma. *Br J Surg* **69:** 725–8

KEY POINTS

- Current surveillance methods are insensitive for detecting early colorectal cancer recurrences, and intensive surveillance with conventional modalities confers marginal survival benefits.
- Improvements in surveillance will require more sensitive and specific tests, e.g. molecular or immunocytochemical screening of blood, bone marrow or stools.
- The reappearance of tumour cells might herald early cancer recurrence when effective treatment is more likely.
- New surveillance methods require validation through clinical trials to determine whether they impart survival benefit.