British Journal of Cancer (2007) 96, 222 – 225
© 2007 Cancer Research UK All rights reserved 0007 – 0920/07 $30.00
www.bjcancer.com

Clinical Studies

C-reactive protein as a predictor of prognosis following curative resection for colorectal liver metastases

VKH Wong[1], HZ Malik[1], ZZR Hamady[1], A Al-Mukhtar[1], D Gomez[1], KR Prasad[1], GJ Toogood[1] and JPA Lodge*[,1]

[1]*HPB and Transplant Unit, St. James's University Hospital, Leeds LS9 7TF, UK*

There is increasing evidence that systemic inflammatory response has a positive correlation with a poorer outcome in patients undergoing resection for solid tumours. The aim of this study was to analyse the impact of an elevated C-reactive protein (CRP), an outcome following curative resection for colorectal liver metastases. One hundred and seventy patients who underwent curative resection for colorectal liver metastases were included in the study. Laboratory measurements of haemoglobin, white cell, platelets, albumin and CRP were taken on the day before surgery. Elevated CRP ($>10\,mg\,l^{-1}$) was present in 54 (31.8%) patients. The median survival of patients with an elevated CRP was 19 months (95% CI 7.5–31.2 months) compared to 42.8 months (95% CI 33.2–52.5 months) for those with a normal CRP, $P=0.004$. Similarly, when assessing disease-free survival, patients with an elevated CRP had poorer disease-free survival (median of 11.8 months (95% CI 6.4–17.3) compared to median of 15.1 months (95% CI 11.1–19.1)), $P=0.043$. The result of the study showed that an elevated preoperative CRP is a predictor of poor outcome in patients undergoing curative resection for colorectal liver metastases.

British Journal of Cancer (2007) **96,** 222–225. doi:10.1038/sj.bjc.6603558 www.bjcancer.com
Published online 9 January 2007
© 2007 Cancer Research UK

Keywords: C-reactive protein; colorectal liver metastases; inflammatory response; survival

Colorectal cancer is the third commonest malignancy in UK with around 32 000 people diagnosed with colorectal cancer each year (Cancerstats, 2003; www.cancerresearchuk.org). Of that, around 20–25% of patients will have liver metastases (CRLM) at presentation and a further 40–50% will develop metachronous CRLM following colorectal surgery. Over the last two decades, liver resection has been established as the standard therapy for CRLM and offers the best chance of a potential cure with a 5-year survival of over 40% (Finch *et al*, 2006; Simmonds *et al*, 2006). However, disease recurrence is common with about two-thirds of patients who had liver resection for CRLM developing recurrent disease, and half of these patients had the disease recur in the remnant liver (Steele *et al*, 1991; Nordlinger *et al*, 1994; Fong *et al*, 1997; Hamady *et al*, 2006).

Several studies have looked for possible prognostic factors indicating poor survival outcome and disease recurrence after initial liver resection for CRLM (Fong *et al*, 1999; Seifert *et al*, 2000; Takahashi *et al*, 2003; Tanaka *et al*, 2004; Hamady *et al*, 2006). Primary colorectal adenocarcinoma stage and grade, size, distribution and number of liver metastases, presence of extrahepatic disease, resection margins and lymph nodes status are among the potential prognostic factors but to date, no consensus have been reached.

Recently, there is increasing evidence that inflammation, both local and systemic, has a causal link in the pathogenesis of many solid tumours (Balkwill and Mantovani, 2001; Coussens and Werb, 2002). Infiltration of proinflammatory macrophages, cytokines and chemokines in the tumour microenvironment predispose the tumour to further progression, growth, invasion and metastasis. Gunter *et al* (2006) showed an association between chronic low-grade inflammation, as evidenced by elevated C-reactive protein (CRP), with an increased risk of colorectal cancer. In addition, raised CRP is associated with an increased risk of developing early recurrence and poor outcome following colorectal surgery (McMillan *et al*, 1995, 2003; Canna *et al*, 2005). This suggests that it is not only the intrinsic properties of tumour cells that determine invasion and metastasis, but also the tumour microenvironment.

The aim of this study is to examine the relationship between inflammation, as evidenced by elevated CRP measured before surgery and outcome in patients who had liver resection for CRLM.

MATERIALS AND METHODS

Patients undergoing resection for colorectal liver metastases had CRP measured preoperatively. CRP (reference range being $10\,mg\,l^{-1}$ or less) measurements were taken on the day before surgery with none of the patients showing clinical signs of sepsis. The criteria for acceptance for surgery included fitness for major resection and lack of disseminated or irresectable extrahepatic disease identified by computerised tomography (CT) or MRI scan. In all cases, the colorectal primary had been previously resected and the patients had recovered fully from that procedure. Patients who underwent neo-adjuvant therapy were excluded from this study. Intraoperative ultrasound was used as an adjunct to the preoperative radiological investigations. Resection was performed using the Cavi-Pulse Ultrasonic Surgical Aspirator (CUSA, Model

*Correspondence: Dr JPA Lodge;
E-mail: Peter.Lodge@leedsth.nhs.uk
Received 4 October 2006; revised 23 November 2006; accepted 23 November 2006; published online 9 January 2007

200 T, Valley Lab., Boulder, CO, USA). If necessary, an intermittent Pringle manoeuvre was used with 15 min of ischaemia followed by 5 min of reperfusion.

In accordance with our unit protocol, all patients undergoing liver resection were offered adjuvant therapy in the form of 5-FU/folinic acid, unless they had received adjuvant therapy following their colonic resection within the past one year.

Patients were followed up at specialist clinics, with a minimum follow-up period of 1 year at the time of writing (range 1–5 years; median 28 months). No patients were lost to follow-up. An intensive policy of postoperative surveillance exists within this unit. Patients have three monthly chest and abdominal CT performed during the first postoperative year, then 6 monthly during year 2. From year 3 to 5, a CT scan is performed yearly and finally at year 7 and year 10 of follow-up. Tumour markers carcinoembryonic antigen ((CEA), CA19-9) and liver function tests are performed during each clinic visit. The data examined included patient demographics; liver resection histology; prehepatectomy CEA and CA19-9 tumour marker; prehepatectomy CRP; postoperative morbidity/mortality results as well as recurrence and survival figures.

STATISTICS

An SPSS version 9 statistical programme was used to analyse the data. The Student's *t*-test and χ^2 tests were used to analyse differences among groups of patients with high or normal CRP. Where variables did not follow a normal distribution, the Mann–Whitney test was applied. Kaplan–Meier survival curves were used to analyse patient outcome. Patients who died in the postoperative period were excluded from the analysis of outcome. A Cox regression analysis was then performed in a step-wise manner in order to perform a multivariable analysis of clinico-pathological factors that impact both overall and disease-free survival.

RESULTS

A total of 170 patients were included in this study. Of these patients, 106 (62%) were males and 64 (38%) females. The mean age of patient at time of surgery was 64 years (range 37–87 years; s.d. 9.86 years). A total of 86 (50.6%) patients had synchronous disease. All patients underwent liver resection. There were 76 (44.7%) patients who underwent an anatomical resection, a further 45 (26.5%) patients underwent a combination of anatomical and nonanatomical resection whereas the remaining 49 (28.8%) patients underwent a nonanatomical resection. A total of 57% of patients had a 'major' (three or more Couinaud segments) resection performed. The in-hospital mortality rate was 3% and 29 (17%) patients had postoperative complications.

Preoperative CRP was elevated ($>10\,mg\,l^{-1}$) in 54 (31.8%) patients. The differences in the clinico-pathological features of patients with a normal compared to an elevated CRP are presented in Table 1. Of note is that patients with an elevated CRP had no significant differences in the 'T' or 'N' stage of the primary tumour. However, patients with an elevated CRP tended to have larger metastases as well as increased CA19-9 levels compared to those with normal CRP.

Table 1 Clinico-pathological features

Factor	Normal CRP ($10\,mg\,l^{-1}$ or less) ($N=116$)	Elevated CRP ($>10\,mg\,l^{-1}$) ($N=54$)	Significance
Age (mean)	63.7	64.7	0.577
Synchronous disease	56	30	0.502
Male gender	73	33	0.802
Multiple (4 or more) metastases	27	12	0.568
Primary nodal status			
N0	32	10	0.371
N1	51	27	
N2	9	6	
Primary T stage			
T1	1	3	0.111
T2	8	3	
T3	57	19	
T4	24	15	
CEA	61.5	63	0.820
CA19-9	53.9	70.9	0.013
Large metastases size (> 50 mm)	34	31	0.003
Positive margin	23	15	0.641

CEA = carcinoembryonic antigen; CRP = C-reactive protein. Mann–Whitney *U*-test.

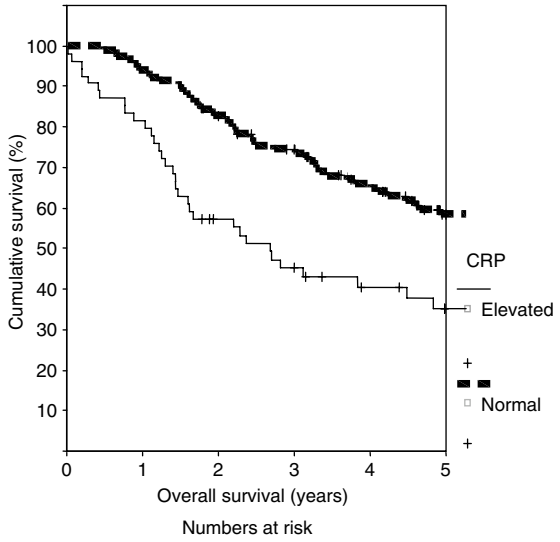

Figure 1 Overall survival stratified according to CRP.

Outcome

Overall there were 80 (47%) patients who died during the time period of this study. Of these, there were six non-cancer-related deaths. Thus, the cancer-specific survival was 56%. The median survival of patients with an elevated CRP was 19 months (95% CI 7.5–31.2 months) compared to 42.8 months (95% CI 33.2–52.5 months) for those with a normal CRP, $P=0.004$ (Figure 1). Similarly, when assessing disease-free survival, patients with an elevated CRP had poorer disease-free survival (median of 11.8 months (95% CI 6.4–17.3) compared to median of 15.1 months (95% CI 11.1–19.1)), $P=0.043$ (Figure 2). The results of univariate and multivariable analysis of the predictors of overall survival are shown in Tables 2 and 3, respectively. Of note is the fact that an elevated CRP was the only predictor of poor survival on univariate analysis. However on multivariable analysis, an elevated CRP as well as primary 'T' stage both predicted for poorer overall survival. When the multivariable analysis was repeated for disease-free

© 2007 Cancer Research UK

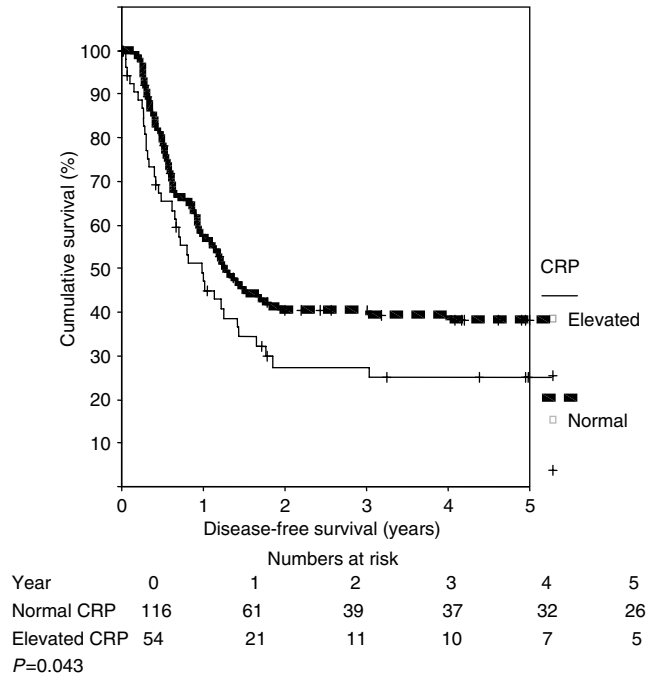

Figure 2 Disease-free survival stratified according to CRP.

Table 2 Univariate analysis of overall survival

Factor	*P*-value
Older age (years)	0.536
Gender (males)	0.522
CEA	0.353
CA19-9	0.838
Large (>50 mm) metastases size	0.661
Positive resection Margin	0.461
Synchronous disease	0.309
Primary tumour nodal positivity	0.754
Poorer tumour primary T-stage	0.124
Multiple (4 or more) Metastases	0.244
Poor clinical risk score	0.972
Elevated CRP	<0.001

CEA = carcinoembryonic antigen; CRP = C-reactive protein. MSKCC clinical risk score – poor scores defined as scores 3–5 (Fong *et al*, 1999).

survival, only the presence of an elevated CRP predicted for poorer outcome, $P = 0.011$ (HR 4.07; 95% CI 1.36–12.19).

DISCUSSION

Tumour progression is a complex process that depends not only on the intrinsic properties of the tumour, but also on its interaction with the host cells. Although the link between inflammation and cancer was first proposed by Virchow in 1863, it is only in last two decades that we are beginning to delineate and have an understanding of this intricate network of interactions.

Table 3 Multivariable analysis of overall survival

Factor	Hazard ratio (95% confidence interval)		*P*-value
Older age (years)	1.04	1.00–1.09	0.051
Gender (males)	1.09	0.51–2.32	0.816
CEA	0.99	0.99–1.00	0.785
CA19-9	0.99	0.99–1.00	0.766
Large (>50 mm) metastases size	0.99	0.97–1.01	0.827
Positive resection Margin	0.56	0.11–2.86	0.488
Synchronous disease	0.92	0.43–1.95	0.836
Primary tumour nodal positivity	0.60	0.30–1.19	0.149
Poorer tumour primary T-stage	1.82	1.10–3.00	0.019
Multiple (4 or more) Metastases	2.06	0.91–4.66	0.785
Poor clinical risk score	0.707	0.21–2.61	0.747
Elevated CRP	2.86	1.09–7.49	0.032

CEA = carcinoembryonic antigen; CRP = C-reactive protein. MSKCC clinical risk score – poor scores defined as scores 3–5 (Fong *et al*, 1999).

This study showed that elevated preoperative CRP present in almost one-third of patients with CRLM and is associated with a poor overall as well as disease-free survival in patients who had liver resection for colorectal metastases. This is consistent with other studies that found a positive correlation between elevated CRP concentrations, before surgery and a poor outcome in patients who had curative primary tumour resection (Nozoe *et al*, 2001; McMillan *et al*, 2003; Canna *et al*, 2005; Crumley *et al*, 2006). However, this is the first study to identify such a relationship among patients who have undergone curative resection for CRLM. This finding has important implications for selection of patients for surgery and the presence of an elevated CRP should be considered when counselling patients upon the likelihood of a 'curative resection'.

We also found that elevated CRP was associated with presence of larger metastases size and elevated CA19-9. It is possible that any impact upon survival of an elevated CRP may be as a result of this association. However, as neither of these factors were independent predictors of survival on multivariable analysis, it appears that the elevated CRP is the main factor contributing to the poorer outcome among these patients. Interestingly, there was no association between 'T' and 'N' characteristics of the primary and an elevation in CRP.

The basis for the relationship between elevated CRP and poor prognosis is unclear and there are several possible explanations. Elevated CRP level may simply reflect a nonspecific inflammatory response to tumour necrosis or local tissue damage. Alternatively, it may be indicative of a favourable environment for the establishment and growth of distant metastases. Serum level of vascular endothelial growth factor (VEGF), an angiogenic factor, is increased in the presence of raised CRP concentration (Xavier *et al*, 2006). Angiogenesis plays an important role in tumour growth and is associated with a poor outcome in patients with GI tumours (Tanigawa *et al*, 1997; Fondevila *et al*, 2004). In addition, interleukin (IL) -1 and -6 network is upregulated (Vidal-Vanaclocha *et al*, 2000; Miki *et al*, 2004). Interleukin 1 is involved in the development of metastasis in animal studies and IL-6, apart from being a growth factor, promotes resistance to apoptosis (Vidal-Vanaclocha *et al*, 1994, 2000; Chauhan *et al*, 1997; Frassanito *et al*, 2001; Jee *et al*, 2001). This creates a micro-environment that favours tumour angiogenesis, proliferation, growth and metastases.

© 2007 Cancer Research UK

Host immune response plays a role in the evolution of tumour growth. An impaired host immune response, evidenced by a weak lymphocyte infiltration at tumour margin, is associated with a poor prognosis in patients who had liver resection for CRLM (Okano *et al*, 2003). There is an inverse relationship between CRP levels and tumour lymphocyte infiltration, with a raised CRP concentration indicative of a weak infiltration of lymphocytes at the periphery of the tumour (Canna *et al*, 2005). The significance of systemic inflammatory response in the pathogenesis of cancer has important clinical implications.

Several novel therapies targeting the inflammatory pathways are in clinical trial (Balkwill and Mantovani, 2001). Tumour necrosis factor (TNF) antagonists, chemokine and IL-6 antagonism, nonsteroidal anti-inflammatory agents and statin drugs are among the potential therapies. Selective Cox-2 inhibitors were of particular interest with promising initial results but adverse cardiovascular risks have limited their usage (Mukherjee *et al*, 2001; Thun *et al*, 2002; Yau *et al*, 2003).

In summary, the results of this study showed that elevated CRP levels, measured before surgery, are present in a significant proportion of patients with CRLM. This is found to predict for a poor survival outcome in patients who had liver resection performed.

REFERENCES

Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? *Lancet* **357:** 539 – 545

Cancer Research UK Information Centre (2003) CancerStats. http//:info.cancerresearchuk.org/cancerstats

Canna K, McArdle PA, McMillan DC, McNicol A-M, Smith GW, McKee RF, McArdle CS (2005) The relationship between tumour T-lymphocyte infiltration, the systemic inflammatory response and survival in patients undergoing curative resection for colorectal cancer. *Br J Cancer* **92:** 651 – 654

Chauhan D, Kharbanda S, Ogata A, Urashima M, Teoh G, Robertson M, Kufe DW, Anderson KC (1997) Interleukin-6 inhibits Fas-induced apoptosis and stress-activated protein kinase activation in multiple myeloma cells. *Blood* **89**(1)**:** 227 – 234

Coussens LM, Werb Z (2002) Inflammation and cancer. *Nature* **420:** 860 – 867

Crumley ABC, McMillan DC, McKernan M, Going JJ, Shearer CJ, Stuart RC (2006) An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer. *Br J Cancer* **94:** 1568 – 1571

Finch RJB, Malik HZ, Hamady ZZR, Al-Mukhtar A, Adair R, Prasad KR, Lodge JPA, Toogood GJ (2006) Outcome following liver resection for colorectal liver metastases: effect of type of resection. *Br J Surg* (in press)

Fondevila C, Metges JP, Fuster J, Grau JJ, Palacin A, Castells A, Volant A, Pera M (2004) p53 and VEGF expression are independent predictors of tumour recurrence and survival following curative resection of gastric cancer. *Br J Cancer* **90:** 206 – 215

Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, Marrero AM, Prasad M, Blumgart LH, Brennan MF (1997) Liver resection for colorectal metastases. *J Clin Oncol* **15:** 938 – 946

Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* **230:** 309 – 318

Frassanito MA, Cusmai A, Iodice G, Dammaco F (2001) Autocrine interleukin-6 production and highly malignant multiple myeloma: Relation with resistance to drug-induce apoptosis. *Blood* **97:** 483 – 489

Gunter MJ, Stolzenberg-Solomon R, Cross AJ, Leitzmann MF, Weinstein S, Wood RJ, Virtamo J, Taylor PR, Albanes D, Sinha R (2006) A prospective study of serum C-reactive protein and colorectal cancer risk in men. *Cancer Res* **66:** 2483 – 2487

Hamady ZZR, Cameron IC, Wyatt J, Prasad RK, Toogood GJ, Lodge JPA (2006) Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: A critical appraisal of the 1 cm rule. *Eur J Surg Onco* **32:** 557 – 563

Jee SH, Shen SC, Chiu HC, Tsai WL, Kuo M (2001) Overexpression of interleukin-6 in human basal cell carcinoma cell lines increases anti-apoptotic activity and tumorigenic potency. *Oncogene* **20:** 198 – 208

McMillan DC, Canna K, McArdle CS (2003) Systemic inflammatory response predicts survival following curative resection of colorectal cancer. *Br J Surg* **90:** 215 – 219

McMillan DC, Wotherspoon HA, Fearon KC, Sturgeon C, Cooke TG, McArdle CS (1995) A prospective study of tumor recurrence and the acute-phase response after apparently curative colorectal cancer surgery. *Am J Surg* **170:** 319 – 322

Miki C, Konishi N, Ojima E, Hatada T, Inous Y, Kusunoki M (2004) C-reactive protein as a prognostic variable that reflects uncontrolled up-regulation of the IL-1 – IL-6 network system in colorectal carcinoma. *Dig Dis Sci* **49:** 970 – 976

Mukherjee D, Nissen SE, Topol EJ (2001) Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* **286:** 954 – 959

Nordlinger B, Vaillant JC, Guiguet M, Balladur P, Paris F, Bachellier P, Jaeck D (1994) Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie.. *J Clin Oncol* **12:** 1491 – 1496

Nozoe T, Saeki H, Sugimachi K (2001) Significance of preoperative elevation of serum C-reactive protein as an indicator of prognosis in esophageal carcinoma. *Am J Surg* **182:** 197 – 201

Okano K, Maeba T, Modoguchi A, Ishimura K, Karasawa Y, Izuishi K, Goda F, Usuki H, Wakabayashi H, Maeta H (2003) Lymphocytic infiltration surrounding liver metastases from colorectal cancer. *J Surg Oncol* **82**(1)**:** 28 – 33

Seifert JK, Bottger TC, Weigel TF, Gonner U, Junginger T (2000) Prognostic factors following liver resection for hepatic metastases from colorectal cancer. *Hepato-Gastroenterology* **47:** 239 – 246

Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M (2006) Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Canc* **94:** 982 – 999

Steele Jr G, Bleday R, Mayer RJ, Lindblad A, Petrelli N, Weaver D (1991) A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: Gastointestinal Tumor Study Group Protocol 6584. *J Clin Oncol* **9:** 1105 – 1112

Takahashi S, Inoue K, Konishi M, Nakagouri T, Kinoshita T (2003) Prognostic factors for poor survival after repeat hepatectomy in patients with colorectal liver metastases. *Surgery* **133:** 627 – 634

Tanaka K, Shimada H, Fujii Y, Endo I, Sekido H, Togo S, Ike H (2004) Pre-hepatectomy prognostic staging to determine treatment strategy for colorectal cancer metastases to the liver. *Arch Surg* **389:** 371 – 379

Tanigawa N, Amaya N, Matsumura M, Shimomatsuya T (1997) Correlation between expression of vascular endothelial growth factor and tumor vascularity, and patient outcome in human gastric carcinoma. *J Clin Oncol* **15:** 826 – 832

Thun MJ, Henley SJ, Patrono C (2002) Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst* **94:** 252 – 266

Vidal-Vanaclocha F, Amezaga C, Asumendi A, Kaplanski G, Dinarello CA (1994) Interleukin 1 receptor blockade reduces the number and size of murine B16 melanoma hepatic metastases. *Cancer Res* **54:** 2667 – 2672

Vidal-Vanaclocha F, Fantuzzi G, Mendoza L, Fuentes AM, Anasagasti MJ, Martin J, Carrascal T, Walsh P, Reznikov LL, Kim SH, Novick D, Rubinstein M, Dinarello CA (2000) IL-18 regulates IL-1b-dependent hepatic melanoma metastasis via vascular cell adhesion molecule-1. *Proc Natl Acad Sci USA* **97:** 734 – 739

Xavier P, Belo L, Beires J, Rebelo I, Martinez-de-Oliveira J, Lunet N, Barros H (2006) Serum levels of VEGF and TNF-a and their association with C-reactive protein in patients with endometriosis. *Arch Gynecol Obstet* **273:** 227 – 231

Yau M, Kargman S, Lam EC, Kelly CR, Zheng Y, Luk P, Kwong E, Evans JF, Wolfe MM (2003) Inhibition of cycooxygenase-2 by rofecoxib attenuates the growth and metastatic potential of colorectal carcinoma in mice. *Cancer Res* **63:** 586 – 592

© 2007 Cancer Research UK