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Evaluation of the prognostic value of systemic inflammation and socioeconomic deprivation in patients with resectable colorectal liver metastases

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ABSTRACT

Background: There is increasing evidence that the presence of a pre-operative systemic inflammatory response (SIR) independently predicts poor long-term outcome in patients with colorectal cancer (CRC). Socioeconomic deprivation was reported to correlate with the presence of the SIR and to independently predict poor outcome following primary CRC resection. The aim of this study was to determine the prognostic value of pre-operative systemic inflammatory biomarkers and socioeconomic deprivation in patients undergoing resection of colorectal liver metastases (CLM) and to examine correlations between these variables in this context.

Patients and methods: Clinicopathological data, including the Memorial Sloan-Kettering Cancer Centre Clinical Risk Score (CRS), were obtained from a prospectively maintained database for 174 patients who underwent hepatectomy for CLM between January 2000 and December 2005 at a single United Kingdom (UK) tertiary referral hepatobiliary centre. Inflammatory biomarkers (total and differential leucocyte counts, neutrophil-lymphocyte ratio, platelet count, haemoglobin, and serum albumin) were measured from routine pre-operative blood tests. Socioeconomic deprivation was measured using the Carstairs deprivation score.

Results: On multivariable analysis, poor CRS (3–5), high neutrophil count ($>6.0 \times 10^9/l$) and low serum albumin (<40 g/dl) were the only independent predictors of shortened overall survival following metastasectomy, with neutrophil count representing the greatest relative risk of death. These factors were also the only independent predictors of shortened disease-free survival following hepatectomy. Socioeconomic deprivation was associated with neither systemic inflammation nor long-term outcome in this context.

Conclusions: The presence of a pre-operative systemic inflammatory response, but not socioeconomic deprivation, independently predicts shortened survival following resection of CLM.

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1. Introduction

Hepatectomy offers the only hope of cure for patients with colorectal liver metastases (CLM), resulting in 5-year survival rates of 30–50%.^{1–3} Recurrence in the liver that is remnant and/or extrahepatic sites is common, however, affecting up to two-thirds of patients despite optimal metastasectomy.³ The ability to predict individual patient prognosis prior to hepatectomy is desirable in order to guide surgical and chemotherapeutic treatment according to individual recurrence risk. This is particularly pertinent given the increasing rates of hepatic resection for CLM. Clinicopathological factors have been shown to predict recurrence risk following metastasectomy,^{1,4} but lack the sensitivity for accurate individual prognostication. The role of molecular tumour biomarkers in determining disease recurrence is also under investigation, but requires further validation.⁵

In addition to intrinsic tumour factors, patient prognosis is also influenced by the host inflammatory response to malignancy, with data supporting a direct role for inflammatory cells and mediators in the promotion of both primary tumour growth and disease dissemination.^{6,7} At the local level, the immune response involves infiltration of the tumour environment by both lymphocytes and cells of myeloid lineages.^{7,8} This local inflammatory cell infiltration has been shown to have prognostic significance in numerous malignancies, including primary colorectal cancer (CRC).^{7,9,10}

A systemic inflammatory response (SIR), more easily assessable pre-operatively, accompanies the local immune response, driven by the production of pro-inflammatory cytokines, including interleukin-1 β , interleukin-6 and tumour necrosis factor- α , by both tumour cells and recruited immune cells.¹¹ These cytokines stimulate the release of acute phase proteins, most notably C-reactive protein (CRP).¹¹ Elevated CRP has been shown to predict shortened long-term survival in a range of solid and haematological malignancies^{12–14} and in CRC, independently predicted decreased survival following both primary tumour and CLM resection.^{2,15,16}

Cellular components of the SIR have also been shown to have prognostic significance in malignancy, though published data are scarce compared to that relating to CRP. Elevated neutrophil, monocyte and/or total leucocyte counts have been reported to predict adverse outcome in patients with a variety of solid tumours,^{17–19} including primary CRC.²⁰ In resectable CLM, examination of cellular indices of the SIR has been limited to the assessment of the neutrophil-lymphocyte ratio (NLR), an index derived as a marker of the systemic inflammation associated with cardiovascular disease and critical illness.^{21,22} The NLR was recently reported to independently predict poor outcome following hepatectomy for CLM and to do so as well as CRP.² Available data suggest, however, that the NLR is not the optimal prognostic cellular index of the SIR in malignancy,²⁰ due to the frequent lack of association between circulating lymphocyte count and survival in this context.^{20,23,24} Indeed, in a recent study of resectable primary CRC, whilst neutrophil count predicted cancer-specific survival, neither lymphocyte count nor the NLR showed any association with the outcome.²⁰ These results indicate that examination of the prognostic role of individual

leucocyte subtypes is also required in the context of resectable CLM.

A further biomarker of systemic inflammation is the ‘negative’ acute phase protein serum albumin. Hypoalbuminaemia correlates with poor outcome in patients with advanced malignancy,²⁵ an association presumed to be due to nutritional depletion secondary to the tumour. Recently, however, it has been postulated that hypoalbuminaemia develops secondary to the SIR.^{26,27} Hypoalbuminaemia predicts poor outcome in several cancer types,²⁸ and has been combined with CRP to form inflammatory prognostic scores in a number of malignancies.^{20,28,29} The prognostic value of serum albumin and its relationship to other systemic inflammatory biomarkers have yet to be examined in the context of resectable CLM.

Factors influencing malignancy-associated inflammation are poorly understood. Recent data have demonstrated that socioeconomic deprivation is associated with shortened overall and cancer-specific survival in patients with primary CRC.^{30,31} Neither clinicopathological factors nor treatment modality explained this correlation, but a significant association was noted between deprivation and the SIR,^{30,31} suggesting that the tumour-host response may be altered in deprived patients. The basis for this association is unclear, but it is postulated to relate to the increased rates of smoking and obesity in deprived patients.³² The association of socioeconomic deprivation with systemic inflammation and prognosis in the context of CLM has yet to be explored.

The primary aim of the current study was, therefore, to validate the prognostic value of systemic inflammatory biomarkers in resectable CLM, including determination of the cellular index with optimum prognostic value. In addition we sought to explore possible correlations between socioeconomic deprivation, systemic inflammation and patient outcome in this context.

2. Patients and methods

All patients who underwent hepatectomy for CLM between January 2000 and December 2005 at a single hepatobiliary tertiary referral centre (Leicester General Hospital, UK) were identified from a hepatobiliary database. During the study period, clinical data had been recorded prospectively in the database. These data were analysed retrospectively, with any additional information gathered from medical records. Radiology reports, pathology results, inpatient records and clinic notes from all follow-up appointments, as well as from any other clinical encounter, were also scrutinised.

Variables constituting the Clinical Risk Score (CRS), devised by the Memorial Sloan-Kettering Cancer Centre,¹ were recorded for each patient. The score is derived from five independent prognostic variables, with each scoring one point: positive nodal status of the primary tumour, disease-free interval from the diagnosis of primary lesion to the discovery of liver metastases of 12 months or less, number of hepatic metastases greater than one, diameter of the largest hepatic tumour greater than 5 cm and pre-operative carcinoembryonic antigen (CEA) level greater than 200 ng/ml. As reported

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