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Staging the tumor and staging the host: A two centre, two country comparison of systemic inflammatory responses of patients undergoing resection of primary operable colorectal cancer

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ABSTRACT

Background: How systemic inflammation-based prognostic scores such as the modified Glasgow Prognostic Score (mGPS) and neutrophil:lymphocyte ratio (NLR) differ across populations of patients with colorectal cancer (CRC) remains unknown. The present study examined the mGPS and NLR in patients from United Kingdom (UK) and Japan.

Methods: Patients undergoing resection of TNM I-III CRC in two centres in the UK and Japan were included. Differences in clinicopathological characteristics and mGPS (0-CRP≤10 mg/L, 1-CRP>10 mg/L, 2-CRP>10 mg/L, albumin<35 g/L) and NLR (≤5/>5) were examined.

Results: Patients from UK ($n = 581$) were more likely to be female, high ASA and BMI, present as an emergency (all $P < 0.01$) and have higher T stage compared to those from Japan ($n = 559$). After controlling for differences in tumor and host characteristics, patients from Japan were less likely to be systemically inflamed (OR: mGPS: 0.37, 95%CI 0.27–0.50, $P < 0.001$; NLR: 0.53, 95%CI 0.35–0.79, $P = 0.002$).

Conclusion: Systemic inflammatory responses differ between populations with colorectal cancer. Given their prognostic value, reporting of systemic inflammation-based scores should be incorporated into future studies reporting patient outcomes.

Summary: Although the systemic inflammatory response is recognised as a prognostic factor in patients with colorectal cancer, it is not clear how these may differ between distinct geographical populations. The present study examines differences in the prevalence of elevated systemic inflammatory responses (modified Glasgow Prognostic Score and neutrophil:lymphocyte ratio) between two populations undergoing resection of colorectal cancer in the United Kingdom and Japan.

1. Introduction

Colorectal cancer is the third most commonly diagnosed cancer worldwide.[1] Although prognosis of patients with early stage disease may be excellent, ultimately 40% of patients across all disease stages die from their disease within five years.[2] Staging and additional treatment is primarily based upon assessment of pathological characteristics of the tumor, with the presence of regional lymph node metastases (TNM stage III) an indication for adjuvant chemotherapy. Similarly, other pathological characteristics, such as venous invasion, may also identify patients with high-risk, node negative disease likely to benefit from chemotherapy.[3]

In addition to tumor-based characteristics, the host systemic inflammatory response is now recognised as an important determinant of disease progression.[4] Assessment of the host systemic inflammatory response, utilising routinely measured circulating biomarkers, such as acute phase proteins and components of the differential white cell count,[5] has prognostic value across a number of cancers, and several inflammation-based prognostic scores have been proposed to this effect.

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One such score is the modified Glasgow Prognostic Score (mGPS), a cumulative score based on pre-operative serum concentrations of the routinely measured acute phase proteins C-reactive protein (CRP) and albumin.[6] In patients with colorectal cancer, the mGPS has complimentary prognostic value to routine TNM-based staging of patients undergoing resection of stage I-III disease, and may potentially select for patients with stage III colon cancer less likely to derive benefit from adjuvant chemotherapy.[7] Therefore, it is of interest that the mGPS has been validated internationally in patients with colorectal cancer.[6,8] Similarly, the systemic inflammation-based neutrophil: lymphocyte ratio (NLR), has been shown to hold independent prognostic value in patients with colorectal cancer internationally.[8–10] Given their routine availability, objectivity and potential role as both prognostic and predictive markers, such inflammation-based scores would be a useful adjunct to the routine staging of patients with colorectal cancer.

However, although individual studies and pooled analyses have confirmed the prognostic value of both the mGPS and NLR in patients from distinct ethnic populations,[7–13] it is recognised that ethnicity itself may confound the presence of a systemic inflammatory response. For example, population studies have found individuals of Black and South Asian origin have higher CRP concentrations than those of Caucasian descent,[14–16] whereas individuals of East Asian heritage have consistently been reported to having significantly lower concentrations.[17–19] Although studied in healthy subjects and cardiovascular disease screening programmes, it is not clear whether the presence of a cancer-associated systemic inflammatory response similarly differs with ethnicity. Given the prognostic implications, it would be of interest to examine whether the prevalence of an elevated systemic inflammatory response was comparable or varied across different ethnic populations after controlling for clinical and pathological characteristics. Also, if different, it would suggest that routine reporting of the systemic inflammatory response would be necessary alongside TNM-based reporting to allow for comparison of both disease stage and outcomes. Indeed there is some evidence that the proportion of patients with elevated prognostic scores varies with ethnicity in patients with cancer.[20] However, to our knowledge the basis of this observation is not clear since a number of potential confounding clinicopathological factors have not been examined. Many Asian research groups (in particular in Japan) have confirmed the prognostic value of systemic inflammation-based prognostic scores. As such, it is of interest to compare, in detail, patients with colorectal cancer from the UK and Japan.

Therefore, using two cohorts of patients in which the mGPS has previously been shown to hold prognostic value,[7,12] the aim of the present study was to compare systemic inflammatory profiles across two distinct populations of patients undergoing resection of stage I-III colorectal cancer in the United Kingdom (UK) and Japan.

2. Methods

2.1. UK cohort

Patients from a single surgical unit at Glasgow Royal Infirmary, UK, (GRI) were identified from a prospectively collected database of elective and emergency colorectal cancer resections. For the purposes of the present study, consecutive patients who on the basis of preoperative staging and intra-operative findings had undergone potentially curative resection of TNM stage I-III colorectal adenocarcinoma between January 1997 and May 2013 were included. Patients with inflammatory bowel disease-related cancer, or who received neoadjuvant chemoradiotherapy were excluded.

Patients undergoing elective resection had differential white cell count, serum CRP and albumin measured routinely at preoperative assessment within 30 days of surgery, whereas patients undergoing emergency resection had values on admission recorded. Body mass index (BMI) was recorded at time of admission, and categorised using World Health Organisation classification. Comorbidity was measured using American Society of Anaesthesiologists' (ASA) grade, which was recorded at time of surgery. Tumors were staged according to the fifth edition of the TNM classification as is current practice in the UK.[21] Elastica staining has been used routinely in GRI since 2003, with selected retrospective staining performed on a cohort of patients before this date for a previous study.[3] West of Scotland Research Ethics Committee approved the study.

2.2. Japanese cohort

Patients were identified from a prospectively maintained database of elective and emergency colorectal cancer resections performed by a single surgical team in the Department of Gastroenterological Surgery, Dokkyo Medical University, Japan (DMU). For the present study, patients who underwent potentially curative resection of TNM stage I-III colorectal adenocarcinoma between November 2005 to December 2015 were included. Exclusion criteria were identical to those applied to the GRI cohort, with pre-operative measurement of differential white cell count, CRP and albumin performed on day of admission. Both BMI and ASA grade were recorded at time of admission. Patients were staged according to the seventh edition of the TNM classification.[22] Elastica staining was not used routinely for detection of venous invasion, and was only used at the discretion of the reporting pathologist. The local institutional review board approved the study.

2.3. Systemic inflammatory scores

The mGPS was calculated for both cohorts as previously described.[6] Patients with CRP$\leq$10 mg/L were given a score of 0, patients with CRP>10 mg/L a score of 1, and patients with CRP>10 mg/L and albumin<35 g/L a score of 2. On the basis of a previous literature review, a NLR>5 was considered elevated.[23]

2.4. Statistical analysis

The relationship between study cohort, mGPS and clinicopathological characteristics was examined using the χ^2 method for linear trend. In order to adjust for multiple comparisons, a $P < 0.01$ was considered significant. Univariate binary logistic regression was used to examine the relationship between clinicopathological characteristics, including study cohort, and the presence of a systemic inflammatory response (mGPS$\geq$1 or NLR>5), calculating odds ratio (OR) and 95% confidence intervals (95% CI). Clinicopathological factors associated with the presence of a systemic inflammatory response that on univariate analysis had a $P < 0.05$ were taken into a multivariate model using a backward conditional model to identify independently significant factors, with $P = 0.05$ considered statistically significant. All analyses were performed using SPSS version 22.0 for Mac (IBM SPSS, IL, USA).

3. Results

The final study population comprised 1140 patients (581 patients from GRI and 559 patients from DMU). Data on BMI were missing for 175 patients from GRI. Data on BMI, lymph node yield, venous invasion and margin involvement were missing for 4, 2, 6 and 8 patients respectively from DMU.

A comparison of characteristics of the two cohorts is displayed

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