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The rate of false-positive diagnosis of colorectal liver metastases in patients undergoing resection with the development of a novel, externally validated risk score☆

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ABSTRACT

Background: Diagnostic error in patients undergoing resection of colorectal liver metastases (CRLM) is unusual but exposes patients to unnecessary risks associated with treatment. The primary aim of this study was to determine the rate of and risk factors for a false-positive diagnosis of colorectal liver metastases in patients undergoing hepatic resection. The secondary aim was to develop and validate a risk score to predict a false-positive diagnosis.

Methods: Patients were identified from prospectively maintained databases. Patients who underwent a first liver resection for presumed colorectal liver metastases were divided into 2 groups: $CRLM_{POS}$ (colorectal liver metastases present on histology or appearance of complete pathologic response to preoperative chemotherapy) and $CRLM_{NEG}$ (all others). Univariable analysis and multivariable binary logistic regression were used to identify risk factors for $CRLM_{NEG}$. Risk scores were developed for $CRLM_{NEG}$ both with and without the use of preoperative carcinoembryonic antigen and were validated on an external cohort.

Results: 3.1% of patients in both test and validation cohorts were $CRLM_{NEG}$ (39/1,252 and 59/1,900, respectively). $CRLM_{NEG}$ patients had fewer ($P = .006$) and smaller lesions ($P < .001$) with lower serum levels of carcinoembryonic antigen ($P < .001$), T ($P = .031$) and N ($P < .001$) and a lower Dukes' stage of the primary ($P < .001$). The risk score performed well (area under the receiver operating characteristic curve 0.869; standard error = 0.030; $P < .001$) with reasonable performance on validation (area under receiver operating characteristic curve 0.743; standard error = 0.058; $P < .001$]).

Conclusion: A false-positive diagnosis of colorectal liver metastases affected the same proportion of patients in 2 unrelated cohorts. This study identified risk factors for false-positive diagnosis with development of a novel risk score supported by external validation.

Liver resection is the principal form of curative treatment for colorectal liver metastases (CRLM), offering 5-year survival of 40%,[1] compared with virtually no survivors among unresected patients.[2] Improvements in selection, technique, and perioperative care allow an aggressive approach to liver-dominant disease, with operative mortality in specialist centers as low as 0.3%–3%.[3,4] National-level data, however, typically report greater rates of mortality than single-center series.[5,6] Liver resection is a major undertaking, with substantial risks of morbidity and mortality. Accurate diagnosis of preoperative CRLM is, therefore, of the utmost importance.

Cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) are the established means of detecting CRLM preoperatively. Positron emission tomography (PET) can be a useful adjunct, especially in the detection of extrahepatic disease.[7] A meta-analysis found that the sensitivity estimates of CT, MRI, and flurodeoxyglucose PET on a per-lesion basis

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were 74.4%, 80.3%, and 81.4%, respectively.[8] These forms of imaging, however, have less ability to detect CRLM or to discriminate between them and other diagnoses under certain conditions, such as when the lesion is small. Additionally, the positive predictive value of an imaging finding will also be affected by the pretest probability of the patient having CRLM; in other words, a false-positive diagnosis is more likely in cases where the risk of CRLM is low.

Hepatic resection for an incorrect diagnosis of CRLM is a rare event, but one that exposes a patient to clinical risk. This study, therefore, sought to identify the rate of and risk factors for making a false-positive diagnosis of CRLM. The secondary aim was to develop a model to predict the occurrence of an incorrect diagnosis of CRLM. The findings of the study and model were evaluated in an external cohort.

Methods

This was a retrospective cohort study of patients undergoing their first liver resection for a presumed diagnosis of CRLM at the Queen Elizabeth Hospital, Birmingham. This cohort served as the main dataset to study risk factors and to develop and test a predictive model. An external cohort of patients treated at St James Hospital, Leeds, was used to validate the study findings. The study period was 2002 to 2015.

The preoperative (imaging) diagnosis was available in the prospectively maintained databases for both cohorts. This diagnosis was compared to the postoperative histopathologic result, which was defined as being the correct diagnosis. Patients undergoing hepatic resection for non-CRLM indications or who had previously undergone a hepatic resection of CRLM were excluded. Patients were divided into 2 groups, CRLM-positive ($CRLM_{POS}$) and CRLM-negative ($CRLM_{NEG}$), on the basis of whether CRLM were detected in any resection specimen for each patient. Patients who underwent neoadjuvant chemotherapy and had histopathologic findings consistent with a complete pathologic response were included in $CRLM_{POS}$. Where a patient had multiple lesions, of which only some were found to be CRLM, they were assigned to the $CRLM_{POS}$ group. A per-lesion analysis is not appropriate, because it is often impossible (in retrospect) to definitively correlate the CRLM and non-CRLM lesions in a pathology report with the lesions seen on preoperative imaging. Synchronous disease was defined as diagnosis of the putative CRLM before resection of the primary.

Imaging protocols

For staging, we performed a CT of the abdomen, thorax, and pelvis with arterial and portal venous enhancement with 1-mm slices. If the suspected CRLMs were synchronous (within 12 months of diagnosis of the colorectal cancer) or when lesions seen on initial CT were considered indeterminate, an additional MRI of the liver was performed with contrast enhancement. CT PET was used occasionally among high-risk patients where there were concerns of widespread disease; however, CT PET was not within our standard protocol for staging. For our surveillance protocol, we perform a CT of the abdomen, thorax, and pelvis with portal venous enhancement with 1-mm slices at 6 and 12 months and then annually to 5 years of follow-up if no recurrence. MRI was performed selectively when lesions were indeterminate.

Statistical analysis

Continuous variables were reported as medians and quartiles and compared between the 2 groups using the Mann-Whitney *U* test. Discrete and ordinal variables were reported as percentages, with comparisons between groups made using Fisher's exact test for the former and Kendall's tau for the latter to account for the ordering of the categories.

Factors found to be statistically significant in univariable analysis were then entered into a multivariable binary logistic regression model, with the group as the outcome and $CRLM_{POS}$ as the reference category. Although Dukes' classification has been superseded by the TNM system, full staging of the primary under the latter system was missing from the datasets in many cases. To minimize missing data, and because Dukes' stage is calculable from the TNM status but the reverse is not true, only Dukes' staging was used in the multivariable analysis. A backward stepwise method was used to remove nonsignificant terms from the model. Prior to this, the relationships between continuous variables and the outcome were assessed, with factors being $\log_2$ transformed, as necessary, to improve the fit of the model.

Use of carcinoembryonic antigen levels within statistical models

Carcinoembryonic antigen (CEA) levels were originally included as a factor in the analysis. However, because CEA is not useful in patients with nonsecreting tumors and, as a practical matter, is often not available when making an initial assessment of patients' suitability for liver surgery, a second analysis was performed to consider both patients who do and do not secrete CEA.

Model development and external validation

The resulting models were then converted into risk scores. The coefficients from the continuous variables were evaluated at a range of values to convert them into categorical cutoffs, thereby making the final score possible to calculate manually. The resulting coefficients were then multiplied by 2 to remove fractions while maintaining accuracy. The performance of the resulting scores was then assessed using receiver operating characteristic (ROC) curves. Data from the Hepatobiliary Surgery Unit at St James's University Hospital, Leeds, were used to validate the scores on an external patient cohort.

Missing data were excluded on a per-analysis basis, and the numbers of cases used in each analysis are quoted throughout. All analyses were performed using IBM SPSS Statistics 22 (IBM Corp, Armonk, NY), with $P < 0.05$ deemed to be indicative of statistical significance.

Results

Final pathologic diagnosis

Of 2,206 patients undergoing their first liver resection, 1,252 had a preoperative diagnosis of CRLM. Of these, 39 (3.1%, 95% confidence interval: 2.2%–4.2%) were $CRLM_{NEG}$. Histologic analysis demonstrated that hemangiomata predominated ($n = 20$), and most of these were reported as having a sclerosed or hyalinized appearance. Other benign diagnoses (which may coexist in separate lesions from the same patient) included inflammatory lesion ($n = 5$), abscess ($n = 3$), lymphoid lesion ($n = 1$), focal fat ($n = 1$), granuloma ($n = 1$), cyst ($n = 1$), and no lesion identified ($n = 3$; patients had not received prior chemotherapy). Overall, 10 $CRLM_{NEG}$ had an alternative malignant diagnosis (hepatocellular carcinoma $n = 5$, cholangiocarcinoma $n = 3$, other metastatic tumor $n = 2$).

Comparison of patients with or without CRLM

Comparisons between the 2 groups are reported in Table 1. The demographics of the 2 groups were similar, with no significant differences in age ($P = .99$) or sex ($P = .87$). The temporal relationship between the primary and metastatic disease was not found to

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