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Serum metabolomic profile as a means to distinguish stage of colorectal cancer

Farshad Farshidfar[1], Aalim M Weljie[2], Karen Kopciuk[3], W Don Buie[4], Anthony MacLean[4], Elijah Dixon[4,5], Francis R Sutherland[4], Andrea Molckovsky[5], Hans J Vogel[2] and Oliver F Bathe[4,5*]

Abstract

Background: Presently, colorectal cancer (CRC) is staged preoperatively by radiographic tests, and postoperatively by pathological evaluation of available surgical specimens. However, present staging methods do not accurately identify occult metastases. This has a direct effect on clinical management. Early identification of metastases isolated to the liver may enable surgical resection, whereas more disseminated disease may be best treated with palliative chemotherapy.

Methods: Sera from 103 patients with colorectal adenocarcinoma treated at the same tertiary cancer center were analyzed by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy and gas chromatography-mass spectroscopy (GC-MS). Metabolic profiling was done using both supervised pattern recognition and orthogonal partial least squares-discriminant analysis (O-PLS-DA) of the most significant metabolites, which enables comparison of the whole sample spectrum between groups. The metabolomic profiles generated from each platform were compared between the following groups: locoregional CRC (N = 42); liver-only metastases (N = 45); and extrahepatic metastases (N = 25).

Results: The serum metabolomic profile associated with locoregional CRC was distinct from that associated with liver-only metastases, based on ^{1}H NMR spectroscopy ($P = 5.10 \times 10^{-7}$) and GC-MS ($P = 1.79 \times 10^{-7}$). Similarly, the serum metabolomic profile differed significantly between patients with liver-only metastases and with extrahepatic metastases. The change in metabolomic profile was most markedly demonstrated on GC-MS ($P = 4.75 \times 10^{-5}$).

Conclusions: In CRC, the serum metabolomic profile changes markedly with metastasis, and site of disease also appears to affect the pattern of circulating metabolites. This novel observation may have clinical utility in enhancing staging accuracy and selecting patients for surgical or medical management. Additional studies are required to determine the sensitivity of this approach to detect subtle or occult metastatic disease.

Background

While most individuals with metastatic colorectal cancer (CRC) receive treatments with palliative intent, there are some who may benefit from more aggressive surgical therapy with curative intent. The prototypical situation in which cure can still be achieved in the face of metastatic disease is when metastases are isolated to the liver. In patients with limited intrahepatic disease, and in the absence of extrahepatic disease, resection can result in a median survival of 40 to 58 months and a 5-year survival of 40 to 58% [1-4]. Presently, only 25 to 30% of patients with colorectal liver metastases have resectable disease. It is possible that earlier identification of the presence of liver metastases could increase the proportion of patients who could undergo surgery with curative intent. Therefore, biomarkers that facilitate early detection of liver-only metastases could be useful. In addition, biomarkers that reveal the presence of radiographically occult extrahepatic disease could help to better select patients who would benefit from resection of liver metastases.

Biomarkers may be defined as any biomolecule or panel of biomolecules that can aid in the diagnosis of disease, prognostication, prediction of biology, or prediction of sensitivity to specific therapies. Recent biomarker discovery efforts have focused largely on the genome, the transcriptome and the proteome, using technologies that

* Correspondence: bathe@ucalgary.ca
[4]Department of Surgery, University of Calgary, 3330 Hospital Dr NW, Calgary, AB, Canada, T2N 4N1
Full list of author information is available at the end of the article