Detecting Cancer of the Bile Duct: Multivariate Analysis of ^{1}H MRS of Bile

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Introduction

Cholangiocarcinoma (CC), cancer of the bile duct, is the leading cause of mortality in patients with primary sclerosing cholangitis (PSC). Due to the absence of an effective treatment in PSC, liver transplantation is the only option for patients with end-stage disease. The result after liver transplantation is excellent in PSC patients without CC. On the contrary, the prognosis in PSC patients with CC is dismal (1). Therefore, it is important to identify PSC patients who are at risk for the development of malignancy so that the transplant can be done early. Diagnostic tools such as brush cytology and the measurement of tumor markers in serum (e.g., CA 19-9, CEA) have been evaluated for this purpose, but they lack the desired sensitivity and specificity (2). CT, ERCP (endoscopic assessment), and MRI have also been used, but an early diagnosis is hard to achieve with these techniques (3). The objective of this study was to determine if ^{1}H MRS of bile, analysed by multivariate methods, could be of value in diagnosing CC in patients with and without PSC.

Patients and Methods

Bile from fifty subjects (12 normal, 38 patients with suspected biliary disease) was studied using ^{1}H MRS. Twenty of the patients had cancer, and 18 had PSC. During the ERCP examination, 2-10 ml bile sample was taken for analysis in plain tubes. A contrast agent, Omnipaque, was used during ERCP. Samples were run on an Avance 360 MHz NMR Spectrometer (Bruker Instruments) with no spinning. The following acquisition parameters were employed in the 1-D experiments: NS (number of scans) = 32, P1 (90° pulse) = 9 μsec, PL9 (water presaturation power) = 40 dB, TD (number of points in time domain) = 16K, D1 (interpulse delay) = 3.0 sec, SW (spectral width) = 4990.02 Hz, AQ (acquisition time) = 1.64 sec. The spectra were analysed using a computerized multivariate analysis, according to the statistical classification strategy previously employed (4). Given the problem of contamination with the contrast agent, MR spectrum of Omnipaque was also obtained to determine the extent of overlap with the resonances of bile.

Results and Discussion

Most of the prominent resonances in ^{1}H MRS of bile have been identified based on literature values and the results of 2-D experiments (5, 6). As can be seen in the figure, it was possible to obtain spectra of diagnostic quality without the need for lyophilization and reconstitution (which can result in loss of some volatile and/or unstable components). The non-malignant groups (normals and PSC) were combined together and compared against the patients who had CC. Since there was a possibility for the peaks from Omnipaque to overlap with those from bile samples, we excluded from the analysis all the spectral regions where Omnipaque could give a signal. Our optimal region selection algorithm found 4 regions that were discriminatory. Using the 4 spectral regions, only 2 spectra were misclassified, 1 normal and 1 cancer. This resulted in an overall accuracy of 96%, sensitivity of 95%, and specificity of 97%. The biochemical compounds that contribute signals to the above 4 regions include: choline, deoxycholic acid, acetoacetate, glutamine and cholesterol. Unlike the conventional analysis, these regions were not *a priori* selected. A lactate doublet (at 1.33 ppm) was frequently present in the bile spectra from CC patients, but not in normal and PSC spectra (see insert in Fig. 1). However, this was not selected by our algorithm as being discriminatory – possibly due to lipid contamination.

Conclusion

^{1}H MRS analysis of bile from patients with cholangiocarcinoma could be a useful tool to detect the cancer at an early stage. Moreover, by identifying those PSC patients that are harboring cancer or are at high risk for developing cancer, a more selective and urgent intervention could be adopted. These results are exciting, and therefore a study with a larger sample size is underway to confirm the method as a useful clinical tool.

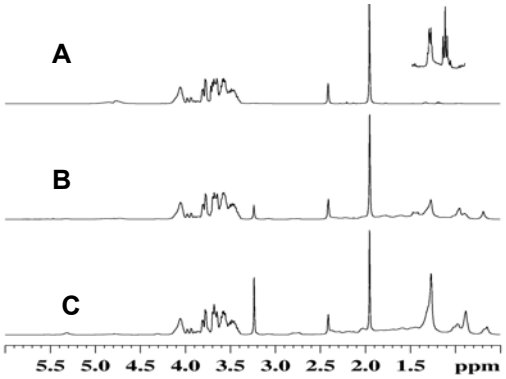

Figure 1. ^{1}H MR spectra (360 MHz, 25 °C) of bile specimens: (A) Cholangiocarcinoma, (B) PSC, and (C) Normal.

References

1. Goss J, et al., *Annals of Surgery* 225: 472 (1997). **2**. Ponsioen CY, et al., *Endoscopy* 31 : 305 (1999). **3.** Lindberg B, et al., *Endoscopy* 34: 909 (2002). **4**. Lean CL, et al., *Annu. Rep. NMR Spectrosc*. 48: 71 (2002). **5**. Nicholson JK, et al., *Prog NMR Spec* 21: 449 (1989). **6**. Khan SA, et al., *Eur J Gastroenterol Hepatol.* 17: 733 (2005).