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ScienceDirect

EJSO 41 (2015) 1020–1027

EJSO the Journal of Cancer Surgery

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Digital histology quantification of intra-hepatic fat in patients undergoing liver resection

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Accepted 7 May 2015
Available online 28 May 2015

Abstract

Background: High intra-hepatic fat (IHF) content is associated with insulin resistance, visceral adiposity, and increased morbidity and mortality following liver resection. However, in clinical practice, IHF is assessed indirectly by pre-operative imaging [for example, chemical-shift magnetic resonance (CS-MR)]. We used the opportunity in patients undergoing liver resection to quantify IHF by digital histology (D-IHF) and relate this to CT-derived anthropometrics, insulin-related serum biomarkers, and IHF estimated by CS-MR.
Methods: A reproducible method for quantification of D-IHF using 7 histology slides (inter- and intra-rater concordance: 0.97 and 0.98) was developed. In 35 patients undergoing resection for colorectal cancer metastases, we measured: CT-derived subcutaneous and visceral adipose tissue volumes, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), fasting serum adiponectin, leptin and fetuin-A. We estimated relative IHF using CS-MR and developed prediction models for IHF using a factor-clustered approach.
Results: The multivariate linear regression models showed that D-IHF was best predicted by HOMA-IR (Beta coefficient$_{\text{per doubling}}$: 2.410, 95% CI: 1.093, 5.313) and adiponectin ($\beta_{\text{per doubling}}$: 0.197, 95% CI: 0.058, 0.667), but not by anthropometrics. MR-derived IHF correlated with D-IHF (rho: 0.626; $p = 0.0001$), but levels of agreement deviated in upper range values (CS-MR over-estimated IHF: regression versus zero, $p = 0.009$); this could be adjusted for by a correction factor (CF: 0.7816).
Conclusions: Our findings show IHF is associated with measures of insulin resistance, but not measures of visceral adiposity. CS-MR over-estimated IHF in the upper range. Larger studies are indicated to test whether a correction of imaging-derived IHF estimates is valid.

Keywords: Hepatic steatosis; Obesity; Insulin resistance; Visceral adiposity; Liver surgery

Introduction

Excess intra-hepatic fat (IHF), commonly termed steatosis, is present in approximately one third of patients with colorectal liver metastases (CLM).[1–3] Moderate to severe steatosis (triglyceride content >33%[4]) and steatohepatitis (steatosis with hepatocyte ballooning, lobular inflammation and fibrosis[4]) are associated with increased post-operative morbidity (two-fold increase) and peri-operative mortality (2.8- to 10-fold increase).[5,6] Retrospective studies have shown excess body mass index (BMI), diabetes and pre-operative chemotherapy are associated with steatosis and/or steatohepatitis in the resection specimen.[3,5,7]

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http://dx.doi.org/10.1016/j.ejso.2015.05.003
0748-7983/

Within the general population, visceral adipose tissue (VAT) but not subcutaneous adipose tissue (SAT), correlates with intra-heaptic fat (IHF).[8–10] Consistent with this, serum surrogate biomarkers of insulin resistance independently predict for IHF.[9–11] However, IHF is determined indirectly by non-invasive imaging modalities, either using ultrasound scans in large cohorts,[12] or in clinical practice, by pre-operative chemical-shift MR (CS-MR).[13] Magnetic resonance (MR) spectroscopy may offer greater performance characteristics but its utility is limited to the research setting.[14,15]

To directly inform the above relationships, and pre-operative assessment, we used the opportunity in patients undergoing liver resection, to quantify IHF by digital histological assessment (D-IHF) and related this with CT-derived anthropometrics (VAT and SAT), insulin-related serum biomarkers, and IHF estimated by CS-MR.

Methods

Patients

The study schema is outlined in (Fig. 1). Patients planned for resection of colorectal liver metastases (CLM) at North Manchester General Hospital, Manchester, United Kingdom, were prospectively recruited between January 2012 and June 2013; all gave informed consent. All patients underwent pre-operative CT, CT-PET and

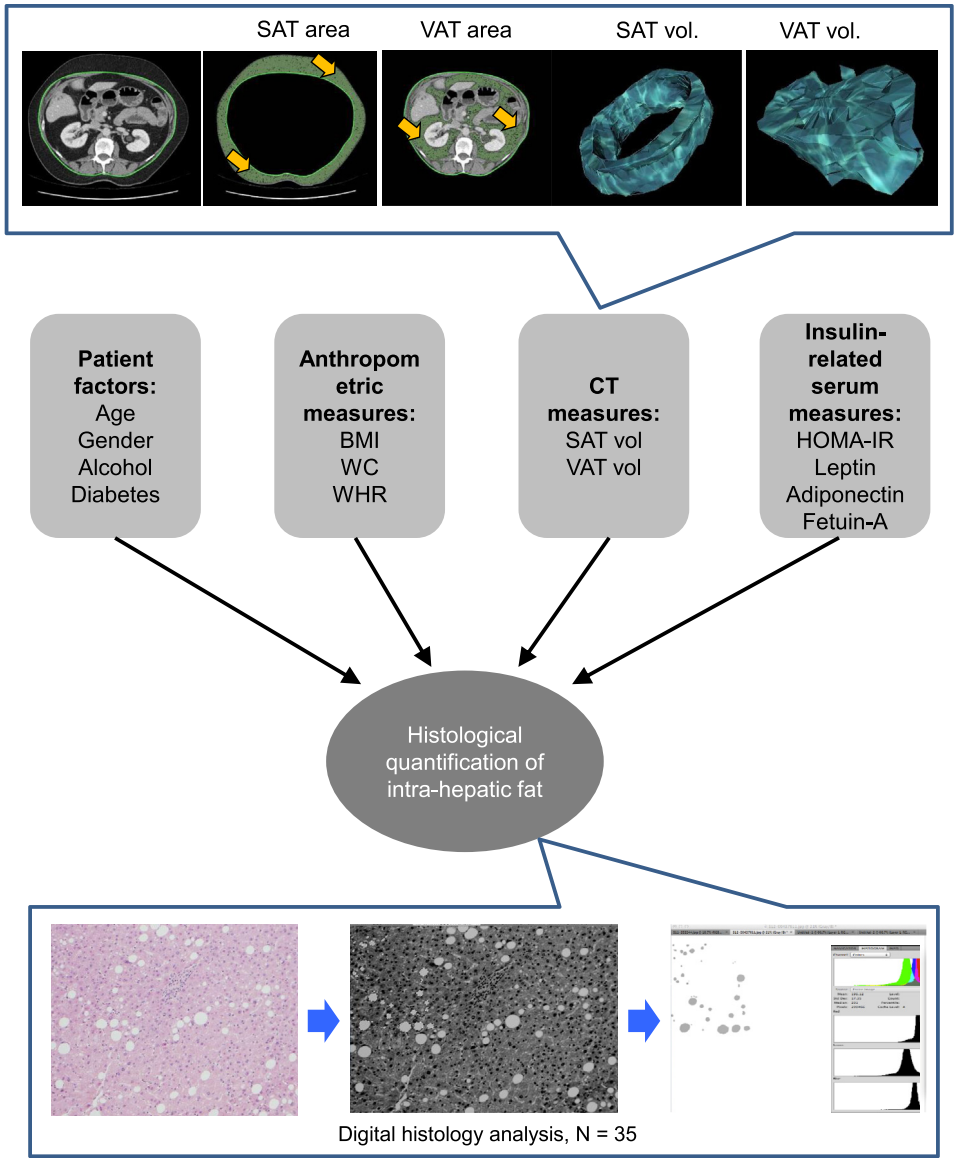

Figure 1. Study design. Upper panel: Pre-operative CT scans were analyzed using OsiriX software to determine subcutaneous (SAT) and visceral adipose tissue (VAT) areas and volumes (indicated by yellow arrows). Lower panel: Digital quantification with Adobe Photoshop. Areas of fat are highlighted using the magic wand; the size of the highlighted area is recorded as a pixel count.