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Research paper

Whole liver CT texture analysis to predict the development of colorectal liver metastases—A multicentre study

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ABSTRACT

Objectives: CT texture analysis has shown promise to differentiate colorectal cancer patients with/without hepatic metastases.

Aim: To investigate whether whole-liver CT texture analysis can also predict the development of colorectal liver metastases.

Material and methods: Retrospective multicentre study (n = 165). Three subgroups were assessed: patients [A] without metastases (n = 57), [B] with synchronous metastases (n = 54) and [C] who developed metastases within ≤24 months (n = 54). Whole-liver texture analysis was performed on primary staging CT. Mean grey-level intensity, entropy and uniformity were derived with different filters (σ0.5–2.5). Univariable logistic regression (group A vs. B) identified potentially predictive parameters, which were tested in multivariable analyses to predict development of metastases (group A vs. C), including subgroup analyses for early (≤6 months), intermediate (7–12 months) and late (13–24 months) metastases.

Results: Univariable analysis identified uniformity (σ0.5), sex, tumour site, nodal stage and carcinoembryonic antigen as potential predictors. Uniformity remained a significant predictor in multivariable analysis to predict early metastases (OR 0.56). None of the parameters could predict intermediate/late metastases.

Conclusions: Whole-liver CT-texture analysis has potential to predict patients at risk of developing early liver metastases ≤6 months, but is not robust enough to identify patients at risk of developing metastases at later stage.

1. Introduction

Survival in colorectal cancer (CRC) is influenced by several factors, including the local T- and N-stage (tumour- and nodal stage), age and sex [1,2]. The most important factor, however, is the presence of metastases. Approximately 20% of patients have metastatic disease at time of diagnosis, with the liver being the most common site of metastases (77%) [3–5]. Another 5% of patients with primary non-metastatic disease develop metachronous metastases within the first year, increasing to up to 15% at five-year follow-up [2]. Several

Abbreviations: AUC, area under the ROC curve; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CT, computed tomography; E, entropy; LoG, Laplacian of Gaussian; M, mean grey-level intensity; MRI, magnetic resonance imaging; N-stage, nodal stage; OR, odds ratio; PET-CT, Positron emission tomography–computed tomography; PVP, portal venous phase; ROC, receiver operating characteristic; T-stage, tumour stage; U, uniformity; VOI, volume of interest

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strategies have been explored to predict which patients are at risk of developing metachronous metastases. By identifying these patients, a different strategy with additional chemotherapy or intensified follow-up might be chosen. A known predictor for the development of colorectal metastases is an increased carcinoembryonic antigen (CEA) level [6]. Other factors are higher T-stage, lymph node metastases and male sex [3,7,8]. From an imaging perspective, a potentially promising tool is CT-texture analysis. Texture analysis refers to a mathematical approach to analyse variations in grey-level intensities within an image or region of interest to provide quantitative measures ('texture features') reflecting spatial heterogeneity [9–11]. Although several methods of texture analysis have been described in literature, the most commonly used technique is statistical-based texture analysis. The most basic form of statistical texture analysis involves first-order statistics, which focuses on the distribution of grey-level frequencies within an image, derived from the histogram of pixel intensities [11–13]. Commonly reported texture features include the 'mean intensity', 'entropy' and 'uniformity'. The mean intensity reflects the average pixel value or 'intensity' of a region of interest. Entropy is a measure that gives an indication of the irregularity of the grey-level distribution, while conversely the uniformity is indicative of its regularity. A higher entropy (and low uniformity) typically reflects a more "heterogeneous" distribution of pixels (and thus a more heterogeneous underlying tissue structure) while on the other hand a high uniformity is associated with a more "homogeneous" distribution of pixels (and therefore a more homogeneous tissue structure).

Single-centre studies have demonstrated that changes in the CT-texture of the liver (increase in entropy and decrease in uniformity) can be observed when the liver is affected by metastatic disease, thereby suggesting that these texture features have potential to differentiate between patients with and without colorectal liver metastases [10,14]. It has been suggested that these changes may be related to the presence of occult micro metastases throughout the liver and/or diffuse changes in hepatic perfusion caused by the presence of metastatic liver disease [15–19]. Hypothetically, similar changes – albeit to a lesser extent – may already be present in an earlier phase, i.e. before the metastatic lesions become visible on morphological CT (computed tomography) assessment. If this were the case, CT-texture may also have potential as an imaging biomarker to predict upfront (at the time of primary staging) which patients who initially present without metastases are at risk of developing metastases at a later stage. This would be beneficial as CT is to date still the most widely used modality for staging of liver metastases and texture parameters can readily be obtained from routinely acquired clinical CT examinations.

The aim of this study was to evaluate in a multicentre study setting whether CT-texture analysis of the apparently non-diseased liver at the time of primary diagnosis has potential to predict patients at risk of developing liver metastases at a later stage.

2. Material and methods

Patients

This multicentre study analysed 165 patients (106 male, 59 female, median age 64 years, range 16–86 years) who were treated for colorectal cancer in one of three university hospitals between December 2006 and October 2013 (a time period selected based on adequate documentation of clinical patient data, availability of consistent quality imaging data and allowing for an adequate clinical follow-up period of at least 2 years). Patients routinely underwent contrast-enhanced liver or abdominal CT as part of their primary staging work-up. According to our country's national law, institutional review board approval and informed consent were not required for this retrospective study. Patients were divided into three ± equally sized subgroups:

- Group A, the 'no metastases group', consisted of 57 patients who had no evidence of liver metastasis at primary staging, or during ≥24 months of follow-up (established by means of clinical, laboratory (CEA) and imaging follow up).
- Group B, the 'synchronous metastases group', consisted of 54 patients who presented with synchronous liver metastases at the time of primary staging. The presence of metastases was confirmed by pathology (biopsy/surgery) in 17 patients, by corresponding positive findings on PET-CT in 7 patients, and by imaging follow-up in the other 30 patients who all had unresectable metastases, which were palliatively managed.
- Group C the 'metachronous metastases group', consisted of 54 patients who had no evidence of metastatic disease at primary staging but developed liver metastases (i.e. new and/or growing lesions on follow-up imaging) within 24 months after primary staging (median interval 12 months, range 2–24). In 21 patients these lesions were histopathologically proven to be colorectal liver metastases.

Inclusion criteria consisted of *(a)* histopathologically confirmed colorectal adenocarcinoma; *(b)* no evidence of extrahepatic metastatic sites on primary or follow-up imaging (CT, MRI and/or PET-CT); *(c)* availability of a primary staging CT including a portal venous phase; *(d)* no history of previous liver surgery; *(e)* no history of previous systemic treatment (chemotherapy); *(f)* no history of diffuse liver disease such as steatosis or cirrhosis; *(g)* no history of diffuse hepatic metastases, as this would leave too little 'normal' liver parenchyma to perform whole-liver texture analysis. Clinical follow-up (after resection of the primary tumour) was performed according to routine clinical guidelines as advocated in the participating centres. This included routine (3–6 monthly) clinical examination, CEA testing and follow-up imaging with CT, MRI and/or FDG-PET when indicated.

CT acquisition

A contrast-enhanced CT was performed as part of the routine work-up for CRC in all centres. All CT scans included a portal venous phase (PVP) scan of the liver and were acquired using different CT scanners (Philips Brilliance 64, Philips Medical Systems, Best, The Netherlands; Siemens Somatom Sensation 16, Somatom Sensation 64, Somatom Definition AS or Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany; Toshiba Aquilion 64, Toshiba Medical Systems, Tokyo, Japan; GE Lightspeed VCT 64, GE Healthcare, Little Chalfont, United Kingdom). PVP images were routinely obtained with a tube voltage of 100–120 kVp. The contrast medium (Ultravist 300–370 mgI/ml; Iopromide, Bayer Healthcare, Berlin, Germany or Visipaque 320mgI/ml; Iopromide, GE Healthcare, Eindhoven, The Netherlands) was prewarmed to 37° C (99°F) and administered intravenously as a bolus injection of 100–150 ml at a rate of 1,8–3,5 ml/s, followed by a saline flush of 20–40 ml. The scan delay for the PVP was set at 70–80 s. Slice thickness was 5 mm in two of the three study centres. In the third center the original slice thickness was 3 mm, which was reconstructed to 5 mm for assessment in this study.

Image assessment

CT images were transferred to an offline workstation for texture analyses and analysed using the open source software tool MRIcron [20]. An experienced reader (RCJB) manually traced the surface of the whole liver on the PVP images on each consecutive slice including all normal (apparently non-diseased) liver parenchyma, excluding the border of the liver, any visible lesions (any benign focal liver lesions or metastases), the caudate lobe (as this is often ill defined and difficult to discern from the vena cava), the inferior vena cava and large portal and hepatic veins to obtain volumes of interest (VOIs) of the whole liver volume, according to methods previously reported (Fig. 1) [10,14].