Texture analysis in colorectal liver metastases

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TEXTURE ANALYSIS IN COLORECTAL LIVER METASTASES

A potential imaging biomarker

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de
Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof.dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
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door

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1. General Introduction

1. General introduction

Colorectal cancer (CRC) is the most common form of cancer in The Netherlands, with 15.550 new cases in 2015¹. Incidence is expected to rise to 17.000 new cases in 2020 because of the implementation of the nationwide screening program, the growing incidence (especially in men) and the growing and ageing population¹. Nowadays, CRC is the second-most common cause of cancer-related death in Western countries^{2, 3}. Mortality is mainly related to the presence of metastatic disease. The liver is the most frequent and often unique site of metastasis in CRC, with metastases occurring both at the time of diagnosis (synchronous) in 14.5% as well as within five years after surgery on the primary tumour (metachronous) in 3.7% to up to 30.4%⁴.

In the last two decades, treatment of metastatic CRC has rapidly evolved with the availability of more effective chemotherapy regimens and more targeted therapies such as monoclonal antibodies (e.g. bevacizumab, cetuximab and panitumumab) that target the endothelial growth factor receptor or epidermal growth factor receptor⁵. Moreover, local treatment options have evolved with the introduction of minimally invasive techniques such as local ablative therapies (radiofrequency and microwave ablation) and chemo- and radioembolization techniques. As a result of these developments, median overall survival rates have improved considerably with reported 5-year overall survival rates of 30-60% for radically treated patients in recent studies compared to 9-16% in studies from 1999-2010^{4, 6, 7}.

These recent advances in the treatment of colorectal liver metastases (CRLM) have led to an increasing demand for more precise diagnostic imaging techniques to help guide and optimise personalised patient management. Although certainly not (yet) standard in all clinics, an important development is the increasing use of MRI to stage the liver. Particularly MRI with liver-specific contrast has proven superior sensitivity to detect even very small liver metastases, resulting in optimised treatment planning^{8, 9}. Nevertheless, in most hospitals to date, CT (computed tomography) remains the main 'workhorse' for the staging of CRC, also because it allows simultaneous staging of other potential metastatic sites including the lungs and peritoneal cavity⁹.

Apart from detecting and determining the extent of the metastatic disease, there are two important clinical issues in the imaging of CRLM: [1] analysing the response to systemic therapy and [2] predicting the course of the disease. Approximately 14.5% of patients initially present without metastases but develop metachronous liver metastases somewhere during the course of their disease. We

have yet to find the tools to help us determine which factors best predict the course of the disease and consequently to help us identify which patients are at risk. Moreover, once the metastatic disease is present it remains unclear which patients will likely show a good response to treatment and which patients will not. Here might be a window of opportunities because improved knowledge on these issues could help us to further tailor treatment according to a patient's individual risk profile. Imaging could play an important role in this regard.

So far, the mainstay of imaging evaluation has been to assess tumour morphology (e.g. shape, signal) and size, for example in the Response Evaluation Criteria in Solid Tumours (RECIST), one of the most widely used imaging assessment techniques to evaluate response¹⁰. In other words, we have so far mainly focussed on things that can be appreciated by the 'naked eye'. There is, however, much more information 'hidden' in images that could potentially provide us with more in-depth knowledge about the underlying tumour biology. This information can be distilled when we look at images with more sophisticated image post-processing methods.

Several methods of image post-processing and quantification exist, varying from relatively simple statistical methods such as histogram analysis of signal values within an image to more novel methods like Radiomics, which extract large amounts of imaging features using more advanced data-quantification algorithms¹¹. Within a broad spectrum of imaging features used in Radiomics, features related to image "texture" appears to be amongst the most promising¹². Image texture refers to the spatial distribution of signals intensities within a selected region of an image, for example within a tumour on CT¹³. When this spatial distribution is more irregular, this is associated with a more heterogeneous underlying tissue architecture¹². Tumours with a high heterogeneity have been shown to be associated with a more aggressive biology leading to poorer prognosis and treatment resistance. This heterogeneity may be captured by quantitative features derived from image texture analysis and therefore may have potential to act as imaging biomarkers to predict response and outcome^{12, 14-16}. The major additional benefit is that texture features can 'freely' be derived from any routinely acquired clinical imaging examination (for example CT or MRI) without the need for extra acquisitions or sophisticated image acquisition techniques.

So far most experience exists with texture analysis using CT data. At the start of this thesis project, evidence for CT texture analysis in oncology was scarce but promising. In a small number of (technical) pilot studies in relatively small patient cohorts (typically 10 to up to 50 patients) it was shown that CT texture

features from oesophageal tumours, primary and metastatic liver tumours, metastasized kidney tumours and colorectal malignancies hold promise to predict treatment response, disease progression and long-term outcome¹⁷⁻²³. In colorectal liver metastases in specific, the group of Ganesan et al were the first to show a potential benefit for texture analysis to predict disease outcome²⁴⁻²⁶. They also showed various correlations between liver texture features and related measures of disease such as hepatic perfusion and the presence of nodal and hepatic metastases²⁷. Whether there could be any meaningful role for CT texture analysis in the clinical management of patients with colorectal liver metastases remains to be determined by further research and was the main focus of this thesis.

Aims of this thesis

The aims of this thesis are to review current evidence on the role of imaging in the assessment of colorectal liver metastases and to investigate what can be the potential added clinical role of novel more advanced image quantification techniques, in particular, textural analysis.

The main study questions are:

1. What is the diagnostic performance of currently available imaging techniques to assess response to of colorectal liver metastases to chemotherapy?
2. What is the added value of CT texture analysis for the assessment of colorectal liver metastases?

Outline of this thesis

Chapter 2 presents a comprehensive overview of current literature on the potential of different imaging modalities and techniques to predict the response to chemotherapy in colorectal liver metastases.

In **Chapter 3**, we conducted a multicentre study to investigate whether whole liver CT texture analysis is capable of predicting the presence of metastatic liver disease and the development of metachronous colorectal liver metastases.

In **Chapter 4**, we aimed to improve our method of texture analyses by investigating whether performing a segmental liver texture analysis instead of a whole liver approach has added benefit to predict metachronous disease.

Chapter 5 evaluates more in depth the relation between the CT texture of colorectal liver metastases and the surrounding liver parenchyma in order to get a better insight into the underlying mechanism of disease. The aim was to assess if the ratio between the texture of the metastases and background liver can be of added value as a predictive or prognostic imaging marker.

Finally, in **Chapter 6**, we performed a pilot study to investigate potential correlations between CT texture features of the liver and corresponding quantitative imaging characteristics derived from liver diffusion-weighted MRI in patients with colorectal cancer.

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2. Advanced imaging to predict response to chemotherapy in colorectal liver metastases – a systematic review

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Abstract

Background

The assessment of colorectal liver metastases (CRLM) after treatment with chemotherapy is challenging due to morphological/functional without changes in size. The aim of this review was to assess the value of FDG-PET, FDG-PET-CT, CT and MRI in predicting response to chemotherapy in CRLM.

Methods

A systematic review was undertaken based on PRISMA statement. PubMed and Embase were searched up to October 2016 for studies on the accuracy of PET, PET-CT, CT and MRI in predicting RECIST or metabolic response to chemotherapy and/or survival in patients with CRLM. Articles evaluating the assessment of response after chemotherapy were excluded.

Results

Sixteen studies met inclusion criteria and were included for further analysis. Study results were available for 6 studies for FDG-PET(-CT), 6 studies for CT and 9 studies for MRI. Generally, features predicting RECIST or metabolic response often predicted shorter survival. The ADC (apparent diffusion coefficient, on MRI) seems to be the most promising predictor of response and survival. In CT-related studies, few attenuation-related parameters and texture features show promising results. In FDG-PET(-CT), findings were ambiguous.

Discussion

Radiological data on the prediction of response to chemotherapy for CRLM is relatively sparse and heterogeneous. Despite that, a promising parameter might be ADC. Second, there seems to be a seemingly counterintuitive correlation between parameters that predict a good response and also predict poor survival.

Introduction

Approximately 15-25% of patients with colorectal cancer will present with synchronous metastases, with the liver as the predominant site^{1,2}. Patients with potentially resectable synchronous colorectal liver metastases (CRLM) usually receive neoadjuvant chemotherapy in order to achieve shrinkage of the liver metastases, which increases the chance of a curative resection³. Response assessment after chemotherapy is mainly done using cross-sectional imaging and is used to help determine whether the response is sufficient to treat a patient with curative intent⁴. The most commonly used system for the assessment of response after neoadjuvant chemotherapy is Response Evaluation Criteria In Solid Tumours (RECIST)⁵. RECIST is based on size measurements, which are known to have limitations. For example, as a result of successful treatment, metastatic lesions can undergo necrotic changes without a notable reduction in lesion size^{6,7}. In such cases, RECIST will fail to recognise a treatment response. Moreover, chemotherapy can affect the liver parenchyma in such a way that it impairs the assessment of lesions. Diffuse fatty changes may conceal metastases on CT, while focal steatosis may mimic tumour^{8,9}. To overcome these issues, it has been suggested to explore imaging techniques that are capable of predicting the response *before* the onset of chemotherapy instead of assessing it *after* treatment has been completed. An additional benefit of such an approach is that it may create opportunities to adapt and optimise the neoadjuvant treatment based on the anticipated treatment response. Several imaging studies have addressed the topic of pre-treatment response prediction in patients with CRLM, using PET, CT and MRI as data sources. More advanced (functional) imaging and image post-processing techniques such as diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI or texture analyses are currently being explored^{10,11}. So far, there is no clear consensus on which imaging modality is the most promising technique. Therefore, the objective of the present study was to perform a systematic review in order to identify the most promising imaging technique for predicting the response to chemotherapy in patients with CRLM with the aim of identifying areas for future research.

Methods and materials

PubMed, MEDLINE and Embase were searched from January 1985 to October 2016 using the following free search terms: 'colorectal neoplasms or carcinoma or

cancer', 'neoplasm metastasis or hepatic or liver metastases', 'chemotherapy, adjuvant', 'positron emission tomography' or 'PET', 'magnetic resonance imaging' or 'MRI', 'computed tomography' or 'CT' and 'PET-CT' or 'PET/CT'. Also, Mesh terms were used for the search ('Colorectal Neoplasms', 'Neoplasm Metastasis', 'Chemotherapy, Adjuvant', 'Positron-Emission Tomography', 'Magnetic Resonance Imaging' and 'Computed Tomography'. No language restriction was used. Studies were included when they met the following criteria: (1) inclusion of patients with CRLM, (2) systemic chemotherapy in a non-experimental regime (capecitabine, 5-fluorouracil combined with leucovorin, oxaliplatin, irinotecan and/or bevacizumab)³, (3) PET-CT, MRI or CT before the start of chemotherapy (4) outcome consisting of either histology, RECIST, progression-free survival (PFS)/time to progression (TTP) or overall survival (OS) as a reference standard. Case reports, reviews, articles that evaluated detection of CRLM and studies that evaluated response after chemotherapy were excluded.

Two reviewers (RB & MM) independently searched for eligible studies. Titles and abstracts were checked in order to select studies, which potentially met the inclusion criteria. Full-text copies of the selected studies were independently reviewed by both reviewers to evaluate which studies met the inclusion criteria. In case of disagreement consensus was reached. References were checked for additional eligible studies. Data that were extracted from the studies were: (1) number, gender and age of patients, (2) study objective, (3) type of reference standard, (4) duration of follow-up, (5) parameter of analysis (e.g. maximum diameter of a lesion) and (6) unit of analysis (lesion or patient-based analysis). Study quality was assessed with the QUADAS-2 checklist¹². Results are reported according to the PRISMA statement¹³.

Results

Literature Search

The search yielded 208 studies of which 16 met inclusion criteria for further analysis, Figure 1 shows the study selection procedure in a PRISMA flowchart. 45 studies were selected based on titles and abstracts. Of these 45 articles, 29 were excluded¹⁴⁻⁴², leaving 16 articles for inclusion^{10,11,43-56}. More information on the excluded articles and the reason for exclusion is available in the supplementary data.

Of the included studies, 12/16 studies had a low risk of selection bias^{10,11,44,45,47,48,50-52,54-56}. Selection bias was introduced in four studies due to unclear enrolment or inappropriate exclusions^{11,43,46,53}. The most encountered quality issue concerned the reference standard (RECIST) and its blinding^{10,11,43-46,49,50,52,55,56}. There were no concerns regarding index test and reference standard applicability. Results of the quality assessment with the QUADAS-2 checklist are available as supplementary data. Based on the overall quality of the studies, none of them was excluded.

Of the 16 articles included, 11 studied a single modality^{10,43,45,46,48-52,54,55} and 5 studies compared two modalities^{11,44,47,53,56}. In total, 5 articles studied FDG-PET^{11,44,50,53,56}, 1 article studied the FDG-PET-CT⁴⁷, 6 articles studied CT^{43,45-47,51,53} and 9 articles studied MRI^{10,11,44,48,49,52,54-56}. The number of patients ranged from 10 to 145 patients per study, with a total of 560 patients evaluated in all studies. The percentage of male patients varied from 54-80%. The reference standards/outcome measures were as follows: 11 studies used RECIST (1.1)^{10,11,43,46-50,52,53,55}, 5 studies used PFS, TTP and OS^{44,45,50,54,56} and only one study used histology after surgery (tumour regression grade, TRG)⁵¹. Individual study characteristics are presented in the supplementary data.

Figure 1. PRISMA flow chart

FDG-PET studies

Table 1 provides the most important results from the studies on PET. The main input variables were SUV_{max} (maximum standardised uptake value), SUV_{mean} (mean standardised uptake value), MR_{glc} (glucose metabolic rates), TLG (total lesion glycolysis) and MTV (metabolic tumour volume). Several reports showed that SUV_{max} before treatment is significantly lower in patients with a favourable outcome, including RECIST responders^{11,50}, and patients with longer OS⁴⁴. However, other studies found no correlation between SUV_{max} (or SUV_{mean}) and OS^{47,53} or PFS^{44,47,50}. Kim et al. even found contradictory results with higher SUV_{mean} value in responders⁴⁷. According to Vriens et al. a lower MR_{glc} resulted in a better OS and PFS ($P=0.002-0.005$)⁵⁶. A higher TLG resulted in a lower OS ($P=0.01$) but had no influence on the PFS⁴⁴.

CT studies

Table 1 shows the most important results from the studies on CT. A wide range of parameters was tested, including perfusion-related parameters (blood flow, blood volume, portal/arterial liver perfusion, AEF (arterial enhancement fraction)), size and volume metrics (maximum diameter, measured in one, two or three planes, tumour to liver ratios or tumour volume), attenuation parameters (maximum, mean or minimum Hounsfield units (HU)) and texture features (e.g. entropy, uniformity, skewness). Joo et al. reported a lower AEF measured in the tumour in responders ($P=0.005$)⁴⁶, reflecting hypervascular lesions. A higher minimum HU of the three largest lesions leads to a longer OS ($P=0.02$) without any influence on TTP⁴⁵. According to Ahn et al. higher mean HU in the tumour was independently associated with response to chemotherapy ($P=0.017$)⁴³, while Huellner et al. found no significant difference in PFS or OS ($P=0.13-0.81$)⁴⁵. Skewness (measured in 2D texture analysis) was significantly lower in responders ($P=0.025$)⁴³. All other perfusion-, metric- or attenuation related parameters and textural features were not significantly different between responders and non-responders^{34,47,51,53}.

MRI studies

Table 1 shows the most important results from the studies on MRI. Various sequences and techniques were evaluated, with three studies focusing on ADC (apparent diffusion coefficient; the quantification of diffusion in a lesion or area, where a lower ADC reflects more dense tissue, corresponding to tumour⁵⁷) related parameters, others focusing on DCE-MRI (dynamic contrast-enhanced MRI in which the inflow and outflow of contrast is assessed) related parameters, such as k_{ep} (rate constant of Gd-DTPA uptake), k^{trans} (transfer constant), v_e (extravascular extracellular space per unit volume of tissue), and the remaining studies focusing on HPI (hepatic perfusion index), T2* MRI (susceptibility-weighted MRI) or T2 relaxation times. Two studies described a significantly lower ADC in responders ($P=0.000-0.002$)^{48,49}. In contrast, Heijmen et al. described that a lower ADC value was associated with a worse outcome in terms of shorter PFS and OS⁴⁴. ADC skewness, kurtosis and variance were not associated with response to chemotherapy ($P=0.21-0.85$)⁴⁹. Coenegrachts et al. stated that k_{ep} was lower in responders, when measured on the slice level through the largest diameter of the target lesion ($P<0.001$)¹⁰. Other studies did not confirm this and reported no difference in k_{ep} between responders and non-responders and no association with PFS or OS^{55,56}. K_{trans} , v_e and HPI were not predictive of response to chemotherapy and were not related to PFS or OS^{11,54-56}. A smaller maximum axial diameter, measured on T2,

indicated a better PFS and OS ($P=0.032$ - 0.039)⁵⁶. A higher T2* lead to a shorter OS, but was not related to PFS ($P=0.01$)⁴⁴. T2 relaxation time was not significantly different between responders and non-responders ($P=0.83$)⁵².

Data and details on FDG-PET(-CT), CT and MRI from all the included studies are provided in supplementary tables.

Table 1. Overview of most promising results per modality

Author	Reference standard	Parameter	Lesion by lesion / Per patient	Outcome
FDG-PET				
De Bruyne	RECIST	SUV _{max}	Lesion by lesion	Lower SUV _{max} in responders
Heijmen	Survival	SUV _{max} TLG	Per patient	Lower SUV _{max} → longer OS Lower TLG → longer OS
Kim	RECIST	SUV _{mean3D}	Per patient	Higher SUV _{mean3D} in responders
Mertens	RECIST	SUV _{max} SAM	Per patient	Lower SUV _{max} in responders Lower SAM in responders
Vriens	Survival	MR _{gdc}	Per patient	Lower MR _{gdc} → longer OS Lower MR _{gdc} → longer PFS
CT				
Ahn	RECIST	Skewness 2D Mean attenuation 3D SD attenuation 3D	Per patient	Lower Skewness 2D in responders Higher Mean attenuation 3D in responders Narrower SD attenuation 3D in responders
Huellner	Survival	Minimum attenuation	Per patient	Lower minimum attenuation → longer OS
Joo	RECIST	AEF	Per patient	Higher AEF in responders
MRI				
Coenegrachts	RECIST	K _{ep}	Lesion by lesion	Higher K _{ep} in responders
Heijmen	Survival	ADC T2* ADC	Per patient	Higher ADC → longer OS Lower T2* → longer OS Higher ADC → longer PFS

Koh	RECIST	Mean ADC 0-500 Mean ADC 150-500	Lesion by lesion	Lower ADC in responders Lower ADC in responders
Liang	RECIST	ADC mean ADC 1 st percentile ADC 10 th percentile ADC 50 th percentile ADC 90 th percentile ADC 99 th percentile	Per Patient	Lower ADC mean in responders Lower ADC 1 st percentile in responders Lower ADC 10 th percentile in responders Lower ADC 50 th percentile in responders Lower ADC 90 th percentile in responders Lower ADC 99 th percentile in responders
Vriens	Survival	Max axial diameter	Per patient	Larger max axial diameter à longer OS

Note. – P -values < 0.05 were considered significant, when both univariate and multivariate results are studied, only significant results of multivariate analyses are reported.

SD: standard deviation

K : exchange between plasma and extravascular extracellular space

SUV_{max} : maximum standard uptake value

ADC: apparent diffusion coefficient

T2*: susceptibility-weighted

TLG: total lesion glycolysis

AEF: arterial enhancement fraction of the lesions

SUV_{mean30} : average value of SUV of the voxels which show $\geq 30\%$ value of SUV_{max}

SAM: standardised added metabolic activity

Discussion

The aim of this systematic review was to explore which imaging techniques may be of value for the pre-treatment prediction of response to chemotherapy in CRLM. The literature on this topic is rather heterogeneous with regard to outcome and techniques used per modality. Therefore, the results should be interpreted with care. Most studies focus on advanced imaging techniques. The ADC derived from diffusion weighted imaging in MRI seems to be the most promising predictor of response and survival. For CT, most results are disappointing; only a few attenuation-related parameters and texture features show promising results. These results are mostly described in one single study, which makes them less robust than the data on ADC. In FDG-PET, the findings were ambiguous. Some reports showed that SUV_{max} before treatment is significantly lower in patients with a favourable outcome, while other studies found no correlation or even a contradictory correlation.

Despite the heterogeneity in techniques and outcome parameters, there was an unexpected counterintuitive finding that parameters that predict a good response to chemotherapy (in terms of RECIST) also seem to be predictive of a worse prognosis. For example, in CT, a higher attenuation was associated with a better response, but a shorter survival^{43,45}. Similarly, in MRI, ADC was lower in responders while it was higher in patients with a longer OS^{48,49}. One possible explanation for this phenomenon might be related to angiogenesis and tumour vascularization. Angiogenesis is a key cancer hallmark involved in tumour growth and metastasis that leads to the formation of new blood vessels^{58,59}. As a general rule, patients with highly vascular tumours have a beneficial outcome when treated with radiotherapy or chemotherapy⁶⁰, as these tumours exhibit an oxygen-rich environment, which makes them more sensitive to therapy^{58,60,61}. Although highly vascular tumours usually respond better, they are also more aggressive, leading to faster tumour growth and a higher propensity to metastasize⁶⁰, which might explain the poorer survival in these patients. In other malignancies, such as non-small cell lung carcinoma (NSCLC) and cervical cancer, similar contradictory findings have been described⁶²⁻⁶⁶. Contrary to the findings for MRI and CT, for FDG-PET the relation between a good response and poor survival was not clearly found. Tumours with a high glucose metabolism are likely to have a higher vascularization to supply sufficient glucose for growth⁶⁷. This would be expected to lead to a good response and poor survival, if the abovementioned hypothesis is followed. Two studies indeed reported lower glucose metabolism to be associated

with longer survival^{44,56}. However, the reported results regarding the association between glucose metabolism and response were conflicting: Kim et al. found a higher SUV_{mean} in responders⁴⁷, but Mertens et al. reported a lower baseline SUV_{max} in patients that showed a good response^{11,50}. As suggested by the authors, this difference in the ability to predict response might be explained by the use of bevacizumab in their treatment regimen⁵⁰, which does improves survival⁶⁸, but does not lead to an increase in RECIST-defined response.

Another explanation for the counterintuitive finding that a good response is correlated with a poorer survival could be the definition of response in radiological studies. Most studies use RECIST as the reference standard, which limits the quality of studies on CRLM in general, as RECIST is a suboptimal reference standard due to the use of size as a response parameter. Up until now, only one study has been conducted to determine the accuracy of RECIST in the assessment of CRLM, which has been conducted before the wide introduction of targeted therapies⁶⁹. In the era of targeted therapies, evaluation based on tumour size alone might no longer be the best option for response assessment because of necrosis and cavitation⁵. Another study showed that neither RECIST nor mRECIST is able to assess the amount of residual viable burden in CRLM⁷⁰. This could imply that the use of RECIST as an indication for long-term outcome, is not reliable, which could explain the counterintuitive finding in our study. Despite these critics, there is yet no other reliable method of response assessment that can replace histopathology⁷¹. In the specific case of CRLM, histopathology is often unavailable, as many patients will not undergo a surgical resection. Alternative endpoints have been proposed. Prolongation of OS is generally the most relevant measure of clinical response in oncological research^{72,73}. The fact that the current review showed that factors predicting a good response seem to be associated with poor survival, supports the advice against using alternative endpoints in clinical research with targeted therapies and stress the need for a reliable non-invasive tool to assess response other than RECIST.

There are some limitations to this study. The main limitation is that studies are heterogeneous with regard to the study population, scan protocols, types of chemotherapy and the use of targeted therapy. This made it impossible to conduct a meta-analysis. Second, as described above, the lack of histopathology as a reference standard reduces study quality significantly. However, it is difficult to overcome this issue as this is a problem in almost all studies focusing on imaging (and treatment) of CRLM. Third, the quality of the studies was assessed by the

QUADAS-2 guidelines, but subgroup analyses for good quality studies could not be performed due to a small sample size and because the main reason for lower quality was the lack of histopathology as a reference standard. Last, this systematic review aimed at predicting response by imaging, while from a clinical perspective prediction of non-response is very relevant. The results of this systematic review can be used when new studies are designed that focus on prediction of response as well as non-response to therapy.

In conclusion, this systematic review shows that the data on prediction of response to chemotherapy for CRLM are relatively sparse and heterogeneous. Despite that, a promising parameter to predict response to chemotherapy in CRLM before treatment might be ADC. There seems to be a correlation between parameters that predict a good response and also predict poor survival. Although the underlying mechanism is not entirely clear, it might be explained by increased angiogenesis and vascularization which makes tumours more responsive, but also more aggressive. Alternatively, the known limitations of the use of RECIST for response assessment may play a role in this counterintuitive finding. RECIST was mainly used as a reference standard, despite the known limitations of a size-based response assessment system. Therefore - especially with the increasing use of new targeted chemotherapeutic agents - there is a strong need for studies that use histopathology as a reference standard or the development of an alternative reliable reference standard other than RECIST.

Supplementary tables

Table S1. QUADAS

Author, year	Risk of Bias			Flow & Timing			Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow & Timing	Patient selection	Index test	Reference standard		
Ahn, 2016	?	☹	☺	☺	☺	☺	☺		☺
Coenegrachts, 2012	☺	?	☺	☺	☺	☺	☺		☺
De Bruyne, 2012	☹	?	☺	?	☹	☺	☺		☺
Heijmen, 2015	☺	?	☹	☺	☺	☺	☺		☺
Huellner, 2012	☺	?	☺	☺	☺	☺	☺		☺
Joo, 2011	?	?	☺	☺	☺	☺	☺		☺
Kim, 2012	☺	☺	☺	☺	☺	☺	☺		☺
Koh, 2007	☺	☺	☺	☺	☺	☺	☺		☺
Liang, 2015	☹	?	☺	☺	☺	☺	☺		☺
Mertens, 2013	☺	?	☺	☺	☹	☺	☺		☺
Rao, 2016	☺	?	☺	?	☺	☺	☺		☺
Raza, 2012	☺	?	☺	☺	☺	☺	☺		☺
Seyal, 2015	?	☺	☺	☺	☺	☺	☺		☺
Tampellini, 2016	☺	☺	☺	☺	☺	☺	☺		☺
van Laarhoven, 2007	☺	?	☺	☺	☺	☺	☺		☺
Vriens, 2009	☺	?	☺	?	☺	☺	☺		☺

Table S2. Study information

Author	Year	Modality	N	Male (%)	Mean age (range)	Population	Chemotherapy	Blinding	Study design	Reference Standard
Ahn	2016	CT	145	66%	63.6 (36-87)	Pathologically confirmed synchronous or metachronous CRLM	FOLFOX / FOLFIRI	One radiologist performed textual analyses, one other radiologist used the reference standard	Retrospective case-control study	RECIST
Coene-grachts	2012	MRI	10	80%	62.3 (48-82)	Pathologically confirmed synchronous, inoperable CRLM	FOLFIRI-B	Image analysis in consensus (two radiologists), unclear assessment of reference standard	Prospective	RECIST
De Bruyne	2012	PET / MRI	19	63%	61	Synchronous or metachronous, potentially resectable CRLM	FOLFOX-B / FOLFIRI-B / none (N=1)	One nuclear medicine physician performed PET analysis, unclear assessment of MRI and reference standard	Prospective	RECIST / metabolic response
Heijmen	2015	PET / MRI	39	72%	62 (29-77)	Pathologically confirmed, inoperable CRLM with Karnovsky performance status > 70	CAPOX / CAPOX-B / Capecitabine-B / FOLFOX / UFT	No blinding of assessment of MRI, PET or reference standard	Prospective	Survival (PFS / OS)

Huellner	2012	CT	55	64%	64* (20-84)	Synchronous CRLM, pathologically confirmed CRC	FOLFOX / CAPOX / XELOX / XELIRI / FOLFIRI +/- bevacizumab or cetuximab	Image analysis by two radiologists (no consensus, no blinding)	Retrospective	Survival (TTP / OS)
Joo	2011	CT	28	67%	61.4 [†]	Pathologically confirmed hepatic metastases of i.a. CRC origin	Unknown	Image analysis in consensus (two radiologists), unclear assessment of reference standard	Retrospective	RECIST
Kim	2012	CT / PET-CT	17	76%	58.1 (37-75)	Pathologically confirmed CRLM, ECOG performance status 0-2	XELOX / FOLFOX / FOLFIRI	Image analysis by two radiologists or three nuclear medicine physicians (consensus, blinded), unclear assessment of reference standard	Prospective	RECIST
Koh	2007	MRI	20	60%	57.3 (45-72)	Pathologically confirmed CRLM, potentially resectable	CAPOX	Image analysis by one radiologist and one MR technologist (consensus, blinded), unclear assessment of reference standard	Prospective	RECIST
Liang	2015	MRI	53	64%	59.9	Synchronous or metachronous CRLM, without extrahepatic metastases	FOLFOX / XELOX +/- bevacizumab or cetuximab	Image analysis by one radiologist, unclear assessment of reference standard	Retrospective	RECIST

Mertens	2013	PET	19	63%	61*	Synchronous or metachronous, potentially resectable CRLM	FOLFOX-B / FOLFIRI-B / none (N=1)	Image analysis by one radiologist, unclear assessment of reference standard	Prospective	Survival (PFS / OS)
Rao	2016	CT	21	71%	69* (46-83)	Synchronous CRLM, pathologically confirmed CRC, without extrahepatic metastases	XELOX +/- bevacizumab	No blinding of assessment of CT, RECIST or reference standard	Retrospective	Pathology
Raza	2012	MRI	11	55%	59 (30-79)	CRLM, pathologically confirmed CRC	CAPOX	No blinding of assessment of MRI or reference standard	Retrospective	RECIST
Seyal	2015	CT / PET	20	75%	54.5 (29-68)	CRLM treated with bevacizumab-containing chemotherapy	FOLFOX-B / FOLFIRI-B / Capecitabine-B	Image analyses MDCCT by two radiologists (blinded to PET results), image analysis PET and reference standard unclear	Retrospective	RECIST
Tampel- lini	2016	MRI	43	58%	64.5* (48-79)	CRLM	(Chronomodulated) FOLFOX / XELOX	No blinding of assessment of MRI or reference standard	Prospective	Survival (PFS / OS)
van Laar- hoven	2007	MRI	37	54%	59 (33-77)	CRLM, pathologically confirmed CRC	5FU/LV / Capecitabine / CAPIRI / FOLFOX	Reference standard assessed by one radiologist (blinded to results of image analysis), unclear image analysis	Prospective	RECIST

Vriens	2009	MRI / PET	23	74%	61.5 (44-78)	Synchronous or metachronous CRLM, patho- logically con- firmed CRC	Irinotecan / Capecitabine / CAPIRI / CAPOX / FOLFOX / 5FU/LV	No blinding of as- sessment of MRI or reference standard	Prospective	Survival (PFS / OS)

Note. –

* median

† mean age of entire study population (72)

Table S3. Results CT

Author	Reference standard	Parameter	Mean responder - non-responder	Lesion by lesion / per patient	P	Outcome
Ahn	RECIST	Mean attenuation 2D *	78.59 – 65.98 HU	Patient	<0.001	Higher Mean attenuation 2D in responders
		SD attenuation 2D *	21.69 – 22.59 HU		0.214	
		Skewness 2D *	0.02 – 0.33		0.001	Lower Skewness 2D in responders
		Kurtosis 2D *	-0.11 – 0.13		0.063	
		Entropy 2D *	4.28 – 4.35		0.147	
		Homogeneity 2D *	0.01 – 0.02		0.004	Lower Homogeneity 2D in responders
		5 th percentile 2D *	44.34 – 30.75 HU		<0.001	Higher 5 th percentile 2D in responders
		10 th percentile 2D *	50.5 – 37.06 HU		<0.001	Higher 10 th percentile 2D in responders
		25 th percentile 2D *	61.98 – 48.58 HU		<0.001	Higher 25 th percentile 2D in responders
		50 th percentile 2D *	76.52 – 63.34 HU		<0.001	Higher 50 th percentile 2D in responders
		75 th percentile 2D *	92.65 – 80.17 HU		<0.001	Higher 75 th percentile 2D in responders
		90 th percentile 2D *	106.78 – 96.20 HU		0.001	Higher 90 th percentile 2D in responders
		95 th percentile 2D *	114.89 – 105.37 HU		0.003	Higher 95 th percentile 2D in responders
		Effective diameter 2D *	19.21 – 23.51 mm		0.090	
		Surface area 2D *	737.27 – 1383.74 mm ²		0.184	
		Sphericity 2D *	0.41 – 0.38		0.091	
		Discrete compactness 2D *	-1.74 – -1.79		0.361	
		GLCM moments 2D *	0.65 – 0.52		0.001	3D in responders
		GLCM ASM 2D *	0.0008 – 0.0006		0.224	Higher 50 th percentile 3D in responders
		GLCM IDM 2D *	0.08 – 0.08		0.22	Higher 75 th percentile 3D in responders
		GLCM Contrast 2D *	319.70 – 447.99		0.15	Higher 90 th percentile 3D in responders
		GLCM Entropy 2D *	3.23 3.31		0.069	Higher 95 th percentile 3D in responders
		Mean attenuation 3D *	82.94 – 71.76 HU		<0.001	
		SD attenuation 3D *	21.69 – 25.06 HU		0.001	
		Skewness 3D *	0.05 – 0.12		0.265	
		Kurtosis 3D *	0.04 – 0.64		0.334	
		Entropy 3D *	4.38 – 4.49		0.017	
		Homogeneity 3D *	0.01 – 0.02		0.002	Higher GLCM moments 3D in responders

5 th percentile 3D *	47.65 – 33.87 HU	< 0.001	Higher GLCM moments 2D in responders
10 th percentile 3D *	54.38 – 40.98 HU	< 0.001	
25 th percentile 3D *	66.52 – 53.74 HU	< 0.001	
50 th percentile 3D *	81.60 – 69.64 HU	< 0.001	
75 th percentile 3D *	96.96 – 87.08 HU	0.001	
90 th percentile 3D *	110.43 – 102.26 HU	0.005	Higher Mean attenuation 3D in responders
95 th percentile 3D *	117.85 – 111.45 HU	0.02	Narrower SD attenuation 3D in responders
Volume 3D *	7973.63 – 41858.58 mm ³	0.375	
Effective diameter 3D *	38.66 – 58.39 mm	0.481	
Surface area 3D *	1290.81 – 3007.38 mm ²	0.265	
Sphericity 3D *	0.64 – 0.63	0.481	Lower Entropy 3D in responders
Discrete compactness 3D *	0.22 – 0.26	0.52	Lower Homogeneity 3D in responders
GLCM moments 3D *	0.71 – 0.58	0.001	Higher 5 th percentile 3D in responders
GLCM ASM 3D *	0.0003 – 0.0002	0.343	Higher 10 th percentile 3D in responders
GLCM IDM 3D *	0.08 – 0.07	0.093	Higher 25 th percentile
GLCM Contrast 3D *	577.39 – 703.07	0.15	
GLCM Entropy 3D *	3.50 – 3.59	0.46	
Skewness 2D †	0.02 – 0.33	0.025	Lower Skewness 2D in responders
Mean attenuation 3D †	82.94 – 71.76 HU	0.017	Higher Mean attenuation 3D in responders
SD attenuation 3D †	21.69 – 25.06 HU	0.002	Narrower SD attenuation 3D in responders

Huelhner	OS	Minimum attenuation § Maximum attenuation § Mean attenuation § Longest diameter 1D Longest diameter 2D Longest diameter 3D Sum Longest Diameters Tumour To Liver Ratio § Tumour To Liver Ratio all Volume largest lesion Minimum attenuation § Maximum attenuation § Mean attenuation § Longest diameter 1D Longest diameter 2D Longest diameter 3D Sum Longest Diameters Tumour To Liver Ratio 3 Tumour To Liver Ratio all Volume largest lesion	7.9 HU 68.2 HU 126.5 HU 46.3 mm 2919 mm ² 231650 mm ³ 74.5 mm 6.28 % 9.66 % 185342 mm ³ 7.9 HU 68.2 HU 126.5 HU 46.3 mm 2919 mm ² 231650 mm ³ 74.5 mm 6.28 % 9.66 % 185342 mm ³	Patient	0.02 0.75 0.81 0.21 0.19 0.21 0.15 0.34 0.39 0.84 0.5 0.46 0.13 0.74 0.72 0.39 0.35 0.96 0.19 0.11	Lower minimum attenuation → longer OS
Joo	RECIST	AEF (tumour) AEF (adjacent parenchyma) AEF (parenchyma)	65.5 – 51.3 37.6 – 28.0 27.5 – 24.2	Patient	0.005 0.072 0.051	Higher AEF (tumour) in responders
Kim	RECIST	Blood flow Blood volume Flow extraction product Arterial liver perfusion Portal liver perfusion Hepatic perfusion index	43.9 – 38.1 ml/100ml/min 4.6 – 3.9 ml/100ml 26.4 – 25.4 ml/100ml/min 32.6 – 22.8 ml/100ml/min 19.5 – 19.2 ml/100ml/min 58.2 – 55.8 %	Patient	0.370 0.321 0.815 0.673 0.481 0.673	

Rao	Histology (TRG)	Mean intensity (no filtration)	55.54 – 54.32 -1.89 – -3.12 -15.15 – -20.64 -33.76 – -44.38 6.37 – 6.30 7.53 – 7.34 7.27 – 7.22 7.12 – 7.08 0.015 – 0.016 0.0072 – 0.0080 0.0079 – 0.0083 0.0092 – 0.0094	Patient	ns ns ns ns ns ns ns ns ns ns ns
		Mean intensity ($\sigma = 0.5$)			
		Mean intensity ($\sigma = 1.5$)			
		Mean intensity ($\sigma = 2.5$)			
		Entropy (no filtration)			
		Entropy ($\sigma = 0.5$)			
		Entropy ($\sigma = 1.5$)			
		Entropy ($\sigma = 2.5$)			
		Uniformity (no filtration)			
		Uniformity ($\sigma = 0.5$)			
		Uniformity ($\sigma = 1.5$)			
		Uniformity ($\sigma = 2.5$)			
Seyal	RECIST	LAD	32.97 mm	Lesion	0.566
		Volume	24.78 mL		0.617

Note. - OS: overall survival; PFS: progression free survival; TRG: tumour regression grade; ns: not significant

SD: standard deviation

GLCM: gray-level values in the matrix

ASM: angular second moment

IDM: inverse difference moment

AEF: arterial enhancement fraction

LAD: longest axial diameters of RECIST lesions

* tested in univariate analysis

† tested in multivariate analysis

§ measured in the three largest lesions

Table S4. Results MRI

Author	Reference standard	Parameter	Mean responder – non-responder	Lesion by lesion / per patient	P	Outcome
Coenegrachts	RECIST 1.1	K _{ep}	0.09852 – 0.07829 0.10622 – 0.10651	Lesion (whole ROI) Lesion (selective ROI)	<0.001 0.897	Higher K _{ep} in responders
De Bruyne	Metabolic response	AUC iAUC K _{trans}		Lesion	ns ns ns	
	OS / PFS	AUC iAUC K _{trans}		Patient	ns ns ns	
Heijmen	OS	ADC	1,21 * 10 ⁻³ mm ² /s	Patient	0.03	Higher ADC → longer OS
		T*	30,2 ms		0.01	Lower T* → longer OS
	PFS	ADC	1,21 * 10 ⁻³ mm ² /s		0.05	Higher ADC → longer PFS
		T*	30,2 ms		ns	
Koh	RECIST	Mean ADC 0-500 Mean ADC 150-500	1.63 – 2.21 * 10 ⁻³ mm ² /s 1.15 – 1.93 * 10 ⁻³ mm ² /s	Lesion	0.001 <0.001	Lower ADC in responders Lower ADC in responders
Liang	RECIST 1.1	ADC mean ADC variance ADC skewness ADC kurtosis	104.3 – 150.1 469.4 – 494.0 0.1 – 0.2 -0.3 – 0.1	Patient	0.001 0.85 0.66 0.21	Lower ADC mean in responders
		ADC 1 st percentile ADC 10 th percentile ADC 50 th percentile ADC 90 th percentile ADC 99 th percentile	64.5 – 108.8 78.7 – 124.5 103.0 – 149.0 130.6 – 177.1 149.7 – 197.8		0.002 0.002 <0.001 <0.001 <0.001	Lower ADC 1 st percentile in responders Lower ADC 10 th percentile in responders Lower ADC 50 th percentile in responders Lower ADC 90 th percentile in responders Lower ADC 99 th percentile in responders
Raza	RECIST	T ₂ relaxation time	67.3 – 71.4 ms *	Lesion	0.83	

Table S5. Results FDG-PET

Author	Reference standard	Parameter	Mean responder - non-responder	Lesion by lesion / per patient	P	Outcome
De Bruyne	RECIST Metabolic response	SUVmax	3.77 – 7.20 g/ml *	Lesion	0.021	Lower SUVmax in responders
		SUVmax	4.78 – 5.57 g/ml *			
Heijmen	OS	SUVmax	11,4 g/cm ³	Patient	0.02	Lower SUVmax → longer OS
		TLG	1084 g		0.01	Lower TLG → longer PFS
	PFS	SUVmax	11,4 g/cm ³		ns	
		TLG	1084 g		ns	
Kim	RECIST	SUVmax	9.2 – 6.5	Patient	0.074	Higher SUVmean30 in responders
		SUVmean30	5.2 – 3.5		0.046	
		MTV30	150.1 – 66.7		0.277	
		LG30	749.7 – 214.3		0.167	
Mertens	OS	SUVmax	5.8	Patient	0.88	Lower SUVmax in responders Lower SAM in responders
		SAM	376.9		0.88	
	PFS	SUVmax	5.8		0.81	
		SAM	376.9		0.38	
	RECIST	SUVmax	3.8 - 7.2 *		0.021	
		SAM	34 - 211 *		0.002	
Seyal	RECIST	SUVmax	0.27 – 0.23	Lesion	0.617	
Vriens	OS	MRglc	0.128 µmol/mL/min *	Patient	0.002 †	Lower MRglc → longer OS
					0.005 ‡	Lower MRglc → longer OS
	PFS	MRglc	0.128 µmol/mL/min *		0.002 †	Lower MRglc → longer PFS
					0.006 ‡	Lower MRglc → longer PFS

Note. - ns = not significant, not otherwise specified; OS: overall survival; PFS: progression free survival; TTP: time to progression
SUVmax: maximum standard uptake value
TLG: total lesion glycolysis
SUVmean30: average value of SUV of the voxels which show $\geq 30\%$ value of SUVmax
MTV30: 30% metabolic tumour volume
LG30: 30% lesion glycolysis
SAM: standardized added metabolic activity
MRglc: glucose metabolic rates
* median
† based on univariate analysis
§ based on multivariate analysis

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An abstract graphic in the top-left corner consisting of several overlapping, semi-transparent geometric shapes in shades of gray, creating a layered, crystalline effect.

3. 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 was 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 ($\sigma 0.5$ -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 ($\sigma 0.5$), 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.

Conclusion

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.

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-up². Several 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) level⁶. 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 heterogeneity⁹⁻¹¹. 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 intensities¹¹⁻¹³. 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 disease¹⁵⁻¹⁹. 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.

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 $\pm$ equally sized subgroups:

1. 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).
2. 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.

3. 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 300-370mgI/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 1,8-3,5ml/s, followed by a saline flush of 20-40 ml. The scan delay for the PVP was set at 70-80 sec. Slice thickness was 5 mm in two of the three study centres. In the third centre 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 MRICron²⁰. An experienced reader (RB) 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 (Figure 1)^{10, 14}.

Figure 1. Example of VOI's drawn on a portal venous phase computed tomography (CT) image of the liver with no filtration (a), fine filtration (0.5)(b), medium filtration (1.5)(c) and coarse filtration (2.5)(d). The border of the liver, any visible lesions, the inferior vena cava and large portal and hepatic veins were excluded.

Texture analysis

Texture analysis was performed using a dedicated script written in MATLAB (The MathWorks Inc., Natick, MA, 2000) by one of the authors (RS), according to methods previously reported^{14, 21}. It comprised two main stages: (a) image filtration, followed by (b) quantification of texture. Fine image filtration highlights very small structures (in the order of 1-2 mm), while coarse image filtration highlights larger structures (in the order of 6 mm). For image filtration, a Laplacian of Gaussian (LoG) band-pass filter was applied to the VOI using sigma (σ) values

of 0.5 (fine scale filtration), 1.5 (medium scale filtration) and 2.5 (coarse scale filtration). For each CT scan with a resolution different than 0.84 mm, the value of σ was modified to keep the physical size (in mm) of the filter constant. The texture of the liver parenchyma was characterized by mean grey-level intensity (M), entropy (E) and uniformity (U). The mathematical analysis technique used for this study is described in detail in the Appendix.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and Stata (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). Baseline patient characteristics were assessed using descriptive statistics. Further analysis comprised two steps:

1. Step 1: univariable multilevel logistic regression analyses were performed to identify potentially predictive clinical and texture parameters ($P < 0.1$) to differentiate between group A (no metastases) and group B (synchronous metastases). Multilevel analyses per CT scanner ($n = 10$ scanners, 3-4 different scanners per centre) were performed to account for potential differences in scan protocol (e.g. contrast timing, kVp) and CT software and hardware between scanners/centres.
2. Step 2: multivariable multilevel logistic regression analysis was performed to test the predictive value of the clinical and texture parameters identified in step 1 to differentiate between patients without metastases (group A) and patients who later developed metastases (group C). CT scanner was chosen as level for the multilevel analysis. Results were separately analysed for patients who developed metastases within 6 months (early), between 7-12 months (intermediate) and between 13-24 months (late).

Receiver operating characteristics (ROC) curves were constructed to determine the diagnostic performance of the various clinical/texture features in predicting the development of liver metastases. The diagnostic performance of different combinations of parameters was assessed using predicted probabilities derived from the logistic regression as input variables. Differences in diagnostic perfor-

mance between the different approaches were compared using the method described by Delong et al²².

Results

Patient characteristics

Patient characteristics are given in Table 1. The primary tumour was located in the colon in 88 patients and in the rectum in the other 77 patients. Fifty-seven patients had no metastases (during a follow-up of at least 24 months after primary diagnosis); 54 patients had synchronous metastases; 11 patients developed metastases within 6 months, 20 within 7-12 months and 23 after 13-24 months.

Table 1. Baseline characteristics of the 165 study patients

Characteristics	Group			
	A (N=57)	B (N=54)	C (N=54)	Total
Age (y)				
Mean	61	66	64	64
Range	16-86	22-85	46-81	16-86
Sex				
Male	32 (56.1)	40 (74.1)	34 (63.0)	106 (64.2)
Female	25 (43.9)	14 (25.9)	20 (37.0)	59 (35.8)
Primary tumour site				
Rectum	34 (59.6)	19 (35.2)	24 (44.4)	77 (46.7)
Colon	23 (40.4)	35 (64.8)	30 (55.6)	88 (53.3)
Tumour stage*				
T1	1 (1.8)	0	0	1 (0.6)
T2	8 (14.0)	2 (3.7)	3 (5.6)	13 (7.9)
T3	42 (73.7)	42 (77.8)	39 (72.2)	123 (74.5)
T4	6 (10.5)	1 (1.9)	12 (22.2)	19 (11.5)
Nodal stage*				
N0	25 (43.9)	15 (27.8)	15 (27.8)	55 (33.3)
N1-2	32 (56.1)	30 (55.6)	39 (72.2)	101 (61.2)
Interval until metastases (m)†				
	N/A	N/A	12 (2-24)	N/A
Carcinoembryonic antigen (CEA) at the time of primary diagnosis				
Normal (< 5 mcg/L)	24 (42.1)	7 (13.0)	20 (37.0)	51 (30.9)
Elevated (≥ 5 mcg/L)	18 (31.6)	39 (72.2)	25 (46.3)	82 (49.7)

Note. – Unless otherwise indicated, data are numbers of patients and data in parentheses are percentages.

Group A: patients without liver metastasis (N=27/11/19 per centre);

Group B: patients with synchronous liver metastasis (N=18/8/28 per centre);

Group C: patients with liver metastasis occurring within 24 months (N=30/6/18 per centre);

N/A: not applicable

* Primary tumour/nodal stage based on histopathology for patients undergoing direct surgery and based on MRI for patients undergoing neo-adjuvant treatment.

† Median interval between the primary staging CT and the detection of liver metastases.

Step 1 – Identification of potential predictive parameters

The mean ($\pm$ standard deviation) of the texture parameters for the different subgroups are presented in Table 2. Detailed results of the univariable multilevel logistic regression analyses are presented in Table 3. There is no significant difference within the scanners ($P > 0.05$). Of the texture parameters, uniformity at fine scale filtration ($U_{0.5}$) offered the best results to differentiate between patients without (group A) and patients with synchronous metastases (group B). In addition, nodal status, primary tumour site, sex and CEA were identified as potentially predictive clinical parameters.

Step 2: Prediction of metachronous metastases

Table 4 shows the results of the multivariable logistic regression of the different parameters identified in step 1 to discriminate between group A (no metastases) and C (metachronous metastases). For the whole group of patients with metachronous disease neither texture analysis ($U_{0.5}$), nor any of the clinical parameters showed significant predictive value (OR 0.52-1.67, $P = 0.16$ -0.44). In the sub-analysis of patients who developed early metastases (within 6 months) $U_{0.5}$ resulted in an OR of 0.56 ($P = 0.05$). Representative imaging examples of patients from the no metastases and early metastases group are provided in Figure 2. Nodal stage in this subgroup resulted in an OR of 3.19 ($P = 0.06$).

Figure 2. Representative examples of the CT scans of a patient from the no metastases group (upper row, A1-A3) and a patient from the metachronous metastases group (bottom row, B1-B3). The dotted lines represent the delineations of the VOIs used to derive the texture features. On primary staging CT, patient A had no visible liver lesions (A1) and patient B had a haemangioma in segment 6 (arrowhead in B1) that was excluded from the VOI. On the scan performed at six months after diagnosis (A2), as well as a late follow-up scan performed 5 years after diagnosis (A3), patient A remained free of metastases. Patient B developed a metastatic lesion of 17 mm in segment 6 (arrow in B2, performed 6 months after diagnosis), which was later confirmed on PET (arrow in B3) and pathologically confirmed after resection of the lesion. The haemangioma remained unchanged (arrow in B2) and was negative on PET. On the primary staging CT, uniformity with a fine filter was 8,665 in patient A who remained without metastases, while it was 6,591 in the patient with metachronous metastasis, illustrating that lower uniformity may be used as a marker to predict patients at risk of developing early metastatic disease.

Diagnostic performance to predict metachronous metastases

ROC-curves illustrating the diagnostic performance of texture and clinical parameters to predict the development of liver metastases are provided in Figure 3. For the whole group of patients with metachronous disease, AUCs to predict the development of metastases ranged between 0.51 and 0.61 for (combinations of) $U_{0.5}$, and the clinical parameters CEA and nodal stage. For prediction of early metastases (occurring within six months), the AUC was 0.74 for $U_{0.5}$ versus AUC

0.70 for CEA + N-stage ($P = 0.72$). Combining $U_{0.5}$ with CEA + N-stage resulted in an AUC of 0.78, which was not a significant improvement compared to either $U_{0.5}$ ($P = 0.53$) or N-stage + CEA ($P = 0.08$).

Table 2. CT texture features of the apparently non-diseased liver parenchyma

Texture features	A (n=57)	B (n=54)	C (n=54)	C ¹ (n=11)	C ² (n=20)	C ³ (n=23)
Mean grey-level intensity						
unfiltered	105.38±18.73	103.09±17.34	101.68±16.56	100.61±12.67	98.02±17.05	105.37±17.59
σ=0.5	0.001±0.07	0.011±0.10	-0.023±0.06	-0.008±0.04	-0.021±0.07	-0.031±0.6
σ=1.5	0.45±0.19	0.50±0.23	0.40±0.17	0.45±0.18	0.37±0.17	0.40±0.18
σ=2.5	1.42±0.44	1.49±0.49	1.34±0.44	1.44±0.42	1.23±0.38	1.40±0.49
Entropy						
unfiltered	5.69±0.26	5.69±0.22	5.65±0.34	5.74±0.26	5.68±0.38	5.59±0.34
σ=0.5	7.16±0.33	7.04±0.37	7.14±0.52	7.36±0.23	7.17±0.54	7.00±0.58
σ=1.5	6.87±0.35	6.88±0.31	6.78±0.38	6.79±0.35	6.83±0.44	6.73±0.34
σ=2.5	6.27±0.36	6.35±0.30	6.17±0.35	6.17±0.35	6.20±0.38	6.15±0.32
Uniformity						
unfiltered	23.24±4.06	23.17±3.66	24.08±5.54	22.26±3.76	23.76±5.88	25.23±5.86
σ=0.5	8.43±1.76	9.37±3.00	9.12±4.72	7.29±1.14	8.87±4.46	10.21±5.73
σ=1.5	10.47±2.54	10.35±2.28	11.16±2.66	11.04±2.50	10.89±3.03	11.46±2.47
σ=2.5	16.10±4.13	15.21±3.32	17.15±3.99	17.18±3.87	16.89±4.51	17.36±3.71

Note.- Data are the mean $\pm$ standard deviation

σ : different image filtrations

Group A: patients without liver metastasis;

Group B: patients with synchronous liver metastases;

Group C: patients with liver metastases occurring within 24 months;

Group C¹: early metastases (≤ 6 months following primary staging);

Group C²: intermediate metastases (7-12 months following primary staging);

Group C³: late metastases (13-24 months following primary staging);

Table 3. Univariable multilevel logistic regression analysis to differentiate between group A and B

Parameters	Odds Ratio	<i>P</i>
Mean grey-level intensity		
unfiltered	0.99 (0.97 – 1.01)	0.50
$\sigma=0.5$	3.99 (0.06 – 279.24)	0.52
$\sigma=1.5$	3.32 (0.54 – 20.64)	0.20
$\sigma=2.5$	1.37 (0.61 – 3.10)	0.44
Entropy		
unfiltered	0.99 (0.21 – 4.60)	0.99
$\sigma=0.5$	0.32 (0.10 - 1.05)	0.06*
$\sigma=1.5$	1.14 (0.36 – 3.60)	0.82
$\sigma=2.5$	2.00 (0.64 - 6.24)	0.23
Uniformity		
unfiltered	1.00 (0.90 – 1.10)	0.93
$\sigma=0.5$	1.21 (0.99 - 1.46)	0.06*
$\sigma=1.5$	0.98 (0.84 – 1.14)	0.79
$\sigma=2.5$	0.94 (0.85 - 1.04)	0.21
Age on diagnosis (y) †	1.02 (0.99 – 1.05)	0.18
Sex †‡	0.45 (0.20 – 1.00)	0.05
Primary tumour site †§	2.72 (1.26 – 5.88)	0.01
Tumour stage	1.27 (0.53 – 3.06)	0.60
Nodal stage †	1.52 (0.96 – 2.39)	0.07
Node positive / Node negative	1.56 (0.69 – 3.52)	0.28
CEA level (mcg/L) †	1.05 (1.02-1.09)	0.00

Note. - Data in parentheses are 95% confidence intervals.

Group A: patients without liver metastasis;

Group B: patients with synchronous liver metastases;

* Since entropy and uniformity are correlated parameters, only uniformity was selected for multivariable logistic regression analysis because of the smaller confidence interval.

† Parameters with $P < .2$ were selected for multivariable logistic regression analysis.

‡ Male (vs. female)

§ Location in rectum (vs. colon)

Table 4. Multilevel multivariable logistic regression analysis to differentiate between group A and C

Parameters	A vs. C		A vs. C ¹ (n=11)		A vs. C ² (n=20)		A vs. C ³ (n=23)	
	Odds Ratio	P	Odds Ratio	P	Odds Ratio	P	Odds Ratio	P
Uniformity $\sigma=0.5$	1.08 (0.92-1.26)	0.35	0.56 (0.31-1.00)	0.05	1.04 (0.85-1.28)	0.68	1.20 (0.97-1.47)	0.09
Nodal stage	1.50 (0.85-2.68)	0.16	3.19 (0.96-10.66)	0.06	2.02 (0.93-4.40)	0.08	0.87 (0.42-1.80)	0.70
Primary tumour site *	1.67 (0.68-4.10)	0.26	4.18 (0.70-25.02)	0.12	1.95 (0.58-6.60)	0.28	1.49 (0.46-4.81)	0.50
CEA (mcg/L)	1.01 (0.98-1.05)	0.44	1.02 (0.98-1.06)	0.41	1.02 (0.98-1.06)	0.37	1.00 (0.94-1.06)	0.93
Sex †	0.52 (0.21-1.31)	0.17	0.63 (0.12-3.38)	0.59	0.69 (0.19-2.49)	0.57	0.45 (0.13-1.58)	0.21

Note. - Data in parentheses are 95% confidence intervals.

Group A: patients without liver metastases.

Group C: with liver metastases occurring within 24 months following primary staging;

Group C¹: early metastases (≤ 6 months following primary staging);

Group C²: intermediate metastases (7-12 months following primary staging);

Group C³: late metastases (13-24 months following primary staging);

* Location in rectum (vs. colon)

† Male (vs. female)

Figure 3. ROC curves illustrating the diagnostic performance of clinical parameters (N-stage and CEA), texture analysis ($U_{0.5}$) and a combination of clinical and texture features to predict patients at risk to develop metachronous disease for the whole patient group (left) and for the subgroup of patients who developed metastases within six months.

Discussion

The aim of our study was to evaluate in a multicentre setting whether CT-texture analysis of the apparently non-diseased liver at the time of primary diagnosis has the potential to predict upfront which patients who initially present without metastases are at risk of developing liver metastases at later stage. Our results suggest that texture analysis has some promise to differentiate patients that will develop liver metastases early (≤ 6 months) after initial diagnosis, but is not robust enough to identify patients at risk to develop metastases after a longer interval (within 7-24 months).

Our findings are in line with those of previous single-centre studies that reported that changes in the overall texture of the liver parenchyma can be observed when metastatic disease is present within the liver. Both Rao et al¹⁴ and Ganeshan et al¹⁰ reported significant differences in CT-texture between patients with and without liver metastases. Rao et al¹⁴ also reported a similar subtle change in texture in patients who had no metastases at the time of primary diagnosis but later developed metachronous liver metastases, but the number of patients with metachronous

disease in their cohort was too small ($n=4$) to draw any meaningful conclusions. Our current multicentre study follows up on these previous works and confirms that – at least to predict metastases occurring within 6 months – texture analysis may be of added value. In ROC-curve analysis there was a trend towards improved results compared to more well-known clinical markers (CEA + N-stage) with an AUC of 0.78 for texture + clinical markers versus an AUC of 0.70 for only clinical markers, albeit not statistically significant ($P = 0.08$). From a clinical point of view, however, these very early metastases are more considered occult synchronous metastases, that were probably already present but too small to detect by visual assessment on CT at the time of primary staging. Moreover, one could wonder whether these lesions might have been detected if patients would have been imaged with MRI instead of CT, given the known superiority of MRI over CT for the detection of small liver metastases^{23, 24}. For the prediction of ‘true’ meta-chronous metastases occurring at later stage, texture analyses were not beneficial. If in these patients changes were already present within the liver at time of primary diagnosis and staging, they were too small to be detected with texture analyses.

Despite the fact that the texture analysis and the delineation were performed in the same way as previous reports, there are some remarkable discrepancies between the findings^{10, 14, 21}. First, in our study the best results were obtained for texture measures using fine image filtration, whereas previous reports found better results for medium to coarse filters^{10, 14}. Fine image filtration highlights very small structures (in the order of 1-2 mm), while coarse image filtration highlights larger structures (in the order of 6 mm). The size of the structures that can be detected, however, also depends on the chosen slice thickness which influences image noise and intrinsic contrast. Therefore, one could expect a correlation between the slice thickness and the optimal image filtration to detect structures of a certain size. Since the above-mentioned studies (including the current) were performed with CT images of varying slice thickness (ranging between 3-10 mm), this may have contributed to the varying results for different image filtrations between studies. Also, previous studies performed by Ganeshan et al use a single slice, while our report is based on the average of multiple slices resulting in whole liver analysis^{10, 17}.

Although the exact mechanism is not fully known, changes in liver texture as a result of metastatic involvement have been proposed to be related to changes in liver perfusion or changes on a cellular level caused by the presence of micro metastases^{16, 18, 25}. With this in mind, it would be logical to assume that entropy would increase (more heterogeneous/irregular liver structure) and vice

versa uniformity would decrease in patients with synchronous metastases and that by extension this effect may also already be observed in patients who later develop metachronous disease. However, as illustrated in Table 2, entropy and uniformity values fluctuated inconsistently between the different subgroups of patients with synchronous, early, intermediate and late metastases for reasons not well understood. Previous studies also found conflicting results; some indeed reported higher entropy and corresponding lower uniformity in patients with metastases^{10, 14}, while others reported the opposite effect⁹. Further research is therefore needed to understand the complex relations between texture parameters and underlying biological tissue characteristics in these different settings.

Apart from biologic tissue properties, there are also several other factors that may influence texture measures, amongst which the image acquisition parameters. For example, Bezy-Wendling et al reported that texture values are highly dependent on the slice thickness of the CT images²⁶. As described above, slice thickness varies considerably between published reports. Moreover, Ganeshan et al reported that timing of acquisition after contrast injection has a considerable effect on entropy and uniformity values (even with slight variations in timing) with typically an increase in entropy and decrease in uniformity over time^{9, 27}. Since contrast timing differs between studies (some used non-enhanced CT and others contrast-enhanced CT with various contrast timings) and even within studies, this will likely also have contributed to the variations in results^{9, 17, 25, 28}. Other factors such as contrast volume, kVp and slice collimation may also affect results, although effects of these items have so far not been specifically addressed in literature. We tried to compensate for such effects by performing a multilevel analysis per CT scanner used in our study (thereby aiming to take into account hardware, software and acquisition protocol related variation between scanners and centres). However, we cannot fully rule out potential confounding effects and more detailed research on the precise effects of acquisition-related factors is therefore urgently needed. All together these issues make it difficult to perform multicentre texture research and ultimately generalize and translate findings to daily use. These issues are also part of the reason why texture analysis is not yet ready for use in clinical practice. Before texture features may truly be used as clinical imaging biomarkers, further standardisation of acquisition- and technical parameters is thus required. Moreover, discrimination threshold values will need to be defined and properly validated.

There are some other limitations to our study design. First, because we aimed to obtain three equally sized patient cohorts, patients (particularly in the meta-chronous group, being the least prevalent outcome) are non-consecutive. Second, VOI's were drawn by a single observer, which does not account for potential interobserver variations (though we believe that for whole-liver analysis this effect will probably be limited). Finally, slice thickness was relatively large (5mm) and in one of the three centres the slice thickness was reconstructed from an original slice thickness of 3 mm, which may have affected image noise. Finally, as described above, for our study we only looked at CT, as this still represents the most routinely used modality for staging CRC in daily practice. Routine staging with MRI was not performed. For future studies, it will be worthwhile to look at the potential added value of MRI in this regard.

Conclusion

In conclusion, it is our experience that it is technically challenging to analyse CT-texture in a multicentre setting and fully take into account potential confounding factors such as differences in CT acquisition protocols. Apart from these challenges, our results suggest that CT-texture analysis may have promise as an adjunct to known clinical risk factors such as N-stage and CEA to predict which patients that are at risk of developing liver metastases early (≤ 6 months) after initial diagnosis, but is not robust enough to identify patients at risk of developing metastases at later stage, i.e. within 1-2 years.

Appendix

Texture analysis consists of two main stages: (a) image filtration and (b) quantification of texture.

1. Image filtration:

For image filtration, a Laplacian of Gaussian (LoG) band-pass filter was chosen. Before applying the filter, regions outside the VOI were set to the average value of the pixels inside the VOI, to prevent non-target regions to influence the analysis. The LoG filter is mathematically defined as $\Delta G(x,y)$, with Δ the Laplace operator and $G(x,y)$ a two-dimensional Gaussian. We have chosen to normalize the Gaussian as follows:

$G(x, y) = -e^{-(x^2+y^2)/(2\sigma^2)}$, which results in a LoG filter that is described by

$$\Delta G = \nabla \cdot \nabla G = \frac{4}{2\sigma^2} \left(1 - \frac{x^2 + y^2}{2\sigma^2} \right) e^{-(x^2+y^2)/(2\sigma^2)}$$

We applied the filter in the Fourier space, as this is less computationally demanding. To calculate the convolution of the data and our filter, we multiplied their Fourier transforms in Fourier space. This has the additional benefit of reducing the discretization errors, as the filter has a larger width in Fourier space. The Fourier transform of the filter is given by

$$F(\Delta G) = 2\pi\sigma^2 4\pi^2 (k_x^2 + k_y^2) e^{-\pi^2 2\sigma^2 (k_x^2 + k_y^2)},$$

with k_x and k_y in the range $[-0.5, 0.5]$. The LoG-filter was applied for a range of σ values. The width of the filters in pixels (at the reference resolution of 0.84 mm) and mm is shown in Table 5. For each CT scan with a resolution different than 0.84 mm, the value of σ was modified to keep the physical size (in mm) of the filter constant. We defined the width of the filter as the distance between the zero crossings (see Figure 4). These occur for $x^2+y^2=2\sigma^2$, so the total width of the filter is given by $2\sqrt{2}\sigma$.

Table 5. Filter widths for different values of σ

σ [pixels]	Full width [pixels]	Full width [mm]
0.5	1.4	1.2
1.5	4.2	3.6
2.5	7.0	5.9

Figure 4. Example of the LoG filter with $\sigma=2.5$

2. Quantification of texture:

For image quantification of texture, mean grey-level intensity, entropy and uniformity were used. These parameters were calculated from a histogram of the points within the VOI with a bin size of 1 HU. From the histogram, the parameters were calculated using:

$$mean = \sum_{i=1}^M f(i) \cdot h(i),$$

$$entropy = - \sum_{i=1}^M f(i) \cdot \log_2(f(i)),$$

$$uniformity = 1000 \cdot \sum_{i=1}^M f(i)^2$$

where M is the number of bins in the histogram, $f(i)$ the fraction of the voxels in the vOI in bin number i of the histogram and $h(i)$ the HU value of bin i . The entropy gives an indication of the width of the histogram and the uniformity of the narrowness.

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4. Whole volume versus segmental CT texture analysis of the liver to assess metachronous colorectal liver metastases

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Abstract

Purpose

It is unclear whether changes in liver texture in patients with colorectal cancer are caused by diffuse (e.g. perfusional) changes throughout the liver or rather based on focal changes (e.g. presence of occult metastases). The aim of this study is to compare a whole-liver approach to a segmental (Couinaud) approach for measuring the CT texture at the time of primary staging in patients who later develop metachronous metastases and evaluate whether assessing CT texture on a segmental level is of added benefit.

Methods

46 Patients were included: 27 patients without metastases (follow-up >2 years) and 19 patients who developed metachronous metastases within 24 months after diagnosis. Volumes of interest (VOIs) covering the whole liver were drawn on primary staging portal-phase CT. In addition, each liver segment was delineated separately. Mean grey-level intensity, entropy (E) and uniformity (U) were derived with different filters (σ 0.5-2.5). Patients/segments without metastases and patients/segments that later developed metachronous metastases were compared using independent samples T-tests.

Results

Absolute differences in entropy and uniformity between the group without metastases and the group with metachronous metastases group were consistently smaller for the segmental approach compared to the whole-liver approach. No statistically significant differences were found in the texture measurements between both groups.

Conclusions

In this small patient cohort, we could not demonstrate a clear predictive value to identify patients at risk of developing metachronous metastases within 2 years. Segmental CT-texture analysis of the liver probably has no additional benefit over whole-liver texture analysis.

Introduction

With $\pm 750,000$ new cases every year worldwide, colorectal cancer (CRC) constitutes one of the most common forms of cancer¹. The most prevalent site of metastases in CRC is the liver (77%). At time of diagnosis approximately 20% of patients have metastatic disease²⁻⁵. An additional 5% of patients will develop metachronous metastases within the first year, increasing to 15% after five years³. The exact pathogenesis of the development of colorectal liver metastases is still not fully understood⁶⁻⁸. A recent review suggested that there might be a difference in biological characteristics between synchronous and metachronous metastases with synchronous metastases showing a more aggressive disease profile with poorer survival rates⁹. However, other studies reported no difference in survival after resection of liver metastases, whether they appeared synchronously or metachronously¹⁰⁻¹². A better understanding of the exact pathogenesis of the development of metachronous metastases could be of great influence on clinical practice; knowing which patients are at risk of developing metachronous disease might create opportunities for (neo-) adjuvant treatment and could affect the intensity of follow-up.

Imaging might play a role in this regard. The idea would be that at the early stage of metachronous disease development, changes are already occurring within the liver before any focal liver lesions become apparent. These early changes cannot be observed with common morphological imaging techniques, but may be detected with more sophisticated imaging or post processing techniques. A specific technique that has shown promise is CT texture analysis. Texture analysis is a mathematical approach to quantify the distribution of grey-level values within tissues, thereby providing a measure of tissue heterogeneity¹³. Texture features derived from colorectal liver metastases as well as from the surrounding liver parenchyma have both been reported to correlate with patient survival^{14, 15}. Moreover, previous reports have shown that differences in the overall liver texture can be observed on CT between patients with and without liver metastases. Similarly, even at the time of primary staging in patients that develop metachronous metastases, texture changes can be observed, particularly in patients who develop metastases early (within 6 months) after diagnosis^{16, 17}. However, results reported so far are ambiguous and convincing evidence supporting the role of CT texture analysis to predict patients at risk for developing metachronous liver disease has yet to be provided.

A potential limiting factor could be the methodology of obtaining texture measures. So far, whole liver texture analyses have been performed, based on the assumption that early changes in the liver preceding the manifestation of visible focal liver lesions occur diffusely in the liver parenchyma and are likely to be related to changes in liver perfusion¹⁸⁻²⁰. An alternative hypothesis would be that these early changes are more localized to a certain area within the liver (i.e. the specific site where at a later stage the metastases will become visible) and are more related to focal changes on a cellular level (i.e. presence of occult micro metastases) and/or focal perfusional changes^{14, 21}. In the latter case, a whole liver approach will likely not be sensitive enough to detect these focal changes and a segmental analysis of the liver texture might provide better results.

The aim of this study therefore was to evaluate this hypothesis and get a better insight in the distribution of textural changes within the liver (i.e. diffuse versus focal) by comparing the CT liver texture of patients without metastases and patients with metachronous liver disease using a ‘whole liver’ versus ‘segmental’ approach.

Method and materials

Patients

This study retrospectively analysed 46 patients who were treated for colorectal cancer at Maastricht Medical Center between August 2009 and November 2013. Informed consent was waived by the local ethical committee. Part of the study patients (44/46) were included in a previously reported multicentre study cohort¹⁷. As part of their primary staging all patients routinely underwent contrast enhanced abdominal or liver CT. Two groups of patients were defined: (A) the ‘no metastases’ (control) group, consisting of 27 patients who had no evidence of liver metastases at primary staging, nor during at least 2 years of follow-up and (B) the ‘metachronous metastases’ group consisting of 19 consecutive patients who had no evidence of liver metastases at primary staging but developed metachronous liver metastases within 24 months after the primary staging. The inclusion criteria consisted of (a) histopathologically confirmed colorectal adenocarcinoma; (b) no extrahepatic metastases; (c) a primary staging CT including a portal venous phase (PVP). Exclusion criteria consisted of (a) previous liver surgery, (b) previous systemic treatment (chemotherapy), (c) diffuse hepatic metastases, leaving no normal segments to compare and (d) evidence of other diffuse liver disease such as steatosis or cirrhosis.

CT acquisition

All CT scans included a PVP scan of the liver and were acquired using multi-slice CT equipment (Philips Brilliance 64, Philips Medical Systems, Best, The Netherlands; Siemens Somatom Sensation 16 or Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany). PVP images were obtained with a tube voltage of 120 kVp. The contrast medium (Ultravist 300mgI/ml; Iopromide, Bayer Healthcare, Berlin, Germany) was prewarmed to 37°C (99°F) and administered intravenously as a bolus injection of 110 ml at a rate of 3.5ml/s, followed by a saline flush of 40 ml. The scan delay for the PVP was set at 70 sec with a (reconstructed) slice thickness of 5 mm.

Whole-volume versus segmental liver delineation

All delineations were performed on the initial staging CTs (when all patients were still without any visible colorectal liver metastases). The PVP images were transferred to an offline workstation for liver delineation which was performed using the open source software tool MRIcron²². Liver delineation was performed in two ways (Figure 1): (a) whole-liver delineation, and (b) segmental delineation. For the whole-liver delineation a single reader (RB) delineated the whole liver volume (excluding the border of the liver, any visible benign lesions, the inferior vena cava, caudate lobe, large hepatic veins, arteries and biliary vessels) according to methods previously reported^{16, 17}. For the segmental delineation individual liver segments were delineated, based on Couinaud's classification²³. Seven segments were included (2, 3, 4ab, 5, 6, 7, 8). The caudate lobe was excluded, since it is often difficult to discern from the border of the vena cava.

Figure 1. Illustration of the hypothetical concept that textural changes are caused either (a) by changes (e.g. perfusional and/or cellular) occurring diffusely throughout the liver, which can be expected to become most apparent with a whole-volume liver delineation, or (b) by more focally situated changes in the liver caused for example by the presence of occult micrometastases,

which can be expected to become more apparent with a segmental liver delineation.

Texture analysis

2D Texture analysis was performed with a dedicated script written in MATLAB (The MathWorks Inc., Natick, MA, 2000) by one of the authors (RS), according to methods previously reported^{16, 17, 24}. The mathematical analysis technique used for this study comprised two main stages: image filtration followed by the quantification of texture. For image filtration, a Laplacian of Gaussian (LoG) band-pass filter was chosen which was applied in the Fourier space. A reference resolution of 0.84 mm was chosen and for each CT scan with a different resolution, the width of the LoG-filter (σ) was modified to keep the physical size (in mm) of the filter constant. A fine ($\sigma=0.5$), medium ($\sigma=1.5$) and a coarse filter ($\sigma=2.5$) were used. For quantification of the texture of the liver parenchyma, mean grey-level intensity (M), entropy (E) and uniformity (U) were used. These features were calculated from a histogram based on the points within the region of interest with a bin size of one Hounsfield unit. M is the number of bins in the histogram; entropy is based on the width of the histogram and uniformity is based on the narrowness.

Standard of reference

In the patients without metastases, the absence of metastases was confirmed by means of clinical follow up including regular carcinoembryonic antigen (CEA) level and imaging (CT and in some cases US and/or MRI). The median follow-up time was 54 months (range 35-57 months). In the metachronous metastases group, the presence of metachronous liver lesions was confirmed by histopathology in 10 patients, by growth over time in 5 patients and by corresponding FDG-PET positivity (after initial CT diagnosis) in 4 patients.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and Stata (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). Baseline patient characteristics were assessed and compared using descriptive statistics. Patients/segments without metastases and with metachronous metastases were compared using independent samples T-test, Mann Whitney U test was used for non-parametric data. For the segmental analysis segments analysed on the initial staging

CT were matched to segments where disease occurred during follow up. A P -value < 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

Of the 46 patients enrolled in the study, 29 patients were male and 17 were female. Median age was 66.5 years (range 44-81 years). The primary tumour was located in the colon in 24 patients and in the rectum in the other 22 patients. Baseline characteristics of the study patients including results per subgroup are given in Table 1. Nineteen patients developed metachronous metastases with a median diagnosis-metastases interval of 12 months (range 4-20 months). In 1 patient metastases occurred within 6 months, in 9 within 7-12 months and in 9 within 13-24 months. A total of 322 segments were delineated. Of these, 189 segments (58.7%) remained without metastases; in 37 segments (11.5%) metastases occurred during follow up. Only segments of the patients who remained without metastases were included in the analysis.

Whole liver versus segmental approach

Table 2 compares the texture values between the no metastases and metachronous metastases group for the whole liver versus the segmental approach. The absolute difference in entropy and uniformity values between the no metastases and metachronous metastases group was consistently smaller for the segmental approach (difference 0.00-0.11 for entropy and 0.13-1.53 for uniformity) compared to the whole volume approach (difference 0.03-0.15 for entropy and 0.70-2.29 for uniformity). For mean intensity at fine image filtration, the same effect was observed. None of the whole liver nor segmental texture measurements resulted in any statistically significant differences between the no metastases and metachronous metastases group.

Table 1. Baseline characteristics of the 46 patients

Characteristics	Group A (N=27)	B (N=19)	Total (N=46)
Age (y)			
Median	66	67	66.5
Range	44-76	47-81	44-81
Sex			
Male	17 (63)	12 (63.2)	29 (63)
Female	10 (37)	7 (36.8)	17 (37)
Primary tumour site			
Rectum	15 (55.6)	7 (36.8)	22 (47.8)
Colon	12 (44.4)	12 (63.2)	24 (52.2)
Tumour stage *			
T1	0	0	0
T2	7 (25.9)	0	7 (15.2)
T3	17 (63.0)	12 (63.2)	29 (63.0)
T4	3 (11.1)	7 (36.8)	10 (21.7)
Nodal stage *			
N0	11 (40.7)	3 (15.8)	14 (30.4)
N1	4 (14.8)	6 (31.6)	10 (21.7)
N2	12 (44.4)	10 (52.6)	22 (47.8)
Histology of primary tumour			
Adenocarcinoma n.o.s.	19 (70.4)	14 (73.7)	33 (71.7)
Mucinous	6 (22.2)	3 (15.8)	9 (19.6)
Signet-ring cell carcinoma	1 (3.7)	2 (10.5)	3 (6.5)
Focal neuroendocrine diff.	1 (3.7)	0	1 (2.1)
Time until metastases (m)†			
Median	N/A	12	N/A
Range	N/A	4-20	N/A
Carcinoembryonic antigen (CEA) at time of primary diagnosis			
Normal (< 5 mcg/L)	18 (66.7)	9 (47.4)	27 (58.7)
Elevated (≥ 5 mcg/L)	8 (29.6)	8 (42.1)	16 (34.8)

Note. – Unless otherwise indicated, data are numbers of patients and data in parentheses are percentages.

Group A: patients without liver metastases;

Group B: patients with metachronous liver metastases within 24 months after primary staging;

N/A: not applicable

* Primary tumour/nodal stage was based on histopathology for patients undergoing direct surgery and based on MRI for patients undergoing neoadjuvant treatment.

† Interval between the primary staging CT and the detection of liver metastases.

Table 2. Mean ($\pm$ Standard Deviation) of CT texture features of the apparently non-diseased liver parenchyma measured at different scale values (σ) on PVP CT

Texture features	Whole liver		Segments	
	A (n=27)	B (n=19)	A (n=189)	B (n=37)
Mean grey-level intensity				
Unfiltered	114.33 $\pm$ 18.38	113.35 $\pm$ 15.68	114.53 $\pm$ 18.27	117.34 $\pm$ 17.92
$\sigma=0.5$	-0.018 $\pm$ 0.087	-0.044 $\pm$ 0.081	0.034 $\pm$ 0.147	0.043 $\pm$ 0.130
$\sigma=1.5$	0.36 $\pm$ 0.18	0.34 $\pm$ 0.22	0.44 $\pm$ 0.25	0.51 $\pm$ 0.29
$\sigma=2.5$	1.25 $\pm$ 0.40	1.20 $\pm$ 0.52	1.33 $\pm$ 0.45	1.44 $\pm$ 0.56
Entropy				
Unfiltered	5.71 $\pm$ 0.18	5.67 $\pm$ 0.36	5.65 $\pm$ 0.19	5.63 $\pm$ 0.32
$\sigma=0.5$	7.02 $\pm$ 0.21	6.87 $\pm$ 0.66	7.02 $\pm$ 0.21	6.91 $\pm$ 0.53
$\sigma=1.5$	7.06 $\pm$ 0.18	6.97 $\pm$ 0.33	7.03 $\pm$ 0.20	6.98 $\pm$ 0.30
$\sigma=2.5$	6.52 $\pm$ 0.17	6.45 $\pm$ 0.24	6.45 $\pm$ 0.19	6.45 $\pm$ 0.24
Uniformity				
Unfiltered	22.82 $\pm$ 2.94	24.12 $\pm$ 6.80	23.84 $\pm$ 3.29	25.01 $\pm$ 6.45
$\sigma=0.5$	9.26 $\pm$ 1.41	11.55 $\pm$ 7.07	9.16 $\pm$ 1.41	10.69 $\pm$ 5.33
$\sigma=1.5$	8.99 $\pm$ 1.14	9.75 $\pm$ 2.42	9.16 $\pm$ 1.28	9.61 $\pm$ 2.16
$\sigma=2.5$	13.32 $\pm$ 1.58	14.02 $\pm$ 2.38	13.88 $\pm$ 1.87	14.01 $\pm$ 2.43

Group A: patients/segments without liver metastases;

Group B: patients/segments with metachronous liver metastases within 24 months following primary staging

* Differences were not statistically significant between the no metastases and metachronous metastases patients/segments for any of the features

Discussion

The aim of this study was to get a better insight in the underlying cause of textural changes that can be observed on CT of the liver in patients with colorectal liver metastases. We compared a whole liver approach with a segmental approach using Couinaud's segments to study whether changes in liver texture are most likely caused by focal or diffuse liver pathology. The hypothesis was that in case of occult focal disease (micro metastases) the differences on a segmental level would be more apparent, whereas conversely diffuse changes in liver texture would become more apparent using a whole-liver approach. Although the observed differences are altogether small, our results suggest that differences in texture between patients without metastases and patients who develop metastatic liver ≤ 2 years after initial diagnosis are more pronounced for the whole-liver approach. However, no additional effect was found for texture measurements on a segmental level.

It has been suggested that diffuse changes in the liver preceding the development of focal liver metastases are probably related to changes in liver perfusion and hepatic hemodynamics^{14, 18}. Tumour progression towards metastasis is a process with multiple stages in which malignant cells spread from the primary colorectal tumour to colonize the liver^{25, 26}. Paget's "seed and soil" theory for metastasis states that an adequate microenvironment is required for malignant cells to nest into distant tissues and form metastases²⁷. This microenvironment should support malignant cell maintenance and regulate cell function and proliferation so that tumour cells are able to form into clinically detectable metastases^{28, 29}. One of the key elements in the progression from micro metastasis to visible metastases is the assembly of a functional vascular structure to enable cellular expansion³⁰⁻³². These changes lead to physiological changes such as increased perfusion, blood volume and capillary permeability³³. It is known that in the liver, tumour angiogenesis occurs when metastases reach approximately 0.5 mm in size, while lesions can only be visualised with conventional morphological imaging techniques when they reach at least 3-5 mm in diameter³⁴. These observations may explain why changes in the liver texture may already be observed on a whole-liver level (as was reported in previous studies^{16, 17}), while no visible metastases have yet become apparent³⁵. Despite the fact that differences in our study also appeared to be most pronounced for the whole liver approach, we could not confirm a statistically significant difference in texture between patients without metastases and patients who later developed metachronous metastases. A possible contributing factor could be that the median interval between the primary staging CT and the

development of metastatic lesions in our study was 12 months whereas Beckers et al. previously reported that CT texture was only able to predict metastases occurring early (within 6 months) after primary CRC diagnosis¹⁷. Our current study cohort was too small to perform meaningful subgroup analyses on the development of early metastases (given that only in 1 patient metastases occurred within 6 months).

Our findings support doubts raised in previous papers with respect to the robustness of texture analysis as a self-contained image quantification method and the current lack of evidence from large-scale prospective studies^{17, 36}. Most likely texture analysis should be used as an adjunct to other parameters, both clinical, laboratory and imaging, with the ultimate aim to develop a comprehensive global clinical prediction model. From the imaging perspective, not only CT texture analysis should be further explored, but also other techniques that have shown promise in previous reports such as diffusion-weighted imaging³⁷, perfusion CT and MR imaging^{38, 39} and ultrasound Doppler⁴⁰.

There are some limitations to our study. The sample size of patients with metachronous metastases (particularly patients with early metastases) was small. Second, slice thickness in our study was relatively large. Third, image segmentations were only performed by a single reader, although we believe that given the method of whole-liver segmentation and segmentations according to the standardised and well-known Couinaud classification potential effects of interobserver variations can be expected to be limited. Finally, a major limitation is that it is not possible to correlate our findings with underlying histopathological changes in the liver as this would require invasive procedures such as routine liver biopsy, which is not feasible from an ethical perspective. Moreover, in the patients who developed metachronous metastases, histopathological confirmation was only available in 10/19 patients.

Conclusion

Our study showed no added value for segmental texture analysis over whole liver CT texture analysis. Despite the lack of pathologic correlation, our results appear to favour the hypothesis that textural changes are more likely based on diffuse, (perfusional) changes, rather than changes occurring on a more focal (segmental) level. Future prospective studies should focus on determining the role of CT texture analysis – as well as other imaging techniques – within the complete spectrum of clinical, laboratory and imaging parameters to develop a clinically meaningful predictive model that can truly impact clinical decision making.

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5. CT texture analysis in colorectal liver metastases and the surrounding liver parenchyma and its potential as an imaging biomarker of disease aggressiveness, response and survival

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Abstract

Objectives

To study the ratio between the CT texture of colorectal liver metastases (CRLM) and the surrounding liver parenchyma and assess the potential of various texture measures and ratios as predictive/prognostic imaging markers.

Materials

Seventy patients with colorectal cancer and synchronous CRLM were included. All visible metastases, as well as the whole-volume of the surrounding liver, were separately delineated on the portal venous phase primary staging CT. Texture features entropy (E) and uniformity (U) were extracted and ratios between the texture features (T) of the metastases and background liver ($T_{\text{metastases}}/T_{\text{liver}}$) calculated. Texture features were compared with clinical outcome parameters: [1] extent of disease (i.e. number of metastases), [2] response to chemotherapy (in 56/70 patients who underwent chemotherapy and CT for response evaluation), and [3] overall survival.

Results

The $E_{\text{metastases}}/E_{\text{liver}}$ ratio was lower in patients with limited disease ($P=0.02$) and associated with overall survival, albeit not statistically significant when tested in multivariable analyses (HR 1.90; $P=0.07$); $U_{\text{metastases}}/U_{\text{liver}}$ was higher in patients with limited disease ($P=0.02$). $E_{\text{metastases}}$ showed a trend towards a higher value in patients that responded well to chemotherapy ($P=0.08$).

Conclusion

The ratio between the texture of liver metastases and the surrounding liver appears to reflect relevant changes in tissue microarchitecture and may be of value to assess the extent of disease and help predict overall survival.

Introduction

Colorectal cancer is one of the most common cancers worldwide ¹. Approximately 15-25% of all patients have colorectal liver metastases (CRLM) at the time of diagnosis ²⁻⁴. These synchronous CRLM patients tend to have a poor prognosis with a reported 1-year survival of less than 30% and a 5-year survival of less than 5% when untreated, with 5-year survival rates of up to 60% in selected groups that can undergo curative surgical resection ³.

Imaging plays a crucial role in the diagnosis and follow-up of CRLM. In many institutions, contrast-enhanced CT remains the primary modality for the staging of patients with colorectal cancer ⁵, although MRI is increasingly applied because of its superiority in detecting small liver metastases ⁶. To date, the mainstay of imaging assessment consists of a visual assessment of lesions and changes in size and morphology as a result of the response to therapy. The most widely adopted method to evaluate treatment response is Response Evaluation Criteria in Solid Tumours (RECIST), which provides standardised measures of response in terms of lesion size ⁷. Although commonly used in clinical trials and daily practice, RECIST is known to have significant limitations as size measurements fail to capture (micro-)structural changes related to for example intralesional perfusion-al or necrotic changes, which are known to be significant factors associated with therapeutic response ⁷⁻⁹.

Therefore, there is nowadays a growing interest in the use of quantitative imaging and image post-processing techniques to gain a more profound insight into the tumour biology. One of such techniques is texture analysis, which is a mathematical approach that uses an algorithm to quantify tissue heterogeneity by assessing the distribution of coarseness and irregularity of pixel intensities within a volume of interest (VOI) derived from a lesion or organ on an image ¹⁰. In patients with CRLM, texture analysis has been studied using both CT and MRI data, although most evidence so far exists for CT. So far, two main settings have been explored: one group of studies focused on the intralesional texture of the liver metastases itself, which was found to significantly correlate with the response to chemotherapy, as well as with survival ¹¹⁻¹⁴. Other studies focused not on the texture of the metastases, but on that of the surrounding apparently disease free liver parenchyma and showed that diffuse parenchymal textural changes may hold promise as a prognostic marker to assess and even predict the occurrence of metastatic disease in the liver ^{15,16}. Although the texture of both liver metastases and surrounding liver have been studied, to our knowledge there have been no

reports so far studying the relation between the two. This would be worthwhile to study as it may potentially provide valuable insights into the relation between texture findings and underlying tumour behaviour.

The aim of our study is twofold: first, we aim to explore the relation between the CT texture of CRLM and the surrounding liver parenchyma and assess if the ratio between the two may be of added value as a predictive or prognostic imaging marker. Second, we want to investigate whether we can confirm results of previous studies that CT texture analysis has a potential value as a biomarker of disease aggressiveness, response and survival in patients with CRLM.

Materials and Methods

Patients

Eighty-three consecutive patients with CRLM treated at Maastricht University Medical Center between April 2008 and December 2013 were considered for inclusion in this retrospective study. The study was approved by the institutional ethical review board; due to the retrospective nature, informed consent was not required. Inclusion criteria were as follows: (a) histopathologically confirmed primary (non-recurrent) colorectal adenocarcinoma; (b) availability of a primary staging CT including (at least) a portal venous phase (PVP); (c) presence of at least one synchronous CRLM at the time of diagnosis and staging; (d) no previous liver surgery; (e) no previous chemotherapy and (f) no clinical or imaging evidence of diffuse liver diseases such as steatosis or cirrhosis. Thirteen patients were excluded because of the presence of concomitant second malignancies at the time of diagnosis (n=3), inadequate CT contrast timing (n=3), and the presence of diffuse hepatic metastases, leaving too little 'normal' liver parenchyma to delineate (n=7). This left a total study population of 70 patients (50 male/20 female, median age 69, range 39-85) for inclusion; see consort diagram in Figure 1. Part of the study patients (29/70) were included in a previously published multicentre study cohort, which focussed on whole liver texture analysis to predict metachronous CRLM and therefore does not overlap with the aims of the current study¹⁵.

Figure 1. Flow-chart of the selection, inclusion and treatment of the studied patients

CT acquisition

All CT scans were acquired using multi-slice CT equipment (Philips Brilliance 64, Philips Medical Systems, Best, The Netherlands; Siemens Somatom Sensation 16 or Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany). PVP images of the liver/abdomen were obtained with a tube voltage of 100-120 kVp. The contrast medium (Ultravist 300mgI/ml; Iopromide, Bayer Healthcare, Berlin, Germany) was prewarmed to 37°C (99°F) and administered intravenously as a bolus injection of 110 ml at a rate of 3.5ml/s, followed by a saline flush of 40 ml. The scan delay for the PVP was set at 70 secs. Images were reconstructed in transverse plane using iterative reconstruction (Siemens Somatom Definition Flash) or filtered backprojection (Philips Brilliance 64 / Siemens Somatom Sensation 16) with a soft tissue filter. Slice thickness was 3 or 5 mm.

Image delineation

All delineations were performed on the primary staging CT. The PVP images were transferred to an offline workstation for delineation, using an open source software tool (MANGO; Multi-image Analysis GUI, version 2.6, Research Imaging Institute, University of Texas Health Science Center, San Antonio, TX). One reader with experience in liver delineation (RB) manually delineated per slice (a) all visible liver metastases, and (b) the surrounding (apparently disease free) liver parenchyma (Figure 2). Delineations were performed according to methods pre-

viously reported^{13,15,16}. For the delineation of the surrounding liver, the border of the liver, any visible focal liver lesions (including both benign lesions as well as any metastases), the inferior vena cava, caudate lobe, large hepatic veins, arteries and biliary ducts were excluded from the VOI.

Figure 2. Representative example of the initial staging portal venous phase CT image of a patient with a solitary CRLM. The dotted lines represent the delineations used to derive the texture features. (A) shows the delineation of the metastasis, while (B) shows the delineation of the background liver. The border of the liver, any visible lesions, the inferior vena cava and large portal and hepatic veins were excluded. The ratio of the texture features (T) between the metastases and background liver were calculated as $T_{\text{metastases}}/T_{\text{liver}}$.

Texture analysis

2D Texture analysis was performed with an in-house software written in Python (Python Software Foundation, version 2.7, <http://www.python.org>) by one of the authors (ST; who was blinded to all clinical patient data and outcomes) largely based on the open source Python package pyradiomics¹⁷, according to methods previously reported^{13,15,16}. The image analysis technique used for this study comprised two main stages: image filtration followed by the quantification of texture. Prior to feature extraction, CT volumes were resampled to isotropy (1x1x1 mm) using b-spline basis functions, whereas nearest neighbour was used for the delineations. In addition to the original image, the Laplacian of Gaussian (LoG) filter was applied to enhance edges and irregularities at two different resolutions: fine ($\sigma=0.5$) and coarse ($\sigma=2.5$). For quantification of the texture, entropy (E) and uni-

formity (U) were the main parameters that were extracted, similar to previously reported research on texture analysis in CRLM¹⁸. The meaning of these two features in relation to tissue microarchitecture is schematically illustrated in Figure 3. Entropy is a measure that gives an indication of the irregularity of the grey-level distribution, while conversely, the uniformity is indicative of its homogeneity. 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)¹⁹⁻²¹. Both features were calculated from a histogram, based on the points within the region of interest with a bin size of one Hounsfield unit. For each texture feature the ratio between the metastases and surrounding liver was calculated according to the following formula:

T represents the respective texture features, $T_{\text{metastases}}$ represents the VOIs of all visible liver metastases combined for each patient, and T_{liver} represents the VOI of the whole volume of the surrounding liver (excluding the metastases). Total time required to delineate and analyse one patient case was approximately 15 minutes.

Figure 3. Illustration of the relationship between entropy (E) and uniformity (U) values. Low values of entropy and uniformity are shown in the bottom left with random displacement of few intensity values. As the image becomes more hypo-intense, with only few spots of hyper-intensity, the uniformity increases (upper left) while the entropy remains unaffected. On the other hand, allowing for a range of hyper-intensities which will induce a more irregular, unpredictable pattern (bottom right) the entropy will increase, as the distribution becomes more uncertain.

Clinical outcome measures/standard of reference

Texture features were compared with three clinical outcome parameters: (1) extent of disease, (2) response to chemotherapy, and (3) overall survival (OS). For the extent of disease, patients were categorised based on the number of liver metastases visible at the time of diagnosis: patients with ≥ 5 liver metastases were classified as the 'extensive disease' group and patients with < 5 liver metastases as the 'limited disease' group (a cut-off based on previous literature)²². Since not all patients underwent surgical resection of their liver metastases, response to

chemotherapy was assessed on post-chemotherapy imaging and patients were categorized according to RECIST 1.1⁷. Patients with complete response (CR) or partial response (PR) were classified as the ‘responders’ group and patients with stable disease (SD) or progressive disease (PD) were classified as the ‘nonresponders’ group. OS was defined as the absence of death during follow-up. Fifty-eight patients died during follow-up, median FU in these patients was 14.5 months (range 1-71). In the twelve patients that were still alive at the time of writing, median FU was 57.5 months (rang 43-103).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). The Shapiro-Wilk Test was used to test for normality. Independent sample T-tests (or Mann-Whitney U test in case of non-normally distributed data) were used to compare mean texture features and ratios between (a) patients with limited (< 5 liver metastases) versus extensive (≥ 5 metastases) disease and (b) responders versus nonresponders (according to RECIST 1.1). The Holm-Bonferroni correction method was used to correct for multiple testing²³.

The predictive value of texture parameters for OS was assessed by use of multivariable Cox proportional hazards models. With univariable analyses, the potentially predictive factors were identified, which were then entered in the multivariable Cox proportional hazards model. Hazard ratios (HRs) with 95% confidence intervals (CI) were calculated. *P*-values ≤ 0.05 were considered statistically significant.

Results

Patients

Baseline patient characteristics are described in Table 1. The primary tumor site was the rectum in 30 and the colon in 40 patients. The median number of CRLMs per patient was 3 (range 1-20); 42 patients had < 5 metastases (limited disease) and 28 had ≥ 5 metastases (extensive disease). Three patients underwent immediate surgical resection. Sixty patients underwent neoadjuvant or palliative chemotherapy; the routine neoadjuvant chemotherapeutic regimen (in 80% of patients) consisted of CAPOX with or without the addition of Bevacizumab. In the patients undergoing chemotherapy, response evaluation with imaging (according to

RECIST 1.1) was available in 56 patients: 31 were responders (all PR), 25 were nonresponders (17 SD, 8 PD). Median OS was 22,5 months (range 1-102 months).

Table 1. Baseline characteristics

Patient characteristics	Total N = 70
Age (y)	
Median	69
Range	39-85
Sex	
Male	50 (71.4)
Female	20 (28.6)
Primary tumor site	
Rectum	30 (42.9)
Colon	40 (57.1)
Number of hepatic metastases	
Median	3
Range	1-20
Extrahepatic metastases	
No	36 (51.4)
Yes	34(48.6)
Intra-abdominal only	7 (10)
Extra-abdominal (+/- intra abdominal)	27 (38.6)
Treatment CRLM	
Immediate surgery	3 (4.3)
Chemotherapy & surgery	22 (31.4)
Palliative chemotherapy	38 (54.3)
Best supportive care	7 (10.0)
Chemotherapy regimen	
CAPOX* + Bevacizumab	39 (65.0)
CAPOX*	9 (15.0)
Capecitabine	7 (11.7)
Other	5 (8.3)

Note. – Unless otherwise indicated, data are numbers of patients and data in parentheses are percentages.

* CAPOX: capecitabine + oxaliplatin

Texture features to assess limited vs. extensive disease

Table 2 compares the texture features and ratios of patients with limited (< 5 lesions) and extensive (≥ 5 lesions) disease. The ratio for the entropy without filter ($E_{\text{metastases}}/E_{\text{liver}}$) was significantly lower in patients with limited disease ($P=0.02$) while correspondingly the ratio for uniformity ($U_{\text{metastases}}/U_{\text{liver}}$) was significantly higher ($P=0.02$). The remaining ratios, as well as the separate texture features (E and U) of the metastases and liver itself, did not show statistically significant differences between the two groups ($P=0.67-1.00$).

Texture features to assess response vs. nonresponse (RECIST 1.1)

Table 2 compares the texture features and ratios between responders and non-responders for the 56 patients for whom a RECIST response assessment after neoadjuvant chemotherapy was available. Only the lesion entropy without filter ($E_{\text{metastases}}$) showed a trend towards a higher value in responders ($P=0.08$). None of the other features or ratios resulted in any significant outcomes ($P=0.48-1.00$).

Texture features to predict survival

Table 3 shows the results for the univariable analyses. Based on these results, the $E_{\text{metastases}}/E_{\text{liver}}$ ratio (without filter) was combined with age at diagnosis, chemotherapy (Y/N), number of CRLM, resection of CRLM (Y/N) and the presence of extrahepatic metastases (none/abdominal only/extra-abdominal metastases) in the multivariable model, the results of which are presented in Table 4.

The $E_{\text{metastases}}/E_{\text{liver}}$ showed a trend towards significance in the multivariable model with a HR of 1.90 (0.95-3.78; $P=0.07$). Resection of CRLM was an independent predictor of OS (HR 0.26; CI 0.11-0.60; $P=0.004$), as was chemotherapy (HR 0.42; CI 0.18-0.98; $P=0.04$).

Table 2. Textural features of patients with < 5 or ≥ 5 lesions and responders and nonresponders according to RECIST 1.1

	< 5 Lesions N = 42	≥ 5 Lesions N = 28	<i>P</i> *	Responders N = 31	Nonre- sponders N = 25	<i>P</i> *
Without filter						
E _{liver}	6.37±0.24	6.29±0.25	1.00	6.32±0.26	6.34±0.25	1.00
U _{liver}	0.02±0.003	0.02±0.003	1.00	0.02±0.003	0.02±0.002	1.00
E _{metastases}	6.57±0.33	6.71±0.24	0.67	6.65±0.26	6.51±0.34	0.08
U _{metastases}	0.01±0.003	0.01±0.002	0.94	0.01±0.002	0.01±0.003	1.00
E _{metastases} /E _{liver}	1.03±0.05	1.07±0.03	0.02	1.05±0.03	1.03±0.06	0.59
U _{metastases} /U _{liver}	0.87±0.21	0.74±0.09	0.02	0.78±0.11	0.89±0.26	0.48
Fine filter						
E _{liver}	5.15±0.25	5.08±0.25	1.00	5.10±0.27	5.12±0.25	1.00
U _{liver}	0.03±0.006	0.04±0.006	1.00	0.04±0.008	0.04±0.006	1.00
E _{metastases}	5.33±0.29	5.27±0.24	1.00	5.31±0.28	5.27±0.25	1.00
U _{metastases}	0.03±0.006	0.03±0.005	1.00	0.03±0.006	0.03±0.006	1.00
E _{metastases} /E _{liver}	1.04±0.04	1.04±0.02	1.00	1.04±0.03	1.03±0.04	1.00
U _{metastases} /U _{liver}	0.87±0.11	0.88±0.06	0.92	0.86±0.08	0.90±0.11	1.00
Coarse filter						
E _{liver}	6.16±0.41	6.11±0.40	1.00	6.19±0.43	6.12±0.41	1.00
U _{liver}	0.03±0.008	0.03±0.009	1.00	0.03±0.008	0.03±0.009	1.00
E _{metastases}	5.90±1.20	6.46±0.65	0.94	6.23±0.79	5.82±1.42	1.00
U _{metastases}	0.03±0.03	0.02±0.009	1.00	0.02±0.01	0.04±0.04	1.00
E _{metastases} /E _{liver}	0.96±0.20	1.06±0.12	0.77	1.01±0.14	0.95±0.23	1.00
U _{metastases} /U _{liver}	1.23±1.32	0.72±0.32	1.00	0.90±0.50	1.38±1.63	1.00

Note. – Data are the mean ± SD, all measurements were performed on primary staging CT before treatment, significant results are printed in bold.

E: Entropy

U: Uniformity

* *P*-values after Holm-Bonferroni correction

Table 3. Univariable Cox proportional hazards model

Parameter	HR	95% Confidence Interval	P
Without filter			
E _{liver}	0.63	0.23-1.73	0.37
U _{liver}	1.04	0.95-1.15	0.41
E _{metastases}	2.59	1.00-6.65	0.05
U _{metastases}	0.90	0.80-1.00	0.05
E _{metastases} /E _{liver} [§]	2.51	1.44-4.36	0.001
U _{metastases} /U _{liver}	0.41	0.24-0.72	0.002
Fine Filter			
E _{liver}	0.81	0.30-2.19	0.67
U _{liver}	1.01	0.97-1.05	0.70
E _{metastases}	0.96	0.39-2.39	0.93
U _{metastases}	1.00	0.96-1.04	0.92
E _{metastases} /E _{liver}	1.23	0.73-2.07	0.43
U _{metastases} /U _{liver}	0.83	0.50-1.40	0.49
Coarse filter			
E _{liver}	0.91	0.47-1.75	0.77
U _{liver}	1.00	0.97-1.03	0.93
E _{metastases}	1.46	1.13-1.89	0.004
U _{metastases}	0.98	0.96-1.00	0.012
E _{metastases} /E _{liver}	1.81	1.06-3.09	0.030
U _{metastases} /U _{liver}	0.49	0.29-0.84	0.009
Clinical parameters			
Age [§]	1.01	0.98-1.04	0.45
Sex	1.09	0.61-1.93	0.78
Location of primary tumour*	0.61	0.32-1.18	0.14
Resection of primary tumour [†]	0.35	0.20-0.62	0.000
Chemotherapy ^{†§}	0.26	0.12-0.57	0.001
Number of CRLM [§]	1.06	1.02-1.10	0.006
Resection of CRLM ^{†§}	0.20	0.10-0.41	0.000
Extrahepatic disease ^{‡§}	1.378	1.04-1.83	0.025

Note. – Texture ratios are dichotomized based on the median value, according to methods previously reported³⁴, uniformity values were multiplied by 1000 in line with previous research¹⁴, significant results are printed in bold.

* left sided (transversum, descendens, sigmoid or rectum) / right sided (ascendens or caecum)

† No / Yes

‡ No / abdominal only / extra-abdominal metastases

Variables indicated with § were included in the multivariable model. To avoid overfitting and because of a relation to other variables, the remaining significant variables were not included in the multivariable model (e.g. the vast majority of patients who underwent resection of their liver metastases also underwent resection of their primary tumour)

Table 4. Multivariable Cox proportional hazards model with entropy ratio

Parameter	HR	95% Confidence Interval	P
E _{metastases} /E _{liver} (without filter)	1.90	0.95-3.78	0.07
Age	1.02	0.99-1.06	0.16
Number of CRLM	1.00	0.96-1.05	0.90
Chemotherapy			
No	1.00		
Yes	0.42	0.18-0.98	0.044
Resection of CRLM			
No	1.00		
Yes	0.26	0.11-0.60	0.004
Extrahepatic disease			
No	1.00		
Abdominal only	1.12	0.59-2.11	0.74
Extra-abdominal	2.10	0.70-6.29	0.19

Note. – Texture ratios are dichotomized based on the median value, according to methods previously reported³⁴, significant results are printed in bold

E: Entropy

Discussion

The aim of our study was twofold: to test if we could confirm results of previous literature that CT texture analysis has potential value as a predictive imaging marker in patients with CRLM and to get a better insight into the relationship between the texture of CRLM and the surrounding liver architecture. Our results suggest that analyzing the ratios between textural changes of the metastases and the surrounding liver parenchyma ($E_{\text{metastases}}/E_{\text{liver}}$ and $U_{\text{metastases}}/U_{\text{liver}}$) may be of added value to assess the burden of disease in the liver. Moreover, the texture ratios showed an association with overall survival, albeit it not statistically significant in multivariate analyses. Finally, we observed a subtle trend towards higher entropy in liver metastases that show a better response to treatment.

As shown in Figure 3, a more irregular distribution of ‘disease’ within a certain VOI will typically lead to a higher entropy (and lower uniformity). One can imagine that in the case of a more aggressive disease profile, the liver lesions become more heterogeneous (higher entropy / lower uniformity) while the surrounding liver remains relatively unaffected. This effect on entropy and uniformity in the liver metastases may be highlighted by comparing it to the surrounding liver (as a normalization factor), which may explain why mainly the ratios were significantly associated with the burden of disease while there was only a subtle, nonsignificant trend for the entropy and uniformity measures itself. An alternative hypothesis would be that the ratio between the texture of the liver metastases and surrounding liver is in itself a unique feature that captures biological properties of the course of metastatic disease within the liver that cannot be identified by looking at either the architecture of the liver lesions or surrounding liver separately.

A higher entropy ratio was also an independent factor that was associated with impaired OS (with a borderline significant HR of 1.90 in multivariate analyses) and may thus be of value as an added biomarker of survival, alongside more well-known clinical predictors such as chemotherapy and resection. This is in line with the findings of previous studies in other tumour types: Ganeshan et al. reported that, for oesophageal cancer, high entropy with a medium to coarse filter was associated with a shorter OS²⁴. Hayano et al. also suggested that high entropy with a medium filter was associated with a shorter OS in non-small cell lung cancer²⁵. In contrast, other groups found the opposite and reported higher entropy (with a fine filter) to be associated with a better OS in patients with head and neck cancer, oesophageal cancer, and colorectal cancer²⁶⁻²⁸. These seemingly

discrepant findings may in part be related to the fact that different studies used different image filters. The use of edge enhancement filters in texture analysis, such as the LoG filter used in this study, is to improve the ability to assess and quantify tissue heterogeneity. Lower filter values highlight small changes in intensity and structures with fine textures, while higher filter values highlight structures with medium and coarse textures in the filtered image ¹⁹. As such, the use of different filters may considerably affect study results. Moreover, these previous studies report on a heterogeneous group of tumour types with various different treatment regimens and inherently different tumour prognostic profiles.

When looking at the texture of the metastatic lesions itself, only a subtle, nonsignificant trend towards higher entropy was observed for responders versus nonresponders according to RECIST 1.1. We acknowledge that RECIST measurements are suboptimal as an outcome variable given the known limitations of RECIST to accurately assess response ^{29,30}. However, since the majority of study patients did not undergo resection of their liver metastases, correlation with histopathology was not feasible in our cohort and we chose RECIST as the main outcome as it is still most commonly used in clinical practice as well as in many previous study reports. Interestingly, our results are in line with a previous report of Rao et al. who did use histologic tumour regression grading (TRG) after surgery as the main outcome of response in a small group of 21 patients with CRLM and reported that – similar to our current findings – a non-significant trend towards higher entropy (without filter) in responders versus nonresponders. Rao et al. did find significant results when looking at relative changes in the texture measures after treatment with significantly decreased entropy compared to pre-treatment measurements in responders and increased entropy in nonresponders ¹³. Ahn et al. found no significant difference in the pre-treatment entropy between responders and nonresponders to chemotherapy in a relatively large cohort of 235 patients with CRLM. However, they did describe a profile of other features (including skewness and standard deviation) that underlined the theory of a more heterogeneous imaging texture of liver metastases in responders versus nonresponders ³¹. Altogether, the results of studies presented so far – including our own – appear to indicate a subtle but not (yet) strong role for pre-treatment textural assessment of CRLM to predict response.

When looking at previous results for whole-liver texture analysis, several studies describe higher entropy in the surrounding liver of patients with CRLM when compared to patients without metastases ^{15,16,32}. Moreover, Beckers et al. found

that differences in the texture of the liver parenchyma can already be observed at the time of primary staging (when no visible lesions are apparent) in patients who develop metachronous metastases in the first 6 months after diagnosis, suggesting that liver texture may serve as a marker to predict the early course of disease ¹⁵. Ganeshan et al. showed that CT texture analysis has potential to identify patients at risk for a reduced survival, based on lower entropy ³³. These findings were however described in a group of patients without metastases. Since our cohort only included patients in whom CRLMs were already present, these previously reported findings could not be explored in the current cohort. When it comes to whole-liver texture analysis for the prediction of the extent of disease, treatment response or survival we could not produce any significant findings.

There are some limitations to our study. First, the sample size is relatively small. Second, despite the standardised protocol, there were some differences between the scanners and slice thickness employed throughout this study, although a previous study suggested that scanner settings are of minor influence on the textural features ¹⁵. Third, as already mentioned above, it was not possible to correlate our findings with underlying histopathology since most patients did not undergo resection of their CRLM. Fourth, in the subgroup undergoing chemotherapy, there were some variations in the chemotherapeutic regimen used. Finally, in the field of texture analysis, many features (derived from both first order as well as higher order statistical models) can be tested, which would result in a risk of false positive findings due to multiple testing (type I error). Therefore, for this study, we chose to only include a selection of first-order texture features commonly used in previous literature within the field of texture analysis in colorectal cancer to allow meaningful comparisons with previous evidence ^{15,18,32}.

In conclusion, our study suggests that the ratio between the texture of liver metastases and the surrounding liver possibly reflects relevant changes in tissue microarchitecture and may be of value in the future to assess the extent of the disease in the liver and to predict overall survival.

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6. Quantitative imaging of the liver in colorectal cancer patients: a comparison between diffusion-weighted MRI and CT texture analysis

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7. General Discussion

7. General discussion

The time that imaging could solely provide information about tumour size and morphology has passed. In recent years, we have seen enormous developments in the field of functional imaging and advanced image post-processing, allowing us to extract imaging biomarkers that can provide novel insights into underlying biological tissue properties. One of such techniques is ‘texture analysis’. Texture analysis is an example of an image post-processing technique where ‘routine’ diagnostic imaging data such as CT or MRI are re-assessed with the help of statistical or mathematical models without the need for extra image acquisitions, or advanced computational software.

A variety of methods exist to derive texture features from an image¹. With the most basic statistical-based methods (such as the ones used in this thesis), we evaluate the frequency and spatial distribution of signal intensities within a certain region of interest in an image, for example within the liver on a routine diagnostic CT image^{1,2}. When this spatial distribution is more irregular, it is associated with a more heterogeneous underlying tissue microarchitecture, while vice versa a more regular distribution of signal intensities correlates with a more homogeneous tissue structure³. Two commonly used texture features in this respect are ‘uniformity’ (a feature reflecting a more homogeneous distribution) and ‘entropy’ (a more or less opposite feature reflecting a higher heterogeneity)⁴. In oncology, heterogeneity is known to be associated with tumour biology. Although the exact bio-oncological substrate for individual texture features is not fully understood, measures of heterogeneity appear to be related to intratumoural spatial variations in cellularity, angiogenesis, extracellular matrix and necrosis³.

Potential clinical applications of texture analysis are emerging and the topic of an increasing number of research studies. So far studies have mainly focussed on texture analysis in a pre-clinical setting, with limited data on its function as a predictor of clinical outcome. With this thesis, we aimed to further build the evidenced base for the potential clinical value of CT texture analysis in oncology, in specific for the clinical management of patients with colorectal liver metastases. To achieve this, we have first focussed on studying the potential of whole-liver CT texture analysis in predicting the course of metastatic disease. Previous work in this field has been conducted by the groups of Rao et al and Ganeshan et al. They both described that texture features derived from the apparently normal (non-diseased) liver parenchyma in patients with colorectal cancer may contain potentially valuable information that can help to establish the presence of met-

astatic disease within the liver^{5,6}. Apparently, the texture of the whole liver is altered when patients are affected by hepatic metastases. Ganeshan et al stated that these changes in liver texture are related to the total hepatic blood flow and glucose metabolism^{7,8}. From a clinical point of view, it is interesting to see whether these changes in liver texture already occur before focal metastatic lesions become apparent within the liver. If so, whole liver texture analysis may have potential to predict the course of metastatic disease. In **Chapter 3**, we confirmed results of previous studies that there is a difference in the whole liver texture of patients with and without present colorectal liver metastases. In particular, we found low uniformity, indicating an overall more heterogeneous liver microarchitecture in patients with metastases. Although the exact mechanism is not fully known, changes in liver texture as a result of metastatic involvement have been proposed to be related to changes in liver perfusion or changes on a cellular level caused by the presence of micro metastases⁸⁻¹⁰. Interestingly, similar changes in liver texture were also observed in patients who presented without metastases at the time of diagnosis but proceeded to develop liver metastases within 6 months. This suggests that whole liver CT texture analysis also has potential to predict patients at risk of developing early metachronous liver metastases during the course of their disease. However, whole liver texture analysis did not prove to be robust enough to identify patients at risk of developing metastases at a later stage (within one or two years), for which there could be two logical explanations. First, it may be that in patients that develop metastases after one to two years, no changes are present yet in the liver parenchyma at the time of primary diagnosis. Alternatively, subtle changes may already be occurring at that time, but too small to be detected with our current techniques.

As a follow-up of the study in **Chapter 3**, we wanted to find out whether the predictive power of our texture approach could be improved by performing a segmental texture analysis instead of a whole liver analysis. The rationale for this approach would be that the textural changes could be more localized to a certain area within the liver (i.e., the specific site where at a later stage the metastases will become visible) and more related to focal changes on a cellular level (i.e., presence of occult micrometastases) compared to more generalized parenchymal changes. If so, we hypothesized that a segmental texture analysis should better predict the occurrence of metastases in specific parts of the liver. The results described in **Chapter 4**, however, do not support this hypothesis as changes in texture on a segmental level were less apparent than texture changes derived from the whole liver, which appears to favour the hypothesis that the texture changes we measure

are related to more diffuse parenchymal changes. We believe that these are likely related to changes in liver perfusion and hepatic hemodynamics^{8,11}. With this in mind, one can imagine that texture measures may be influenced and therefore highlighted according to the timing of image acquisition after contrast injection. It has indeed previously been demonstrated that contrast timing in CT can significantly affect texture measurements. For example, in previous studies by Ganesan et al, results for liver CT analyses were more significant when using arterial phase scans^{7,12}. In our studies we mainly used portal venous phase contrast scans as in common clinical practice this is often the only phase that is routinely acquired. The potential benefit of adding extra (dynamic) contrast phases therefore remains to be investigated by future studies.

Second, we aimed to explore the possibilities of CT texture analysis as a biomarker for the prediction of response to therapy and survival. As a first exploratory step, in **Chapter 2** we performed a literature review to study the available evidence on the prediction of response to chemotherapy in colorectal liver metastases using various imaging techniques, including texture analysis. Most promising results so far have been reported for functional MR imaging, in specific diffusion-weighted imaging. With regard to texture analysis, evidence so far is sparse. Only one report by Rao et al specifically addressed the use of CT texture features of metastatic liver lesions to predict response to chemotherapy in colorectal cancer¹⁵. They found that changes in CT texture measures after treatment (Δ uniformity and Δ entropy) outperformed RECIST and tumour volume measurements to assess the treatment response after completion of chemotherapy, but none of the texture features was beneficial in predicting treatment response beforehand. This is in line with the findings described in **Chapter 5**. Neither texture features derived from the metastatic liver lesions, nor the background liver parenchyma were capable of predicting response to chemotherapy pre-treatment. Similarly, no significant results were found for the prediction of survival using whole liver or lesional texture features. Interestingly, however, when a ratio was calculated by dividing the texture of the metastatic lesion by the texture of the whole liver parenchyma, results improved considerably. Apparently clinically relevant changes in texture can be highlighted by looking at the relation between the texture of the liver lesions itself and the background liver. An increased lesion-to-liver entropy ratio (albeit not significant) was associated with a poorer overall survival. Moreover, texture ratios were associated with the extent of metastatic disease in the liver. Although, to our knowledge, we are the first to report on using ratios between the texture of liver metastases and the background liver in such a way,

our results support the findings of previous studies that reported significant correlations between texture features and survival, both in colorectal liver metastases as well as in other tumour types^{11,13}.

We have encountered some challenges when investigating the clinical potential of CT texture analysis in colorectal liver metastases. Our group is one of the first to perform a clinical study on CT texture in a multicentre setting. This involved dealing with differences in hardware, scan protocols and acquisition-related parameters within the participating centres. An important challenge was to properly take these effects into account. In our multicentre study in **Chapter 3**, we tried to compensate for such effects by performing a multilevel analysis per CT scanner. However, we could not fully rule out potential confounding effects. Several studies have indicated that factors such as slice thickness, contrast timing and CT acquisition parameters (i.e. kVp and slice collimation) may influence texture features, although the exact effects are still unknown^{7,8,11,13,14}. Also, there are several different methods to conduct texture analysis. In this thesis, we have solely explored first order statistics features. As with other imaging techniques, standardisation of protocols and analysis methods is an important item that deserves attention in future research to further facilitate the implementation of texture as an imaging biomarker.

As a final step of this thesis, we aimed to put texture analysis in perspective with regard to other currently highly researched techniques, especially diffusion-weighted MRI (DWI). DWI bases its contrast mainly on changes in tissue cellularity and has been shown to be highly sensitive and superior to CT, PET-CT, and ultrasound for the detection of small focal liver lesions¹⁵. Furthermore, quantification of liver diffusion by means of the apparent diffusion coefficient (ADC) has shown promise for lesion characterization and prognosticating the response of colorectal liver metastases to chemotherapy and radiotherapy^{16,17}. In a previous report by our group (Lambregts et al.) on liver DWI-MRI histogram analysis, significant differences were found when comparing the whole liver ADC of patients with colorectal liver metastases to that of healthy controls¹⁸. In our study in **Chapter 3** on CT texture analysis, we found similar differences in the whole liver texture features between colorectal cancer patients with and without any metastatic liver disease. As such, we believed it would be interesting to compare ADC and texture features of the liver in colorectal cancer patients, which resulted in the study presented in **Chapter 6**. Only a few weakly significant correlations were found between CT texture features and ADC- related

parameters derived from DWI-MRI. This makes sense since the two techniques are distinctly different. Whereas texture analysis focuses on tissue heterogeneity, DWI provides a measure of a tissue's cellular microarchitecture by assessing the diffusivity of water protons. Although a potential relation with corresponding (micro)perfusional changes has been proposed for both DWI¹⁹ and texture analyses⁸, the underlying mechanism of action is thus different for the two techniques. Moreover, there is a considerable difference in image resolution and soft tissue contrast between CT and MRI, which will likely also affect results. Interestingly, in the study in **Chapter 6**, none of the ADC-related parameters showed significant differences between normal liver parenchyma and metastatic liver lesions, while multiple texture features (especially entropy and uniformity with a medium to coarse filter) were distinctly different in the metastases. This at first seems contra-intuitive since – when visually assessing DWI-MRI – the difference in signal between metastases and the normal background liver is much more pronounced. This has to do with the way the diffusion images are displayed. Typically, a very narrow window-width is chosen, which greatly exaggerates differences between the metastases and background liver (although small in an absolute sense), thereby highlighting the metastases. Although DWI can thus certainly be of help to detect metastases, from a quantitative point of view, texture analysis appears to better equipped to characterize metastatic tissue within the liver²⁰⁻²².

Summary and Recommendations

The aim of this thesis was to build on evidence for the use of CT texture analysis as a biomarker in colorectal liver metastases. We have gained a better understanding of the relationship between texture analysis and the amount of metastatic disease in colorectal cancer. We have been able to confirm that there is a potential clinical value in textural analysis particularly for assessing the presence and severity of disease in the liver and thereby estimating the risk of developing metachronous metastases early after diagnosis. In addition, there seems to be valuable information contained in studying the ratio of the texture of metastatic liver lesions and the surrounding liver parenchyma. The main challenge for translating this further into clinical practice is to overcome practical limitations related to variations in measurements caused by hardware and acquisition-related differences, which can make multicentre research challenging. Future studies should, therefore, aim at gaining a better understanding of these effects so that they can be taken into account in upcoming studies to enable potential clinical implementation. Moreover, future research should focus on further establishing the role of quantitative imaging techniques such as textural analysis and on combining different quantitative imaging biomarkers with other histopathological markers, clinical features and genomics to develop comprehensive clinical models to further facilitate personalised cancer treatment. Finally, image quantification typically requires manual delineation of tumours and/or organs, which is time-consuming and influenced by human error. As such deep learning and automated segmentation techniques should be further developed to facilitate more quantitative research in the future.

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8. Summary / Samenvatting

Summary

The aim of this thesis was to investigate the current role of imaging techniques in the assessment of colorectal liver metastases and to determine the possible added value of new techniques, in particular, CT texture analysis.

In **chapter 2** we studied the role of PET, PET-CT, CT and MRI in a systematic review of 16 radiological studies to predict the response to chemotherapy in patients with colorectal liver metastases. First of all, it turned out that the available literature was relatively scarce and extremely heterogeneous, which made it difficult to draw firm conclusions. Nevertheless, ADC appears to be a promising technique in the prediction of response to chemotherapy. A striking finding, moreover, was that techniques that predicted a good RECIST or metabolic response were also often associated with a shorter survival in patients with colorectal liver metastases.

Chapter 3 describes a multicentre study investigating the value of CT texture analysis to assess the presence of synchronous metastatic disease in the liver and predict the development of metachronous colorectal liver metastases. Through CT texture analysis, we were able to distinguish between patients with and without colorectal liver metastases. We were also able to predict the occurrence of liver metastases within 6 months after diagnosis, but the technique was not robust enough to predict the occurrence of metachronous in the longer term.

In the study in **chapter 4**, we aimed to further improve our method of CT texture analysis described in chapter 3 by investigating whether a separate analysis of the texture in different liver segments offers added value above the assessment of the average texture of the whole liver volume. However, the more detailed segmental registration did not prove to be of added value to predict metachronous disease. This indirectly suggests that changes in CT texture measured in the liver appear to be due to changes diffusely distributed throughout the liver parenchyma and less likely to be caused by occult local disease.

In **chapter 5** we analysed the relationship ('ratio') between the CT texture of metastases in the liver and the surrounding normal liver parenchyma with the aim of gaining a better understanding in the underlying disease mechanism. This ratio was significantly different in patients with a limited number of metastases compared to patients with extensive liver metastases, indicating that texture

ratios may be of added value to predict the burden of disease. Moreover, we saw a trend that texture ratios may also be of value for predicting the response to chemotherapy and survival in the longer term.

In **chapter 6** we investigated whether correlations exist between parameters obtained by CT texture analysis and parameters from diffusion-weighted MRI of the liver in patients with colorectal cancer. We compared measurements obtained from liver metastases with measurements from different parts of the healthy liver parenchyma. There were only a few weak correlations between CT texture and DWI-related parameters, but no correlation was found for the majority of the tested parameters. CT texture parameters was better able to quantitatively distinguish between normal liver parenchyma and metastases. In addition, texture measurements were less sensitive to measurement variations within the normal parenchyma and were, therefore, more robust than DWI-related parameters.

Samenvatting

Het doel van dit proefschrift was om de huidige rol van beeldvormende technieken te onderzoeken in de beoordeling van colorectale levermetastasen en om te bepalen wat de mogelijk toegevoegde waarde is van nieuwe technieken, in het bijzonder CT textuur analyse.

In **hoofdstuk 2** bestudeerden we middels een systematische review van 16 radiologische studies de rol van PET, PET-CT, CT en MRI om de respons op chemotherapie te voorspellen in patiënten met colorectale levermetastasen. Allereerst bleek dat de beschikbare literatuur relatief schaars en uitermate heterogeen was, wat het lastig maakt harde conclusies te trekken. Desondanks lijkt ADC een veelbelovende techniek te zijn in de voorspelling van respons op chemotherapie. Een opvallende bevinding was bovendien dat technieken die een goede RECIST of metabole respons voorspelden vaak tevens geassocieerd waren met een kortere overleving in patiënten met colorectale levermetastasen.

Hoofdstuk 3 beschrijft een multicentrische studie waarin de waarde van CT textuur analyse werd onderzocht voor het voorspellen van de aanwezigheid van synchrone metastatische ziekte in de lever en het ontstaan van metachrone colorectale levermetastasen. Middels CT textuur analyse konden we een onderscheid maken tussen patiënten met en zonder colorectale levermetastasen. De techniek was tevens in staat om het ontstaan van levermetastasen binnen 6 maanden na diagnose te voorspellen, maar niet robuust genoeg om het ontstaan van metachrone op langere termijn te voorspellen.

In de studie in **hoofdstuk 4** hebben we getracht onze methode van textuuranalyse beschreven in **hoofdstuk 3** verder te verbeteren door te onderzoeken of het separaat analyseren van de textuur in verschillende leversegmenten meerwaarde biedt boven het beoordelen van de gemiddelde textuur van de gehele lever. De meer gedetailleerde segmentele intekening bleek echter niet van meerwaarde om metachrone ziekte te voorspellen. Dit suggereert indirect dat textuurveranderingen gemeten in de lever lijken te berusten op veranderingen diffuus verspreid door het gehele lever parenchym en minder waarschijnlijk worden veroorzaakt door occulte lokale ziekte.

In **hoofdstuk 5** analyseerden we de relatie ('ratio') tussen de CT textuur van metastasen in de lever en het omringend normaal leverparenchym met als doel

een beter inzicht te krijgen in het onderliggende ziektemechanisme. Deze ratio was significant anders in patiënten met een beperkte hoeveelheid metastasen in vergelijking met patiënten met uitgebreide levermetastasen, indicierend dat textuur ratio's van meerwaarde kunnen zijn om de ziektelast te voorspellen. Bovendien zagen we een trend dat textuur ratio's mogelijk ook van waarde kunnen zijn voor het voorspellen van de respons op chemotherapie en de overleving op langere termijn.

In **hoofdstuk 6** onderzochten we of er correlaties bestaan tussen parameters verkregen middels CT textuur analyse en parameters uit diffusie-gewogen MRI van de lever bij patiënten met een colorectaal carcinoom. We vergeleken hierbij metingen verkregen uit levermetastasen met metingen uit verschillende delen van het gezonde leverparenchym. Er waren slechts enkele zwakke correlaties tussen CT textuur en DWI-gerelateerde parameters, maar voor het merendeel van de geteste parameters werd geen correlatie gevonden. CT textuur parameters bleken daarnaast beter in staat om kwantitatief het onderscheid te maken tussen normaal leverweefsel en metastasen. Textuur metingen bleken bovendien minder gevoelig voor meetvariaties binnen het normale parenchym en waren derhalve robuuster dan DWI-gerelateerde parameters.

9. Valorisation addendum

Valorisation addendum

Colorectal cancer (CRC) is the most common form of cancer in The Netherlands, with 15.550 new cases in 2015¹. Incidence is expected to rise to 17.000 new cases in 2020 because of the implementation of the nationwide screening program, the growing incidence (especially in men) and the growing and ageing population¹. Once CRC is diagnosed, the next step is to determine its stage. The stage of CRC is based on the local tumour extent and on whether there are signs of cancer spread to lymph nodes and other organs. This is typically assessed with imaging, including a CT scan or MRI of the abdomen and a CT scan or X-ray of the chest. In case of stage IV cancer, cancer has spread to distant organs, with one of the most important sites of metastases being the liver. This is considered ‘advanced’ CRC and is generally treated with chemotherapy. Some patients may benefit from chemotherapy with even a curative path in combination with surgery. However, there are still many patients for whom chemotherapy will only be a palliative solution. To date, we still have an insufficient insight into which factors determine the course of the disease and consequently to determine which patients are at risk to develop advanced disease². Moreover, once the metastatic disease is present it remains unclear which patients will likely show a good response to treatment and which patients will not.

So far, the mainstay of imaging evaluation has been to assess the morphology (e.g. shape, signal) and size of tumour lesions³. In other words, we have so far mainly focussed on things that can be appreciated by the ‘naked eye’. There is, however, much more information ‘hidden’ in images that could potentially provide us with more in-depth knowledge about the underlying tumour biology. This information can be distilled when we look at images with more sophisticated methods. An example of such a method is CT texture analysis, which is a mathematical method that assesses the distribution of signal intensities on CT images⁴.

Relevance

The results of this thesis show that CT texture analysis can be a useful adjunct for the imaging of colorectal liver metastases as it can provide quantitative ‘imaging markers’ to predict the course of the disease. For example, texture analysis has shown capable of predicting the occurrence of metastases within six months after diagnosis, which enables an early selection of patients at risk of developing metastases. This is in line with the current trend to promote “personalised medicine”, which means that medical decisions, practices, interventions and/

or products are tailored to the individual patient, based on their predicted disease risk profile. In future practice, novel imaging tools such as texture analysis may thus aid in optimising treatment for individual patients, thereby aiming to ultimately improve outcome and survival. Moreover, when patients can be better informed about their risk profile, this can lead to a better-informed decision-making process between doctor and patient.

Target population

There are several people who could benefit from the results presented in this thesis (once properly validated and confirmed by further studies). First, obviously, all colorectal cancer patients can benefit from CT texture analysis as it is a non-invasive tool that can provide the patient's treating physicians with additional information that provides a better insight into their disease and can thus help optimise treatment to obtain the best possible outcome. Second, healthcare professionals who are in the decision-making process among patients with CRC could benefit from the 'imaging biomarkers' provided by texture analysis. Finally, in the field of radiology, the results obtained with texture analysis in colorectal cancer may be extrapolated and explored further in other malignancies, but also in other non-oncologic conditions including chronic liver disease such as steatosis and cirrhosis. Further research is needed, to explore these opportunities.

Products

Currently, there are a few commercial products available that incorporate texture analysis within daily used imaging software. This is mainly because to date, evidence on the clinical utility of texture analysis is still relatively sparse. Once the clinical added value is confirmed by further and larger studies, the incorporation of texture analysis into clinical imaging tools should be further explored therewith building on the important bridge between research and clinical practice.

Innovation and future

Up until now, CT texture analysis has not been part of daily radiological clinical practice. With this thesis, we aimed to give an overview of the current potential of this method and its possible beneficial role as a clinical diagnostic tool. Future research should focus on building on this preliminary evidence by performing large-scale validation studies, detailed correlation with pathology and standardisation of scanning protocols.

Moreover, it will be interesting to apply texture analysis as a post-processing method not only to CT data but also to MRI sequences including both routine morphological sequences as well as exciting novel functional imaging techniques such as diffusion-weighted and perfusion imaging that focus on more and more specific aspects of the tumour biology. Finally, imaging features such as texture should be combined with other clinical features such as histopathology and genomics in order to build smart multiparametric clinical models that can offer comprehensive insights into a patient's disease profile and prognosis.

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10. List of Publications

List of publications

Beckers RCJ, van der Linden FThMP, Oomen APA. Centralisatie van zorg rondom electieve aneurysmachirurgie – Een retrospectieve analyse in een perifere, niet-opleidingskliniek.

Nederlands tijdschrift voor Heelkunde 23.5 (2014): 46-49

Beckers RCJ, Beets-Tan RGH, Schnerr RS, Maas M, da Costa Andrade LA, Beets GL, Dejong CHC, Houwers JB, Lambregts DMJ. Whole-volume vs. segmental CT texture analysis of the liver to assess metachronous colorectal liver metastases. *Abdominal Radiology* 42.11 (2017): 2639-2645.

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12. Curriculum Vitae

Curriculum Vitae

Rianne C.J. Beckers was born on March 29th 1986 in Brunssum, the Netherlands. After obtaining her gymnasium degree in 2004 at Sint-Janscollege in Hoensbroek, she started a bachelor in Health Sciences with a major in Health, Policy and Management at the Faculty of Health, Medicine and Life Sciences at Maastricht University. In 2006 she started her medical study at the Faculty of Medicine at Maastricht University. In 2008 she finished her bachelor in Health Sciences while continuing her medical study. After obtaining her medical doctor degree in 2013, Rianne immediately started working as a surgical resident at the Maastricht University Medical Center. After one year of working in surgery, she started in 2014 as a PhD student at the GROW School for Oncology and Developmental Biology under supervision of prof. dr. R.G.H. Beets-Tan, prof. dr. G.L. Beets and dr. D.M.J. Lambregts.

In September 2017, she started her residency in Gastroenterology at the Zuyderland hospital in Sittard-Geleen and Heerlen under supervision of prof. dr. A.A.M. Masclee.