

# Clinical value of quantitative imaging in patients with gastrointestinal liver metastases

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# SUMMARY



The aim of this thesis was to explore the use and clinical utility of quantitative imaging and radiomics for GI-tract liver metastases, specifically focused on patients with colorectal liver metastases (CRLM) (part I) and neuroendocrine liver metastases (NELM) (part II).

## **PART I: COLORECTAL LIVER METASTASES**

The current state of the art of radiomics for the prediction of response or long-term outcome in CRC was systematically reviewed in **Chapter 2**. Heterogeneous results were reported in the 76 included studies regarding radiomics methods and included features. CT or MRI were predominantly used for radiomics analyses and a minority was performed on  $^{18}\text{F}$ -FDG-PET/CT. Only 13 out of the 72 included studies were considered high-quality according to both Radiomics Quality score (RQS) and Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, mainly consisting of MRI-based radiomics to predict response in rectal cancer. In general, a model that combined radiomics with clinical features outperformed models that used either clinical or radiomics features only. Although several studies reported a good predictive performance, no specific radiomics features or transformation methods could be identified as most predictive. Lack of (external) validation and reproducibility represent the main problems for implementation into clinical practice. This review identified that future radiomics research in CRC should focus on independent validation of existing models rather than on developing new models for existing aims. No evidence was available for radiomics for the prediction of response or long-term outcome in patients treated with ablation.

In **Chapter 3 to 5** we explored the use of radiomics in thermal ablation for CRLM. First, we studied the value of CT-based radiomics of the ablation zones (AZ) from 127 CRLM treated with thermal ablation in **Chapter 3**. Combining radiomics features with clinical features yielded the best predictive performance for local tumour progression (LTP) (c-statistic 0.78) compared to models with clinical or radiomics features only. Uniformity<sub>1.5</sub> was selected from both the AZ and PAR and seems to have the most potential to predict LTP as. Furthermore, three out of the five selected radiomics features originated from the periablational rim (PAR) which showed a stronger predictive value than AZ features. From a clinical point of view, it makes sense that before LTP occurs microscopical changes are present at the edge (i.e. PAR) of the AZ and, therefore, we concluded that the PAR may have the most potential for LTP prediction. These findings need external validation in larger datasets to confirm these results.

Radiomics analyses of the actual tumour or metastases have shown promising results to predict outcome in tumour types and, therefore, we analysed the CRLM itself before

ablation to predict LTP in **Chapter 4**. This chapter showed that a machine learning model of routine CT images 0-3 months before ablation could act as a valuable biomarker to predict local tumour progression-free survival. The radiomics and combined model both outperformed the clinical model in the identification of lesions at high risk for LTP (c-index 0.78 and 0.79 vs c-index 0.56, respectively). The most important features that were selected as predictors were 'Small Dependence Low Gray-Level Emphasis' and the clinical variable adjuvant chemotherapy. Because this was a single centre retrospective study and a first for this specific aim, the results need to be externally validated in a larger cohort.

Previous radiomics studies of CT data of the healthy liver parenchyma were able to predict the occurrence of metastases within 6 months after diagnosis of CRC, and so, in **Chapter 5** we studied the healthy liver parenchyma before treatment of patients undergoing ablation for CRLM to identify patients at the risk of developing new metastases. To this end, both an existing successful radiomics model for the prediction of CRLM during follow-up and a newly developed machine learning model based on the healthy liver parenchyma on the CT before ablation were tested on a population of patients planned to undergo thermal ablation for CRLM. All models proved to be unable to identify patients at risk of early (<6 months) or late (<24 months) recurrence in the liver (AUCs  $\leq$  0.60). After extensive hypothesis testing, we hypothesized that metastases in the liver potentially affect the whole liver parenchyma permanently. Consequently, radiomics is not able to identify any differences between patients with and without new CRLM during follow-up after thermal ablation.

In **Chapter 6** the reproducibility of gadoxetic acid-enhanced (Gd-EOB) magnetic resonance imaging (MRI) of the liver for the diagnosis of sinusoidal obstruction syndrome (SOS) grade and its relationship with response and long-term outcome was studied. This retrospective single centre study aimed to validate a previously developed scoring system for the diagnosis of SOS on MRI. Twenty-six MRI scans of 26 patients were included and three radiologists independently scored presence and severity of SOS on a 5-point scale. The inter-observer agreement for the diagnosis of SOS was poor ( $\kappa$  0.17–0.40), also for the binary outcome of SOS+ ( $\kappa$  0.03–0.37). Moreover, no significant correlation with relevant outcomes (response or overall survival) was found for any of the readers. Based on this study, MRI for SOS diagnosis might be less useful than previously reported.

## PART II: NEUROENDOCRINE LIVER METASTASES

In Part II, the role of radiomics in GEP-NETs was studied. The systematic review in **Chapter 7** showed that most radiomics analyses were performed on CT, MRI and  $^{68}\text{Ga}$ -DOTA-TATE-PET/CT. The majority of the radiomics studies in GEP-NETs analysed tumour grade or differential diagnosis of GEP-NETs, while few studies analysed response to treatment or long-term outcomes in GEP-NETs. Furthermore, 43 studies analysed pNETs, while only 2 studied other GEP-NET and a majority of the studies was of low quality (RQS < 30%). The higher quality studies were predominantly for the prediction of tumour grade. Only one study developed a model to predict recurrence in pancreas NETs (AUC 0.77). Combining clinical with radiomics features achieved the best performance. Future studies should focus on developing models for prediction of response or long-term outcome, since evidence for these aims is scarce.

In **Chapter 8** we studied the value of radiomics for the classification of patients with stable or progressive disease during somatostatin analogue treatment for neuroendocrine liver metastases (NELM). This single-centre retrospective study included 87 NELM in 46 patients. Two experienced radiologists classified patients according to RECIST 1.1. Nineteen patients had progressive disease (PD) and 27 patients had stable disease (SD) according to RECIST 1.1. Target lesions were manually delineated and both the arterial-phase (AP) and portal-venous-phase (PVP) CT were analysed with radiomics. Contrary to previous studies, univariable analyses found no differences between patients with PD and SD. More robust statistical analyses were not able to develop a model that was able to accurately classify response (AUC 0.44-0.60).