Advanced imaging to predict response to chemotherapy in colorectal liver metastases

REVIEW ARTICLE

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 and/or functional change 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 the 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.

Conclusion: 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.

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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 resection.[3] 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 intent.[4] 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 postprocessing 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 [RCJB and 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 checklist.[12] Results are reported according to the PRISMA statement.[13]

Results

Literature search

The search yielded 208 studies of which 16 met inclusion criteria for further analysis, Fig. 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 excluded,[14–42] 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-CT,[47] 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 to 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.

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 OS.[44] 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 responders.[47] 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 PFS.[44]

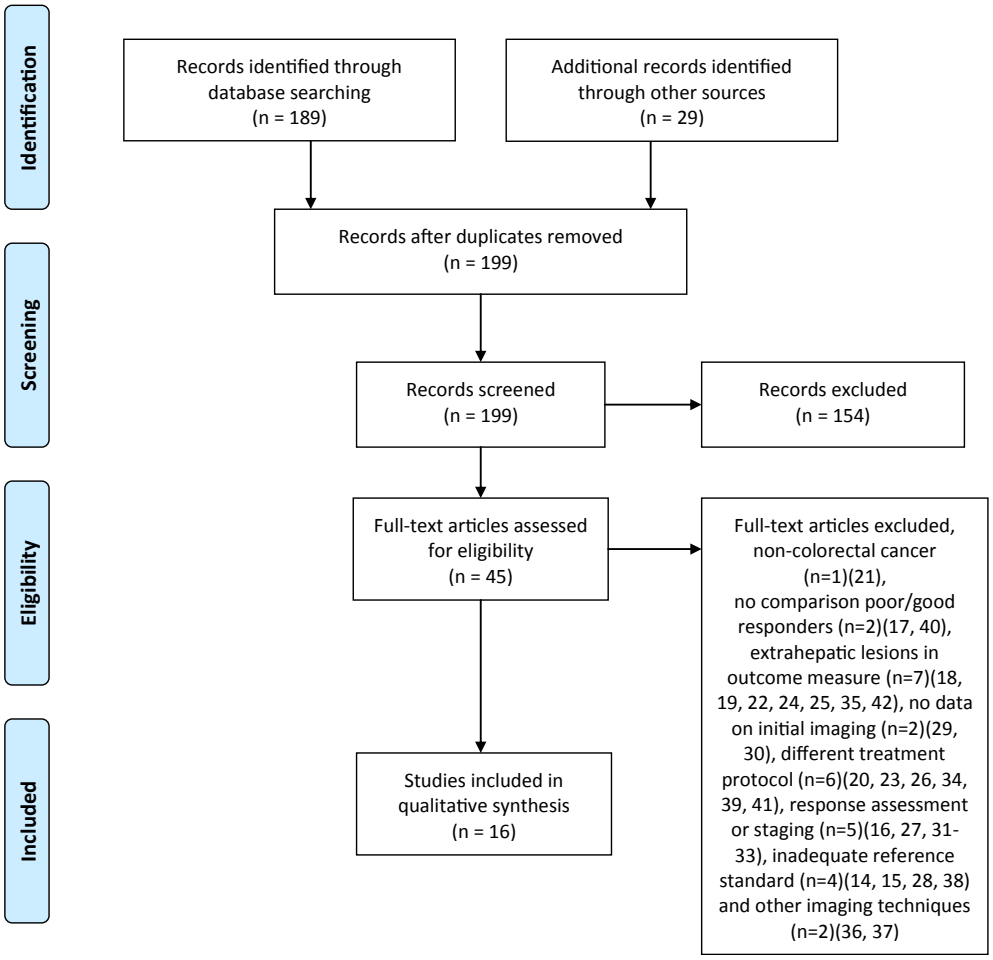

Figure 1 PRISMA flow chart

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 TTP.[45] 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 focussing on ADC (apparent diffusion coefficient; the quantification of diffusion in a lesion or area, where a lower ADC reflects more dense tissue, corresponding to tumour[57]) related parameters, others focussing 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 focussing 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 OS.[44] ADC skewness, kurtosis and variance were

Table 1 Overview of statistically significant data on RECIST responders and survival

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_{mean30}	Per patient	Higher SUV_{mean30} in responders
Mertens	RECIST	SUV_{max} SAM	Per patient	Lower SUV_{max} in responders Lower SAM in responders
Vriens	Survival	MR_{glc}	Per patient	Lower MR_{glc} → longer OS Lower MR_{glc} → 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 1st percentile ADC 10th percentile ADC 50th percentile ADC 90th percentile ADC 99th percentile	Per Patient	Lower ADC mean in responders Lower ADC 1st percentile in responders Lower ADC 10th percentile in responders Lower ADC 50th percentile in responders Lower ADC 90th percentile in responders Lower ADC 99th percentile in responders
Vriens	Survival	Max axial diameter	Per patient	Larger max axial diameter → 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_{ep}: 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 ≥30% value of SUVmax.
SAM: standardised added metabolic activity.

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]

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

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 chemotherapy,[60] 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 metastasize,[60] 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 described.[62–66] 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 growth.[67] 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 responders,[47] 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 regimen,[50] which does improves survival,[68] 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 therapies.[69] 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 cavitation.[5] Another study showed that neither RECIST nor mRECIST is able to assess the amount of residual viable burden in CRLM.[70] 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 histopathology.[71] 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 focussing 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.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hpb.2017.10.013.