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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

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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]

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