Editorial Commentary

Yes, you should do a magnetic resonance imaging (MRI) for patients scheduled for local therapy of colorectal cancer liver metastases: insights into the CAMINO study

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Colorectal cancer (CRC) is the third most frequent solid cancer in the world with about 1.9 million newly diagnosed cases in 2020 worldwide (1). It is the second cause of death by cancer with approximately 915,000 deaths per year worldwide (1). Population-based studies have shown that approximatively 25–30% of patients develop liver metastases (2,3). Over the past decades, locoregional treatments (ablation with or without surgery) for unresectable colorectal cancer liver metastases (CRCLM) (4,5) have been shown to significantly prolong survival, as long as all disease can be addressed (6-8).

In this context, the role of diagnostic imaging has changed dramatically regarding the staging of the disease, going from a patient oriented clinical question (i.e., is there a metastasis) to tumor oriented questions (i.e., can all disease be treated safely with adequate surgical and/or ablative margins).

Over the years, various imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT), have been employed to assess CRCLM. Among these modalities, MRI has emerged as an important imaging method in the pretreatment assessment of CRCLM, offering superior sensitivity and specificity compared to conventional CT scans and PET-CT for local staging. It must be noted that PET/CT offers the benefit of detection of distant metastases, has been shown to change management in 24% of patients (9) and should be considered prior to minimally invasive liver-directed therapies.

The integration of advanced MRI techniques, such as diffusion-weighted imaging (DWI) and hepatobiliary (HPB) contrast-enhanced MRI, has further enhanced the detection and characterization of liver metastases (10-12). It provides unparalleled insights into the extent and characteristics of CRCLM. Studies have consistently demonstrated the superiority of MRI over CT in detecting liver metastases, with sensitivity rates exceeding 90% in several cohorts, as well shown in the meta-analysis of Vilgrain *et al.*, who demonstrated an accuracy of MRI up to 95% when combining HPB sequences with DWI (10). Moreover, surgery and ablation, in order to achieve local cure, require adequate margins (R0 or A0, respectively). Especially with ablation, MRI provides important anatomic detail to ensure that margins (at minimum >5 mm, ideally >10 mm) can be achieved safely. Magnetic resonance cholangiopancreatography (MRCP) and/or delayed biliary excretion phase imaging can also assess the risk for biliary injury with ablation and the relationship between the metastases and the biliary tree prior to surgery.

While MRI offers clear diagnostic advantages over CT in the assessment of CRCLM, its impact on patient

outcomes and treatment strategies warrants further investigation. Some small studies suggest that MRI may change the initial surgical planning done on CT in up to 45% of cases. However, to be fully embraced by the oncological community at large, such approach needs much larger confirmation, especially considering the perceived added costs and organizational challenges of adding MRI with HPB agents to CT, as well as shortage of MRI in some areas.

The CAMINO study, a landmark multicenter trial, sought to elucidate the incremental diagnostic value of adding liver contrast-enhanced MRI to standard contrast-enhanced CT in the preoperative evaluation of CRCLM (13). By comparing surgical plans based solely on CT findings with those incorporating MRI data, the study shed light on the potential benefits of MRI-guided treatment strategies. Notably, the addition of MRI led to significant changes in surgical planning for a substantial proportion of patients, emphasizing its role in refining treatment algorithms and optimizing patient outcomes.

The CAMINO study, conducted across 14 liver surgery centers in Europe (The Netherlands, Belgium, Norway, and Italy), enrolled a diverse cohort of CRCLM patients undergoing evaluation for local therapy. Two hundred and ninety-eight patients were included, and the primary endpoint was the changes in surgical planning from CT to MRI.

By prospectively comparing treatment plans derived from CT alone versus those augmented by MRI findings, the study provided valuable insights into the impact of MRI on treatment decision-making. In 31% of patients, the local therapy plan proposed by the multidisciplinary team meeting based on contrast enhanced CT combined with MRI was changed when compared to the local therapy plan based on both contrast-enhanced CT alone, mostly due to the identification of additional metastatic lesions on MRI that were not visualized on CT scans. In 13% of patients, MRI indicated the need for more extended surgery, less extended surgery in 4% of patients and either no local treatment or induction systemic therapy in 11% of patients.

These changes in planning were significant, as patients were cancelled for surgery, or required a more extensive surgery compared to the initial planning, with lesions being at risk of being missed based on CT alone.

Other endpoints of this study are most interesting. Despite the accuracy of MRI, additional lesions were still found on intra-operative ultrasound (IOUS), showing the necessity of keeping this modality despite an optimal preoperative staging. This was especially noted in patients who received preoperative chemotherapy. This unsurprising as chemotherapy can induce a varied range of changes in the liver parenchyma, including vascular lesions, such as focal areas of peliosis, sinusoidal occlusion syndrome (14) or focal hepatitis, as well as changes related to fatty infiltration, as seen in cases of chemotherapy associated steatohepatitis (15-17). These different changes can create false positive and/or false negatives, and markedly complicate the interpretation of both CT and MRI, as well as IOUS, which is also operator dependent. Chemotherapy can also lead to the disappearance of lesions (so called ghost lesions), which can be missed with MRI and CT, although MRI with HPB agents has shown superiority to other modalities in detecting these lesions (18). These findings raise an interesting question regarding the respective place of surgery and local ablative therapies, as IOUS is of course not possible to perform in the latter case, although imaging assessments performed at the time of ablation (particularly when performed with contrast-enhanced CT (CECT) and/or PET/CT guidance) significantly overcome this limitation. The true impact of these lesions seen on IOUS alone would need to be specifically investigated.

In addition to clinical efficacy, the cost-effectiveness of integrating MRI into standard staging protocols is a critical consideration for healthcare systems. While MRI may incur higher upfront costs compared to conventional CT imaging, its potential to improve treatment outcomes and better triage patients into those needing an intervention and those were such costly operations (including post operative potential complications) would be futile, could translate into long-term cost savings. The CAMINO study's ancillary analysis of cost-effectiveness highlighted the favorable economic profile of MRI-guided treatment strategies, underscoring the value proposition of incorporating MRI into routine clinical practice. Recent advancements in imaging technology and streamlined protocols such as the emergence of abbreviated MRI protocols, which have shown strong diagnostic accuracy, may further enhance the cost-effectiveness of MRI-based approaches in CRCLM management.

This favorable economic profile of MRI is in line with an analysis of Zech *et al.* who demonstrated similar findings (19). However, in the CAMINO study, it does so in a practical, real-life setting, as CT is done no matter what in these patients. As mentioned by the authors, CT would be necessary in searching for lung metastases, and it is also useful for a global assessment of intraabdominal extrahepatic disease, such as retroperitoneal lymph nodes

and carcinomatosis as well as evaluation of the primary tumor in case of liver first strategy. Interestingly, it must be noted that a subset of patients with CRCLM and extrahepatic disease involving the lungs or lymph nodes appear to benefit from local CRCLM treatment (20).

Some limitations remain in this study. First, the evaluation of MRI alone was not performed. It would be interesting to have a third comparison arm where MRI based staging was compared to CT based staging and the sequential CT then MRI staging. It would have been relevant, as one could wonder if some interpretative biases could exist by the sequential read. Second, there is no evaluation of CT versus IOUS. It would have been interesting to know if there were less differences between CT and IOUS than between CT/MRI and IOUS. If it is unlikely that the missing lesions found by IOUS would have been noted by CT, some false positive of MRI may not be present, especially in patient who received neoadjuvant chemotherapy. Third, the authors explain that some centers did not use either DWI or HPB contrast. This is important to consider when analyzing the results of the study as it has been shown that MRI with HPB agents and MRI is superior in its staging ability to MRI with conventional extracellular gadolinium. A subgroup analysis of the MRI done with these varied protocols would have been most informative.

It must be noted that recent advances in CT technology, namely the emergence of spectral CT may significantly affect the accuracy of CT in the staging of these patients (21), but evaluation of the modality for this purpose is still in its infancy. Nevertheless, it will be interesting to know if future strategies will incorporate spectral CT in lieu of MRI or if the addition of the two techniques will emerge as the best combination for patients staging.

Beyond its diagnostic utility and potential to affect treatment strategies as shown by the CAMINO study, MRI holds potential as a surrogate biomarker for predicting treatment response and long-term outcomes in CRCLM patients. In multiple studies (22,23), Cheung *et al*. have identified associations between preoperative MRI phenotypes of tumors and overall survival (OS) (with a 30% OS difference at 3 years) and that this effect was seen both with conventional extracellular gadolinium and HPB agents. This association was also observed in patients receiving chemotherapy only. Additional molecular analysis of this cohort revealed that these MRI changes may be related to mutational burden of the metastases (24), even if further research into the molecular correlates of MRI findings and their implications for treatment selection is warranted to fully realize the transformative potential of imaging biomarkers in clinical practice. By leveraging MRI-derived information on tumor characteristics, clinicians could tailor treatment strategies to individual patients, thereby advancing the paradigm of personalized medicine in CRCLM management. Such analysis would be most interesting to conduct of large cohort of patients, such as the one presented in the CAMINO study.

Additionally, recent reports have shown that gadoxetic acid uptake in the future liver remnant is associated with the probability of post operative liver failure post hepatectomy (25,26), which may be an invaluable information for patient preoperative decision making and reinforce the potential role of MRI as a comprehensive staging and prognostic tool in patients with CRCLM.

In conclusion, the CAMINO study represents a seminal contribution to the evolving landscape of CRCLM management, providing robust evidence supporting the integration of liver HPB-contrast-enhanced MRI into standard staging protocols. By elucidating the incremental diagnostic value of MRI and its implications for treatment decision-making, the study underscores the importance of personalized approaches in optimizing patient outcomes. Moving forward, continued innovation in imaging technology, coupled with advances in molecular profiling and personalized medicine, promises to revolutionize the care of CRCLM patients, ushering in a new era of precision oncology.

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