French Editorial Commentary from the ACHBPT

The role of MRI in modifying surgical management of colorectal liver metastases: a lesson from the CAMINO trial

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The CAMINO trial by Görgec *et al.* (1) assessed the added diagnostic value of contrast-enhanced (CE) magnetic resonance imaging (MRI) using gadoxetic acid and diffusion-weighted imaging for patients with colorectal liver metastases (CRLMs) scheduled for curative treatment (surgical resection, thermal ablation, or both). The study explored how often liver MRI) changes therapeutic strategy compared to using only a CE computed tomography (CT) scan. Despite MRI's widespread use in staging for CRLMs, guidelines remain vague, leaving decisions to the surgeon's preference and expertise.

The CAMINO trial is a multicenter, international, prospective study involving 14 liver surgery centers across Europe. The widespread pre-study use of liver MRI in clinical practice made organizing a randomized controlled trial unfeasible. Treatment decisions based on MRI findings were first made by local multidisciplinary teams and then validated by an independent panel of experts.

From December 17, 2019, to July 31, 2021, 325 patients were assessed, and 301 were enrolled in the study. An overall change in treatment strategy occurred in 92 out of 298 patients (31%). Of these, 40 patients (13%) required more extensive therapy, 11 patients (4%) required less invasive treatment, and curative treatment was canceled for 34 patients (11%) with 26 (9%) found to have unresectable disease and 8 (3%) having benign lesions initially detected as metastases by CT. In 7 patients (2%) a completely different treatment was chosen.

The authors also aimed to create a predictive model to identify patients who would benefit most from liver-specific MRI but found it impractical for daily use. Though not a cost-effectiveness study, a basic analysis suggested that preoperative MRI resulted in a net saving of 128,191 euros, equivalent to 430 euros per patient.

CRLMs are the main indication for liver surgery, accounting for about 50% of all liver resections (2,3). Surgical resection and thermal ablation are currently considered the only curative treatments, with the latter being considered not inferior to the former for lesions smaller than 3 cm (4). For these reasons, preoperative diagnostic accuracy is fundamental to plan the best therapeutic approach and achieve optimal oncological outcomes. Intra-operative ultrasound (IOUS) with the possible use of contrast medium [contrast-enhanced ultrasound (CEUS)], CT scan, MRI and fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT represents the most useful imaging modalities in the detection of CRCLMs. A recent meta-analysis found that MRI has the higher sensitivity for lesions <10 mm and lesions at least 10 mm in size, whereas hepatospecific contrast agent did not improve diagnostic performances (5). Despite the latest evidence, the role of MRI remains highly controversial in

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the different international guidelines (6,7).

The CAMINO trial is the first multicenter, international diagnostic accuracy study aimed to assess the added value of performing an MRI compared to CE CT alone for a patient scheduled for local curative treatment for CRLMs. The extremely pragmatic approach and the simple study design enable a clear and effective communication of the results. MRI proved superior to CT in diagnostic accuracy and in defining with great precision the burden of hepatic disease, thereby avoiding unnecessary surgical or radiological procedures in 34 patients (11%), including 8 patients (3%) with benign conditions, in whom the initial diagnosis of secondary lesion based solely on the CT scan was incorrect. This is consistent with data available in the literature that establish the fundamental role of MRI in recognizing hepatic benign conditions, reducing the rate of misdiagnosis (8,9) as well as to its role in detecting occult metastasis, as already demonstrated for other gastrointestinal tumors (10). The power of MRI to induce a change in therapeutic strategy appears to be particularly valid in the subgroup of patients who have received neoadjuvant chemotherapy compared to those who underwent upfront resection (33.3% *vs.* 21.6%, P=0.049). This seems to suggest a greater sensitivity of MRI compared to CT in identifying hepatic changes induced by chemotherapy, as reported by previous studies (11,12). On the other hand, a post-hoc analysis didn't show a significant advantage of MRI in assessing patients with hepatic steatosis (35% *vs.* 30.6%, P=0.68).

After a careful dissection of the study design and methodology, certain technical aspects of the study protocol could be sources of bias that warrant further investigations. Firstly, according to the study protocol, the maximum time interval admitted between the CE CT scan and actual local therapy was 10 weeks. Furthermore, liver MRI should have been carried out within 4 weeks from the CT scan. Assuming a time frame of 4 weeks between the CT and the MRI, we might speculate that tumors characterized by a more aggressive biology could undergo significant disease progression during this period, especially in the absence of systemic treatment (13). Therefore, the change in therapeutic strategy may not necessarily result from the additional findings detected by MRI, but rather from the natural progression of the disease that occurred during the time interval between the two radiological investigations. However, we must consider that in the present study, the average time interval between the two radiological examinations is only 14 days, which is a significantly shorter time interval than the hypothesized one, reducing the risk of disease progression. Secondly, the decision to change the planned treatment could occur during a second multidisciplinary team meeting if the MRI was not already available during the first one. However, the meeting participants may not necessarily be the same. The radiologist or the surgeon who recommend curative treatment based on the CT scan may sometimes be different from those who modify the indication after MRI findings. Maintaining the same components in both meetings would certainly have increased the accuracy of the decisions made. However, this bias is partly addressed by the introduction of a central, independent panel of experts, which validated the indications of the local meetings for all enrolled patients.

Another point is that liver CE MRI was assessed by an abdominal radiologist who was not blinded to the CE CT results. This, while reflecting what typically occurs in daily clinical practice, can indeed influence the interpretation of the MRI findings. An independent and blinded analysis of both investigations would certainly be advisable. Specific type of indication is another issue to address. For 26 patients (9%) the first indication for curative-intent local therapy was revoked because of disease extension. However, it is well-known that the assessment of unresectability, as well as the type of curative treatment adopted, strongly depends on the expertise of the center and on the surgical volume of hepatic resections performed (14,15). Other 7 patients (2%) had a change of the planned strategy in favor of other options as radiotherapy, liver transplantation without further information of what MRI really found compared to CT scan. In this regard, we have very little information about the 14 liver centers involved. How does the decision to modify or revoke the surgical indication change in low/medium volume centers compared to those with a high volume of hepatic surgery that have greater experience and can handle more complex procedures?

Finally, the international nature of the study is certainly one of the most interesting aspects, providing a snapshot of current clinical practices across different European countries. However, we must consider that surgical indications are strongly influenced by national guidelines and internal protocols, which may vary slightly from a country to another.

A strong point of this trial is the extremely interesting post-hoc cost-effectiveness decision tree analysis. Although a precise cost-effective analysis was not the main objective of the study, the authors claimed that implementing MRI in the preoperative diagnostic phase of CRLMs could result in a total net saving of 128,191 euros (430 euros per

patient), mostly by avoiding unnecessary procedures in 11% of patients. Therefore, in the conclusions, they suggested the implementation of CE MRI as a routine investigation for all patients undergoing local therapy. However, in our opinion, some logistic and economical aspects need to be considered. Firstly, if MRI were performed on a large scale in all patients affected by CRLMs before planning any curative treatment, it would become a significant economic burden for healthcare systems. Secondly, as is well known, MRIs are not always equally distributed across the territory and easily accessible for all patients. Its routine use could result in significant delays before proceeding with curative treatment, potentially harming the patient. From this point of view, it is noteworthy that of the 51 patients excluded due to protocol deviation, 33 patients took more than 4 weeks to undergo MRI and 9 patients were excluded because they received curative treatment more than 10 weeks after the staging CT scan.

Finally, the CAMINO study does not consider patients deemed ineligible for surgical or ablative treatment based exclusively on CT data. In fact, 5 patients were excluded because of unresectable tumors based on CT. In our opinion, liver CE MRI could be equally useful in this group of patients to identify the exact number and location of metastases and to reconsider surgical resectability after induction chemotherapy (12).

In conclusion, beyond some aspects that deserve further investigations, the CAMINO trial represents a valuable study that analyzes the additional value of performing a liver CE MRI during the preoperative phase for patients affected by CRLMs and eligible for curative treatments. We believe that the best take-home message of this work lies in the immediacy of its results: performing an MRI with a dedicated liver protocol changes the therapeutic plan in about 1 out of 3 patients, avoids the execution of unnecessary invasive procedures in 1 out of 10 patients, and in 8 patients (3% of cases) contradicts CT findings by distinguishing benign lesions from metastases. These data should be clear to every physician when treating a patient with liver metastases, and they should represent an important point of reflection for the upcoming guidelines.

Weak spots:

- Rudimental cost-effective analysis;
- Weak clinical utility of proposed predictive model;
- Lack of correlation between outcomes and hepatic surgical volumes of participating centers.

Strong points:

- International and multicentric study;
- Simple and pragmatic outcome;
- Clear and efficacious results.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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