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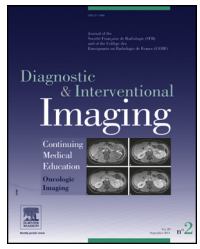

CONTINUING EDUCATION PROGRAM: FOCUS...

Imaging strategies before beginning treatment of colorectal liver metastases

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Metastatic lesions;
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Abstract The management of colorectal intrahepatic metastases before resection is multidisciplinary and radiologists and nuclear medicine specialists play a major role. In accordance with the French National Guide for appropriate use of diagnostic imaging, the approach should be multimodal: a chest-abdomen and pelvic (CAP) CT scan and hepatic MRI are mandatory while PET-CT provides important additional information, in particular on intra-abdominal extrahepatic metastases. This multimodal approach emphasizes the importance of early and appropriate use of imaging in these patients, as well as the central role of multidisciplinary meetings in oncology.

The prognosis of patients with colorectal cancer is dependent upon the presence or not of metastases, in particular in the liver. These hepatic metastases are found in 20 to 70% of patients [1] and they are intrahepatic alone in approximately 30% of the cases. It is now generally accepted that local treatment of liver metastases associated with perioperative adjuvant therapy improves recurrence-free survival as well as overall survival [2—4]. In this

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context, the goal of imaging before resection is to detect all metastatic tumors and identify their location, to determine the feasibility of local resection, as well as to evaluate the response to possible adjuvant therapy and assess its toxicity. Indeed, the risk of morbidity from preoperative chemotherapy is known [5].

The goal of this article is to describe the existing guidelines for imaging before resection of colorectal liver metastases, then suggest the optimal imaging strategy in this context.

Imaging techniques to determine the resectability of liver metastases: comparison of diagnostic values

Several meta-analyses have compared ultrasound, computed tomography (CT scan), magnetic resonance imaging (MRI), fluodeoxyglucose-positron emission tomography (FDG-PET) and positron emission tomography-computed tomography (PET-CT) for the diagnosis of liver metastases. The first meta-analysis published by Kinkel et al. [6] evaluated 111 studies including nine ultrasound studies (509 patients), 25 CT scan studies (1747 patients), 11 MRI based studies (401 patients) and nine PET scan studies (423 patients), with sensitivities of 55% for ultrasound, 72% for CT scan, 76% for MRI and 90% for FDG-PET; the specificity of the different modes was equivalent. These results were recently modified by the study published by Floriani et al. [7], based on a review of 6030 articles and an evaluation of 25 specific studies: the sensitivity of ultrasound was 63—97%, CT scan was 74.8—95.6%, MRI was 80.1—97.2%, and FDG-PET was 93.8-98.7%. MRI seemed to be more sensitive than CT scan in this study, both per patient and per lesion analysis (Fig. 1).

What is the role of PET scan in the management of colorectal cancer liver metastases before resection?

PET scan plays an important role in the management of patients with colorectal cancer before resection. In a study in 2007 including 131 patients, 75 with colorectal cancer, Chua et al. [8] suggested that patient management had been modified because of PET scan results in 25% of patients. However, this study was based on a 5 year follow-up and the parameters used to compare CT scan acquisitions and PET scan varied with CT-slice collimation ranging from 4×1 mm or 4×2.5 mm. Moreover, as in several studies including PET-CT, there was no reference test to evaluate lesions that were missed on CT scan but positive on PET scan, which concerned, in particular, extrahepatic lesions. Researchers at the CHRU Lille [9] evaluated lesions that were found to be positive on PET scan and were not detected by other imaging techniques. The authors performed a preoperative PET scan and CT scan in a series of 53 patients who were eligible for resection of colorectal hepatic metastases, with less than 61 days between the two imaging tests (mean 24 days). All lesions detected by imaging were investigated surgically providing an extensive pathological correlation. A total of 119 tumoral metastases were detected in the study population. There was disagreement between preoperative imaging and the surgical results in 37/119 lesions, or 31% of the cases: 26 cases of disagreement involved the liver and an identical number of lesions were missed by PET scan and CT scan including nine lesions less than 1 cm that were missed on PET scan. Disagreement involved extrahepatic abdominal lesions in 11 cases, in particular peritoneal carcinomatosis most of which (6/8) were missed by CT scan, while a greater number were detected by PET scan. None of the thoracic lesions were missed by either of the imaging techniques. Overall, the authors reported that PET scan had a definite positive influence in the management of five patients (or 9% of the cases), but with false positives in three patients (6% of the cases), in particular regarding the characterization of a mediastinal adenopathy and two bone lesions that were not confirmed as metastases.

The authors of a recent prospective study [10] evaluating the preoperative imaging strategies in patients with metastatic colorectal cancers eligible for surgical resection confirmed the following: the study concluded that CT scan and MRI should be performed for the preoperative assessment of patients with suspected colorectal cancer

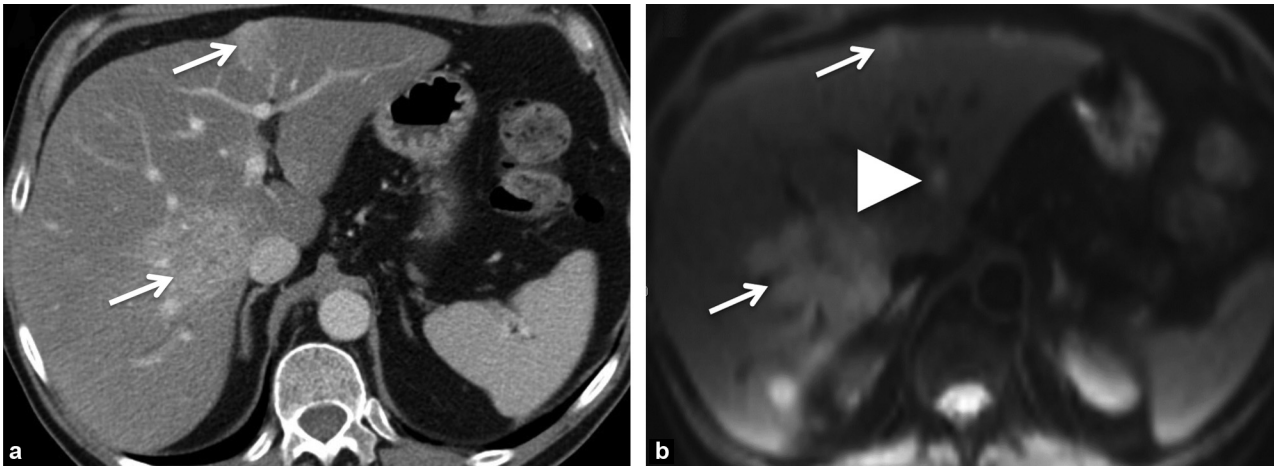


Figure 1. a: axial contrast enhanced portal phase CT scan of the liver hows the presence of two metastases (thin arrows); b: diffusion MRI ($b = 100\,sec/mm^2$): discovery of an additional metastasis in segment 2 (arrowhead).

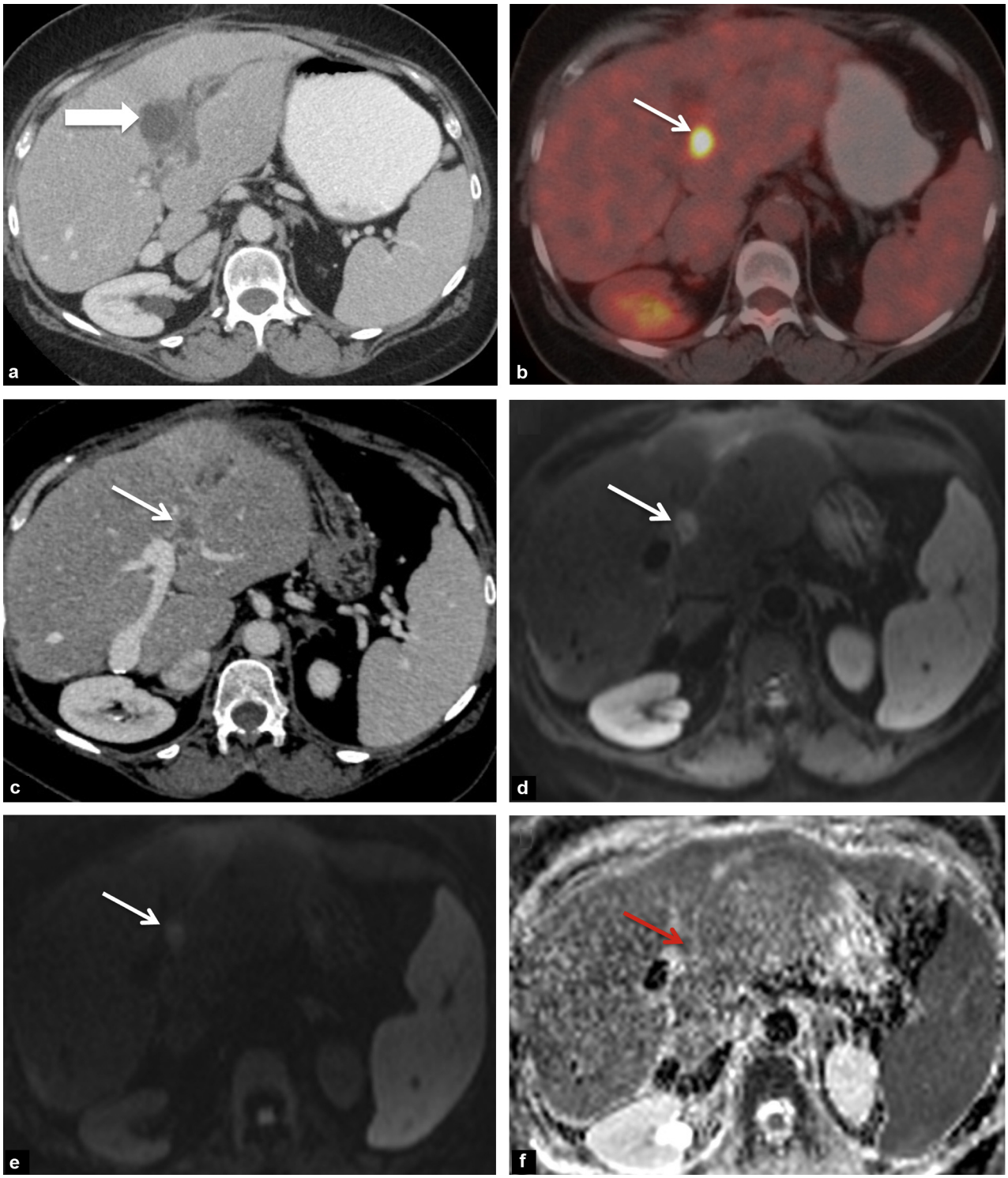


Figure 2. a: contrast enhanced portal venous phase CT scan of the liver: round lesion in segment 4b, measuring 2.9 cm (thick arrow); b: after targeted chemotherapy, the lesion is smaller measuring 1.4 cm; it is hypermetabolic on PET scan (thin arrow); c: it is also detected by portal venous phase CT scan (arrow); d: the lesion shows hypersignal intensity on diffusion MRI ($b = 100\ sec/mm^2$) (arrow); e: this hypersignal persists at $b = 800\ sec/mm^2$ (arrow); f: The lesion shows restricted ADC (low intensity on ADC map: red arrow); g: the lesion shows peripheral contrast enhancement during the portal venous phase (arrow); h—i: note the presence of liver steatosis caused by chemotherapy (signal dropout during the out phase (i) compared to the in phase (h) sequence (arrow head). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

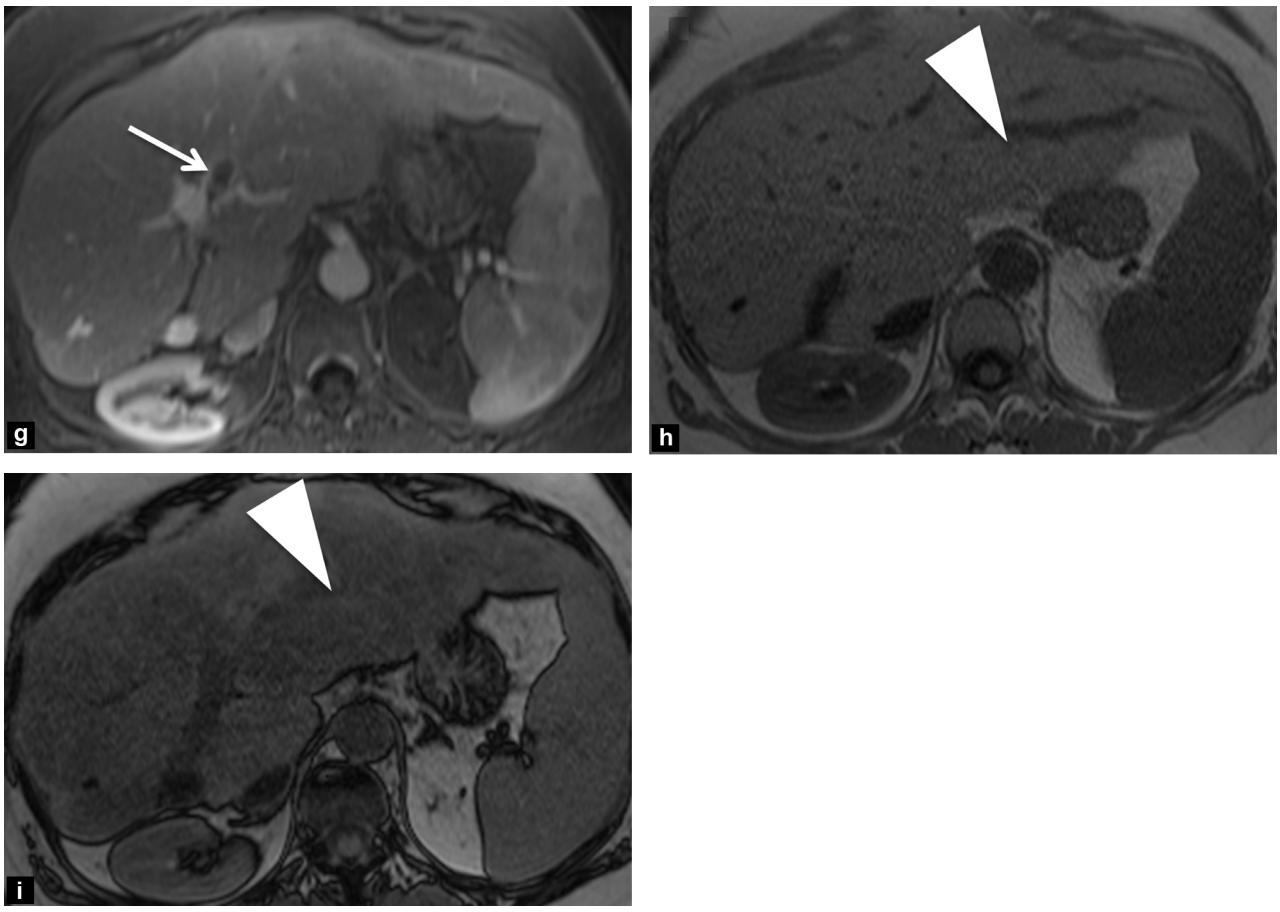


Figure 2. (*Continued*)

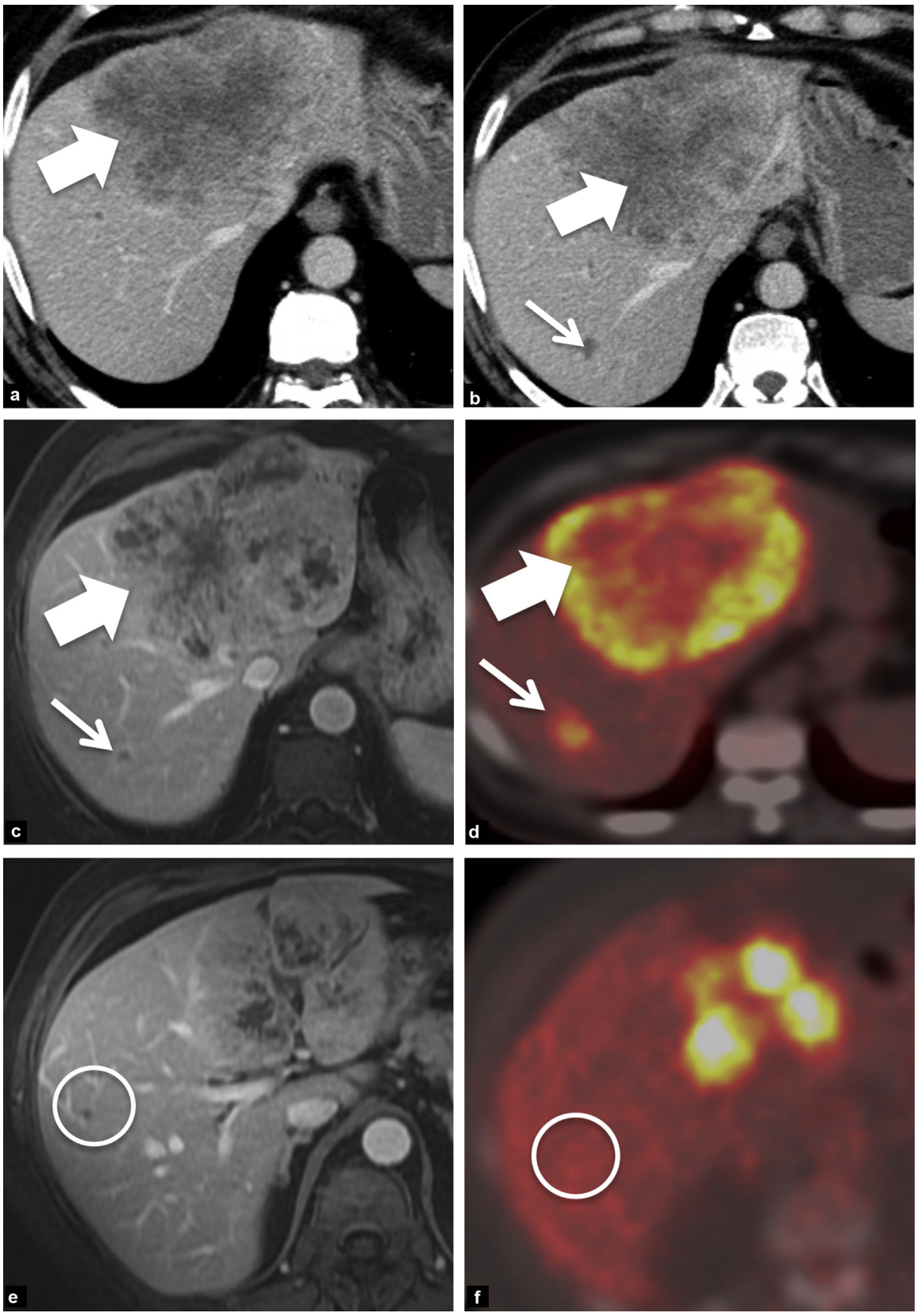
metastases, and suggested that the role of PET scan was especially important for detecting potentially resectable intraabdominal, extrahepatic metastases (Fig. 2). More recently in a retrospective study, Ayez et al. [11] suggested that whatever influence PET-CT had on the detection of metastases before resection, this did not influence survival without progression or overall survival. Determining the influence of technical improvements in morphological, functional and metabolic imaging on overall patient survival in prospective studies, is, in fact, a major challenge.

In any case, it is important to remember that preoperative PET-CT should not be performed for the resection of hepatic metastases less than a month after the last chemotherapy session. A PET scan that is performed earlier is an important source of false negatives, which can reach 86.7%, as shown in the study by Glazer el al. [12] (Fig. 3).

Why is MRI so important?

The optimization of MRI technology is constantly progressing

Besides the development of parallel reconstruction and dynamic acquisitions with millimetric slices, in the past 10 years the detection and characterization of intrahepatic metastases with MRI have improved thanks to two important technological advancements. These are diffusion weighted MRI and the use of hepatocyte-specific contrast agents. The use of these two techniques, independently or combined, provides more sensitive, specific and accurate characterization of liver metastases [13,14] (Fig. 2). In a recent study, Chung et al. evaluated the influence of the use of a hepatocyte-specific contrast agents including iron oxide particles and gadoxetic acid (gadolinium EOB-DPTA, Primovist, Bayer), which both increase contrast enhancement between metastases and the underlying liver [15]. There was no difference in accuracy, sensitivity or the positive predictive value of these two contrast agents for metastases larger than 10 mm. On the other hand, the use of these agents, and in particular gadolinium EOB-DPTA, increased the accuracy and sensitivity for metastases smaller than 10 mm. These results were recently confirmed in the study by Koh et al. [16] This team included 417 lesions including 107 benign lesions and 310 colorectal cancer metastases in 72 patients, and compared the impact of diffusion weighted MRI and gadolinium EOB-DTPA contrast enhanced imaging as well as the combined reading—of diffusion and hepatocyte phase after gadolinium EOB-DTPA injection. The authors reported that the combined use of diffusion MRI and a hepatocyte-specific contrast agent increases detection of lesions because the use of hepatocyte-specific contrast agents helps in detecting a certain number of lesions in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the left lobe that are missed with diffusion imaging owing to heartbeat artifacts. Hence, three lesions were missed (2% of all lesions) by one of the observers using combined diffusion imaging and hepatocyte-specific contrast enhancement, compared to 26 (13%) using diffusion imaging alone as well as other MRI sequences.

The influence of chemotherapy on imaging techniques: the superiority of MRI

Besides improvements in MRI technology, chemotherapies are known to significantly modify the underlying liver parenchyma, either because of vascular modifications or hepatic steatosis [17—21] (Fig. 2 H, I).

In a meta-analysis by Van Kessel et al. [22], 11 studies including 223 patients and 906 colorectal cancer liver metastases were evaluated. The authors studied, in particular, the influence of neoadjuvent chemotherapy on imaging results. The sensitivity of MRI in case of prior chemotherapy was more than 72%, while it was no more than 63.4% for FDG-PET. Thus, adjuvant chemotherapy significantly influences the efficacy of PET-CT. This influence was less marked on CT scan results, even if liver steatosis also reduces the sensitivity of CT scan for accurate detection of all lesions.

What can be expected from PET-MRI under these conditions?

Clinical studies on hybrid PET-MRI imaging for the management of liver metastases have just begun. In a recent study, Catalano et al. [23] compared the results of simultaneous PET-MRI and PET-CT for the detection of metastases. PET-MRI seemed to detect additional lesions in 41% of patients, which had a direct clinical impact on patient management in 17.9% of all cases (or 24 patients) unlike PET-CT. This was especially true for the elimination of certain malignant lesions, the incidental discovery of other cancers, the detection of adenopathies or the confirmation of malignant bone lesions. Beiderwellen et al. [24] also compared the role of PET-MRI to PET-CT in 70 patients presenting with primary tumors (including four colorectal cancers). Characterization of tumors seemed to be better with PET-MRI in particular intrahepatic lesions, but because of the few number of included patients these data are preliminary. Reiner et al. [25] suggested that the diagnostic accuracy was better with use of T1- and T2-weighted sequences combined with PET-MRI than with PET-CT and could therefore play a diagnostic role in the process of patient management. These preliminary data suggest that the combination of metabolic imaging, which effectively detects intraabdominal extrahepatic lesions and MRI which effectively detects and characterizes intrahepatic metastases, could play an important role in the future in the management of patients who are eligible for resection. The problem of detecting and characterizing pulmonary nodules still seems to be better with CT scan.

Management guidelines

Guidelines for appropriate use of diagnostic imaging

The guide for appropriate use of diagnostic imaging by the French Health Authority (Haute Autorité de santé [HAS]), associated with the French Society of Radiology and the French Society of Nuclear Medicine has drafted the imaging strategy before resection of colorectal cancer hepatic metastases. Three tests are recommended in this specific clinical context: MRI of the liver, chest-abdomen-pelvic (CAP) CT scan and PET- CT combined with the use of FDG (gbu.radiologie.fr).

These guidelines are similar to the consensus opinion proposed by Adams et al. [26], which recommends MRI as the first line test in this clinical situation. These experts note that this is especially important for lesions less than 1 cm whose detection is improved by diffusion MRI and hepatocyte directed contrast enhancement but also in case of steatosis after chemotherapy where MRI seems to perform better than other imaging techniques. The experts concluded that PET-CT is useful for identifying intraabdominal extrahepatic metastases, but not intrathoracic lesions or intrahepatic lesions smaller than 1 cm.

Management strategy

As we have seen MRI, PET-CT and CT scan are indicated before resection of colorectal hepatic metastases, each for different purposes of detection and characterization. At present, MRI is the technique that provides optimal detection of intrahepatic metastases.

Overall patient management could be modified in relation to these elements. MRI of the liver could be recommended during initial management to optimize comparison with post-chemotherapy MRI. Indeed, only comparative tests with the same imaging technique can provide an accurate assessment of lesions. Communication between the oncologist, the liver surgeon and the radiologist is essential. Eligibility for curative resection is usually decided during multidisciplinary meetings in specialized centers.

Under these conditions, at baseline, all patients potentially resectable could undergo a liver MRI and an FDG PETCT, as well as a CAP CT scan, so that the progression or response to treatment could then be monitored based on CT scan results [27], while pre-resection MRIs could be compared to initial MRIs, to limit the number of metastases that ''disappear''.

Figure 3. a: portal venous phase contrast enhanced liver CT scan: necrotic mass, with fibrous enhancement centered on segments 2—4 (thick arrow); b: a second hypodense lesion on CT scan is visible in segment 7 (thin arrow); c: MRI shows peripheral enhancement of both lesions (arrows); d: both lesions are hypermetabolic on PET-CT (arrows); e: discovery of an additional lesion on portal venous phase contrast enhanced MRI (circle); f: this third lesion was not seen on CT scan or PET-CT (circle).

Conclusion

Patient management before resection of intrahepatic metastases is multidisciplinary with radiologists and nuclear medicine specialists playing an important role. CAP CT scan and MRI of the liver are essential. PET-CT provides important information especially on intraabdominal, extrahepatic metastases. The development of PET-MRI will probably influence the future management of these patients.

TAKE-HOME MESSAGES

- MRI is the first line-imaging test for intrahepatic metastases.
- All patients with intrahepatic metastases should be considered as potential candidates for resection.
- A liver MRI as well as CAP CT scan should be recommended at the beginning of the patient management process enabling the comparison with pre-resection MRI
- PET-CT is indicated in the pre-resection assessment of liver metastases.
- PET-CT is useful in particular for the detection of intraabdominal extra-hepatic locations.
- There must be a 4-week delay between the end of chemotherapy and the PET-CT examination.

Disclosure of interest

The authors declare that they have no conflict of interests in relation to this article.

References

[1] Cromheecke M, de Jong KP, Hoekstra HJ. Current treatment for colorectal cancer metastatic to the liver. Eur J Surg Oncol 1999;25(5):451—63.

[2] Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 2006;93(4):465—74.

[3] Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery *versus* surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371(9617):1007—16.

[4] Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240(4):644—57 [discussion 657—8].

[5] Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006;243(1):1—7.

[6] Kinkel K, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. Radiology 2002;224(3):748—56.

[7] Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, et al. Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. J Magn Reson Imaging 2010;31(1):19—31.

[8] Chua SC, Groves AM, Kayani I, Menezes L, Gacinovic S, Du Y, et al. The impact of 18F-FDG PET/CT in patients with liver metastases. Eur J Nucl Med Mol Imaging 2007;34(12):1906—14.

[9] Truant S, Huglo D, Hebbar M, Ernst O, Steinling M. Pruvot F-R. Prospective evaluation of the impact of [18F]fluoro-2-deoxy-D-glucose positron emission tomography of resectable colorectal liver metastases. Br J Surg 2005;92(3):362—9.

[10] Bonanni L, De'liguori Carino N, Deshpande R, Ammori BJ, Sherlock DJ, Valle JW, et al. A comparison of diagnostic imaging modalities for colorectal liver metastases. Eur J Surg Oncol 2014;40(5):545—50, http://dx.doi.org/10.1016/j.ejso.2013.12.023 [Epub 2014 Jan 15].

[11] Ayez N, de Ridder J, Wiering B, Oyen WJ, de Wilt JHW, Verhoef C. Preoperative FDG-PET-scan in patients with resectable colorectal liver metastases does not improve overall survival: a retrospective analysis stratified by clinical risk score. Dig Surg 2014;30(4—6):451—8.

[12] Glazer ES, Beaty K, Abdalla EK, Vauthey JN, Curley SA. Effectiveness of positron emission tomography for predicting chemotherapy response in colorectal cancer liver metastases. Arch Surg 2010;145(4):340—5 [discussion 345].

[13] Nasu K, Kuroki Y, Nawano S, Kuroki S, Tsukamoto T, Yamamoto S, et al. Hepatic metastases: diffusion-weighted sensitivity-encoding *versus* SPIO-enhanced MR imaging. Radiology 2006;239(1):122—30.

[14] Koh D-M, Brown G, Riddell AM, Scurr E, Collins DJ, Allen SD, et al. Detection of colorectal hepatic metastases using MnDPDP MR imaging and diffusion-weighted imaging (DWI) alone and in combination. Eur Radiol 2008;18(5):903—10.

[15] Chung W-S, Kim M-J, Chung YE, Kim Y-E, Park M-S, Choi J-Y, et al. Comparison of gadoxetic acid-enhanced dynamic imaging and diffusion-weighted imaging for the preoperative evaluation of colorectal liver metastases. J Magn Reson Imaging 2011;34(2):345—53.

[16] Koh DM, Collins DJ, Wallace T, Chau I, Riddell AM. Combining diffusion-weighted MRI with Gd-EOB-DTPA-enhanced MRI improves the detection of colorectal liver metastases. Br J Radiol 2012;85(1015):980—9.

[17] Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA. Hepatic toxicity associated with fluorouracil plus levamisole adjuvant therapy. J Clin Oncol 1993;11(12):2386—90.

[18] Sorensen P, Edal AL, Madsen EL, Fenger C, Poulsen MR, Petersen OF. Reversible hepatic steatosis in patients treated with interferon alfa-2a and 5-fluorouracil. Cancer 1995;75(10):2592—6.

[19] Peppercorn PD, Reznek RH, Wilson P, Slevin ML, Gupta RK. Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. Br J Cancer 1998;77(11):2008—11.

[20] Kooby DA, Fong Y, Suriawinata A, Gonen M, Allen PJ, Klimstra DS, et al. Impact of steatosis on perioperative outcome following hepatic resection. J Gastrointest Surg 2003;7(8):1034—44.

[21] Vauthey J-N, Pawlik TM, Ribero D, Wu T-T, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24(13):2065—72.

[22] Kessel CS, Buckens CFM, Bosch MAAJ, Leeuwen MS, Hillegersberg R, Verkooijen HM. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol 2012;19(9):2805—13.

[23] Catalano OA, Rosen BR, Sahani DV, Hahn PF, Guimaraes AR, Vangel MG, et al. Clinical impact of PET/MR imaging in patients with cancer undergoing same-day PET/CT: initial experience in 134 patients — a hypothesis-generating exploratory study. Radiology 2013;269(3):857—69.

[24] Beiderwellen K, Gomez B, Buchbender C, Hartung V, Poeppel TD, Nensa F, et al. Depiction and characterization of liver lesions in whole body [(18)F]-FDG PET/MRI. Eur J Radiol 2013;82(11):e669—75.

[25] Reiner CS, Stolzmann P, Husmann L, Burger IA, Hullner MW, Schaefer NG, et al. Protocol requirements and diagnostic value of PET/MR imaging for liver metastasis detection. Eur J Nucl Med Mol Imaging 2014;41(4):649—58.

[26] Adams RB, Aloia TA, Loyer E, Pawlik TM, Taouli B, Vauthey JN. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB 2013;15(2):91—103.

[27] Chun YS, Vauthey J-N, Boonsirikamchai P, Maru DM, Kopetz S, Palavecino M, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA 2009;302(21):2338—44.