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ARTICLE

Molecular Diagnostics

Clinical impact of PET/MRI in oligometastatic colorectal cancer

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BACKGROUND: Oligometastatic colorectal cancer (CRC) is potentially curable and demands individualised strategies.
METHODS: This single-centre retrospective study investigated if positron emission tomography (PET)/magnetic resonance imaging (MR) had a clinical impact on oligometastatic CRC relative to the standard of care imaging (SCI). Adult patients with oligometastatic CRC on SCI who also underwent PET/MR between 3/2016 and 3/2019 were included. The exclusion criterion was lack of confirmatory standard of reference, either surgical pathology, intraoperative gross confirmation or imaging follow-up. SCI consisted of contrast-enhanced (CE) computed tomography (CT) of the chest/abdomen/pelvis, abdominal/pelvic CE-MR, and/or CE whole-body PET/CT with diagnostic quality (i.e. standard radiation dose) CT. Follow-up was evaluated until 3/2020.
RESULTS: Thirty-one patients constituted the cohort, 16 (52%) male, median patient age was 53 years (interquartile range: 49–65 years). PET/MR and SCI results were divergent in 19% (95% CI 9–37%) of the cases, with PET/MR leading to management changes in all of them. The diagnostic accuracy of PET/MR was 90 ± 5%, versus 71 ± 8% for SCI. In a pairwise analysis, PET/MR outperformed SCI when compared to the reference standard ($p = 0.0412$).
CONCLUSIONS: These findings suggest the potential usefulness of PET/MR in the management of oligometastatic CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, and the fourth most common in the USA, following lung and breast cancers globally, and also prostate cancer in the USA. It is the second deadliest cancer after lung cancer both worldwide and in the USA [1, 2]. The current standard imaging workup for CRC includes computed tomography (CT) scans of the chest, abdomen, and pelvis in addition to pelvic magnetic resonance imaging (MR) in rectal cancer patients [3]. A multidisciplinary approach is optimal for management planning in these patients, with input from gastroenterologists, radiologists, surgeons, radiation oncologists, and medical oncologists. Imaging plays a crucial role in the approach to their care, both initially and on subsequent restaging and surveillance.

Metastatic disease is common in CRC patients, seen in about 20–25% of patients at initial diagnosis, with almost 50% developing metastases during the course of their disease. The most common site of metastases is the liver, followed by the lungs and peritoneum [4–6]. In patients with liver metastases, about 70–80% have metastatic disease solely confined to the liver without metastases elsewhere, these patients may be potentially cured following hepatectomy [7, 8].

Currently, there is mounting evidence supporting invasive treatment in oligometastatic CRC to increase patient survival, with the possibility of cure [8–11]. This can be achieved either by surgery alone (which is the gold standard in terms of potential for cure but only applicable to a minority of patients) or in combination with local ablative treatments such as thermal ablation and stereotactic ablative radiotherapy; or potentially local ablative therapy alone in patients where surgery is not feasible [12].

Perioperative chemotherapy is the most common approach for liver confined oligometastatic CRC. However, especially if risk factors are present such as multiple foci, lesions larger than 5 cm, primary lymph node involvement, and/or elevated tumour marker levels, there is often some individualisation of the approach [3]. This includes decisions regarding the ideal sequence of procedures (e.g. whether metastasectomy should precede or follow primary tumour resection, or even done synchronously) [13, 14]. For patients with initially unresectable metastases, chemotherapy may lead to lesion shrinkage and subsequent resectability. Although positron emission tomography (PET)/CT is often a useful imaging adjunct to CT or MR, current research has not shown a statistically significant benefit for PET/CT in terms of disease-free or overall survival [15]. PET/CT follow-up also did not significantly

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detect more asymptomatic recurrences after surgery compared to standard CT and biomarkers [16], which contradicts the assumption that PET/CT might lead to earlier detection.

PET/MR is an emerging modality that may prove useful in the management of CRC patients. The superior soft-tissue resolution of MR combined with the picomolar sensitivity of PET might, besides a reduced radiation dose compared to PET/CT, offer several potential improvements over the current standard of care imaging (SCI) [17, 18]. Preliminary studies have touted these advantages, particularly in regard to lesion detection and characterisation, across a variety of neoplasms outside of the central nervous system [19–24]. Moreover, in studies specifically focused on CRC, PET/MR has demonstrated value both in the staging and in the subsequent management [25–28].

However, the utility of PET/MR in the management of oligometastatic CRC patients has not yet been established. The goal of this study is to evaluate the impact of PET/MR on the management of patients with oligometastatic CRC as compared to SCI.

METHODS

Patient selection

A retrospective observational review was performed of all adult patients with oligometastatic colorectal cancers who underwent PET/MR between March 2016 and March 2019. The study received approval from the internal institutional review board (Protocol #2018P001334). Informed written consent was waived given the retrospective nature of the study.

Inclusion criteria encompassed patients with pathologically confirmed CRC and oligometastatic disease, as determined by SCI, who also underwent a PET/MR scan during their disease course. Oligometastatic disease was defined as greater than one but fewer than five metastases in one or more organs. Lesions confined to a single liver lobe were considered a single metastasis due to the possibility of *en bloc* resection with partial hepatectomy. Both synchronous metastases (i.e. that present with the initial tumour) or metachronous metastases (i.e. those that present after initial treatment) were considered for inclusion [29, 30]. Patients that underwent PET/MR and SCI for restaging purposes were not included if they had more than five metastases at the initial staging but later regressed to oligometastatic disease after treatment effect (i.e. those with induced oligometastatic disease).

Patients were excluded from the study if the PET/MR and SCI findings could not be confirmed; either by pathology, or by an intraoperative description when no pathology specimen was collected due to gross neoplastic involvement, or by follow-up imaging in cases where the disease was not invasively evaluated. The maximum time interval accepted between the most recent SCI and PET/MR was 4 weeks. This interval is narrower than the one determined by the National Comprehensive Cancer Network guidelines for reevaluating patients with metastatic colon cancer, which is 60 days [31]. It is anticipated this shorter timeframe should have diminished the chance of occurrence of significant tumour variation.

PET/MR acquisition

Simultaneous PET/MR was acquired with a hybrid Biograph mMR Scanner (Siemens, Erlangen, Germany). Patients were requested to fast for at least 6 h and had their blood glucose levels checked just before the examination to ensure it was less than 140 mg/dL. The injected activity was 4.5 MBq/Kg of FDG. Subjects were invited to void before being scanned to avoid radiotracer accumulation in the bladder. FDG incubation time was approximately one hour. For patients with a colonic primary, the PET/MR protocol included whole-body imaging from the base of the neck to the thighs, followed by dedicated upper abdominal sequences. For those with a rectal primary, an additional dedicated pelvic protocol was run before acquiring whole-body and dedicated upper abdominal sequences. The PET/MR technical protocol details are shown in Supplementary Table 1.

Standard of care imaging

Standard of care imaging was defined as the most recent contrast-enhanced (CE)-CT of the chest/abdomen/pelvis and/or CE-MR abdomen/pelvis, and/or CE-PET/CT with diagnostic quality (i.e. standard radiation dose) CT prior to the PET/MR. A combination of these modalities was also considered if both were performed within 4 weeks of the PET/MR, based on the same principle under the National Comprehensive Cancer Network guidelines on metastatic tumour reevaluation [31].

Data collection and analyses

A careful review of the electronic medical record was performed, including demographics, the reason for imaging (initial staging versus restaging), the primary organ of origin (rectum versus colon), previous/ongoing treatments, and management plans. The initial original reports from SCI and PET/MR, extracted from the medical records, were compared. These reports had been provided by board-certified radiologists and nuclear medicine physicians. For each patient, SCI and PET/MR reports were randomly and separately compared to the standard of reference and accordingly classified to calculate their respective diagnostic accuracy. To reduce recall bias, an interval of at least 4 weeks passed between the comparison of standard of reference with SCI or PET/MR reports. In cases where they disagreed with each other, the accuracy of SCI and PET/MR original reports was validated by a board-certified radiologist with more than 8 years of experience in clinical PET/MR. Management changes were defined as the cancellation of a previously planned surgical procedure, proceeding to surgery in a patient previously considered not eligible or extending the originally planned resection (e.g. including another resection site), a change in the prescribed chemotherapy and/or radiotherapy regimen, or institution of chemotherapy and/or radiotherapy. A subsequent analysis investigating a possible influence of the primary organ of origin, namely rectum versus colon, on management changes was also performed. The same was done to evaluate the association between management changes and the type of SCI, disease stages, and primary study purpose.

Standard of reference

Electronic medical records and follow-up imaging were evaluated to establish the diagnostic accuracy of PET/MR and SCI. When pathology results, defined as a pathology report by a board-certified pathologist from our institution, were available, they served as the reference standard. If there was no pathology confirmation, the gross description of the lesions, as written on the operative notes, was considered the reference standard. When none of the aforementioned options were available, follow-up imaging reports served as the standard of reference. Follow-up imaging consisted of CE-CT of the chest, abdomen, and pelvis and/or CE-MR of the abdomen and pelvis and/or whole-body CE-PET/CT with diagnostic quality (i.e. standard radiation dose) CT. In patients with more than one lesion, the index lesion(s) and/or the one(s) that was/were deemed the most useful to be biopsied underwent tissue sampling. All lesions, including the one(s) that were biopsied or intra-operatively assessed and the others which were not sampled, were also followed up with imaging over time to assure they were of the same nature. Follow-up was evaluated through March 2020.

Statistical analyses

Categorical variables are given as counts and percentages, ±standard errors (SE) when applicable. Continuous variables are reported as medians and interquartile ranges (IQR). The 95% confidence interval (CI) for management changes was obtained using the modified Wald method. For the inferential statistics, the association of categorical variables with dichotomous outcomes was evaluated using Fisher's Exact Test. Diagnostic accuracy was calculated using the reference standard to classify PET/MR and SCI findings into true-negatives, true-positives, false-positives, and false-negatives according to lesion detection at a patient level. Matched pairs of SCI and PET/MR results were then compared against the reference standard to evaluate the diagnostic performance using McNemar's test with continuity correction. A p-value of 0.05 was adopted for statistical significance, all reported p-values are two-tailed. Statistical calculations were performed in R. Studio (R. Studio, Inc, version 1.2.5001/19, 2019), an open-source software.

RESULTS

Patient data

Thirty-three consecutive patients with oligometastatic colorectal cancer underwent PET/MR between March 2016 and March 2019. Two patients were excluded because the interval between their SCI and PET/MR scans exceeded 4 weeks. Thus, 31 patients who

Table 1. Sites of metastatic involvement and relative frequency.

Number of metastatic sites	Number of patients	% of patients
1	20	65%
2	9	29%
3	1	2%
4	1	2%
Metastases location	**Number of occurrences**	**% of sites**
Liver	14	31%
Non-regional lymph nodes	13	29%
Lung	6	13%
Peritoneum	5	11%
Pelvis	4	9%
Retroperitoneum	1	2%
Bile ducts	1	2%
Adnexa	1	2%

underwent SCI and PET/MR constituted our final cohort. Of these, 16 (16/31, 52%) were male, and 15 (15/31, 48%) were female. The median patient age was 53 years (IQR 49–65 years). The rectum was the most common primary site with 65% (20/31) of the cases, followed by the colon with 35% (11/31). The sites of metastatic involvement and their respective frequency of occurrence are detailed in Table 1.

Regarding the SCI that preceded PET/MR, 16% (5/31) of the patients had CE-CT only, 3% (1/31) had CE-MR only, 13% (4/31) had PET/CT only, 23% (7/31) had CE-MR and CE-CT, 32% (10/31) had PET/CT and CE-CT, and 13% (4/31) had CE-MR and PET/CT. The median time interval between PET/MR and the temporally closest SCI was 0 (IQR 0–20 days).

Regarding the purpose of the SCI and PET/MR, 32% (10/31) of the scans were ordered for initial staging and had not received any treatment, while 68% (21/31) were acquired for restaging after various treatments, represented by: chemotherapy only in 6% (2/31), chemoradiation in 10% (3/31), resection of the primary lesion only in 16% (5/21), chemoradiation and resection of the primary lesion in 19% (6/31), and chemotherapy and resection of the primary lesion in 16% (5/31) of the cases.

Reference standard

The reference standard consisted of pathology in 27 cases (87%, 27/31), follow-up imaging in 3 cases (10%, 3/31), and gross description of the intraoperative findings in 1 case (3%, 1/31). Follow-up imaging consisted of CE-MR in 2 instances and CE-CT in 1 occurrence.

PET/MR versus SCI

When compared to the reference standard, both modalities were correct in 22 cases (71%, 22/31); PET/MR was correct and SCI wrong in 6 cases (19%, 6/31) and they both were wrong in 3 cases (10%, 3/31), 2 of which were false-positives and 1 was false-negative. In all the 6 cases of discordant results, PET/MR correctly upstaged the disease burden compared to SCI, which was then confirmed by the reference standard. These cases were false-negative results for SCI, where it failed to identify lesions or underestimated their extent. More details from the discordant cases are shown in Table 2. Of the 25 remaining occasions when PET/MR and SCI results agreed, in 22 of them both PET/MR and SCI results were ultimately confirmed as true-positives by the standard of reference, meanwhile, in 2/24 cases both modalities produced false-positive results, in one instance calling metastatic lymph nodes that turned out to be negative for malignancy on pathology, while in another case SCI and PET/MR raised suspicion of peritoneal carcinomatosis which was later disproved by pathology. In the other 1/24 case, both modalities had false-negative findings, misinterpreting a metastasis as an atypical hemangioma.

A pairwise analysis comparing both tests showed significant superiority of PET/MR over SCI ($p = 0.0412$, McNemar's test). The diagnostic accuracy of PET/MR was 90% (SE ± 5%), versus 71% (SE ± 8%) for SCI. Representative cases are shown in Figs. 1 and 2.

Clinical impact of PET/MR

The retrospective ad hoc imaging reader found only one case where he dissented from the original disagreeing reports. This patient, according to the original PET/CT reading, was eligible for surgery. Meanwhile, the PET/MR reading alerted the clinicians about a more extensive spread of disease that favoured the final adoption of chemotherapy and the cancellation of surgery. On the other hand, the ad hoc imaging reader felt that the disease was widely spread also on the basis of the original PET/CT. Therefore, this case, despite not undergoing pelvic surgery in the real scenario due to PET/MR, was classified as concordant between PET/CT and PET/MR with no management changes for the sake of uniform quality readings. The other cases of disagreeing PET/MR and SCI reports were classified as adequate by the ad hoc reviewer.

Therefore, after final review PET/MR and SCI findings ultimately agreed in 81% (25/31) of the patients. Management changed in all the remaining 19% (6/31) disagreeing cases. The changes were as follows: cancellation of a surgical procedure (33%, 2/6), adding para-aortic lymphadenectomy to the original metastasectomy plan (17%, 1/6), changing the original chemotherapy regimen (17%, 1/6), performing a newly planned metastasectomy (17%, 1/6), and adoption of a different multidisciplinary strategy/surgical approach for the operation (17%, 1/6). Regarding the contribution of local versus metastatic findings for management change, 50% (3/6) were from metastases not seen on SCI, such as to non-regional lymph nodes, the peritoneum, and the liver. The other 50% (3/6) were related to local factors, such as newly detected recurrences or previously underestimated tumour extension. The rationale for each change, as well as the corresponding findings for SCI and PET/MR, are detailed in Table 2.

The estimate for the probability of change in management with the addition of PET/MR was 19% (95% CI 9–37%). In regard to the possible influence of the type of SCI on PET/MR's superiority in guiding patient management, there was no significant relationship between SCI being morphologic (i.e., CT or MR only) or hybrid (i.e. PET/CT) and management changes ($p = 0.3589$), neither between SCI being a single modality or a combination of them and management changes ($p = 0.6342$).

Regarding the comparison between rectal and colon primaries, PET/MR had a larger effect on the management of rectal cancer patients, with 30% (SE ± 8%) of them having their treatments modified, rather than those with colon cancer, who did not have any instances of management changes. However, the aforementioned relationship was not statistically significant ($p = 0.0658$).

DISCUSSION

In this single-centre, retrospective observational analysis, we sought to demonstrate the role of PET/MR, if any, in the evaluation of oligometastatic CRC. Oligometastatic CRC is considered a disease spectrum between loco-regional and multi-metastatic disease, with an intermediate prognosis [12, 30]. As of yet, oligometastatic disease is not uniformly defined. Some studies consider oligometastatic cases with metastases confined only to the lung or to the liver [32–34]. This approach is similar to the AJCC 8th Edition classification for CRC, which despite not defining oligometastases, divides the M stage according to the involvement of one site/organ (M1a), more than one site/organ (M1b), or of the peritoneum (M1c) [35]. The 2016 European Society for

Table 2. Detailed description of the cases whose management was changed.

SCI: Relevant findings (proposed management)	PET/MR: Relevant findings (proposed management)	Final management and reason for change in management (Interval between PET/MR and SCI)	Means of result confirmation
CE-MR of the abdomen/pelvis and CE-CT of the chest/abdomen/pelvis: One lesion in hepatic segment VII/VIII suspicious for metastasis. Soft-tissue nodule near the resection bed concerning for recurrence. (Hepatic metastasectomy and pelvic recurrence resection)	In addition to the segment VII/VIII metastasis, there are peritoneal lesions in the pelvis highly suspicious for peritoneal metastases. The soft-tissue nodule near the resection bed is benign. (Chemotherapy)	Chemotherapy. Peritoneal seeding, demonstrating widely spread metastatic disease, precluded liver metastasectomy. Additionally, local recurrence was ruled out[a]. (Scans were 19 days apart)	Follow-up imaging (CE-MR).
Whole-body CE-PET/CT and CE-CT of the chest/abdomen/pelvis: Lesion in hepatic segment I suspicious for metastasis. No other lesions identified. (Hepatic metastasectomy)	In addition to the suspected liver metastasis, there is also left para-aortic lymphadenopathy. (Left para-aortic lymphadenectomy and hepatic metastasectomy)	Left para-aortic lymphadenectomy and hepatic metastasectomy. Demonstration of metastatic lymphadenopathy. (Scans were performed on the same day)	Pathology results from hepatic metastasectomy and lymphadenectomy 20 days after the scans.
Whole-body CE-PET/CT and CE-CT of the chest/abdomen/pelvis: Eccentric lower rectal thickening compatible with biopsy-proven rectal adenocarcinoma with non-regional metastatic lymphadenopathy. (Total neoadjuvant therapy)	Low-mid rectal cancer infiltrating the most caudal portion of the *levator ani* bilaterally and the upper portion of the sphincter, tumour invades into the left posterior lateral mesorectal fascia. There is also non-regional metastatic lymphadenopathy. (Chemoradiation with folinic acid, fluorouracil, and oxaliplatin)	Chemoradiation with folinic acid, fluorouracil, and oxaliplatin. Demonstration of bilateral *levator ani* involvement. (Scans were 9 days apart)	Pathology results from surgery 277 days after the PET/MR.
Whole-body CE-PET/CT and CE-MR of the abdomen/pelvis: Combined CT and PET appearances of the distal rectum may represent post-radiotherapy change or recurrent cancer. Increase in size of the left pulmonary nodule, suspicious for metastasis. (Pulmonary wedge resection)	The lower rectum is extensively replaced by infiltrative residual/recurrent disease. There are also post-radiation changes. Left lung metastasis is increased from prior. (Palliative care)	Palliative care. The lung wedge resection was canceled, and the patient was referred to palliative care since PET/MR showed extensive residual disease at the primary site. Intraoperative findings confirmed the lesion to be unresectable. (Scans were performed on the same day)	Rectsosigmoidoscopy 7 days after scans.
Whole-body CE-PET/CT and CE-CT of the chest/abdomen/pelvis: The liver metastases described in prior studies seem resolved. There is still non-regional lymphadenopathy. (Chemoradiation)	A hepatic segment VII metastasis remains viable. In addition, there is still non-regional lymphadenopathy. (Liver metastasectomy in addition to chemoradiation)	Liver metastasectomy in addition to chemoradiation. Demonstration of persistent metastatic involvement of the liver[b]. (Scans were performed on the same day)	Pathology from hepatic metastasectomy 57 days after scans.
Whole-body CE-PET/CT: Unchanged locally confined pelvic infiltrative mass that may represent post-treatment changes OR recurrent disease. Surgical resection.	The pelvic mass infiltrates the posterior acetabulum, the junction with the left posterior inferior bladder wall, and also involves the prostate. The appearance of the mass suggests combined post-treatment changes and recurrent disease. Surgical resection requiring coordination of a multidisciplinary team.	Surgical resection requiring coordination of a multidisciplinary team. PET/MR demonstrated more extensive local infiltration, leading to changes in the surgical approach which involved a collaborative effort of colorectal surgery, orthopaedic oncology, urology, and plastic surgery, besides intraoperative radiation oncology. (Scans were performed on the same day)	Pathology from surgery 97 days after scans.

CE contrast-enhanced, *CT* computed tomography, *FDG* 2-deoxy-2-[18F] fluoroglucose, *MR* magnetic resonance imaging, *PET* positron emission tomography, *SCI* standard of care imaging.
[a]Shown in Fig. 1.
[b]Shown in Fig. 2.

Medical Oncology guidelines for the management of metastatic colorectal cancer defines oligometastatic disease as the existence of up to 3 separate anatomical sites with up to 5 or occasionally more lesions, predominantly in visceral locations, and, occasionally, in lymph nodes [36]. For the purposes of this study, according to prevalent clinical practice at our institution, oligometastatic disease was defined as at least one but fewer than five metastatic lesions, potentially amenable to surgical

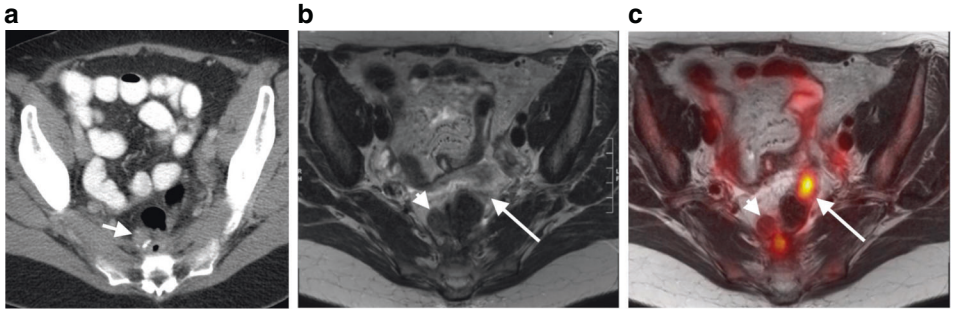

Fig. 1 Peritoneal disease detected at PET/MR only. Axial CE-CT (**a**), PET/MR axial T2-weighted high resolution (**b**), and fused PET/MR (**c**), from a 55-year-old female patient with oligometastatic rectal cancer, who had already undergone rectal surgery. The axial CT shows a presacral soft-tissue nodule, inseparable from the anastomosis, suspicious for tumour recurrence (arrow in **a**). On the PET/MR, the same lesion did not demonstrate increased FDG uptake (short arrow in **b**, **c**). There is, however, unexpected peritoneal disease involving the serosa of the sigmoid colon that was not seen on CT (long arrow in **b**, **c**). Both scans were performed 19 days apart. Due to the demonstration of peritoneal metastases by PET/MR, the patient was placed on chemotherapy instead of the original surgical approach which included liver metastasectomy and pelvic recurrence resection. The findings were confirmed by follow-up CE-MR performed 73 days later.

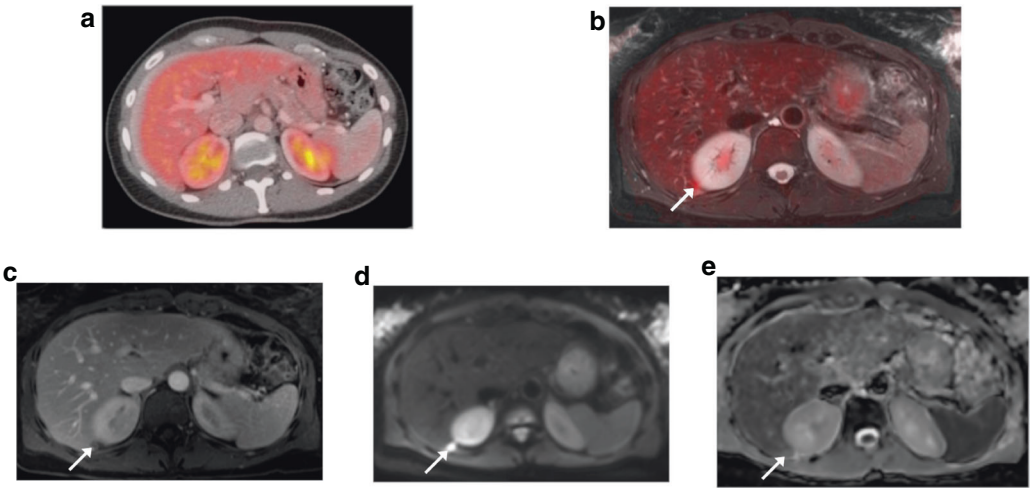

Fig. 2 Viable metastasis diagnosed by PET/MR. Axial fused PET/CT (**a**), axial fused PET/MR (**b**), PET/MR contrast-enhanced VIBE (**c**), low b-value diffusion-weighted imaging (DWI) (**d**), and apparent diffusion coefficient (ADC) map (**e**). 50-year-old female patient with oligometastatic rectal cancer. PET/CT did not show residual hepatic metastases. However, a residual metastasis in segment VI/VII (arrow) was diagnosed by PET/MR. The lesion is harder to call a metastasis on PET/CT. Compared to PET/CT, the longer PET acquisition time along with the combined information from restricted diffusion and enhancement pattern on PET/MR allowed lesion detection and characterisation. Therefore, the patient underwent a liver metastasectomy in addition to the already planned chemoradiation therapy. Both scans were performed on the same day, and the pathology report from the liver metastasectomy specimen confirmed the PET/MR finding.

resection. The involvement of a single lobe of the liver was considered a single metastatic lesion as there is potential for *en bloc* resection of the lesions with partial hepatectomy. Imaging is especially important in this context, as it might guide directed therapies that impact patient survival.

PET/MR is an emerging modality that became commercially available only in 2011 [37], and has higher costs associated with acquisition, maintenance, and operation. However, given its superior diagnostic yield, it might be cost-effective when factoring in the cost of biopsies and surgeries that would be proven unnecessary. This was recently demonstrated by Gassert et al. in the context of rectal cancer M staging [38]. Although more expensive than separate pelvic MR and chest/abdomen CT, as recommended per the National Comprehensive Cancer Network Guidelines [39], the increased overhead with follow-up diagnostic tests with the standard strategy might counterbalance on a large enough sample. Furthermore, early metastasis detection and intervention improves the quality of life which also has associated value.

Regarding the heterogeneous SCI in our sample, it should be understated that this is truly representative of the different pathways that patients may go through among referrals and continued care. The current recommendations are not strict in this regard, allowing flexibility, especially when substituting abdominal CT for MRI. Thus, it is anticipated that in the population patients will be staged with different modalities. Nevertheless, we find in the literature comparative evaluations of PET/MR against each of the SCI modalities separately, demonstrating similar effects. For example, when comparing PET/MR to PET and MR separately, the synergy between the two imaging methods results in a superior performance [40]. PET/MR's superior performance is also sustained when comparing it to MR [28], CT [27] and PET/CT [26]. Therefore, even though in our manuscript these modalities were joined under the SCI label, their differences to PET/MR are known separately and are expected to maintain their behaviour as such.

Our findings support the importance of PET/MR in the diagnosis and management of oligometastatic CRC, where PET/MR altered clinical management in 19% of the cases (95% CI 9–37%). The

management changes rates in our cohort are comparable to the 22% rate reported by Kang et al. when comparing PET/MR to CT in the setting of colorectal cancer regardless of treatment status and with the 36% rate reported by Amorim et al. in the setting of treated colorectal cancers [25, 27]. This suggests PET/MR might also have an important role in the settings of oligometastatic colorectal cancer management. To the best of our knowledge, to date, this is the first study comparing the diagnostic performance and even more so the clinical implications of PET/MR to other available imaging techniques in the specific setting of oligometastatic colorectal cancer.

Overall, PET/MR outperformed SCI, with accuracies of 90% (SE ± 5%) and 71% (SE ± 8%) for tumour burden evaluation at a patient level, respectively. In the one case where PET/MR was false-negative, the SCI findings were also inaccurate. These findings suggest that PET/MR has a greater diagnostic yield when compared to SCI. This is further reiterated by the matched comparison of SCI and PET/MR pairs for each patient regarding their correspondence to the reference standard. Moreover, this is consistent with the available literature which has shown the superior diagnostic performance of PET/MR versus SCI in treated and untreated colorectal cancer [25–28, 41]. One limitation of PET/MR that should be pointed out is the worse sensitivity for lung metastases detection when compared to chest CT and PET/CT, especially for lesions below 7 mm [42]. This can be explained by the intrinsic low signal of the lungs on MR, and the fact that lesions below this size approach PET's current detection threshold due to limitations from spatial resolution [43]. In our cohort, no lung metastases were missed when comparing PET/MR to PET/CT and/or chest/abdomen CT.

Our initial observations support the role of PET/MR as a potential tool in determining the best, individualised, plan for these patients. In an era of precision medicine in which the profiling of tumour types guides progressively more specifically targeted cytotoxic and biologic agents, it is natural for the imaging tests to also adapt to such reality [44]. While radiomics and radiogenomics might provide new answers using old imaging modalities [45, 46], the introduction of PET/MR to the clinical management of such neoplasms may provide yet another pathway for a patient-centred treatment approach.

Limitations

Our study has several limitations. The data were collected in a retrospective manner, which can introduce inadvertent selection bias. Furthermore, the fact that PET/MR was read after SCI meant that readers might have been aware of the latter's findings, which could have been a confounder. However, as extensively described in Table 2, the changes in management were not related to any information that could be translated from one modality to another. Conversely, this approach may have contributed to the two false-positives and the one false-negative results that were in agreement on both modalities, due to confirmation bias.

The number of cases studied is small; however, as this study is the first on PET/MR efficacy for oligometastatic CRC to our knowledge, we feel that the contribution might be useful to point out potential areas of research and clinically meaningful applications. Moreover, the number of subjects is also compatible with previously reported studies of PET/MR in CRC which ranged from 12 to 62 patients [25, 27, 28, 47, 48].

Another limitation is related to the heterogeneity of our population, especially in regard to the SCI, stages of care, and primary cancer origin. In fact, the standard of care imaging was non-uniform in our patient population with patients receiving either CT, MR, or PET/CT; however, we did not find that the difference in types of SCI employed significantly impacted the likelihood of a change in management by PET/MR. The lack of such association should be interpreted with caution, as there was no sufficient power to rule it out. Nevertheless, the existing literature supports PET/MR superiority over each one of those modalities when individually compared [26–28].

Additionally, the PET/MR examinations studied were performed at different stages of care, either at initial staging or for restaging. In patients imaged for restaging, patient treatments prior to PET/MR varied, with patients receiving different regimens of chemotherapy, radiation, and/or surgery.

Furthermore, rectal cancers constituted the vast majority of our study population (65% rectal primary versus 35% colon primary) which might have impacted the observed predominance of treatment changes in rectal primaries. In rectal cancer, pelvic MR is considered standard in staging and restaging. The same is true for abdominal MR in cases in which surgery and/or liver-directed therapy are being considered [39]. However, MR was not necessarily included in SCI for all of the rectal cancer patients due to the evaluation-time bias relative to PET/MR imaging which might have instead acted as a confounder. Notwithstanding, the patients underwent imaging as directed by their providers, and all available previous imaging was also comparatively evaluated by SCI and PET/MR readers. Therefore, it is not anticipated that the lack of direct comparison of pelvic/abdominal MR and PET/MR would result in different results from those presented here.

Lastly, although in theory, the heterogeneity of the reference standard might be a potential confounding factor, 87% of our cases had pathology confirmation and 3% had intraoperative confirmation. Only 10% of them were confirmed only by follow-up imaging.

CONCLUSIONS

PET/MR has the potential to impact the clinical management of oligometastatic CRC patients in about 19% of cases (95% CI 9–37%). This is the result of the incremental value of PET/MR, versus the standard of care imaging (CT, MR, or PET/CT), in evaluating the extent of supposedly oligometastatic CRC. Additionally, our findings suggest that PET/MR might be more useful in the evaluation of rectal cancers rather than colonic primaries.

DATA AVAILABILITY

The de-identified dataset is available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualisation: OAC, JWC, TH, DG, JCC, LB and KSW; Methodology: HDL, OAC and AM; formal analysis, MV and FSF; Investigation: RS, OAC, JW, LU, RR, LB, MQ, CRF, FSF, MA and KSW; Resources: LU and DG; Writing—original draft preparation: KSW, OAC, FSF, MA and DG; Writing—review and editing: MV, JWC, TH, JCC, LB, RS, JW, LU, RR, LB, MQ, CRF, AM, HDL, MA, and AM; Supervision: OAC; Project administration: OAC and RS. All authors have read and agreed to the published version of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Mass General Brigham (protocol code #2018P001334 approved on 7/10/2018). Patient consent was waived due to the retrospective nature of the study.

CONSENT TO PUBLISH

No individual and/or identifiable patient data is reported.

ADDITIONAL INFORMATION

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