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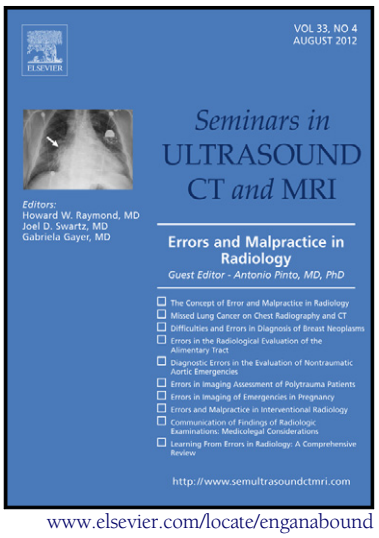

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Invited Review:

Positron emission tomography/magnetic resonance imaging of gastrointestinal cancers

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ABSTRACT:

As an integrated system, hybrid positron emission tomography/magnetic resonance imaging (PET/MRI) is able to provide simultaneously complementary high-resolution anatomic, molecular and functional information, allowing comprehensive cancer phenotyping in a single imaging examination. In addition to an improved patient experience by combining two separate imaging examinations and streamlining the patient pathway, the superior soft tissue contrast resolution of MRI and the ability to acquire multi-parametric MRI data is advantageous over computed tomography (CT). For gastrointestinal cancers this will improve tumor staging, assessment of neoadjuvant response and of the likelihood of a complete (R0) resection in comparison to PET/CT.

BODY:

The number of installed hybrid positron emission tomography/magnetic resonance imaging (PET/MRI) scanners has increased steadily since their clinical introduction in 2010. Current scanners combine a PET system with a 3-tesla (3T) MRI, either as an integrated or sequential system [1,2]. In an integrated system, PET and MRI are co-located with the PET detectors embedded within the MRI system. In a sequential scanner, the MRI and PET are linked with a shuttle system, allowing the patient to be transferred directly from one system to another yet maintaining the same patient table position to facilitate co-registration of PET and MRI (**Table 1**).

Integration of PET with MRI has been challenging but eventually achieved through substantial engineering advances [3]. The MRI static B0 and radiofrequency B1 magnetic field and radiofrequency pulse will affect electron paths, cause heating, vibration and interference with PET electronics. Likewise, PET components may affect the homogeneity of the MRI B0 field and radiofrequency detection. Integration has required the replacement of standard PET photomultiplier tubes with magnetic field-insensitive avalanche photodiodes or silicon photomultipliers; incorporation of additional shielding around the PET system and redesign of electronics [3]. MRI radiofrequency surface coils also have been designed to be 'PET transparent' with minimal attenuation of emitted photons.

Integration has brought new challenges for PET attenuation correction, an essential part of PET imaging [4]. PET radionuclide decay results in the emission of two opposing 511 keV annihilation photons. Some photons are attenuated or scattered by body tissues before being detected causing signal loss proportional to the distance from the surface and regional tissue density. Non-attenuation-corrected PET data will generally underestimate tracer activity deep within the body. With a hybrid PET/computed tomography (CT) system, attenuation correction using CT based X-ray attenuation, scaled to reflect the attenuation of higher energy 511keV emission photons, enables accurate quantification [5].

With hybrid PET/MRI this is not possible, as MRI signal intensity is not based on tissue density as with CT but on proton density and relaxation properties, requiring alternative methods [4]. In current systems, dedicated attenuation correction sequences may be acquired, most commonly a 2-point Dixon 3D gradient echo, deriving an attenuation map (μ map) based on four tissue types: background air, lungs, soft-tissue, and fat. A limitation of such methodology is the classification of bone as soft-tissue, which may lead to

standardized uptake value (SUV) underestimations of bone lesions by as much as 30% [6-8]. Ongoing work on ultra-short time-to-echo (TE) MRI sequences may improve bone classification at the expense of a longer acquisition time and possible artefacts with large field-of-view imaging (which is the norm for whole body imaging) [9]. Alternatives, including atlas-based methods and software-based artificial intelligence algorithms (e.g. neural networks and fuzzy logic) to segment anatomical structures such as soft tissue and bone for attenuation correction, are also under consideration [10].

Another issue for attenuation correction is that the MRI field-of-view is smaller than the PET field-of-view. This can affect MR attenuation correction if anatomical structures lie outside the field-of-view, e.g. in obese patients. The arms may also be truncated by the MRI field-of-view. A current workaround in clinical systems is to iteratively extract the contours of the arms from PET data (maximum likelihood reconstruction of attenuation and activity [11]) and to use this information to complete the MR based attenuation correction map of the body.

Currently, hybrid PET/MRI is evolving from being just a research tool to include clinical applications, as the high sensitivity of PET acts synergistically with the high contrast and spatial resolution of MRI. It is also possible to include locoregional MRI functional sequences, including diffusion weighted MRI, dynamic contrast enhanced MRI and blood oxygenation level dependent MRI to provide a more comprehensive evaluation of underlying tumor biology and physiology. This is particularly promising for imaging gastrointestinal cancers.

Nevertheless, a 3T MRI system does bring some challenges for body imaging [12]. While the signal-to-noise ratio increases approximately linearly with field strength, and thus an advantage of imaging at 3T, the energy deposition will increase also, as the square of field strengths. Specific absorption ratio (SAR) limits are likely to be reached more often, typically restricting acquisition parameters, e.g. lengthening the acquisition time.

Standing wave effects are also relevant at 3T. The ^{1}H Larmor resonance frequency increases with field strength, e.g. from 63.9 MHz at 1.5T to 127.8MHz at 3T; consequently, the wavelength of the applied radiofrequency (in the medium water and thus 'body tissue') is shortened, e.g. from 52cm at 1.5T to 26cm at 3T in body tissue (versus 470cm to 235cm in the medium air). This 26cm wavelength is similar to the dimensions of the body trunk in axial sections, and relevant as radiofrequency excitation is undertaken perpendicular to the body long axis. The shorter wavelength inside the body at 3T results in a negative interference of superimposed radiofrequency waves emanating into the body from the surface. Near complete cancellation of radiofrequency excitation may occur in central parts of the abdomen or pelvis. Further radiofrequency effects may also arise from induced eddy currents in conductive parts of the body. Both effects result in marked B1 field inhomogeneity (and local irregular flip angles), which are relevant to centrally located gastrointestinal cancers and quantitative functional MRI techniques and may be worse in patients with increased conductivity, e.g. with ascites that acts as a conductive medium. Workarounds in clinical systems include improved coil designs, more flexible radiofrequency shimming, and draining of ascites prior to imaging.

Another issue is that the chemical shift effect is greater at 3T. Chemical shift results from partial shielding of the outer magnetic field at the location of the nuclei by the electron sheath of the molecule. This is proportional to the field strength: the Larmor frequency

difference between nuclei with different chemical bonds increases linearly, e.g. the difference between water and methylene (in fatty acid and triglycerides) doubles from 220 Hz to 440 Hz at 3T. This is relevant to gastrointestinal imaging due to the fat/water interface at the bowel wall, which may lead to chemical misregistration artefacts. This has to be considered when assessing tumor stage (T stage).

Finally, magnetic susceptibility effects also increase linearly with field strength and is two times greater at 3T compared to 1.5T for the same volume. Microscopic gradient differences at the interfaces of materials of different magnetic susceptibility, e.g. air/soft tissue and metal/soft tissue are accentuated at 3T and challenging for gastrointestinal cancers, where luminal gas often lies in proximity of the tumor. MRI acquisition optimization is necessary to mitigate these effects, for example by increasing receiver bandwidth, using spin echo over gradient echo sequences or less B0-sensitive fat suppression techniques.

Imaging Workflow for Gastrointestinal Cancers

Patient preparation for PET/MRI has to consider the requirements of both modalities. For ^{18}F-FDG PET, pregnancy is a contraindication. A 4-6 hour fast, control of the blood glucose level (<120mg/dL) and minimization of patient movement after FDG injection is also necessary to minimize skeletal muscle uptake. Consideration also has to be made for diabetic patients on metformin. Metformin is known to increase bowel activity diffusely and has been shown to be associated with false negative cancer detection [13]; replacement of metformin with alternative therapies may be required if this is considerable. The risks for MRI are related to its strong static magnetic field, pulsed magnetic field and radiofrequency field. MRI cardiac pacemakers are an absolute contraindication due to possible device

malfunction, localized heating and possible arrhythmias. At 3T some metal implants are also contraindicated due to possible movement and localized heating effects.

For ^{18}F-FDG, a dose of 2.5-5 MBq/kg is typically injected (up to maximum dose of 740 MBq) [14] and, following a 60- to 90-minute uptake period, the PET/MRI acquisition commenced.

A typical half-body simultaneous hybrid PET/MRI acquisition is shown in **Figure 1**. Patient positioning to optimize the MRI signal and to minimize artefacts related to B0 inhomogeneities requires the patient to be centered within the magnetic field and for the surface coils to be positioned appropriately. This can potentially add to technologists' radiation exposure compared to PET/CT, and has to be considered when training technologists.

MR attenuation correction is performed using a 2-point Dixon 3D volume interpolated breath-hold sequence. Large field-of-view, T2 weighted (T2-W) single shot TSE (HASTE) sequences either in the axial or coronal plane are acquired for anatomical localization; these have a lower spatial resolution than standard diagnostic sequences but are ideal due to their rapid acquisition time (<30s per bed position). A standard half body scan from vertex to mid-thigh will typically take 20 minutes [15,16]. Concurrent acquisition of free breathing diffusion weighted MRI and PET acquisitions can streamline workflow if diffusion weighted imaging is required.

A number of additional locoregional higher resolution MRI sequences may be selected following the half-body acquisition, that can be varied flexibly according to body region and the clinical question (**Figure 2**). For rectal cancer, this would include a T2-W turbo spin echo (TSE) sagittal and coronal of the pelvis and T2-W TSE axial oblique and coronal oblique sequences centered on the rectal cancer. For esophageal cancer this would include a T2-W TSE sagittal, coronal and axial sequence. Cardiac and respiratory gating may be required for

lower thoracic esophageal and gastro-esophageal junction cancers. This may result in a large number of multi-planar sequences [16].

A possible approach is to read the whole body images, which provide an overview of both the PET molecular and MRI anatomical information as a fused set, and then the locoregional images, which are typically of higher spatial resolution for MRI and acquired in the appropriate planes for gastrointestinal cancers, e.g. parallel and perpendicular to the bowel lumen.

PET/MRI assessment of gastrointestinal cancers

Staging and restaging

Due to its high contrast and spatial resolution, and its ability to depict the relationship of the primary tumor to the potential resection margin, MRI is the standard of care for TNM (tumor-node-metastasis) staging of rectal cancer [17, 18]. Further staging improvement may be gained in terms of nodal and distant metastatic disease by combining PET and MRI information. Similarly, assessment of pelvic recurrent disease may also be improved by combining PET and MRI (**Figure 3**). This is supported by a recent small study which compared the performance of FDG PET/CT versus FDG PET/MRI for lesion detection in 15 colorectal cancer patients with 180 lesions of which 110 were malignant (using histology and/or follow-up imaging as the reference standard). This investigated the use of anatomical MRI alone, anatomical MRI with diffusion MRI, anatomical MRI with PET, anatomical MRI with diffusion MRI and PET and PET/CT [19]. Lesion-based diagnostic accuracy was highest when combining anatomical, diffusion MRI and PET and lowest with anatomical MRI alone, highlighting the potential added value.

To date there have been few published data. One study of 51 patients with colorectal cancer who underwent ^{18}F-FDG PET/MRI and contrast enhanced CT within 90-days investigated the added value of PET/MRI to CT for lesion detection and characterization, and changes to treatment strategies. The reference standard was histopathology, imaging and clinical follow-up [20]. This study found added value in 14/ 51 patients (27.5%) with 12/51 (23.5%) demonstrating better characterization of lesions and in 2/51 (3.9%) the additional detection of extra-colonic disease. There was a change in treatment strategy in 11/51 (21.6%). In another small study of 12 patients comparing PET/MRI to PET/CT for restaging (10/12 patients) and staging (2/12 patients) [21], where PET/MRI was performed at a median of 60min post PET/CT, there appeared to be more detailed T staging with PET/MRI and comparable N and M staging. On a per-patient basis the true positive rate was 5/7 (71%) for PET/CT and 6/7 (86%) for PET/MRI with the same true negative rate, 5/5 (100%). On a per-lesion basis PET/CT identified 26 of 29 (90%) correctly detected PET/MRI lesions.

For resectable esophageal cancer, an imaging approach combining endoscopic ultrasound (EUS) with contrast enhanced CT and FDG PET/CT is currently the standard of care. However, MRI has been shown to be capable of high resolution imaging of the esophagus and the surgical anatomy, particularly with respect to T stage [22,23], and potentially allows patient imaging to be more streamlined. To date a small study has compared EUS, CT, PET/MR & PET/CT for locoregional staging in 19 patients with resectable esophageal cancer with a pathological reference standard in the 15/19 patients treated surgically [24]. Primary tumors were correctly T staged in 13 (86.7%), 10 (66.7%) & 5 (33.3%) patients at EUS, PET/MR and CT respectively: p-value 0.021 to 0.375. T staging accuracy was highest for EUS, but comparable with PET/MRI. For T1 lesions, accuracy was 86.7%, 80.0%, & 46.7% for EUS,

PET/MR & CT respectively. For T3 lesions accuracy was 93.3%, 86.7% & 86.7% for EUS, PET/MR & CT respectively. Nodal staging accuracy was also high for PET/MRI with an accuracy of 83.3%, 75.0%, 66.7% & 50.0% for PET/MR, EUS, PET/CT & CT respectively, highlighting a potential advantage of combining PET & MRI where diffusion weighted imaging is highly sensitive for nodes, and specificity may be improved with the addition of PET.

A few studies have specifically assessed PET/MRI for detecting and characterizing liver lesions. One study of 26 patients with 113 liver lesions (68 benign, 45 malignant; with a reference standard of follow-up imaging in all patients and additional histology in 8 patients) who underwent both PET/CT and PET/MRI (including contrast enhanced and diffusion MRI sequences) reported an improvement in sensitivity, specificity, and accuracy with PET/MRI, with a sensitivity, specificity, and accuracy of 91.1-93.3%, 100% and 95.6-96.7% for PET/MRI versus 64.4-71.1%, 97.1% and 80.8-84.1% for PET/CT, respectively for two different readers [25]. Another study comparing PET/MRI and PET/CT in 70 patients, 51% of whom had liver lesions, found that PET/MRI detected more lesions than PET/CT and resulted in an increase in diagnostic confidence of both malignant and benign lesions with PET/MRI [26].

Therapy response assessment

Another promising area for PET/MRI is therapy response assessment, as a multi-parametric approach is possible providing comprehensive information beyond size change. To date there has been a lack of data with integrated PET/MRI. One study comparing PET alone, MRI alone with combined fused PET-MRI data in locally advanced rectal cancer treated with chemoradiation has suggested an improvement in the sensitivity, specificity and accuracy of

fused PET-MRI data: sensitivity, specificity and accuracy of 60% versus 80%; 20% versus 66.7% and 80% versus 86.7% for MRI data alone versus fused PET-MRI data, respectively [27]. Further data in the field are awaited from planned studies.

In summary, hybrid PET/MRI is an emerging technique, showing promise for gastrointestinal cancers due to the high contrast and spatial resolution of MRI, the high sensitivity of PET and the ability to include multiple sequences for comprehensive functional and anatomical evaluation. Accurate staging is important for appropriate therapeutic triage and PET/MRI is potentially able to improve on nodal and metastatic staging in rectal cancer and tumor and nodal staging in esophageal cancer. A higher sensitivity for disease is also important in restaging disease recurrence in order to improve outcomes of patients planned for further surgery of local recurrence or oligometastatic disease. For therapy response assessment, the ability to assess response/non-response with a comprehensive approach may allow therapeutic switching or earlier surgery where there is a lack of response. However, published evidence remains scarce with early initial data only. Further work is required before full clinical adoption is possible.

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Figure Captions

Figure 1. Schema showing typical hybrid PET/MRI acquisitions. AC = attenuation correction; DWI = diffusion weighted imaging.

Figure 2. PET/MRI imaging of a locally advanced rectal cancer planned for pre-operative chemoradiotherapy (gray arrowheads). A multi-parametric approach is shown, including ^{18}F-FDG PET, perfusion MRI, diffusion MRI and ^{1}H MRI spectroscopy.

Figure 3. PET/MRI increases diagnostic confidence of a local anastomotic rectal cancer recurrence in a patient with rising CEA (gray arrowheads). From the top left corner, clockwise: ^{18}F-FDG PET 3D maximum intensity projection (MIP) reconstruction, axial HASTE, ADC map, fused anatomical-diffusion MRI, fused PET/MRI.

Figure 4. Fused PET/MRI image of an FDG-avid, mid-thoracic esophageal cancer (gray arrowhead).

Table 1. Comparison of current hybrid PET/MRI systems.

Systems	**Integrated**		**Sequential**
Manufacturer	Siemens	General Electric	Phillips
Scanner Bore	60cm	60cm	60cm
MRI: **Field Strength** **Gradients** **Slew Rate**	 3-tesla 45mT/m 200 mT/m/s	 3-tesla 50mT/m 150 mT/m/s	 3-tesla 40 or *80mT/ms 200 or*100mT/m/s
MRI Field-of-View (FOV)	50x50x45cm	45x45x45cm	50x50x45cm
PET Detectors	Lutetium oxyorthosilicate avalanche photodiodes	Lutetium based scintillator with silicon photomultipliers	Lutetium oxyorthosilicate photomultiplier detector modules
PET Axial FOV	25 cm	25 cm	18 cm
Simultaneous Acquisition	Yes	Yes	No

*Enhanced mode

Figure 1

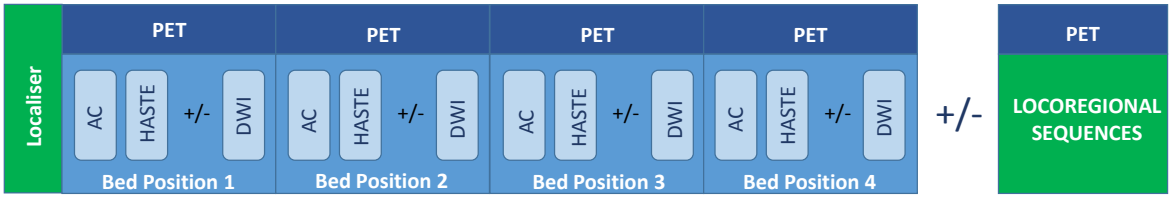

Figure 2

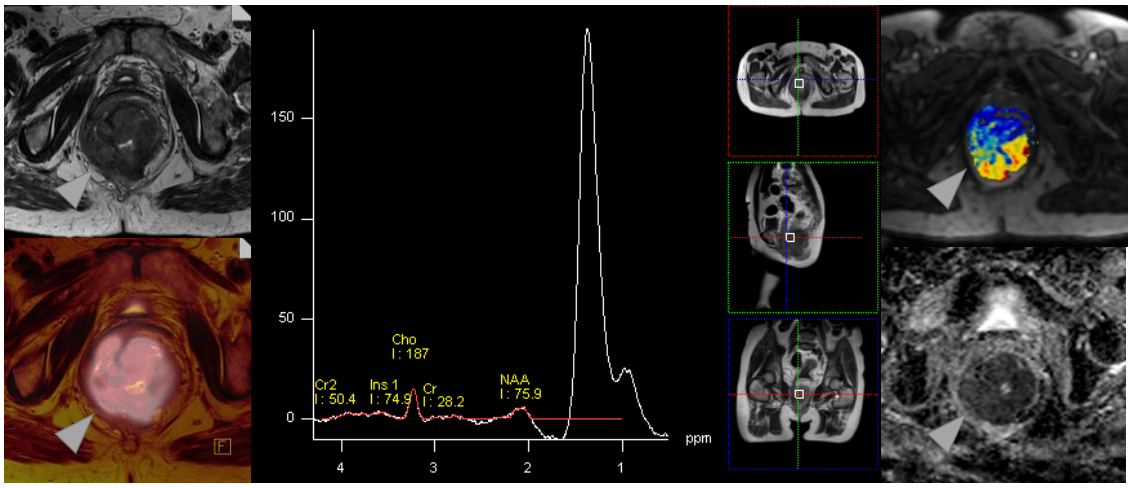

Figure 3

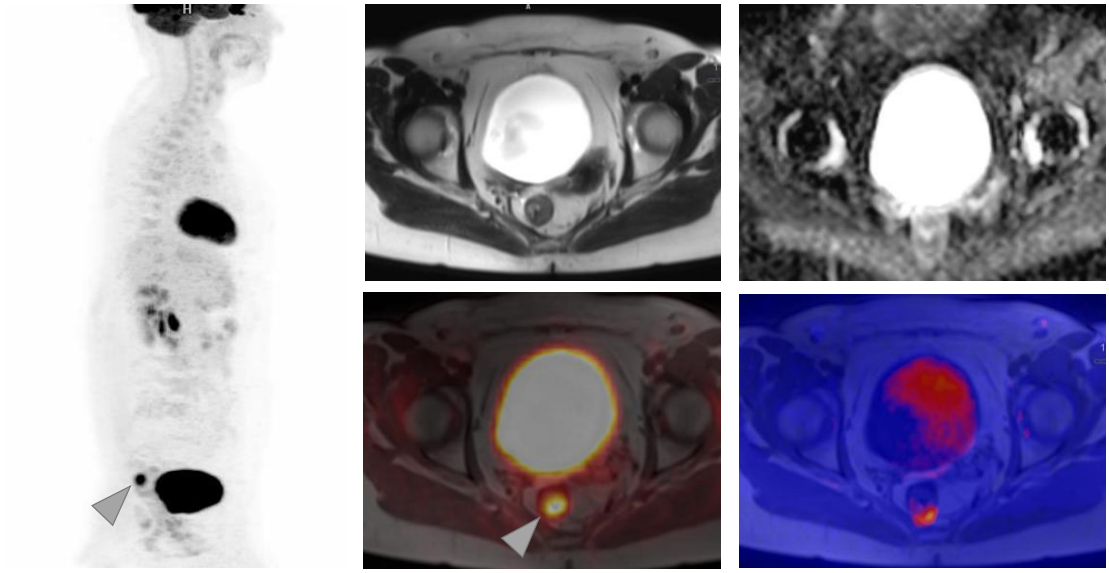

Figure 4