Hybrid PET/MRI in non-small cell lung cancer (NSCLC) and lung nodules—a literature review

Dahlsgaard-Wallenius, Sara E.; Hildebrandt, Malene Grubbe; Johansen, Allan; Vilstrup, Mie Holm; Petersen, Henrik; Gerke, Oke; Høilund-Carlsen, Poul Flemming; Morsing, Anni; Andersen, Thomas Lund

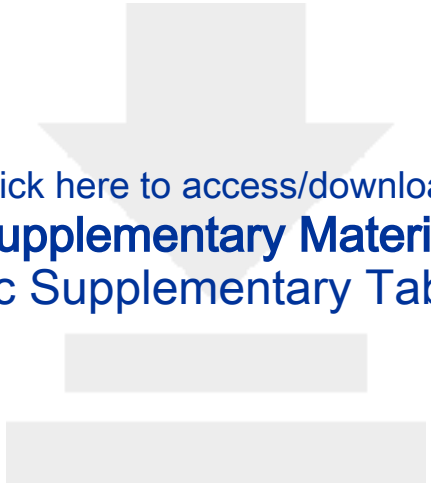
Published in:
European Journal of Nuclear Medicine and Molecular Imaging

DOI:
10.1007/s00259-020-04955-z

Publication date:
2020

Document version
Accepted manuscript

Citation for pulished version (APA):
Dahlsgaard-Wallenius, S. E., Hildebrandt, M. G., Johansen, A., Vilstrup, M. H., Petersen, H., Gerke, O., Høilund-Carlsen, P. F., Morsing, A., & Andersen, T. L. (2020). Hybrid PET/MRI in non-small cell lung cancer (NSCLC) and lung nodules—a literature review. *European Journal of Nuclear Medicine and Molecular Imaging*. https://doi.org/10.1007/s00259-020-04955-z



Eur J Nucl Med Mol Imaging

Review article

Hybrid PET/MRI in non-small cell lung cancer (NSCLC) and lung nodules - a literature review

Sara E. Dahlsgaard-Wallenius[1], Malene Grubbe Hildebrandt[1,2,3], Allan Johansen[1], Mie Holm Vilstrup[1], Henrik Petersen[1], Oke Gerke[1,2,] Poul Flemming Høilund-Carlsen[1,2], Anni Morsing[4,5,*]& Thomas Lund Andersen[1,4,*]

[1]Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark

[2]Research Unit of Clinical Physiology and Nuclear Medicine, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[3]Centre for Innovative Medical Technology (CIMT), Odense University Hospital, Odense, Denmark

[4]MAgNetic resonance Technology for Response Adapted radiotherapy (MANTRA), Odense University Hospital, Odense, Denmark

[5]Novo Nordisk A/S, Soeborg, Denmark

*These authors contributed equally to this work

Corresponding author:

Sara E. Dahlsgaard-Wallenius

Email: sarawallenius@hotmail.com

Tel.: +45 6611 3333

Abstract

Background: The use of hybrid PET/MRI for clinical staging is growing in several cancer forms and, consequently, PET/MRI has also gained interest in the assessment of non-small cell lung cancer (NSCLC) and lung lesions. However, lung evaluation with PET/MRI is associated with challenges related to technical issues and diagnostic image quality. We, therefore, investigated the published literature on PET/MRI for clinical staging in NSCLC or lung nodule detection specifically addressing diagnostic accuracy and technical issues.

Methods: The data originates from a systematic search performed in PubMed/MEDLINE, Embase, and Cochrane Library on hybrid PET/MRI in patients with cancer for a scoping review published earlier (doi: 10.1007/s00259-019-04402-8). Studies in English and German evaluating the diagnostic performance of hybrid PET/MRI for NSCLC or lung nodule detection in cancer patients were selected. Data reported in peer-reviewed journals without restrictions to year of publication were included.

Results: 3138 publications were identified from which 116 published 2012-2018 were included. Of these, nine studies addressed PET/MRI in NSCLC (4) or lung nodule detection (5). Overall, PET/MRI did not provide advantages in preoperative T and N staging in NSCLC compared to PET/CT. The data on M staging were too few for conclusions to be drawn. The lung nodule detection rate of PET/MRI was comparable to that of PET/CT for FDG-avid nodules larger than 10 mm, but the sensitivity of PET/MRI for detection of non-FDG-avid nodules smaller than 5 mm was low.

Conclusion: PET/MRI did not provide advantages in T and N staging of NSCLC compared to PET/CT. PET/MRI had a comparable sensitivity for detection of FDG-avid lung nodules and nodules over 10 mm, but PET/CT yielded a higher detection rate in non FDG-avid lung nodules under 5 mm. With PET/MRI, the overall detection rate for lung nodules in various cancer types remains inferior to that of PET/CT due to the lower diagnostic performance of MRI than CT in the lungs.

Keywords: PET/MRI, PET/CT, 18F-FDG, NSCLC, lung lesions

Introduction

Lung cancer is a leading cause of cancer-related mortality, and correct staging is vital for appropriate management and prognosis [1]. In non-small cell lung cancer (NSCLC) PET/CT has proven indispensable in lymph node and distant metastases staging and provides useful data for the characterization of morphologically indeterminate pulmonary nodules and has been widely adopted in clinical practice. Lately, hybrid PET/MRI has gained interest in several cancer forms, e.g., located in the upper abdomen [2] or pelvic region [3–5], due to the possibility of combining multiparametric metabolic, functional, and morphological information provided by radioactive tracers and different MRI sequences. In lung cancer, which typically metastasizes to the brain, adrenal glands, and bone marrow [6,7], MRI adds image contrast flexibility compared to CT and holds the potential to provide additional diagnostic value.

Pulmonary lesions are often detected in patients with extra-pulmonary cancer. The identification and evaluation of such nodules as either benign or malignant may be essential for choice of treatment and/or prognosis. It is hypothesized that small lung nodules may be harder to visualize on PET/MRI compared to PET/CT due to the fundamentally different imaging principles of CT and MRI. Particularly, small non-2-[18F] fluoro-2-deoxy-D-glucose (FDG)-avid nodules are of concern as they are usually only detected on the CT part of the PET/CT scan [8,9]. PET/MRI evaluation of the lungs and pulmonary lesions pose special technical challenges related to the MRI technology and FDG-avidity and with varying clinical consequence depending on the primary indication and/or cancer form. Diagnostic quality MRI of the lungs is difficult to obtain due to the inherent low proton density in the lungs resulting in a low signal to noise ratio, cardiac and respiratory motion artifacts, and susceptibility artifacts at the tissue-air interface [10,11]. Hence, the size of the pulmonary nodule is a significant factor for evaluating the diagnostic performance of PET/MRI justifying special mention to studies focusing on pulmonary nodule detection as their primary aim. The purpose of this review was to present studies comparing PET/MRI to PET/CT in staging NSCLC or with the primary aim of detecting pulmonary lesions in cancer patients.

Material and methods

The data in this review originates from a systematic literature search performed on the first of august 2018 on PET/MRI in patients with cancer (excluding the central nervous system). The search strategy has previously been described in detail in a paper dealing with major non-pulmonary cancers [12]. In brief, studies were identified by searching

MEDLINE (via PubMed), EMBASE, and the Cochrane Library databases (Supplementary material Table 1). The search strategy was developed by two senior consultant reviewers (A.M., M.G.H.) and a senior health sciences research librarian from the University Library of Southern Denmark. Both index terms (e.g. MESH terms) and text words were included in the searches. After removal of duplicates, papers were screened by title and abstract and the full-text body was checked for eligibility according to strict inclusion and exclusion criteria. The including criteria were patients with cancer (excluding central nervous system) evaluated for staging, surgical resectability, radiation therapy planning, response or suspected recurrence. Studies in which the primary aim was evaluation of hybrid PET/MRI with no restrictions on comparator modalities. Outcome being diagnostic performance, lesion detection, quantitative evaluation, or feasibility. Only data reported in peer-reviewed journals were included and without restrictions to year of publication. Exclusion criteria were non-human studies, publications not in English or German, case reports, editorials, commentaries, reviews, meta-analyses, guidelines, book chapters, technology assessment reports, and conference proceedings. Studies comprising non-hybrid PET/MRI systems or trimodality PET/CT/MRI systems, studies including ten or fewer patients, and studies on dedicated PET/MRI breast imaging and CNS were also excluded.

In this descriptive review, we present papers on the use of PET/MRI in staging NSCLC or with the primary aim of evaluating pulmonary lesions in cancer patients. We did not use strict criteria for outcome measures, and no critical appraisal was performed.

Results

The database search revealed 3138 papers from which 116 papers published 2012-2018 were included and grouped according to cancer type [12]. Four studies concerned NSCLC and compared initial staging with PET/MRI and PET/CT (Table 1) [13–16]. Five studies addressed the detection of pulmonary lesions in pulmonary and non-pulmonary cancer [17–21] (Table 2); three of those compared the detection of lung nodules on PET/MRI to PET/CT [17,20,21], and two evaluated the outcome of lung nodules missed on PET/MRI [18,19]. All studies used FDG as PET-tracer.

Studies in NSCLC staging

Lee et al. and Heusch et al. compared PET/MRI to PET/CT for staging in 45 and 22 NSCLC patients, respectively. They found complete agreement in T stage (32 vs. 32 patients and 16 vs. 16 patients, respectively) and no statistically

significant difference (p=0.683 and p=0.48) in N stage (24 vs. 22 patients and 20 vs. 22 patients, respectively). Both studies used histopathology and follow-up as reference standard and lung protocols including T2w Half-Fourier Acquisition Single-shot Turbo Spin Echo (TSE) (HASTE) and Volume-interpolated breath-hold examination (VIBE) among others (Table 1). In the study by Lee et al., six patients had metastatic lesions in brain, bone, liver, and pleura of which PET/MRI missed one patient with pleural metastases, and PET/CT overlooked a brain metastasis in one and pleural metastases in two patients, but no statistically significant difference in accuracy of metastatic staging was detected (p=0.48) [14].

The performance of PET/MRI for staging compared to PET/CT in NSCLC patients was also investigated by Fraioli et al. and Schaarschmidt et al. using sequences such as T2w HASTE and diffusion-weighted imaging (DWI) (Table 1) in 50 and 77 patients, respectively. In the former study, the T stage was correctly identified in 37 patients (74%), N stage in 37 patients (74%), and M stage in 47 patients (94%). Metastatic lesions were identified on PET/MRI in ten patients out of which PET/MRI found one liver metastasis and two bone lesions not seen on PET/CT [15]. Schaarschmidt et al. mirrored the findings by Fraioli et al. in their retrospective study, reporting discrepant T stage in 14 patients (18%), N stage in 18 patients (23%) and M stage in 1 patient (1%). In a simulated interdisciplinary tumor board, the differences changed treatment recommendations in six patients (8%) [13].

Studies on detection of pulmonary lesions

In a retrospective study by Sawicki et al. comprising 121 oncologic patients, 241 lung lesions were found in 84 patients (13.1 ± 15.2, range 1-98 mm). The detection rates of MRI with the lung sequence T1w VIBE in deep inspiration breath hold (DIBH) compared to the CT component of PET/CT correlated with lesion size and were 43.1%, 45.9%, and 94.9% for lesions < 5 mm, <10 mm, and ≥10 mm, respectively [17].

Two prospective studies, comparing lesion detection by PET/MRI and PET/CT, yielded similar overall detection rates for all lung nodules of 70% and 68% including T1w VIBE images in 32 and 42 oncological patients, respectively [20,21]. In the study by Chandarana et al., the sensitivity was higher for FDG-avid nodules than non-FDG-avid nodules (95.6% (86/90) and 22.9% (11/48), respectively), and the sensitivity for nodules ≥ 5 mm higher than for nodules < 5 mm (88.6% (78/88) and 38% (19/50)) [21]. Rauscher et al. identified 47 lung lesions in 25 patients (10.0 ± 11.4 mm, range 2-60 mm). The detection rate of the 22 FDG-avid nodules did not differ between PET/MRI and PET/CT. They

also compared the detection rate of T1w Dixon sequence with the T1w VIBE sequence for MRI and found that VIBE increased detection rate of lesions < 10 mm compared to the Dixon sequence (15 vs. 9 of 33 lesions, p <0.0001) [20].

Two studies evaluated the outcome of lung nodules missed on PET/MRI but detected on PET/CT [18,19]. Sawicki et al. retrospectively included 51 oncologic patients, and out of 134 nodules found on PET/CT, PET/MRI using VIBE in free-breathing, missed 42 nodules in 30 patients (3.9 ±1.3 mm, range 2-7 mm) of which 9 nodules (21.4%) in 4 patients were rated malignant. As a result, one patient was upstaged from stage I to IV [18]. Raad et al. prospectively included 208 oncologic patients, 89 lung nodules (4 ± 1.9, range 2-10 mm) in 43 patients were detected only on the CT component of PET/CT and missed on PET/MRI (with the lung sequences T1w gradient-echo imaging with radial stack of stars trajectory (STAR), VIBE in free-breathing and T2w HASTE in breath-hold). Out of the 84 nodules with follow-up, only 3 nodules in 1 patient progressed (3%) and the remaining either subsided or remained stable suggesting benignity [19]. In both studies, all the overlooked nodules were non-FDG-avid.

Discussion

In this descriptive review, we found relatively few, and mostly heterogeneous, studies with outcomes addressing PET/MRI for diagnosing NSCLC and lung nodules. They showed that PET/MRI and PET/CT had similar diagnostic performance for T and N staging in NSCLC, whereas the data material on M stage was too small for meaningful analysis. The lung nodule detection rate of PET/MRI was comparable to that of PET/CT for FDG-avid nodules larger than 10 mm but the PET/MRI detection rate for non-FDG-avid nodules smaller than 5 mm was low in oncologic patients, but the clinical significance hereof is unknown.

Our literature search method was systematic, albeit without following all the rules of a systematic review. The key strength of the present review is that there are both clinician and physicist as senior authors, so that the clinical value is combined with technical assessment, a perspective, that to our knowledge, has not been addressed before.

Our findings are in line with findings in two recent studies. In a prospective study including 84 NSCLC patients, Kirchner et al. concluded that the differences in accuracy between PET/CT and PET/MRI in T and N staging were not statistically significant [22]. In a single center observational study from 2019, Martin et al. comprising 1003 examinations concluded comparable staging outcomes by PET/MRI compared to PET/CT [23]. In some of the studies included in this review, a few cases suggested that PET/MRI may be superior to PET/CT in the detection of metastases

in pleura and in the brain [14] as well as in the liver and bone [15]. This is also in line with results from a prospective single-center study of 330 examinations, where PET/MRI detected brain and liver metastases that were undetected on PET/CT [24]. Thus, the use of a hybrid PET/MRI in lung cancer patients might at times benefit the detection of distant metastases, because NSCLC metastases are mainly located in brain, liver and bone [6,7]. The included studies provided limited data on extra-thoracic metastatic disease and did, therefore, not allow for conclusions regarding the potential superiority of PET/MRI. However, in a recent systematic review, published after the end of our literature survey, comprising 19 studies and four meta-analysis with 22-250 patients, the authors concluded that, compared with CT and FDG-PET of both combined, MRI yielded at least similar or better results with regard to N staging of patients with NSCLC [25].

The included studies in this review were heterogenous and evaluated nodule size differently. This makes it inherently difficult to specify nodule sizes for which PET/MRI performs equivalent to PET/CT in terms of detection of pulmonary lesions. In two of the studies, PET/MRI performed nearly equivalently for lesions larger than 10 mm, but the studies grouped lesion size differently (<5mm, <10 mm and ≥10 mm vs smaller or larger than 10 mm) [17,20]. Chandarana et al. reported high sensitivity in the detection of lesions over 5 mm, with lesions grouped <5 mm, 5-9 mm and ≥10 mm. Sawicki et al. reported low detections rates for lesions smaller than 5 mm, but the detections rates of lesions measuring 5-10 mm is unknown, and a maximum of 10 lung lesions was identified for each patient. In the studies that investigated the outcome of overlooked nodules, the size of these nodules ranged from 2 mm up to 7 [18] and 10 mm [19]. Overall, reported detection rates with PET/MRI and PET/CT were nearly equivalent for pulmonary lesions larger than 10 mm, but compared to PET/CT, PET/MRI suffers from low sensitivity with regard to non-FDG-avid lesions smaller than 10 mm [17–21]. In the study by Sawicki et al., MRI without PET missed more than half of pulmonary lesions smaller than 10 mm [17], and similarly, it missed over 77 % of the non-FDG-avid nodules in the study by Chandarana et al. [21]. The same was applicable for the study by Rauscher et al. in which the reported detection rate for lung lesions <10 mm by PET/MRI was significantly lower for both Dixon and VIBE sequences than with PET/CT [20]. In both studies, the PET datasets for PET/MRI and PET/CT detected the same numbers of lung lesions, despite differences in technology and attenuation correction [20,21]. Hence, the detection rate of fused PET/MRI and PET/CT appears to be identical to that of its respective morphologic imaging components, suggesting that the detection rate of PET/MRI is increased by the PET component for small lesions. For PET/MRI to be a realistic alternative to PET/CT, MRI must perform acceptably well compared to CT, and future research should focus on faster and more sensitive MRI sequences to increase the detection rate of small non-FDG-avid lung nodules.

Despite discordance in NSCLC staging and lung nodules overlooked by PET/MRI but not PET/CT, patient management rarely changed. Regarding staging, clinical management would only have been altered in two patients (4%) [15] and six patients (8%) [13], respectively. However, very few of the included studies compared the changes in clinical management, and as the latter study only compared patient management based on differences between PET/MRI and PET/CT and not according to a standard reference, the question of which modality has the higher accuracy remains unanswered. Although, it is in line with the findings by Catalano et al., who compared the clinical impact of PET/MRI and PET/CT in a retrospective study including 134 oncologic patients [26]. They reported that in two (1.5%) of 134 patients, PET/CT affected management, as it revealed lung nodules smaller than 6 mm in diameter overlooked by PET/MRI.

The vast majority of nodules were found to be benign in both studies elucidating the outcome of lung nodules overlooked by PET/MRI [18,19]. Prior studies have also shown that in patients with a known primary malignancy, small nodules measuring less than 1 cm may not represent metastases [27]. However, despite their lack of identifiable FDG uptake and their small size, the possibility of these small nodules being metastases could not be excluded with certainty. Clinical impact is controversial concerning small overlooked nodules and varies depending on the clinical scenario and, thus, presents a diagnostic dilemma. We suggest that the clinical importance of small non-FDG-avid nodules that are missed on PET/MRI should be a focus of future investigations.

Several limitations apply to the papers included in this review. The studies by Sawicki et al. had an overlap of the patient population, and an upper limit on identified lung nodules (10) for each patient, and therefor did not evaluate the smallest nodules [17,18]. Some studies used follow-up imaging for evaluation of tumor or nodule malignancy. These studies often had different follow-up intervals, some not more than a couple of months that do not consider slow growing lesions and, hence, may result in false negative readings. Another limitation was the varying use of contrast-enhanced and low-dose protocols with both PET/CT and PET/MRI. The studies by Lee et al. and Fraioli et al. uses AC-CT as reference standard, and both studies by Sawicki et al. only uses diagnostic quality CT in some of the patients, which might favor PET/MRI performance. Equally important was the use of a fixed attenuation value assigned to each class after segmentation, something that differs between vendors and, thus, contributes to the total error by not reflecting the intra-patient variability in the PET/MRI setting [28]. When considering also MRI issues such as low proton density and rapid decay of transversal magnetization causing tradeoffs between spatial resolution, image quality

and signal to noise ratio in the lungs, it appears that multiple factors contribute to the inferiority PET/MRI compared to PET/CT with regard to lung lesion detectability and lung cancer staging.

Typically, to visualize lung nodules with PET/MRI a 3D fast spoiled gradient echo type sequence is conventionally used which enables the option of breath-hold imaging. The VIBE sequence, being an example of the former, have in earlier multiple studies demonstrated the highest sensitivity in MRI lung evaluation and lesion detection [11,29]. Rauscher et al. showed that the detection rate of lung lesions can be improved by adding a diagnostic contrast-enhanced VIBE sequence to the PET/MRI protocol compared to a PET attenuation-dedicated Dixon sequence [20]. Almost all the studies used the VIBE sequence, either in breath hold or with free breathing. However, breath hold in deep inspiration as used in many studies may cause misalignment with PET images, which typically are acquired in free breathing. The detection rate of MRI for lung lesions could possibly be improved by multisequence protocols or by respiratory gating the PET data, but this is more time consuming [30–32].

Many of the studies used different slice thicknesses, often with thinner slices on PET/CT than PET/MRI to increase time resolution and signal intensity. This was reflected in the two studies from Sawicki et al. in which CT was acquired with 1 mm and MRI with 3 mm slice thickness, which again may have contributed to the inferior detection rate of small lung lesions with PET/MRI. It requires ultra-fast sequences to get enough signal for thin slices on MRI that are as good as with CT; otherwise, the signal is too small and the movements too large.

Generally, for lung nodules and masses by MRI, a 3D gradient echo T1-weighted volume interpolated sequence performed in breath-hold is the most used MRI sequence. The studies by Raad et al. and Chandarana et al. extended this and used a radial sampling giving a higher degree of motion compensation possibilities, resulting in a higher signal-to-noise ratio (SNR) relevant for the detection of lung nodules [19,21]. A radial k-space acquisition can produce significantly improved images due to the fast nature of the k-space acquisition, especially in patients with poor breath-hold capabilities. Parallel imaging, a means of faster MRI acquisitions, was used in several of the studies in a GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) approach [13,14,16,17,19,20]. An example of an acquisition scheme allowing even higher acceleration factors than GRAPPA, i.e. faster scans, is The Controlled Aliasing In Parallel Imaging Results In Higher Acceleration (CAIPIRINHA) which can be used to reduce breath-hold times or improve the SNR in the final images and will maybe be relevant for lung imaging [33].

To improve lung MRI imaging even further, sequence development has introduced ultra-short echo-time (UTE) and zero echo-time (ZTE). Both sequences acquire data with very low echo times which is relevant in lung tissue imaging which have very short T2/T2* . UTE realizes a few microseconds echo time by gradient ramping after a non-selective radio frequency (RF) pulse. ZTE takes the concept even further by turning on the gradient before the RF pulse, corresponding to zero echo time. Both sequences will produce images largely proton-density weighted and can be obtained on the same time scale as e.g. a 3D VIBE. Ohno et al. found that there was no significant sensitivity difference in nodule detection between methods (standard-dose CT vs. reduced-dose CT, vs. MRI with UTE), not even in the smallest nodules reported (4-6 mm) [34]. Results by Cha et al. mirrored these findings in that all nodules ≥ 5 mm in diameter were identified on spiral 3D UTE (100%), but the detection rate was inferior for nodules <5 mm (76.7 %) compared to the reference standard (thin-section chest CT) [35]. Consistent with these findings, a third study described that the UTE sequence in free breathing on PET/MRI enabled detection of all FDG-avid nodules on PET/CT. The sequence also had a high detection rate for non-FDG-avid pulmonary nodules of at least 4 mm in diameter (79%), but that the detection of pulmonary nodules smaller than 4 mm in diameter remained limited [36]. Bae et al. compared UTE with ZTE in lungs of 20 patients and found that the diagnostic accuracy for sub-centimeter nodules was significantly higher for ZTE, indicating that ZTE can provide high-resolution pulmonary structural information offering an improvement in both diagnostic accuracy and image quality [37]. Together, these recent studies indicate, that the sequences ZTE and UTE may be the way to go for visualizing small lung lesions, preferably in free breathing. An increased number of clinical studies applying these sequences for image improvement will likely make them more clinically useful in the near future.

Conclusion

The included studies were heterogeneous in study design, reference standard, and CT and MRI protocols and included small patient populations resulting in low statistical power. The compiled results should therefore be considered as preliminary requiring further validation. However, PET/MRI appears to be a robust technique that is comparable to PET/CT for T- and N staging in NSCLC. Data were too few to allow for conclusions on M-staging. The detection rate of lung nodules with PET/MRI remains inferior to that of PET/CT depending mainly on nodule size. This makes small lung nodules the only real persistent limitation of PET/MRI when it comes to whole body staging. Issues like consistency, FDG-uptake, sequence use, and breath holding conditions may contribute to higher detection rates with

PET/CT of non-FDG-avid small lung nodules (< 5 mm), while similar sensitivity was reported with regard to FDG-avid nodules and nodules over 10 mm. The lower diagnostic performance of the MRI component of PET/MRI seems to be outmatched by the CT component of PET/CT, suggesting a chest CT might still be considered in those patients undergoing whole body PET/MRI. At present, the disadvantages of PET/MRI are not outweighed by its advantages to a degree that this modality can contend for precedence with PET/CT when it comes to imaging of lung lesions. Future research will demonstrate if faster and more sensitive MRI sequences and other improvements can remedy some of these differences and justify a greater use of PET/MRI for the detection of lung lesions.

Acknowledgements

Research librarian L. Østengaard, PhD, University Library of Southern Denmark and Head of Department, and Associate Professor J.S. Madsen, Biochemistry and Immunology, Institute of Regional Health Research, University of Southern Denmark are acknowledged for help with the literature search.

Compliance with ethical standards

Conflict of Interest: All Authors declare no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Table 1. PET/MRI in non-small cell lung cancer: Study design and outcome

Publication	Patients (n) and study design	Clinical area of application and comparison modality	PET/MRI pulmonary protocol	Reference standard	Findings
Schaarschmidt 2017 [13]	77 Retrospective	If differences in thoracic staging PET/MRI and PET/CT led to different therapeutic decisions	T2w propeller and DWI in free breathing, T2w TrueFISP, T2w HASTE and T1w Fast Low Angle Shot (FLASH) all in DIBH	None	Discrepant TN staging in 27 patients (35%) which changed treatment recommendations in 6 patients (8%)
Lee 2016 [14]	45 Prospective	TNM staging compared to PET/CT	T1w TSE, T2w HASTE with SPAIR, VIBE	Histopathology or follow-up imaging	No difference in preoperative TN staging (T stage 32 vs. 32 patients, N stage 24 vs. 22 patients) or accuracy of M staging (6 patients)
Fraioli 2015 [15]	50 Prospective	TNM staging and resectability compared to PET/CT	T2w HASTE, axial DWI, T1w VIBE with fat suppression	Histopathology, PET/CT, or follow-up	TNM staging in agreement with PET/CT in 26 patients. Specificity 92.3% and sensitivity 97.3% of PET/MRI for resectability
Heusch 2014 [16]	22 Prospective	TN staging compared to PET/CT	T2w TrueFISP, T2w propeller TSE in breath-hold, HASTE, VIBE	Histopathology	No difference in T or N stage

DWI: Diffusion-weighted imaging, TrueFISP: Steady state-free precession, HASTE: Half fourier acquisition angle-shot turbo spin-echo sequence, FLASH: Fast low angle shot, DIBH: Deep inspiration breath hold, SPAIR: Spectral attenuated inversion, VIBE: Volume-interpolated breath-hold examination, TSE: Turbo spin-echo

Table 2. PET/MRI in evaluation of pulmonary nodules: Study design and outcome

Publication	Patients (n) and study design	Clinical area of application and comparison modality	PET/MRI pulmonary protocol	Reference standard	Findings
Sawicki 2016 [17]	121 Retrospective	Lung lesion detection; comparison of MRI component of PET/MRI to PET component of PET/MRI and PET/CT	T1w VIBE in DIBH	CT component of PET/CT	No difference in detection rate of FDG-avid lesions. Detection rate of MRI for lesions < 5 mm, <10 mm, and ≥ 10 mm were 43.1%, 45.9%, and 94.9%, respectively (241 lesions in 84 patients)
Sawicki 2016 [18]	51 Retrospective	Outcome of small nodules detected on PET/CT but overlooked on PET/MRI	T1w VIBE in breath hold	CT or PET/CT follow-up	42 lung nodules (3.9 ± 1.3 mm (SD), range 2-7 mm) in 30 patients were missed by PET/MR
Raad 2016 [19]	208 Prospective	Outcome of small nodules detected on PET/CT but overlooked on PET/MRI	T1w STAR-VIBE in free breathing, T2w HASTE in breath hold.	CT or PET/CT follow-up	89 non-FDG-avid nodules in 34 pts were detected only on the CT component of PET/CT but were missed on PET/MRI.
Rauscher 2014 [20]	40 Prospective	Lung nodule detection compared with PET/CT	Dixon and fat suppressed VIBE in breath hold (end- expiratory and deep inspiration)	CT in deep inspiration	Detection rate for FDG-avid nodules (n =22) did not differ between PET/MRI and PET/CT. VIBE sequence increased detection rate of lesions < 10 mm compared to Dixon sequence on MRI
Chandarana 2013 [21]	32 Prospective	Sensitivity of PET/MRI lung nodule detection	Radial T1w VIBE in free breathing and DWI.	PET/CT	Sensitivity of PET/MRI was 70.3% for all nodules, 95.6% for FDG-avid nodules, 88.6% for nodules ≥ 5 mm, 38% for nodules < 5 mm, and 22.9% for non-FDG-avid nodules (19 pts)

VIBE: Volume-interpolated breath-hold examination, DIBH: Deep inspiration breath hold, STAR: Radial stack-of-stars, HASTE: Half Fourier acquisition single-shot turbo spin-echo sequence, DWI: Diffusion-weighted imaging

References

1. F. Bray, Jacques Ferlay, Isabelle Soerjomataram, Siegel; RL, Torre; LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2018; doi: 10.3322/caac.21492.

2. Gavra M, Syed R, Fraioli F, Afaq A, Bomanji J. PET/MRI in the upper abdomen. Semin. Nucl. Med. 2015. doi: 10.1053/j.semnuclmed.2015.03.00

3. Catalano OA, Coutinho AM, Sahani D V., Vangel MG, Gee MS, Hahn PF, et al. Colorectal cancer staging: comparison of whole-body PET/CT and PET/MR. Abdom Radiol. 2017; doi: 10.1053/j.semnuclmed.2015.03.002

4. Lee DH, Lee JM. Whole-body PET/MRI for colorectal cancer staging: Is it the way forward? J. Magn. Reson. Imaging. 2017. doi: 10.1002/jmri.25337

5. Barbosa F de G, Queiroz MA, Nunes RF, Marin JFG, Buchpiguel CA, Cerri GG. Clinical perspectives of PSMA PET/MRI for prostate cancer. Clinics. 2018. doi: 10.6061/clinics/2018/e586s

6. Milovanovic IS, Stjepanovic M, Mitrovic D. Distribution patterns of the metastases of the lung carcinoma in relation to histological type of the primary tumor: An autopsy study. Ann Thorac Med. 2017; doi: 10.4103/atm.ATM_276_16.

7. Popper HH. Progression and metastasis of lung cancer. Cancer Metastasis Rev. 2016; doi: 10.1007/s10555-016-96180.

8. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: A meta-analysis. J. Am. Med. Assoc. 2001. doi: 10.1001/jama.285.7.914

9. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. Lung Cancer. 2004; doi: 10.1016/j.lungcan.2004.01.009

10. Wild JM, Marshall H, Bock M, Schad LR, Jakob PM, Puderbach M, et al. MRI of the lung (1/3): Methods. Insights Imaging. 2012; doi: 10.1007/s13244-012-0176-x.

11. Biederer J, Beer M, Hirsch W, Wild J, Fabel M, Puderbach M, et al. MRI of the lung (2/3). Why... when ... how? Insights Imaging. 2012; doi: 10.1007/s13244-011-0146-8

12. Morsing A, Hildebrandt MG, Vilstrup MH, Wallenius SE, Gerke O, Petersen H, et al. Hybrid PET/MRI in major cancers: a scoping review. Eur. J. Nucl. Med. Mol. Imaging. Springer Berlin Heidelberg; 2019. p. 2138–51. doi: 10.1007/s00259-019-04402-8

13. Schaarschmidt BM, Grueneisen J, Metzenmacher M, Gomez B, Gauler T, Roesel C, et al. Thoracic staging with18F-FDG PET/MR in non-small cell lung cancer – does it change therapeutic decisions in comparison to18F-FDG PET/CT? Eur Radiol. 2017; doi: 10.1007/s00330-016-4397-0.

14. Lee SM, Goo JM, Park CM, Yoon SH, Paeng JC, Cheon GJ, et al. Preoperative staging of non-small cell lung cancer: prospective comparison of PET/MR and PET/CT. Eur Radiol. 2016; doi: 10.1007/s00330-016-4255-0

15. Fraioli F, Screaton NJ, Janes SM, Win T, Menezes L, Kayani I, et al. Non-small-cell lung cancer resectability: diagnostic value of PET/MR. Eur J Nucl Med Mol Imaging. 2015; doi: 10.1007/s00259-014-2873-9

16. Heusch P, Buchbender C, Kohler J, Nensa F, Gauler T, Gomez B, et al. Thoracic Staging in Lung Cancer: Prospective Comparison of 18F-FDG PET/MR Imaging and 18F-FDG PET/CT. J Nucl Med. 2014; doi: 10.2967/jnumed.113.129825.

17. Sawicki LM, Grueneisen J, Buchbender C, Schaarschmidt BM, Gomez B, Ruhlmann V, et al. Comparative Performance of 18F-FDG PET/MRI and 18F-FDG PET/CT in Detection and Characterization of Pulmonary Lesions in 121 Oncologic Patients. J Nucl Med. 2016; doi: 10.2967/jnumed.115.167486.

18. Sawicki LM, Grueneisen J, Buchbender C, Schaarschmidt BM, Gomez B, Ruhlmann V, et al. Evaluation of the Outcome of Lung Nodules Missed on 18F-FDG PET/MRI Compared with 18F-FDG PET/CT in Patients with Known Malignancies. J Nucl Med. 2016; doi: 10.2967/jnumed.115.162966

19. Raad RA, Friedman KP, Heacock L, Ponzo F, Melsaether A, Chandarana H. Outcome of small lung nodules missed on hybrid PET/MRI in patients with primary malignancy. J Magn Reson Imaging. 2016; doi: 10.1002/jmri.25005.

20. Rauscher I, Eiber M, Furst S, Souvatzoglou M, Nekolla SG, Ziegler SI, et al. PET/MR Imaging in the Detection and Characterization of Pulmonary Lesions: Technical and Diagnostic Evaluation in Comparison to PET/CT. J Nucl Med. 2014; doi: 10.2967/jnumed.113.129247.

21. Chandarana H, Heacock L, Rakheja R, DeMello LR, Bonavita J, Block TK, et al. Pulmonary Nodules in Patients with Primary Malignancy: Comparison of Hybrid PET/MR and PET/CT Imaging. Radiology. 2013; doi: 10.1148/radiol.13130620.

22. Kirchner J, Sawicki LM, Nensa F, Schaarschmidt BM, Reis H, Ingenwerth M, et al. Prospective comparison of 18F-FDG PET/MRI and 18F-FDG PET/CT for thoracic staging of non-small cell lung cancer. Eur J Nucl Med Mol Imaging. 2019; doi: 10.1007/s00259-018-4109-x.

23. Martin O, Schaarschmidt BM, Kirchner J, Suntharalingam S, Grueneisen J, Demircioglu A, et al. PET/MRI versus PET/CT in whole-body staging: results from a unicenter observational study in 1003 subsequent examinations. J Nucl Med. 2019; doi: 10.2967/jnumed.119.233940.

24. Mayerhoefer ME, Prosch H, Beer L, Tamandl D, Beyer T, Hoeller C, et al. PET/MRI versus PET/CT in oncology: a prospective single-center study of 330 examinations focusing on implications for patient management and cost considerations. Eur J Nucl Med Mol Imaging. European Journal of Nuclear Medicine and Molecular Imaging; 2020;47:51–60. doi: 10.1007/s00259-019-04452-y.

25. Brea TP, Raviña AR, Villamor JMC, Gómez AG, de Alegría AM, Valdèc)s L. Use of Magnetic Resonance Imaging for N-Staging in Patients with Non-Small Cell Lung Cancer. A Systematic Review. Arch Bronconeumol (English Ed. 2019;55:9–16. doi: 10.1016/j.arbr.2018.03.013.

26. Catalano OA, Rosen BR, Sahani D V, Hahn PF, Guimaraes AR, Vangel MG, et al. Clinical Impact of PET / MR Imaging in Patients with Cancer Initial Experience in 134 Patients. Radiology. 2013;269:857–69. 10.1148/radiol.13131306/-/DC1

27. Benjamin MS, Drucker EA, McLoud TC, Shepard JO. Small pulmonary nodules: Detection at chest CT and outcome. Radiology. 2003; doi: 10.1148/radiol.2262010556

28. Delso G, Voert E Ter, Barbosa FDG, Veit-Haibach P. Pitfalls and Limitations in Simultaneous PET/MRI. Semin. Nucl. Med. 2015. doi: 10.1053/j.semnuclmed.2015.04.002.

29. Biederer J, Hintze C, Fabel M. MRI of pulmonary nodules: Technique and diagnostic value. Cancer Imaging. 2008. doi: 10.1102/1470-7330.2008.0018.

30. Heye T, Ley S, Heussel CP, Dienemann H, Kauczor HU, Hosch W, et al. Detection and size of pulmonary lesions: How accurate is MRI? A prospective comparison of CT and MRI. Acta radiol. 2012; doi: 10.1258/ar.2011.110445.

31. Boada FE, Koesters T, Block KT, Chandarana H. Improved Detection of Small Pulmonary Nodules Through Simultaneous MR/PET Imaging. Magn. Reson. Imaging Clin. N. Am. 2017. doi: 10.1016/j.mric.2016.12.009.

32. Schleyer PJ, O'Doherty MJ, Barrington SF, Marsden PK. Retrospective data-driven respiratory gating for PET/CT. Phys Med Biol. 2009; doi: 10.1088/0031-9155/54/7/005.

33. Dewes P, Frellesen C, Al-Butmeh F, Albrecht MH, Scholtz JE, Metzger SC, et al. Comparative evaluation of non-contrast CAIPIRINHA-VIBE 3T-MRI and multidetector CT for detection of pulmonary nodules: In vivo evaluation of diagnostic accuracy and image quality. Eur J Radiol. Elsevier Ireland Ltd; 2016;85:193–8. doi: 10.1016/j.ejrad.2015.11.020.

34. Ohno Y, Koyama H, Yoshikawa T, Kishida Y, Seki S, Takenaka D, et al. Standard-, Reduced-, and No-Dose Thin-

Section Radiologic Examinations: Comparison of Capability for Nodule Detection and Nodule Type Assessment in Patients Suspected of Having Pulmonary Nodules. Radiology. 2017; doi: 10.1148/radiol.2017161037.

35. Cha MJ, Park HJ, Paek MY, Stemmer A, Lee ES, Park S Bin, et al. Free-breathing ultrashort echo time lung magnetic resonance imaging using stack-of-spirals acquisition: A feasibility study in oncology patients. Magn Reson Imaging. 2018; doi: 10.1016/j.mri.2018.05.002

36. Burris NS, Johnson KM, Larson PEZ, Hope MD, Nagle SK, Behr SC, et al. Detection of Small Pulmonary Nodules with Ultrashort Echo Time Sequences in Oncology Patients by Using a PET/MR System. Radiology. 2016; doi: 10.1148/radiol.2015150489.

37. Bae K, Jeon KN, Hwang MJ, Lee JS, Ha JY, Ryu KH, et al. Comparison of lung imaging using three-dimensional ultrashort echo time and zero echo time sequences: preliminary study. Eur Radiol. European Radiology; 2019;29:2253–62. doi: 10.1007/s00330-018-5889-x.

Reviewer #1: Dear Authors

Thanks for having improved the quality of the manuscript and having worked on the points we raised.

I would just suggest you to further highlight that missing small lung nodules is the only real persistent limitation of PET/MR versus PET/CT when it gets to whole body staging and that this might translate in clinical management changes.

We thank the reviewer for this suggestion and have added a sentence in the conclusion (page 10, line 54-56) mentioning this.

The study by Chandarna used AC-CT images in all cases, the one by Sawicki used AC-CT images in 33 pts and diagnostic quality CT only in 28 patients; therefore, although important, they might favor PET/MR performance also in assessing potential evolution of missed nodules. In several Institutions AC-CT is not considered adequate for lung interpretation.

After addressing this limitation, we have written a few examples of studies where the use of AC-CT might have affected the results (page 8, line 45-49).

As in the reference PMID: 24009348 (that for unclear reasons the authors decided not to cite) those authors used full dose diagnostic quality CT for assessing the lung and they found "Findings affecting clinical management were noted for PET/CT studies but not for PET/MR studies in two (1.5%) of 134" and were exactly missed lung nodules at PET/MR. This is important since a chest CT might still be considered in those undergoing whole body PET/MR.

The study has now been included in the manuscript (page 8, lines 11-17), and in the conclusion we have added the sentence "*suggesting a chest CT might still be considered in those patients undergoing whole body PET/MRI.*" (page 11, lines 5-7)