TITLE:

DIAGNOSTIC ACCURACY OF FEC-PET/CT, FDG-PET/CT AND DIFFUSION-WEIGHTED MRI IN DETECTION OF NODAL METASTASES IN SURGICALLY TREATED ENDOMETRIAL AND CERVICAL CARCINOMA

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Authors:
Andrea G Rockall [1,2*], Tara D Barwick[1,2*], William Wilson[3], Naveena Singh[4], Nishat Bharwani[1,2], Aslam Sohaib[5], Marielle Nobbenhuis[6], Victoria Warbey[7], Marc Miquel[8,9], Dow-Mu Koh[5], Katja N De Paepe[5], Pierre Martin-Hirsch[10], Sadaf Ghaem-Maghami[1,11], Christina Fotopoulou[1,11], Helen Stringfellow[10], Sudha Sundar[12], Ranjit Manchanda[13,14, 15], Anju Sahdev[16], Allan Hackshaw[3], Gary J Cook[17] and the MAPPING Study Group‡

1. Dept of Surgery and Cancer, Imperial College London
2. Department of Radiology, Imperial College Healthcare NHS Trust, London
3. Cancer Research UK & UCL Cancer Trials Centre, University College London
4. Dept of Pathology, Barts Health NHS Trust
5. Dept of Radiology, Royal Marsden Hospital NHS Foundation Trust, London
6. Dept of Gynaeoncology, Royal Marsden Hospital NHS Foundation Trust, London
7. Dept of Radiology, Guys and St Thomas' NHS Trust, London, UK
8. Clinical Physics, Barts Health NHS Trust, London
9. William Harvey Research Institute, Digital Envoronment Research Institute, Queen Mary University of London
10. Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK
11. Dept of Gynaeoncology, Imperial College Healthcare NHS Trust
12. Pan Birmingham Gynaecological Cancer Centre, City Hospital and Insitute of Cancer and Genomic Sciences, University of Birmingham
13. Wolfson Institute of Preventive Medicine QMUL, Old Anatomy Building, Charterhouse Square, London EC1M 6BQ
14. Department of Gynaecological Oncology, Barts Health NHS Trust, London, UK
15. Department of Health Services Research, London School of Hygiene & Tropical Medicine, London, UK
16. Dept of Radiology, St Bartholomews Hospital, Barts Health NHS Trust, London, EC1A 7BE, UK
17. Cancer Imaging Dept, School of Biomedical Engineering and Imaging Sciences, King's College London

*Equal contribution

‡MAPPING study group authors
Victoria Stewart
Alan Farthing
Maria Kyrgiou
Joseph Yazbek
Roberto Dina
Thomas Ind
Desmond Barton
John Butler
Ayoma Attygalle
Steve Hazell
Alexandra Taylor

Susan Lalondrelle
Imene Zerizer
Diana Rosof-Williams
Mike Dobson
Jonathan Hill
Elly Brockbank
Alexandra Lawrence
Arjun Jeyarajah
David Oram
Raji Ganesan
Peter Guest
Mark Davies
Laura Vosper
Carike Coetzee

Running Title:
Imaging in nodal staging in cervix and endometrial cancer

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Corresponding author:
Professor Andrea Rockall
Imperial College London
Division of Surgery and Cancer,
ICTEM Building, Hammersmith Campus
Du Cane Rd,
London W12 0NS, UK
a.rockall@imperial.ac.uk

Statement of conflict of interest

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Translational Relevance

Nodal status is a highly important prognostic factor in endometrial and cervical cancers and has a significant impact on patient risk stratification and management.

This is the first multicentre prospective study to directly compare the diagnostic performance of FEC-PET/CT, FDG-PET/CT and DW-MRI for the detection of nodal involvement in surgically staged endometrial and cervical cancers, with a strict histological reference standard.

No technique had sufficient sensitivity to obviate the need for surgical nodal staging in radiologically node negative patients, in cases where nodal staging is considered appropriate. However, the low false positive rate may contribute to patient risk stratification in cases with difficult surgical decision making, for arbitration in borderline surgical cases: In cervical cancer, a FDG-positive case could support a decision to redirect patients from radical surgery to chemo-radiotherapy options. In endometrial cancer, a FDG-positive case could allow planning of a more tailored therapeutic approach. By identifying the site and extent of avid nodes, a targeted surgical dissection of the area of interest could be planned avoiding morbidity from unnecessary radicality. Moreover, a preoperative discussion with the patient about her systemic and radiotherapeutic options and how those would complement any surgical approach, would be facilitated.

Abstract

Purpose:

Pre-operative nodal staging is important for planning treatment in cervical cancer (CC) and endometrial cancer (EC) but remains challenging. We compare nodal staging accuracy of ^{18}F-ethyl-choline-(FEC)-PET/CT, ^{18}F-Fluoro-deoxy-glucose-(FDG)-PET/CT and diffusion-weighted-MRI (DW-MRI) with conventional morphological MRI.

Experimetal Design:

A prospective, multicentre observational study of diagnostic accuracy for nodal metastases was undertaken in 5 gyne-oncology centres. FEC-PET/CT, FDG-PET/CT and DW-MRI were compared to nodal size and morphology on MRI. Reference standard was strictly correlated nodal histology. Eligibility included operable CC stage=>1B1 or EC (grade 3 any stage with myometrial invasion or grade 1-2 stage=>II).

Results:

Among 162 consenting participants, 136 underwent study DW-MRI and FDG-PET/CT, and 60 underwent FEC-PET/CT. 267 nodal regions in 118 women were strictly correlated at histology (nodal positivity rate 25%). Sensitivity per-patient (n=118) for nodal size, morphology, DW-MRI, FDG- and FEC-PET/CT were 40%*, 53%, 53%, 63%* and 67% for all cases (*p=0.016); 10%, 10%, 20%, 30% and 25% in CC (n=40); 65%, 75%, 70%, 80% and 88% in EC (n=78). FDG-PET/CT outperformed nodal size (p=0.006) and size ratio (p=0.04) for per-region sensitivity. False positive rates were all <10%.

Conclusions:

All imaging techniques had low sensitivity for detection of nodal metastases and cannot replace surgical nodal staging. The performance of FEC-PET/CT was not statistically different to other techniques that are more widely available. FDG-PET/CT had higher sensitivity than size in detecting nodal metastases. False positive rates were low across all methods. The low false positive rate demonstrated by FDG-PET/CT may be helpful in arbitration of challenging surgical planning decisions.

INTRODUCTION

In patients with endometrial or cervical cancer, nodal metastatic disease adversely affects prognosis (1, 2). In cervical cancer, the 5-year relative survival rates for patients with disease localised to the cervix is 92% compared to 56% for those with positive pelvic lymph nodes (LN) (3). In endometrial cancer, the 5-year disease-free survival is 90% in patients without LN metastasis, but 60-70% in those with pelvic LN metastasis and 30-40% in those with para-aortic LN metastasis (1). Accurate LN staging is required for prognostic stratification and treatment planning, as well as tailoring the surgical approach and delineating the extent of radiotherapy in both cervical and endometrial cancer. Knowledge of LN status is of paramount importance to stratify patients to radical hysterectomy versus primary chemoradiotherapy, particularly in cervical cancer.

In endometrial cancer, most patients will undergo at least a hysterectomy and bilateral salpingo-oopherectomy as primary treatment. The International Federation of Gynecology and Obstetrics (FIGO) include the LN status in the tumor staging of the patients, and so national and international guidelines recommend surgical LN staging in high risk subtypes (4, 5). However, there has not been any prospective evidence so far to demonstrate therapeutic value of systematic lymphadenectomy (LND) in endometrial cancer (6-9). Even though sentinel LN techniques are now gradually replacing systematic LND in multiple guidelines (10-12), its implementation is not yet homogenous around the world due to infrastructural, financial and governance challenges. For that reason many patients still undergo LND with all the associated sequelae such as lymphocyst formation, lymphorrhea and lymphedema in addition to higher surgical morbidity. The accurate and reliable preoperative identification of LN positive patients therefore still represents an unmet need in order to adequately tailor therapeutic management.

In cervical cancer, radical hysterectomy is not recommended in LN positive patients, and so the accurate preoperative identification of even microscopically involved LN would spare those patients unnecessary surgical morbidity and direct them to chemoradiotherapy with exact tailoring of the extended field.

Although the pre-operative detection of nodal metastases would be practice-changing, conventional imaging techniques, including CT and MRI, that rely on LN size criteria and morphology (shape, contour, signal intensity) are largely unreliable (10). Few prospective multicentre trials with a histological reference standard to guide management exist (11).

Several functional imaging techniques have been evaluated in an attempt to improve pre-operative nodal staging. DW-MRI, which assesses tissue diffusion properties and cellularity, is now widely established for routine use in pelvic MRI in cervical and endometrial cancer staging although published results of DW-MRI in nodal diagnosis are variable (13).

FDG-PET/CT is established in staging locally advanced cervical cancer and incorporated into guidelines due to its diagnostic superiority (12, 14). The role of FDG-PET/CT in endometrial cancer has not been clearly established with a lack of evidence to date (15). In general, FDG-PET/CT has high specificity for nodal involvement in advanced cervical and endometrial cancer but low to moderate sensitivity remains problematic, particularly in early stage disease (15-17).

Choline-PET imaging is a surrogate marker of accelerated cell membrane metabolism in cancer and has an established role in imaging of prostate cancer, including nodal assessment for high risk staging (18). In cell line studies of endometrial cancer, the expression and activity of choline

kinase alpha is increased with a several-fold increase in the uptake of ^{3}H choline in endometrial cancer cells compared to normal endometrial stromal cells (19). Early pilot studies of ^{11}C choline in gynecological cancer show promise (20, 21), however ^{18}F-labelled fluoro-methyl and fluoro-ethyl choline have a longer radioactive half-life (110 minutes) and are therefore more practical to use. The use of Fluoro-ethyl-choline (FEC)-PET/CT in detecting nodal metastases in endometrial and cervical cancer has not been previously explored.

Our hypothesis was that any of DW-MRI, FEC-PET/CT or FDG-PET/CT could preoperatively identify LN metastases, with sufficiently high accuracy, in order to replace the need for surgical LN staging but also identify those patients who should not undergo surgery, in eligible patients with seemingly operable cervical and high risk endometrial cancer.

Materials and Methods

Study Design and participants

MAPPING is a multicentre, prospective observational study evaluating the diagnostic accuracy for detecting nodal metastases using different imaging methods. Ethics approval, ARSAC licence and MHRA approvals were obtained (Research Ethics Committee reference number 11/LO/1465). The study was sponsored by Barts Health NHS Trust. The Centre for Experimental Cancer Medicine (CECM), Barts Cancer Institute, Queen Mary University of London had overall responsibility for trial management. All participants gave written informed consent.

Eligible patients were aged ≥18 years, with newly diagnosed histologically confirmed cervical or endometrial cancer and were eligible and fit for surgical lymphadenectomy, as per the decision of a multidisciplinary tumour board and assessment by a specialist surgical and anaesthetic team. Pre-treatment FIGO stage (2009) was established on the basis of clinical examination and standard of care imaging (CT and MRI). Patients with cervical cancer were eligible if the pre-treatment FIGO stage was considered stage IB and local disease appeared operable. Patients with endometrial cancer were eligible if high risk features for LN metastases, i.e. histological grade was high-grade (including grade 3 endometrioid adenocarcinoma, serous, clear cell or carcinosarcoma) with myometrial invasion on MRI, or MRI-based FIGO stage II or above. Patients were ineligible if unable to provide written informed consent, were pregnant or had contra-indications to MRI or PET/CT (Table S1).

Procedures

All imaging tests were performed before surgery and within the national standard time frame of pre-operative care. Standard of care MRI scan was performed first, and as per local practice. FDG- and FEC-PET/CT scans had to be performed on separate days, and the DW-MRI scan could be performed alongside either of these, and at the same time as the conventional MRI (Fig S1).

MRI

Standard of care MRI scan for staging was performed as per local protocol. The MRI field of view included the pelvis and para-aortic regions up to the level of the left renal vein. For nodal evaluation, readers had a minimal dataset that included axial T1, axial T2 and study-specific axial DW-MRI (b values 0, 300, 600, 900 and 1200) with associated calculated ADC maps, following optimization with ice-water phatom (Table S2). The details of standard of

care MRI and DW-MRI are provided in Table S2A-C.

FDG-PET/CT and FEC-PET/CT

FDG- and FEC-PET/CT scans were performed using a standard protocol (Table S2D) based on UK NCRI PET Research Network guidance. Each centre had been accredited by the NCRI PET Research Network for multicentre trials. All scans were acquired from base of skull to upper thighs as 3D acquisitions with TOF if available. Low dose CT acquisitions were made for attenuation correction and image fusion. FDG-PET/CT scans were acquired at a median of 60 mins post injection (range 57-80) and FEC-PET/CT scans at a median 60 mins (range 55-74) and the two scans were acquired on different days.

Participants fasted for =>4 hours prior to FDG injection (median 370 MBq, range 217-436 MBq) and scanning only performed if blood glucose was <10 mmol/L. Fasting was not required prior to FEC injection (median 293 MBq, range 209-369 MBq). Patients were asked to void their bladder before both scans. Both tracers were classified as investigational medical products. Patients were contacted 24 hours following scans to record any adverse events.

Reader evaluations

All imaging scans were read by one local and two central radiologists. The central reviews were co-ordinated through the UK NCRI PET core lab (PET) and the trials unit (MRI), and discordant reviews were resolved by consensus. All radiologists were accredited core members of the gyne-oncology multi-disciplinary team and/or PET/CT experts. All readers were aware of the clinical diagnosis (endometrial or cervical cancer) but when assessing each scan they were blinded to all other imaging scans, surgical findings and final histology. The local radiological assessment was used for the main analyses to be consistent with patient management and treatment being guided by the local MRI evaluation.

Evaluation of nodes using the standard MRI, DW-MRI and PET scans was based on a 6-point confidence score: 1: definitely benign, 2: probably benign, 3: low confidence benign, 4: low confidence malignant, 5: probably malignant, 6: definitely malignant. A score of 5 or 6 was classified as test-positive.

Conventional MRI nodal diagnosis based on MRI size and morphology

The anatomical location of nodes that were $\geq$5mm and their short and long axis diameter were recorded. If there were multiple nodes in one anatomical region, the largest or most suspicious node was used for the nodal descriptors (fatty hilum, homogeneous appearance, necrosis or irregular margin). Nodal diagnosis was then made using the size (in mm), or nodal morphology (based on the 6-point confidence score); both without reference to the DW-MRI.

The diagnosis based on nodal size criteria was considered using three cut-offs, analysed separately: 1) short axis diameter >9mm; 2) short axis >10 mm or 3) 'size ratio' criteria, whereby a node <8 mm short axis is considered benign, node >10 mm short axis is considered metastatic (and therefore positive), but a node with a short axis between 8 and 10 mm is only considered positive if the short axis to long axis ratio is over 0.8 (i.e. a round node) (22).

Nodal diagnosis based on DW-MRI

Nodes were identified on the high b value DW-MRI as non-continuous high signal intensity

(SI) round or ovoid structures that corresponded with a node on the anatomical images. Nodes that retained very high SI on the high b value images, without T2 shine-through, were considered to be positive based on the 6-point confidence score.

Nodal diagnosis based on PET/CT

The anatomical location of any focally increased tracer uptake that was higher than background adjacent tissue corresponding to a node of any size on the CT was recorded and assessed according to a 5-point scale (A: Normal FDG/FEC uptake, B: Mild increased FDG/FEC uptake likely not to represent tumour involvement, C: Equivocal FDG/FEC uptake, D: Moderately increased FDG/FEC uptake likely to represent tumour involvement, E: Intensely increased FDG/FEC uptake representing tumour involvement). The 6-point confidence level was used for nodal diagnosis.

Primary reference standard

The primary reference standard was confirmed nodal histology obtained by surgical lymphadenectomy. The surgeon was made aware of the position of any suspicious node prior to the lymphadenectomy in order to ensure the highest likelihood of correlating all suspected positive nodes based on imaging tests. The surgeon recorded the site of resected nodes which were labelled for histological correlation according to the predefined protocol.

All retrieved nodes were analysed by expert gyne-oncology histopathologists at each site and the anatomical location of all nodes, nodal size and presence of metastatic disease were recorded. The histopathologist was blind to all image findings, although they were aware of the original histopathology results from pre-operative biopsy of the primary tumour, as per standard practice.

In cases where imaging suggested an involved node but histopathology was negative, further reviews were undertaken to avoid an uncertain reference standard due to the possibility that the node was not retrieved at surgery. First, any post-operative imaging was reviewed by an expert consensus to be certain that all suspicious nodes had been retrieved at surgery. If the suspicious node remained in situ, then the case was not eligible for analysis by the primary reference standard, as the correlation with histology was uncertain. Second, the most suspicious node underwent ultra-sectioning and immunostains to ensure very high sensitivity for micro-metastases. Where histopathology was positive but imaging negative, then the imaging was deemed false-negative.

The final histological sub-type and pathological stage of the primary tumour were recorded. If no nodal tissue was obtained in the surgical specimen, the case was not eligible for analysis with the histological primary reference standard.

Secondary reference standard

A secondary reference standard was specified to allow for inclusion of patients in whom definitive histopathology was unavailable (either no surgery, no nodal tissue retrieved or suspicious node not resected), and therefore could not be included in analyses using the primary reference standard. This secondary reference standard was comprised by a consensus panel that reviewed all available imaging and clinical information for 9 months from when the patient was recruited to impute the presence and position of any positive nodal sites, for example by identifying progression in a node or clear regression following treatment. If no follow-up was available, the patient was excluded from analysis.

Outcome measures

The primary outcome measures were sensitivity and false positive rate [FPR]) for histologically confirmed nodal metastatic disease. Sensitivity is the proportion of cases who are test-positive among all who have confirmed metastatic disease. FPR (specificity) is the proportion of cases who are test-positive among all those who do not have metastatic disease. These were estimated for each of the DW-MRI, FEC- and FDG-PET/CT scans, and also (using standard MRI) nodal size criteria and morphology. Secondary outcome measures were positive and negative predictive values. Analyses were performed according to cervical or endometrial cancer, and on a per-patient level (all surgically resected nodal regions considered together) and per-nodal-region level (right pelvis, left pelvis, para-aortic).

Statistical considerations

Sensitivities of DW-MRI, FDG- and FEC-PET/CT were compared with that of nodal size, using a McNemar's paired test. The primary analysis was based on patients who had both DW-MRI and FDG-PET/CT, as these were mandatory for study inclusion and FEC-PET/CT was optional.

Sample size assumptions were based on results for conventional MRI nodal size, DW-MRI (original calculation based on Thoeny HC et al, ESUR 2009 abstract MS8 p45) and FDG-PET/CT (23).

For comparing sensitivity of DW-MRI (93%) with nodal size (47%), at a fixed FPR of 25% (the published estimate for DW-MRI), using a discordant paired analysis, 19 women with confirmed histological nodal disease were required (80% power, and one-sided statistical significance of 0.017 to allow for 3 main comparisons). Assuming 15% of women have nodal disease , 127 patients were needed in total. For comparing the sensitivity of FDG-PET/CT (73%) with nodal size (27%), at a fixed FPR of 3% (the published estimate for FDG-PET/CT), required 23 women with confirmed nodal disease and therefore about 150 in total.

The target study size was taken as the greater of the two main comparisons: N=150 patients. No preliminary data were available for FEC-PET/CT, but we expected that FEC-PET/CT would have a diagnostic performance similar to either DW-MRI or FDG-PET/CT, and thus not require a larger sample size. A statistically significant difference was taken to be <0.034 (two-sided, as per the design and power calculation).

Interrater agreement between local and the central consensus reviews was assessed using Cohen's kappa statistic.

Results

Participants were included from 5 gyne-oncology tertiary referral centres in National Health Service (NHS) hospitals in England (Table S2A). Consent was obtained from 162 women between October 2012 and July 2017 (Figure 1). Among the 145 women who had any study imaging and surgery, surgery was performed laparoscopically in 64, open in 42, robotically-assisted procedure in 32 and 7 did not undergo surgery (advanced disease on PET (n=1), investigator decision (n=2), patient decision (n=1), unable to comply with study schedule (n=2)). The diagnosis was endometrial cancer in 98 and cervical cancer in 47 patients (Table 1).

Our primary analyses were based on the 118 who had both DW-MRI and FDG-PET/CT, and definitive histopathology according to the primary reference standard; baseline patient and tumour characteristics are in Table 1 and Table S3. The median time interval between pre-operative imaging and nodal surgery was 26 days, (range 1-83) for standard of care MRI, 12 days (1-58) for DW-MRI, 7.5 days (0-44), for FDG-PET/CT (one patient being imaged early morning prior to evening surgery) and 7 days (1-28) for FEC-PET/CT. Among 118 cases included with primary reference standard, 4 cases had review of post operative imaging for confirmation of nodal resection.

Metastatic nodal disease was histologically confirmed in 25.4% (30/118) patients in both tumor types, according to the primary reference standard: 10/40 of cervical cancer- and 20/78 of endometrial cancer patients.

Diagnostic accuracy using primary reference standard

On a per patient basis, for all patients combined, diagnosis based on nodal morphology was equivalent to DW-MRI with sensitivites and FPRs of 53% (95%CI 34-72) and 3% (95%CI 1-10), respectively (Table 2). FDG-PET/CT had the same FPR but with a slightly higher sensitivity of 63% (95%CI 44-80), while FEC-PET/CT had sensitivity and FPR of 67% (95%CI 35-90) and 3% (95%CI 0-13), respectively. Diagnosis based on short axis >10mm had a sensitivity of 40% (95%CI 23-59) and FPR of 5% (95%CI 1-11). McNemar's tests found FDG-PET/CT to have significantly better sensitivity than short axis >10mm (p=0.016) while all other comparisons were not statistically significant.

On a per-region basis (N=267 regions among the 118 patients, mean 2.3 regions per patient), diagnostic performances differed only slightly (Table S4A-C) and McNemar's tests found FDG-PET/CT outperformed both short axis >10mm (p=0.006) and size ratio criteria (p=0.04) with regards to sensitivity. Distant metastases were described on PET/CT in 8/162 patients, 6 included in the primary reference standard and 2 excluded due to final histology being ovarian cancer (n=1) and no histology or follow-up imaging therefore no nodal reference standard available (n=1). (Fig. 1).

Among 40 women with cervical cancer, 10 (25%) had confirmed histological nodal metastases, only 1 of which had a LN short axis>10mm. The sensitivities were lower, ranging from 10% (size ratio criteria, morphology and short axis >9mm) to 30% (FDG-PET/CT) (Table 3). There was no significant difference in modalities among these patients in terms of sensitivity or FPR. Only 4 patients had an MRI FIGO stage greater than 1B1 (as expected due to patient selection for operability) and in these cases the FPR was 0% for all tests (Table S5).

Among 78 women with endometrial cancer, 20 (25.6%) had confirmed histological nodal metastases, 15 of which had a LN short axis >10mm. Sensitivities were 75% (95%CI 51-91) for morphology, and 65% (95%CI 41-85) for short axis >9mm, 70% (95%CI 46-88) for DW-MRI, 80% (95%CI 56-94) for FDG-PET/CT, 88% (95%CI 47-100) for FEC-PET/CT. FPRs ranged from 9% (95%CI 3-19) for size ratio criteria to 3% (95%CI 0-12) for DW-MRI (Table 4). No imaging modality had significantly better sensitivity or FPR among patients with endometrial cancer. Of the 27 cases with stage 1A disease based on MRI,

there was no histologically confirmed nodal metastasis, with a single false positive detection on MRI and no false positives on PET/CT with very high NPV on PET/CT (Table S5C). There were 20 cases with stage 1B disease based on MRI of which only one had a suspected nodal metastasis, detected on DW-MRI, and was false-negative on FDG-PET/CT, size and morphology (Table S5D). Among 30 patients with cancer stage higher than 1B on MRI, 19 had nodal metastases and the sensitivity and FPR based on MRI nodal morphology was 79% (95%CI 54-94) and 9% (95%CI 0-41), for DW-MRI was 68% (95%CI 43-87) and 9% (95%CI 0-41) and for FDG-PET/CT was 84% (95%CI 60-97) and 9% (95%CI 0-41) (Table S5E).

The above results were based on patients who had both the DW-MRI and FDG-PET/CT scans. Quantitative values for FDG- and FEC- SUV and ADC in positive and negative nodes are provided in Suppl Table S6.

Secondary reference standard

18 patients were not included in the main analyses because they did not have definitive histopathology correlation using the primary reference standard. This included 4 patients who did not undergo surgery, 3 patients in whom a suspected positive node remained visible on post-operative imaging therefore not considered resected (figure 2, all included in secondary reference standard), 3 in whom lymphadenectomy was attempted but no nodal tissue retrieved and 8 who underwent surgery but lymphadenectomy was abandoned during surgery for clinical reasons. Of these 18 patients, 6 in total had post-operative imaging and follow-up to 9 months. Combining these with the 118 who had the primary reference standard, gave a total of 124 patients for analyses based on the secondary reference standard (Fig. 1). 25.8% (54/124) had nodal metastasis. Results using the secondary reference standard did not differ substantially from results based on the primary reference standard and are available in Table S7A-C. Twelve patients had no histology or imaging follow-up and therefore could not be included (Fig.1).

Central review

Diagnostic performance based on the independent central review did not differ substantially from the local radiologist assessment (Table S8). Interrater agreement between local and central consensus reviews was high for each imaging modality, with kappa statistics of 0.70, 0.86 and 0.79 for DW-MRI, FDG- and FEC-PET/CT, respectively.

Adverse events

The MAPPING study was conducted as a study of investigational medicinal products, according to MHRA guidance. Adverse events were collected for all patients who underwent at least one of the trial PET scans (n=147 participants, Table S9). One patient had mood alteration and another had vomiting, both thought to be related to FEC-PET/CT. One patient had hyperglycaemia and another developed a rash, these were considered related to FDG-PET/CT. There were no serious adverse events.

Discussion

In this multicentre prospective cohort study, with a strict histological reference standard, we failed to demonstrate a significantly higher sensitivity, on a per patient basis (n=118), using FEC-PET/CT, FDG-PET/CT or DW-MRI compared to standard MRI in the radiological detection of nodal metastases in seemingly operable cervical (sensitivities of 20-30% compared to 10%) and in endometrial cancer (sensitivities of 70-87.5% compared to 75%). FEC-PET/CT, studied as a possible alternative to FDG, was not found to improve diagnostic performance compared to FDG-PET/CT, with sensitivity of 66.7% in the entire cohort (25% in CC and 87.5% in EC). As such, we could not establish any

preoperative imaging that had sufficient sensitivity to obviate the need for surgical LN staging in seemingly operable early stage cervical and operable endometrial cancer.

On a per-region basis (N=267), FDG-PET/CT outperformed both short axis >10mm (p=0.006) and size ratio criteria (p=0.04) with regards to sensitivity.

Importantly, we demonstrated very low false positive rates for LN metastases in both cervical and endometrial cancers (ranging from 2.5–6.8%) across all imaging modalities. This high specificity suggests that positive preoperative imaging can be relied upon to indicate nodal involvement, even in the case of non bulky LN, so that indication for surgery and extent of surgical radicality can be appropriately modified.

The performance of functional imaging techniques was better in the cohort of endometrial, compared to cervical cancer patients. This may be attributed to the fact that only early stage cervical cancer patients with non bulky LN on conventional imaging were included, since only those were eligible for surgery, as opposed to endometrial cancer patients, where those with bulky LN were considered operable and hence included in our study.

In the cohort of women with endometrial cancer, radiological detection of nodal metases was demonstrated to be reasonably sensitive (FDG-PET/CT 80%, FEC-PET/CT 87.5%) and highly specific (false positive rate: FDG-PET/CT 5%, FEC-PET/CT 4%). Of all the modalities, PET/CT had higher performance than MRI with or without DW-MRI, although this was not statistically significant. This first study using FEC-PET/CT in endometrial cancer demonstrated good diagnostic performance but not statistically better than FDG-PET/CT. In endometrial cancer, FDG-PET/CT is not currently used routinely but the high negative predictive value (NPV: FDG-PET/CT 93.2%, FEC-PET/CT 95.8%) could be used to re-inforce standard of care imaging in order to arbitrate difficult or borderline surgical decisions concerning surgical lymphadenectomy. Surgical LN staging is recommended in apparent uterine-confined high risk endometrial cancer (5) but there is no prospective evidence so far to demonstrate a therapeutic value of systematic LND (9). A corroboration of a borderline or suspicious morphological imaging test with a functional imaging test could support the decision to proceed with nodal dissection and allow planning of surgical approach and extent in order to minimize morbidity related to the surgery and subsequent increased risk of lymphoedema.

Our study provides prospective multi-centre evidence that would support the use of FDG-PET/CT in endometrial cancer cases with difficult surgical decision-making, in order to direct surgical resection to the positive LN avoiding more extensive lymphadenectomy. In cases with a positive PET/CT, the surgical plan could include limited targeted resection of individual accessible positive nodes at the time of hysterectomy, followed by adjuvant therapy or a decision to avoid nodal dissection altogether to treat with targeted radiotherapy depending on the overall tumor dissemination pattern and patients profile. In cases that are PET/CT-negative, but intermediate to high risk disease, there is increasing evidence for the use of sentinel lymph node technique as a viable alternative for systematic LND (24).

This is the first study to report the use of FEC-PET/CT as an alternative to FDG-PET/CT in the nodal staging of endometrial cancer. The rationale to study this was choline-PET/CT has shown promise in the nodal staging of high risk prostate cancer (25) and supportive feasibility data of 11C-choline-PET in gynecological cancers (20, 21). In our study, FEC-PET/CT performed well, but with no statistical difference to FDG-PET/CT. In daily practice, FDG is more widely available and therefore more practical.

There are no similar multicentre prospective studies in the last five years in gynecological malignancies. Eight prospective studies have evaluated endometrial cancer with FDG-PET/CT and surgical-pathological reference standard between 2009 and 2019 (with inclusion of more than 30 patients, range 37-220) (26-33). The range of sensitivities was between 45.8-93.3% and FPRs between 3.0–8.8% apart from one study with a higher FPR of 17.9% (31). The largest multicentre prospective study of FDG-PET/CT in endometrial cancer (27), reported per patient sensitivity of 59 % (23/39) for nodal metastases in those patients that had histological confirmation, a little lower than 80.0% in our study. Criteria for nodal involvement and details of surgical reference standard were not described. A more recent single centre prospective study in patients with high-risk endometrial cancer found a lower sensitivity of 45.8% (11/24), specificity of 91.1% (72/79) for nodal metastatic disease in 103 patients (33). In this study, there was a similar prevalence of nodal involvement in the cases that underwent nodal dissection (23.3% versus 26% in our study) and more FIGO stage 1A cases, although they did not mention the size of the nodes. Their sensitivity is lower than other studies included in a meta analysis which reported the pooled sensitivity of 68% (34). In addition, the reference standard for false positive PET cases was not clear: in our study, we reviewed post operative imaging to ensure the suspicious node was removed, and excluded cases where the suspicious node was still present on post operative imaging, in order to ensure an accurate reference standard.

There are only three prospective studies assessing diagnostic accuracy of MRI for LN metastases in endometrial cancer with more than 30 evaluable patients with surgical-pathological reference standard (including 46, 181 and 220 patients) between 2009 and 2015 (27, 31, 35). The sensitivities using size criteria (short axis >10 mm) for LN metastases were from 75%, 69.2% and 40% with FPRs of 19%, 6.5% and 3.5% respectively. More recently a prospective study developing and testing radiomic features to predict nodal involvement has been published and this is an exciting area of future research (36).

In early stage presumed operable cervical cancer, we found that no imaging method, including DW-MRI, FDG- or FEC-PET/CT was able to reliably identify nodal metastases in normal sized/non bulky lymph nodes with sufficient sensitivity. Our results confirm the findings of a single centre prospective cohort (32.1% sensitivity FDG-PET/CT compared to 27.3% in our study), that the role of FDG-PET/CT in staging of early cervical cancer is limited as the prevalence of nodal involvement is low, and if present, nodal metastases are often small volume and below the sensitivity of PET (37). Although in our cohort 25% (10/40) had at least one positive node, the majority of these nodes were subcentimetre. Importantly, we had no false positive case on FDG-PET/CT in women with cervix cancer. This information is highly relevant in cases where the choice of surgery may be difficult: a negative FDG-PET/CT could allow a decision for surgery to go ahead, at least for surgical nodal staging, whereas the finding of a positive node could safely and reliably exclude these patients from radical hysterectomy and direct them to chemoradiotherapy. Early data that suggest individual nodal sensitivity of FDG PET/CT in endometrial and cervical cancer could be enhanced by image fusion with DW-MRI with potential complementarity between the modalities but was beyond the scope of our study (38).

There are limitations to our study. Our results are suggestive (but not conclusive) of a difference in diagnostic performance between cervical and endometrial cancer. However, there are insufficient cases to reliably analyse these separately because when the study was designed there were few publications on this, limiting the power calculation. Study recruitment was challenging as patients needed to undertake repeat study MRI for the study diffusion sequence, as well as study-specific FDG-PET/CT and optional FEC-PET/CT prior to the planned surgery. In addition, many recruited women did not complete all the imaging as per study protocol, in particular FEC-PET/CT due to logistical challenges of co-ordinating manufacture timings and radiotracer distribution in a

multicentre study with short time-frames for imaging prior to surgery. Several cases could not be evaluated with the primary reference standard as we could not be fully confident that the suspicious node on imaging had been correlated at histology. By having a stringent primary reference standard, we ensured a high likelihood of correlated imaging and nodal histology. However, this led to several patients excluded from the primary analysis, where the suspicious node was not successfully surgically resected. Nevertheless, analyses based on the secondary (follow-up) reference standard were similar to the primary analyses. Although our main analyses were based on 118 patients (less than the target of 150), the sample size was based on the number of histologically confirmed cases with nodal metastasis, and we observed 30 cases, above the target of 19-23.

In conclusion, in this prospective multicentre study with strict histological reference standard, no imaging technique provided sufficient sensitivity to obviate the need for lymph node dissection in cases where this is considered appropriate, in women with early stage operable cervical cancer and in women with intermediate to high risk endometrial cancer. However, the very low false positive rates, in all modalities, could be helpful in treatment planning. In women with cervical cancer, with borderline appropriateness for radical surgery, MRI findings could be supported by FDG-PET/CT, as false positive scans are highly unlikely and therefore a positive scan would allow avoidance of inappropriate surgery, or could direct surgical resection for confirmation. In women with endometrial cancer, in cases where there is uncertainty regarding the risk/benefits of lymphadenectomy, confirmatory FDG-PET/CT may add support to MRI to decide on proceeding to surgical nodal dissection, as well as directing the surgical approach.

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Tables

Table 1. Baseline characteristics of the 118 patients who had confirmed histopathology using the primary reference standard

Characteristic	Cervical (N=40)		Endometrial (N=78)	
Age (years), median (range)	38 (24 - 75)		67 (27 - 83)	
Ethnic group, N(%)				
Asian (Indian)	1 (2.5)		8 (10.3)	
Asian (Other)	1 (2.5)		3 (3.8)	
Asian Pakistani	1 (2.5)		0	
Black (African)	0		3 (3.8)	
Black (Caribbean)	0		2 (2.6)	
Chinese	0		1 (1.3)	
Other	2 (5.0)		1 (1.3)	
White	35 (87.5)		58 (74.4)	
Unknown	0		2 (2.6)	
Histology, N(%)				
	Adenocarcinoma	13 (32.5)	Endometrioid	42 (53.8)
	Adenosquamous	4 (10.0)	Serous/clear cell	37 (47.4)
	Squamous cell	22 (55.0)	Carcinosarcoma	1 (1.3)
	Unknown	1 (2.5)	Other*	3 (3.8)
			Unknown	1 (1.3)
Lymphovascular space invasion (LVSI), N(%)				
No	22 (55.0)		41 (52.6)	
Yes	16 (40.0)		29 (37.2)	
Unknown	2 (5.0)		8 (10.3)	
Differentiation, N(%)				
Grade 1	5 (12.5)		7 (9.0)	
Grade 2	20 (50.0)		9 (11.5)	
Grade 3	12 (30.0)		59 (75.6)	
Unknown	3 (7.5)		3 (3.8)	
FIGO stage (on MRI), N(%)				
	1B1	36 (90.0)	1A	27 (34.6)
	1B2	1 (2.5)	1B	20 (25.6)
	2A1	2 (5.0)	2	9 (11.5)
	2B	1 (2.5)	3A	3 (3.8)
			3C	13 (16.7)
			4B	5 (6.4)
			Unknown	1 (2.5)

*2 Carcinosarcoma, 1 Mucinous, 2 Unknown

Table 2. Estimates of diagnostic performance using the primary reference standard: Per patient diagnostic performance among all patients.

Diagnostic method#	No. patients	Confirmed node metastatic disease		Confirmed without nodal disease		Sensitivity (95% CI)	False-positive rate (95% CI)	PPV (95% CI)	NPV (95% CI)
		True +ve	False -ve	True -ve	False +ve				
DW-MRI	118	16 (13.6%)	14 (11.9%)	85 (72.0%)	3 (2.5%)	53.3% (34.3-71.7)	3.4% (0.7-9.6)	84.2% (60.4-96.6)	85.9% (77.4-92.0)
FDG-PET/CT	118	19 (16.1%)	11 (9.3%)	85 (72.0%)	3 (2.5%)	63.3% (43.9-80.1)	3.4% (0.7-9.6)	86.4% (65.1-97.1)	88.5% (80.4-94.1)
FEC-PET/CT	52	8 (15.4%)	4 (7.7%)	39 (75.0%)	1 (1.9%)	66.7% (34.9-90.1)	2.5% (0.1-13.2)	88.9% (51.8-99.7)	90.7% (77.9-97.4)
Diagnosis based on morphology	118	16 (13.6%)	14 (11.9%)	85 (72.0%)	3 (2.5%)	53.3% (34.3-71.7)	3.4% (0.7-9.6)	84.2% (60.4-96.6)	85.9% (77.4-92.0)
Short axis >9mm	118	14 (11.9%)	16 (13.6%)	82 (69.5%)	6 (5.1%)	46.7% (28.3-65.7)	6.8% (2.5-14.3)	70.0% (45.7-88.1)	83.7% (74.8-90.4)
>10mm	118	12 (10.2%)	18 (15.3%)	84 (71.2%)	4 (3.4%)	40.0% (22.7-59.4)	4.5% (1.3-11.2)	75.0% (47.6-92.7)	82.4% (73.6-89.2)
Size ratio criteria	118	14 (11.9%)	16 (13.6%)	82 (69.5%)	6 (5.1%)	46.7% (28.3-65.7)	6.8% (2.5-14.3)	70.0% (45.7-88.1)	83.7% (74.8-90.4)

PPV: positive predictive value NPV: negative predictive value

For all imaging, a positive test result is defined as a confidence score of 5 or 6 (see Methods); for short axis a positive result is defined in the table, and for size ratio criteria see Methods.

Table 3: Estimates of diagnostic performance using the primary reference standard: Per patient diagnostic performance patients with cervical cancer.

Diagnostic method#	No. patients	Confirmed node metastatic disease		Confirmed without nodal disease		Sensitivity (95% CI)	False-positive rate (95% CI)	PPV (95% CI)	NPV (95% CI)
		True +ve	False -ve	True -ve	False +ve				
DW-MRI	40	2 (5.0%)	8 (20.0%)	29 (72.5%)	1 (2.5%)	20.0% (2.5-55.6)	3.3% (0.1-17.2)	66.7% (9.4-99.2)	78.4% (61.8-90.2)
FDG-PET/CT	40	3 (7.5%)	7 (17.5%)	30 (75.0%)	0 (0.0%)	30.0% (6.7-65.2)	0.0% (0.0-11.6)	100.0% (29.2-100.0)	81.1% (64.8-92.0)
FEC-PET/CT	20	1 (5.0%)	3 (15.0%)	16 (80.0%)	0 (0.0%)	25.0% (0.6-80.6)	0.0% (0.0-20.6)	100.0% (2.5-100.0)	84.2% (60.4-96.6)
Diagnosis based on morphology	40	1 (2.5%)	9 (22.5%)	30 (75.0%)	0 (0.0%)	10.0% (0.3-44.5)	0.0% (0.0-11.6)	100.0% (2.5-100.0)	76.9% (60.7-88.9)
Short axis >9mm	40	1 (2.5%)	9 (22.5%)	28 (70.0%)	2 (5.0%)	10.0% (0.3-44.5)	6.7% (0.8-22.1)	33.3% (0.8-90.6)	75.7% (58.8-88.2)
>10mm	40	1 (2.5%)	9 (22.5%)	30 (75.0%)	0 (0.0%)	10.0% (0.3-44.5)	0.0% (0.0-11.6)	100.0% (2.5-100.0)	76.9% (60.7-88.9)
Size ratio criteria	40	1 (2.5%)	9 (22.5%)	29 (72.5%)	1 (2.5%)	10.0% (0.3-44.5)	3.3% (0.1-17.2)	50.0% (1.3-98.7)	76.3% (59.8-88.6)

PPV: positive predictive value NPV: negative predictive value

For all imaging, a positive test result is defined as a confidence score of 5 or 6 (see Methods); for short axis a positive result is defined in the table, and for size ratio criteria see Methods.

Table 4. Estimates of diagnostic performance using the primary reference standard: Per patient diagnostic performance patients with endometrial cancer.

Diagnostic method#	No. patients	Confirmed node metastatic disease		Confirmed without nodal disease		Sensitivity (95% CI)	False-positive rate (95% CI)	PPV (95% CI)	NPV (95% CI)
		True +ve	False -ve	True -ve	False +ve				
DW-MRI	78	14 (17.9%)	6 (7.7%)	56 (71.8%)	2 (2.6%)	70.0% (45.7-88.1)	3.4% (0.4-11.9)	87.5% (61.7-98.4)	90.3% (80.1-96.4)
FDG-PET/CT	78	16 (20.5%)	4 (5.1%)	55 (70.5%)	3 (3.8%)	80.0% (56.3-94.3)	5.2% (1.1-14.4)	84.2% (60.4-96.6)	93.2% (83.5-98.1)
FEC-PET/CT	32	7 (21.9%)	1 (3.1%)	23 (71.9%)	1 (3.1%)	87.5% (47.3-99.7)	4.2% (0.1-21.1)	87.5% (47.3-99.7)	95.8% (78.9-99.9)
Diagnosis based on morphology	78	15 (19.2%)	5 (6.4%)	55 (70.5%)	3 (3.8%)	75.0% (50.9-91.3)	5.2% (1.1-14.4)	83.3% (58.6-96.4)	91.7% (81.6-97.2)
Short axis >9mm	78	13 (16.7%)	7 (9.0%)	54 (69.2%)	4 (5.1%)	65.0% (40.8-84.6)	6.9% (1.9-16.7)	76.5% (50.1-93.2)	88.5% (77.8-95.3)
>10mm	78	11 (14.1%)	9 (11.5%)	54 (69.2%)	4 (5.1%)	55.0% (31.5-76.9)	6.9% (1.9-16.7)	73.3% (44.9-92.2)	85.7% (74.6-93.3)
Size ratio criteria	78	13 (16.7%)	7 (9.0%)	53 (67.9%)	5 (6.4%)	65.0% (40.8-84.6)	8.6% (2.9-19.0)	72.2% (46.5-90.3)	88.3% (77.4-95.2)

PPV: positive predictive value NPV: negative predictive value

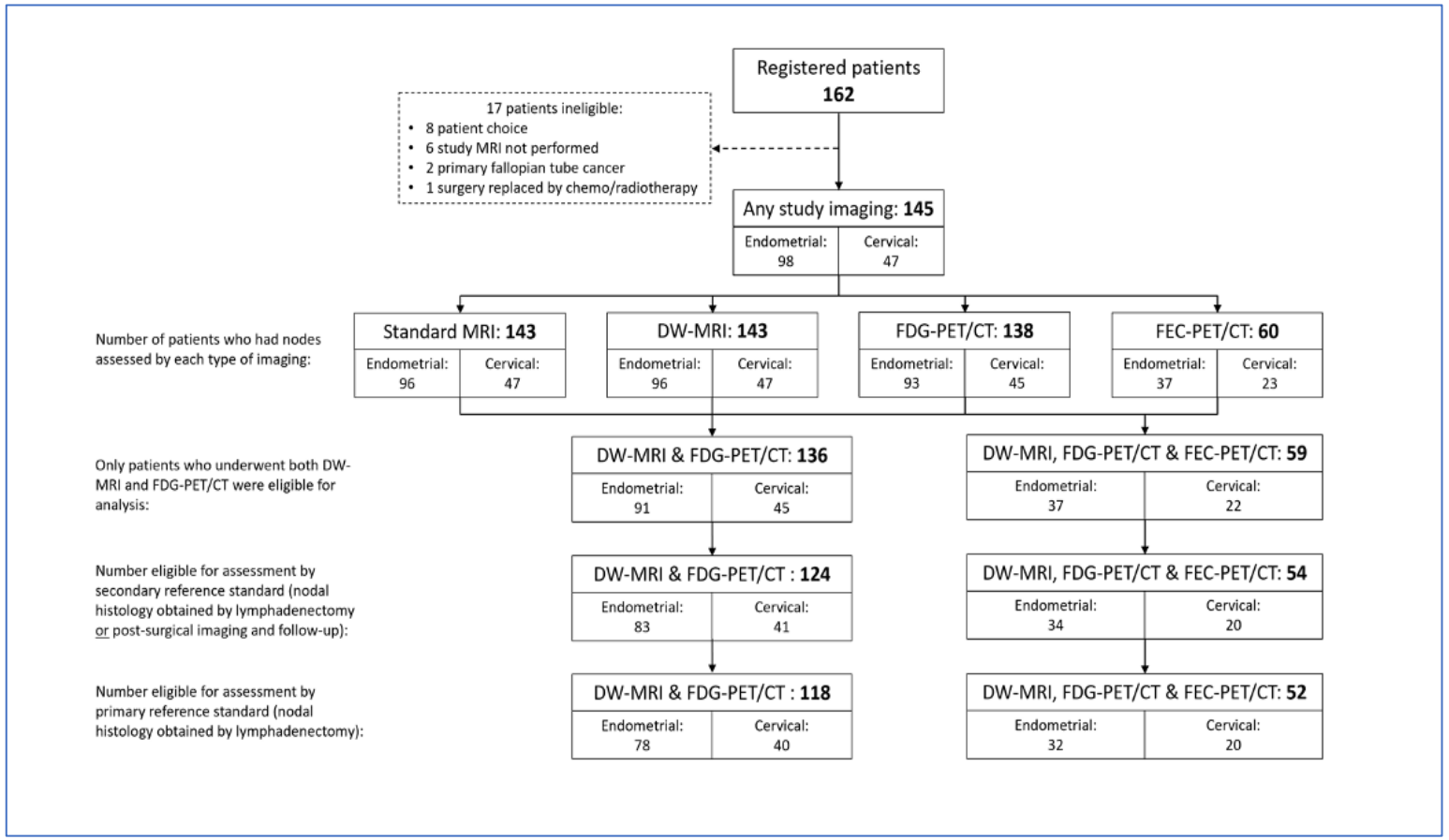
For all imaging, a positive test result is defined as a confidence score of 5 or 6 (see Methods); for short axis a positive result is defined in the table, and for size ratio criteria see Methods.

Figure legends

Figure 1. Study consort diagram

Figure 2. A 55 year old with endometrial carcinoma. Cor/ axial T2 weighted MRI (i), axial ADC (ii), axial FDG fused (iii), axial FEC fused (iv) shows focal tracer uptake in a 8 mm rounded left external iliac node (row A, arrows, * tumor, ^ ureter), and a 9 mm rounded righ common iliac node (row B, arrows). Histopathology was negative. Follow up axial FDG fused (v) and axial contrast enhanced CT (CECT) (vi) confirmed the nodes were not removed at surgery.

Figure 1. Study consort diagram



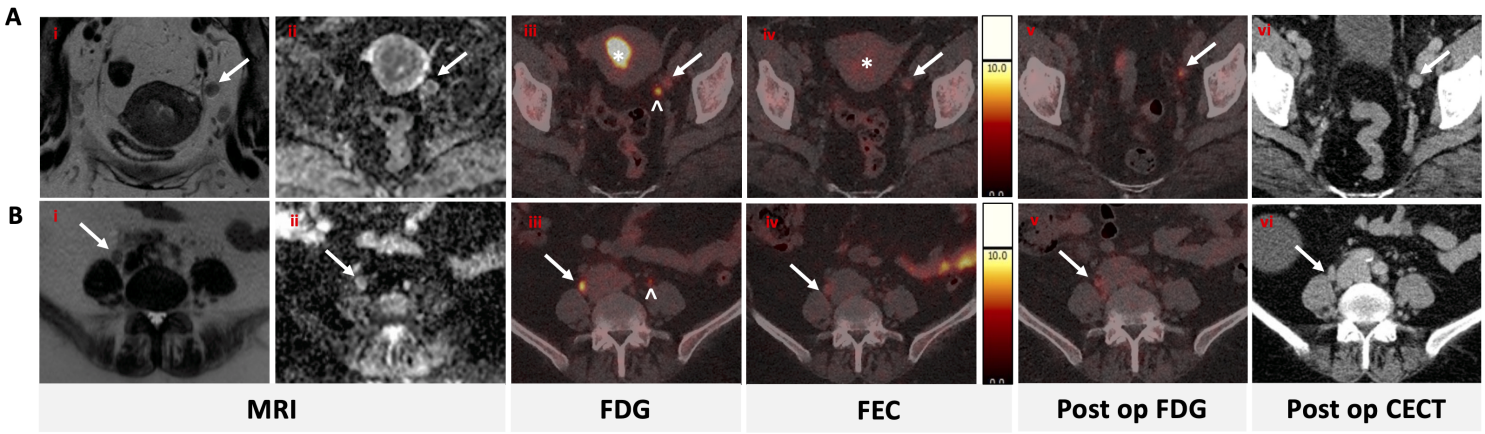


Figure 2.

AACR American Association for Cancer Research

Clinical Cancer Research

DIAGNOSTIC ACCURACY OF FEC-PET/CT, FDG-PET/CT AND DIFFUSION-WEIGHTED MRI IN DETECTION OF NODAL METASTASES IN SURGICALLY TREATED ENDOMETRIAL AND CERVICAL CARCINOMA

Andrea G. Rockall, Tara D. Barwick, William Wilson, et al.

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