

FAPI PET/MRI in Endometriosis: A Practical Approach to Mapping Complex Disease Beyond Standard Pelvic MRI

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Abstract

Endometriosis is a common yet under-recognized disease affecting young and reproductive-aged women. Often, symptoms are dismissed or attributed to gastrointestinal, urological, or nonspecific pelvic pain syndromes. This leads to repeated consultations, imaging tests, endoscopies, analgesic therapies, and sometimes diagnostic surgeries before a confident diagnosis is reached. This diagnostic odyssey incurs direct healthcare costs, results in productivity losses, and imposes a significant personal burden. Therefore, for MR teams, the practical question is not only whether endometriosis is present but also how to map the extent of the disease in a way that reduces uncertainty and supports targeted care. Our initial experience with fibroblast activation protein (FAP)-targeted PET/MRI

suggests its potential as an adjunctive tool for selected patients with suspected deep infiltrating, multifocal, or extrapelvic endometriosis. MRI provides the anatomical language for #Enzian-based reporting, while fibroblast activation protein inhibitor (FAPI) PET can act as a molecular searchlight for tissue remodeling, prompting a focused re-review of subtle or equivocal compartments. The expected benefits are a more complete preoperative disease map, improved multidisciplinary communication, and fewer inconclusive steps in complex cases. However, because FAP expression is not disease-specific, PET/MRI should be interpreted in the clinical context and validated prospectively rather than being used as a stand-alone diagnostic label.

Key points

- Clinical benefit: Better visualization of complex, multifocal, peritoneal, tubo-ovarian, and extrapelvic diseases, which may improve preoperative planning and patient counseling.
- Operational benefit: An MRI-first, PET-guided second read can transform molecular hot spots into a structured, #Enzian-based map for the multidisciplinary team.
- Financial and societal benefit: Earlier and more targeted diagnoses could reduce the need for repeated consultations, duplicate tests, unnecessary procedures, and lost productivity in a disease that is often not diagnosed until years after the onset of symptoms.

Although endometriosis is often described as a pelvic disease, daily practice teaches us that the relevant question for patients and surgeons is broader. The important questions are: Where is the active disease? Which organs or compartments are involved? And which lesions could

change the operative strategy? Our initial experience with fibroblast activation protein (FAP)-targeted PET/MRI indicates that molecular information can serve as a practical guide during MRI interpretation, particularly in anatomically challenging areas.

Why this topic matters for MR teams

Endometriosis is a condition that affects women of reproductive age. It is often associated with chronic pelvic pain, infertility, recurrent symptoms after surgery, and a lengthy diagnostic process [1, 2]. Many centers use transvaginal sonography as the initial test, reserving MRI for complex cases, deep infiltrating endometriosis, extrapelvic symptoms, and preoperative decision-making [3, 4].

While MRI provides gynecologic surgeons with the anatomic information they need, even high-quality MRI can be limited when the disease is subtle, multifocal, adhesive, peritoneal, or outside the expected pelvic compartments

[4, 5]. This is where combined PET/MRI can be useful: PET may enhance the diagnostic accuracy of MRI by molecularly marking endometriosis lesions and may provide valuable information regarding disease activity by visualizing fibroblast activation.

Why FAP-targeted PET is biologically plausible

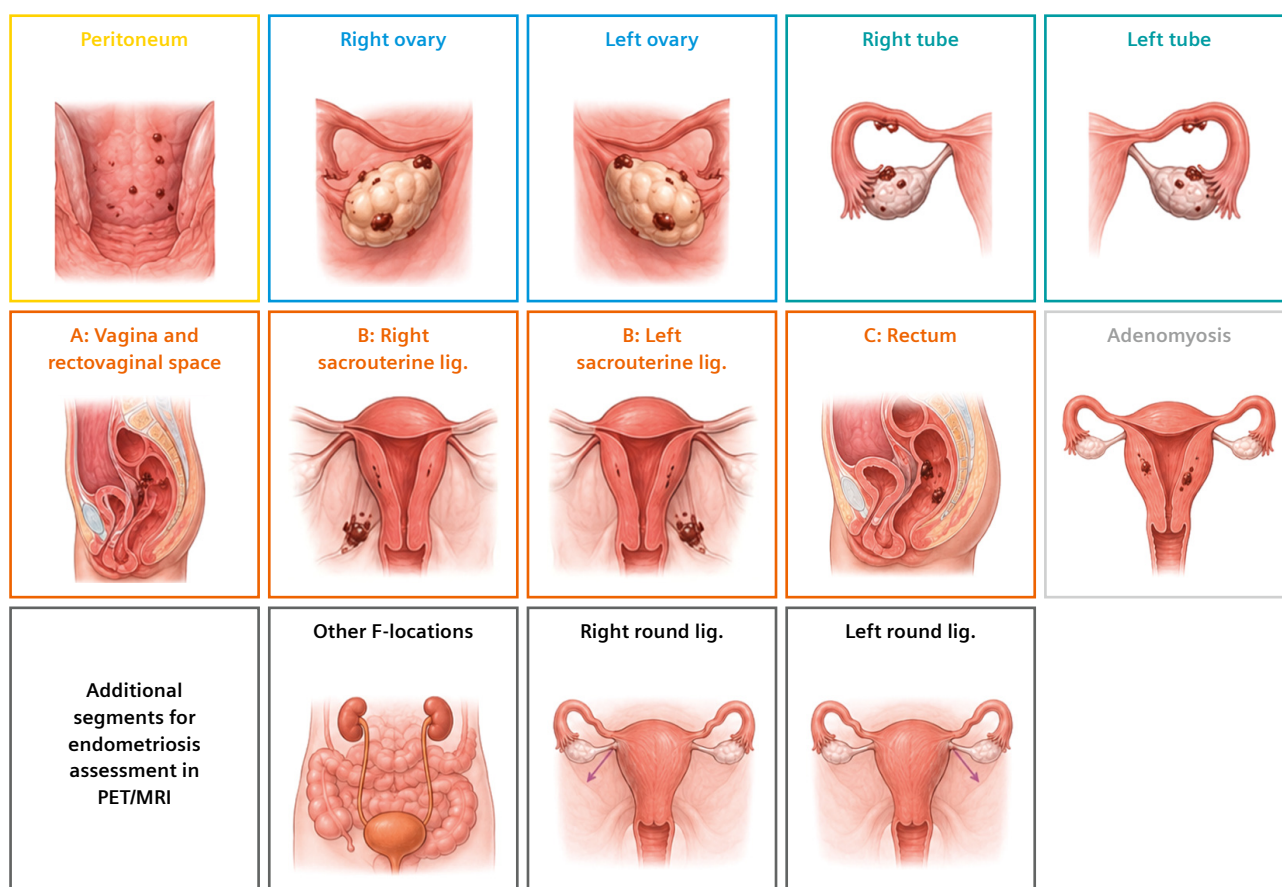
FAP plays a role in tissue remodeling. This is important in endometriosis because lesions undergo repeated injury, repair, inflammation, and fibrosis. FAP expression has also been observed in endometriotic tissue, and physiological FAP inhibitor (FAPI) uptake occurs in the healthy endometrium of premenopausal women [1, 6–8].

This biology is helpful but also humbling for interpretation, because FAP expression can't be regarded as highly specific for endometriosis lesions [6, 7]. Therefore, we

emphasize interpretation of FAPI uptake only in the anatomical, clinical, and surgical context. Focal uptake should prompt a targeted MRI review and structured discussion about confidence and differential diagnosis.

Our initial experience: Lessons rather than statistics

In the initial retrospective cohort, we evaluated premenopausal patients with suspected or confirmed endometriosis, as well as a premenopausal reference cohort without known endometriosis. Among the seven patients in the endometriosis group who underwent PET/MRI, an MRI-only review identified suspicious findings in 17 of 91 #Enzian-derived segments (Fig. 1). When PET and MRI were reviewed together, the disease map expanded to 45 of 91 segments. Most of the combined PET/MRI-positive segments showed focal FAPI uptake.



1 Segment-based evaluation scheme used for the combined PET/MRI test dataset. Thirteen anatomical segments were assessed, including ten #Enzian classification compartments: peritoneum, left ovary, right ovary, left fallopian tube, right fallopian tube, vagina and rectovaginal space (deep infiltrating endometriosis, DIE Group A), left and right uterosacral ligaments (DIE Group B), rectum (DIE Group C), and focal adenomyosis of the uterus. To enable a more comprehensive assessment, the original #Enzian classification was expanded by three additional segments: the left and right ligamentum teres uteri and a combined category of extrapelvic manifestations ("other F-locations"), comprising the bladder, intestines, ureters, and other abdominal structures.

Across all PET datasets, focal extrauterine uptake was more frequent in the endometriosis group than in the reference group. This was most evident in peritoneal, ovarian, tubal, and selected extrapelvic or “F-location” disease, where conventional imaging can be particularly challenging. Where laparoscopy was available, several PET/MRI findings were concordant with the operative assessment. One instructive case involved diaphragmatic

disease in a patient with cycle-dependent shoulder pain (Fig. 2).

While the numbers are encouraging, the clinical lesson is more important: PET/MRI changed the way the imaging team approached the examination. PET-positive foci often prompted a second, more focused look at the MRI. However, MRI morphology remained essential for determining if a focus was a likely endometriotic lesion.



2 Images from a patient who presented with menstrual cycle-dependent right shoulder pain. **(2A)** Maximum-intensity projection PET images demonstrate abnormal tracer uptake in the right diaphragm, bilateral round ligaments, the peritoneum surrounding both ovaries, and the left fallopian tube (indicated by arrows). On fused PET/MRI, a T2-hyperintense lesion with focal tracer uptake is identified inferior to the right hemidiaphragm, consistent with diaphragmatic endometriosis (arrows, **2B**). Subsequent laparoscopic confirmation revealed extensive pelvic endometriosis and diaphragmatic implants (**2C**).

A practical workflow for selected patients

Patient selection: Where PET/MRI may be worth studying or considering in selected cases

- High clinical suspicion for deep infiltrating endometriosis with equivocal or incomplete conventional imaging.
- Preoperative mapping when multifocal disease could change the surgical team, surgical route, or counseling.
- Symptoms suggesting extrapelvic disease, such as cyclic shoulder pain, thoracic or upper abdominal symptoms, or unexplained pain beyond the pelvis.
- Recurrent disease after prior surgery, when adhesions, fibrosis, and subtle residual lesions complicate anatomical interpretation.
- Research settings in which PET/MRI findings can be validated against surgery, histology, and longitudinal outcomes.

- 1. Start with the clinical map.** Before opening the images, gather information on symptoms, prior surgeries, hormonal treatments, previous ultrasounds or MRIs, endoscopies (if relevant), and the surgeon's main question. Record the menstrual cycle phase, if possible, even if the scan is not scheduled around it.
- 2. Read the MRI first.** Reading the MRI first helps preserve the strengths of conventional endometriosis imaging and reduces the risk of misinterpreting non-specific uptake as endometriosis. Document lesions according to the #Enzian classification.
- 3. Add PET as a searchlight.** Review the PET maximum-intensity projections and the fused PET/MR images. Focal uptake at or above background muscle uptake should prompt a targeted anatomical review but not an automatic diagnosis.
- 4. Assign confidence rather than binary certainty.** Classify each site as having definite, probable, possible, or unlikely endometriosis based on the uptake pattern, the MRI correlate, the location, the symptoms, and previous interventions.
- 5. Translate the results for the surgeon.** Report whether a lesion is present and, if so, whether it involves the rectovaginal space, uterosacral ligaments, bowel, urinary tract, ovary/tube, round ligament, diaphragm, abdominal wall, or another extrapelvic site. Comment on the likely surgical implications.

Interpretation principles

Imaging situation	Practical interpretation	Reporting safeguard
Focal FAPI uptake with convincing MRI correlate	High confidence, especially when location and symptoms fit endometriosis.	Describe the segment, morphology, uptake, and expected surgical relevance.
Focal FAPI uptake with subtle or no MRI correlate	Potentially useful signpost, but not definitive. Review prior imaging and clinical symptoms.	Use words like "suspicious" or "possible." Recommend targeted correlation rather than overcalling.
MRI-suspicious lesion without focal FAPI uptake	May still represent endometriosis. Biology and lesion age can vary.	Do not downgrade a convincing MRI lesion solely because PET is negative.
Homogeneous uterine/endometrial uptake	Expected physiologic finding in premenopausal patients and not specific for adenomyosis.	Adenomyosis assessment should remain MRI-led.
Uptake near adhesions or prior operative sites	FAP expression can reflect remodeling and fibrosis. False positives are possible.	Mention adhesions, inflammation, and post-surgical change as differential considerations.
Extrapelvic uptake in symptomatic patient	Potentially high impact for treatment planning, particularly if symptoms are cyclic.	Flag for multidisciplinary review and consider whether additional targeted imaging or surgical expertise is needed.

Structured reporting: Make the disease map usable

A PET/MRI report for endometriosis should offer more than just a list of hot spots. It should provide the clinical team with a map that can be compared with the clinical examination, ultrasound, prior operative findings, and the

surgical plan. We recommend using #Enzian terminology whenever possible, along with a few practical additions for sites that are particularly important in extra-pelvic imaging.

Report item	Example content	Why it matters	Suggested wording
Segment	#Enzian compartment or added site such as diaphragm or round ligament	Allows direct comparison with clinical and surgical maps.	"Focal uptake and T2-hypointense nodular thickening in the right round ligament region."
Morphology	Fibrotic nodule, plaque-like lesion, cystic ovarian lesion, suspected adhesion	MRI remains essential for lesion characterization.	"Morphology is compatible with deep infiltrating endometriosis."
PET signal	Focal uptake relative to muscle; SUV optional but not threshold-based	Supports confidence but should not be used alone.	"Abnormal focal FAPI uptake."
Confidence	Definite/probable/possible/unlikely	Communicates uncertainty in an emerging technique.	"Possible endometriotic implant; clinical and surgical correlation recommended."
Surgical relevance	Bowel, ureter, bladder, diaphragm, ovary/tube, adhesions, access route	Supports planning, referral, and patient counseling.	"This site may be relevant for preoperative planning because of its proximity to the ureter."

Pitfalls and safeguards

The biggest pitfall is treating FAP uptake as disease-specific. It is not. FAP uptake reflects tissue remodeling, which can occur in normal endometrium, adhesions, post-surgical fibrosis, inflammation, and other conditions. In our cohort, focal uptake was also observed in some locations within the reference group, and adhesions led to false-positive interpretations in a few cases.

The second pitfall is expecting a universal standardized uptake value (SUV) threshold. We do not yet have validated uptake cutoffs for endometriosis. Differences in tracer, timing, menstrual cycle phase, hormonal treatment, scanner performance, and reconstruction can influence uptake and contrast. For now, readers should combine visual assessment with anatomical and clinical context.

The third pitfall is underestimating the importance of reader training. PET/MRI scans for endometriosis are best interpreted jointly by radiologists and nuclear medicine physicians who have access to gynecologic expertise. While subtle findings can be meaningful, they can also be misleading when interpreted outside the context of the patient.

How PET/MRI changes the multidisciplinary discussion

The strongest practical value may lie in the multidisciplinary conference. A focal PET signal can help focus the discussion on an equivocal MRI site, while an MRI can help determine if the signal corresponds to a plaque, nodule, ovarian/tubal lesion, or adhesion. This combination can influence the need for colorectal, urologic, thoracic, or other surgical expertise.

Regarding the patient, the aim is not simply to detect more lesions. Rather, the goal is to reduce uncertainty before treatment, avoid incomplete mapping of multifocal disease, and provide a clearer explanation of why a specific surgical or conservative strategy is recommended.

Current role: An adjunct, not a replacement

Our data are preliminary. The study was retrospective and small. It was also heterogeneous in terms of tracer and modality. Not all patients underwent surgical validation after PET. Additionally, examinations were not scheduled according to the phase of the menstrual cycle. Due to these limitations, it is not yet possible to define the sensitivity, specificity, and diagnostic thresholds.

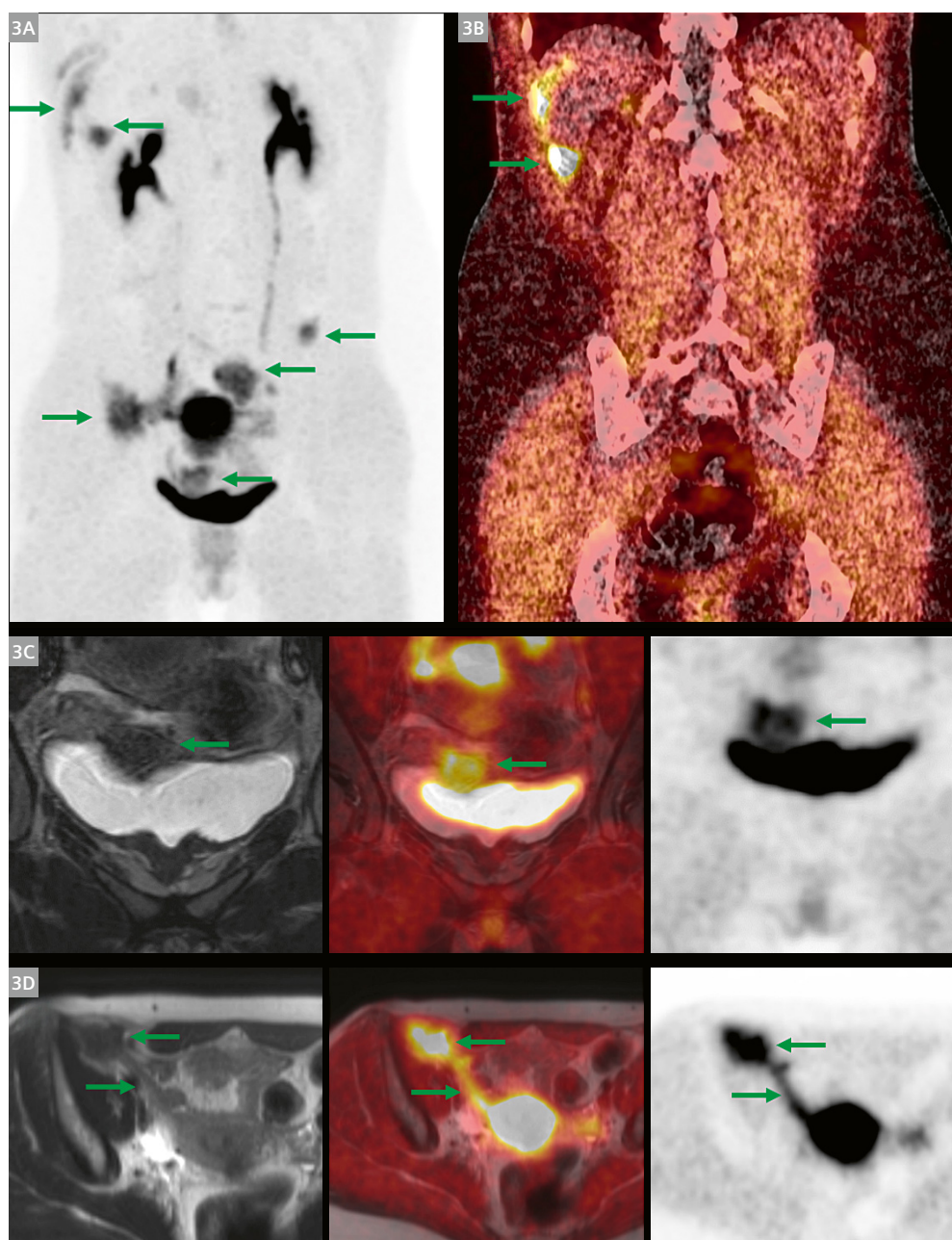
Accordingly, the current role of FAPI PET/MRI should be considered as an emerging adjunct for complex cases and a research tool for prospective validation. FAPI PET/MRI should complement, not replace, expert history taking, clinical examination, advanced ultrasound, high-quality MRI, and multidisciplinary endometriosis care.

Outlook: Whole-body screening and targeted PET/MRI characterization

The next step for our group is to transition from the feasibility stage to a defined patient pathway. One promising approach is a two-stage molecular imaging strategy

for patients suspected of having complex or multifocal endometriosis.

First, we could investigate the use of high-sensitivity long axial field of view (LAFOV, "whole-body") FAPI PET/CT as a screening or triage examination. The rationale is practical: PET/CT provides rapid whole-body molecular coverage and can help identify suspicious sites beyond the standard pelvic field of view. These sites include the abdominal wall, diaphragm, and other extrapelvic areas. Higher-sensitivity systems could facilitate this whole-body step by enabling lower administered activity, shorter acquisitions, or improved detection of small foci, depending on the protocol and local regulatory framework.



3 Images from a patient with extensive endometriosis. **(3A)** Maximum-intensity projection PET images demonstrate abnormal tracer uptake in the right diaphragm, peritoneum, bilateral round ligaments, and the dome of the urinary bladder (arrowheads). On fused PET/ultra-low-dose CT, focal tracer uptake localizes to the right hemidiaphragm, consistent with diaphragmatic endometriosis (arrows, **3B**). Fused PET/MRI further demonstrates an endometriotic lesion infiltrating the bladder dome (arrows, **3C**) and an additional lesion involving the right round ligament (arrows, **3D**).

Second, suspicious lesions identified by PET/CT, symptoms, or ultrasound could be characterized using PET/MRI. PET/MRI would then provide decisive anatomical context, including soft-tissue contrast, compartment assignment, and the relationship to the bowel, ureters, bladder, ovaries, tubes, ligaments, diaphragm, and adhesions. This imaging would provide the language necessary for surgical planning (Fig. 3).

This future pathway would also allow research questions to be answered systematically: Which patients benefit most? Which compartments show the highest incremental value? How does the phase of the menstrual cycle affect uptake? Can uptake patterns predict fibrosis, pain, recurrence, or surgical complexity? Most importantly, does molecular imaging change management in a way that improves patient outcomes?

Take-home messages

- FAPI PET/MRI can help map complex endometriosis by combining molecular markers with high-resolution MRI anatomy.
- The technique appears to be most promising for patients with clinically important disease extent, multifocality, peritoneal involvement, tubo-ovarian disease, or extrapelvic manifestations.
- PET findings should be interpreted using a structured, #Enzian-based framework, and should not be used as a standalone diagnostic label.
- Physiologic uterine uptake, adhesions, inflammation, prior surgery, and subtle uptake patterns are key pitfalls.
- Future studies should test a pathway using high-sensitivity, whole-body FAPI PET/CT for screening or triage, and PET/MRI for the detailed characterization of suspicious lesions.

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