Assessment of endometriosis angiogenesis using ^{99m}Tc-maraciclatide imaging (DETECT): a single-centre, exploratory, open-label, non-randomised, phase 2 study

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Summary

Background Novel non-invasive or minimally invasive diagnostic tests for endometriosis are a research priority. Superficial peritoneal endometriosis, the most prevalent subtype of endometriosis (80% of all laparoscopically diagnosed disease), currently eludes reliable detection by standard imaging techniques (eg, transvaginal ultrasound and MRI). We aimed to evaluate the diagnostic potential and accuracy of ^{99m}Tc-maraciclatide, a gamma-emitting radiotracer that binds to αvβ3 integrins for imaging inflammatory diseases, in people with endometriosis.

Methods The DETECT study was a prospective, single-centre, exploratory, open-label, non-randomised, phase 2 study in a tertiary hospital setting that generated single-photon-emission CT-CT (SPECT-CT) imaging data before surgery (the reference standard). The Women's Centre and Oxford Endometriosis CaRe Centre (University of Oxford, Oxford, UK) served as the recruiting site, with scans performed at the Royal United Hospital (Bath, UK). Female participants aged 18 years and older with confirmed or suspected endometriosis based on previous clinical investigation and who were due to have a diagnostic or therapeutic laparoscopy or thoracoscopic surgery were recruited to the study. Participants underwent preoperative imaging with 10-min or 20-min SPECT-CT, with intravenous ^{99m}Tc-maraciclatide administered as a bolus followed by saline flush. The primary outcome was agreement of radiological and surgical findings in participants completing both imaging and surgery and was assessed per protocol. The surgical report and World Endometriosis Research Foundation surgical form on lesion type and location were compared with images for alignment. Safety was assessed in all participants who underwent the SPECT-CT scan from the time of administering ^{99m}Tc-maraciclatide and for the duration of the imaging day. The study is registered with ClinicalTrials.Gov, NCT05623332, and is active.

Findings Between March 6, 2023, and Sept 16, 2024, 20 participants were recruited and imaged. Of the 20 participants recruited, 17 (85%) underwent laparoscopy and two (10%) had thoracoscopy after SPECT-CT imaging. Imaging results were concordant with the surgical presence or absence of endometriosis in 16 (84%, 95% CI 60–97) of the 19 participants who completed the study, with endometriosis imaged in 14 (82%) of 17 surgically positive participants, including two participants with thoracic endometriosis. Although the study was not powered for definitive diagnostic accuracy, participant-level sensitivity was calculated to be 82% (95% CI 57–96) and specificity to be 100% (16–100). There were no serious adverse events during the study or adverse events that resulted in participant withdrawal from the study.

Interpretation The DETECT study highlights the potential of imaging with ^{99m}Tc-maraciclatide to identify endometriosis, especially superficial peritoneal endometriosis. If the effectiveness of this technique is supported in a larger study, there might be a role for ^{99m}Tc-maraciclatide as a novel diagnostic tool for endometriosis.

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Introduction

Endometriosis is a common gynaecological disease that affects approximately 190 million people worldwide.[1] One of the main global challenges facing those with endometriosis and their health-care providers is diagnostic delay, with estimates of up to 12 years in the USA[2] and 8 years in the UK.[3] Chronic pelvic pain and infertility are common presentations of endometriosis, but in most cases the symptoms experienced are varied and non-specific, including fatigue, bloating, dyschezia, dyspareunia, urinary urgency, urinary frequency, and multisite pain, all of which can be mistaken for other conditions.[1] The diagnostic challenge is exacerbated by an absence of clinically validated biomarkers and the limitations of available imaging techniques.[1,4–6] Thus, advancing diagnostic imaging in endometriosis has been identified as a global priority for endometriosis research.[7] Despite enhancements in MRI and ultrasound, superficial peritoneal endometriosis, the most common endometriosis subtype, present in approximately 80% of people with endometriosis, cannot be reliably detected with current imaging techniques.[5,8] Thus, for diagnosis of

Research in context

Evidence before this study

On Jan 10, 2022, we searched MEDLINE (Ovid) from database inception using the search terms "endometriosis" AND "Integrin" OR "CD11a Antigen", "CD11b Antigen", "CD11c Antigen", "alpha1", "alpha-1", "a1", "alpha2", "alpha-2", "a2", "alpha3", "alpha-3", "a3", "alpha4", "alpha-4", "a4", "alpha5", "alpha-5", "a5", "alpha6", "alpha-6", "a6", "alpha7", "alpha-7", "a7", "alpha8", "alpha-8", "a8", "alpha10", "alpha-10", "a10", "alpha11", "alpha-11", "a11", "alphaV", "alpha-V", "av", "Platelet Membrane Glycoprotein IIb", "CD18 Antigens", "beta1", "beta-1", "b1", "beta2", "beta-2", "b2", "beta3", "beta-3", "b3", "beta4", "beta-4", "b4", "beta5", "beta-5", "b5", "beta6", "beta-6", "b6", "beta7", "beta-7", "b7", "beta8", "beta-8", "b8", "Platelet Glycoprotein GPIIb-IIIa Complex", "Vitronectin Receptor", "Collagen receptor", "RGD receptor", "Laminin receptor", "Leukocyte-specific receptor", without language restrictions. 113 results were retrieved, including 20 human studies and four animal studies assessing the roles of integrins in endometriosis pathogenesis, including adhesion (seven studies), invasion (four studies), proliferation (two studies), angiogenesis (three studies), and infertility (seven studies), with αvβ3 being the most commonly studied integrin. The results of the included studies showed that the eutopic and ectopic endometria of individuals with endometriosis show aberrant integrin expression compared with control individuals, contributing to disease pathology. Moreover, integrin expression patterns vary by endometriosis subtype. The endometrium of those with endometriosis was found to express higher levels of vascular αvβ3 than in control individuals, suggesting a greater propensity for angiogenesis before cells are refluxed into the pelvic cavity. No studies examined expression of αvβ3 within ectopic lesions, which could offer new insights into disease pathology, especially if differences in expression patterns were observed by subtype and if these integrins could be visualised in vivo, offering a novel method of visualising endometriosis. ^{99m}Tc-maraciclatide is a marker that binds with high affinity and specificity to the angiogenic integrin αvβ3 and has shown effectiveness in visualising various inflammatory diseases, such as rheumatoid arthritis. This effectiveness has been supported by published papers on maraciclatide or NC100692. Searching for published papers on maraciclatide-containing, NC100692-containing, or RGD-containing imaging agents did not provide any evidence suggesting our hypothesis was unsubstantiated.

Added value of this study

The DETECT study, for the first time to our knowledge, showed that ^{99m}Tc-maraciclatide can visualise endometriosis, including superficial peritoneal endometriosis (the most common subtype, yet often the most challenging to detect without surgery). The study is novel in that it detected endometriosis pathophysiology (ie, inflammatory and angiogenic processes) to diagnose endometriosis rather than using anatomical changes. This is the first study to use single-photon-emission CT-CT (SPECT-CT) detection of αvβ3 in endometriotic lesions to detect endometriosis. Nuclear imaging, including SPECT-CT, is an uncommon modality for detecting non-cancerous gynaecological pathology; however, the DETECT study supports its use, encouraging translation of other nuclear imaging advances to this field.

Implications of all the available evidence

The DETECT study suggests a role for ^{99m}Tc-maraciclatide and SPECT-CT imaging in the diagnostic pathway for endometriosis. If the results of this phase 2 study are replicated in larger studies, the findings would support the use of imaging with ^{99m}Tc-maraciclatide as a novel minimally invasive imaging test for endometriosis, especially in people with imaging-negative endometriosis.

superficial peritoneal endometriosis, clinicians are heavily reliant on laparoscopic identification.

Endometriosis can also exist beyond the pelvis. Estimates suggest that 12% of those with endometriosis have extra-pelvic disease, with thoracic endometriosis being the most common site beyond the abdominopelvic cavity.[9,10] Although imaging modalities, including x-ray, CT, and MRI, can be used to investigate thoracic endometriosis, their accuracy is restricted; therefore, video-assisted thoracoscopic surgery remains the gold standard.[9]

^{99m}Tc-maraciclatide is a gamma-emitting radiotracer that binds to αvβ3 integrins. These integrins are upregulated in endothelial cells of tissues undergoing inflammation-associated angiogenesis. However, in healthy tissue, αvβ3 integrins are minimally expressed, with some physiological exceptions, such as bone (osteoclasts) and endometrium.[11,12] Angiogenesis and inflammation are crucial mechanisms involved in the establishment of endometriosis, allowing lesions to develop a blood supply and proliferate.[13] Angiogenesis is mediated by proangiogenic factors, such as VEGF, which induces αvβ3 expression.[14] The presence of VEGF in ectopic endometriotic lesions varies, with higher expression in red lesions than black lesions, reflecting the belief that red lesions represent an earlier angiogenic phase in the lifecycle of a lesion.[15] This theory could also explain why red lesions are more commonly seen in younger people with endometriosis.[16] Higher vascular expression of αvβ3 integrins has been described in eutopic endometrium in people with endometriosis compared with control individuals, and expression has been shown throughout the menstrual cycle.[17,18]

Results of a phase 1, randomised, placebo-controlled study to assess the safety, biodistribution, and radiation dosimetry of ^{99m}Tc-maraciclatide in healthy volunteers have been reported.[19] ^{99m}Tc-maraciclatide was well tolerated, with no serious adverse events reported. The

mean effective dose per unit injected activity was 7·8 µSv/MBq (SD 0·8).

The detecting endometriosis integrins using technetium-99m imaging (DETECT) study explored the diagnostic potential of ^{99m}Tc-maraciclatide to visualise angiogenesis in endometriosis. We aimed to determine whether endometriosis can be visualised using ^{99m}Tc-maraciclatide in participants undergoing surgery for endometriosis.

Methods

Study design and participants

The DETECT study was a prospective, exploratory, open-label, non-randomised, single-centre, phase 2 study in a tertiary hospital setting that generated single-photon-emission CT-CT (SPECT-CT) imaging data before surgery (the reference standard). The Women's Centre and Oxford Endometriosis CaRe Centre (University of Oxford, Oxford, UK) served as the recruiting site, with scans completed at the Royal United Hospital (RUH; Bath, UK) due to availability of a Veriton-CT scanner (Spectrum Dynamics; Caesarea, Israel), which is a cadmium zinc telluride 360-degree acquisition SPECT-CT scanner and is more sensitive than traditional dual-head SPECT-CT scanners.

The study was sponsored by the University of Oxford and received ethics approval from the South Oxfordshire Research Ethics Committee (22/SC/0130), following approvals from the Administration of Radioactive Substances Advisory Committee and independent nuclear imaging risk assessments. Two people with endometriosis, independent of the study, reviewed and gave feedback on the study design and participant-facing documents before the study commenced. The study is registered with ClinicalTrials.Gov, NCT05623332, and is active. Potential participants were identified during endometriosis clinics or by assessing planned surgical lists within Oxford University Hospital, and approached based on scanner availability at RUH (convenience series), typically 2–4 weeks before planned surgery. After potential participants had sufficient time to consider the study information documents, an in-person or virtual meeting was held to complete an informed consent form, a copy of which was provided to the participant. Written consent was prioritised; however, if this was not possible, remote affirmative verbal consent was obtained. Consent was re-checked on the day of the scan and surgery. A data safety monitoring board was not implemented as maraciclatide was well tolerated in previous clinical studies and the chemical quantity administered was low (<40 nmol). The study protocol is included in the appendix (pp 5–47). Protocol amendments are detailed in the appendix (pp 48–50).

Female participants aged 18 years and older who were willing and able to give informed consent, with confirmed or suspected endometriosis (pelvic, extrapelvic, or both) based on previous clinical investigation (including symptom and examination findings, previous imaging, or both) and who were due to have laparoscopic or thoracoscopic surgery for suspected endometriosis, and who were willing and able to comply with scheduled visits were recruited. Exclusion criteria were pregnancy, breastfeeding, known renal or hepatic impairment, high-dose intravenous steroid use in the past 6 months, clinically significant disease—such as gynaecological cancers—that could put participants at risk or might affect the result of the study, participation in another research study that could affect the results of this study, previous reaction to technetium imaging agents, and inability to attend planned hospital visits or adhere to nuclear imaging safety restrictions. Baseline data for each participant were obtained using a modified World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) patient questionnaire,[20] completed before the SPECT-CT scan.[23] Ethnicity data were self-reported on the patient questionnaire.

Procedures

Maraciclatide is a chelate-peptide conjugate containing an arginine-glycine-aspartic acid amino acid motif in a configuration that specifically binds with nanomolar affinity to the integrin receptor αvβ3.[19] Radiolabelling was done under aseptic conditions in a hospital radiopharmacy. Maraciclatide was supplied as lyophilised kits stored at 2–8°C. Each vial contained approximately 44 nmol maraciclatide (molecular weight 1697) and all the excipients required for radiolabelling with sodium (^{99m}Tc) pertechnetate via incubation at room temperature for 20 min. The radiolabelled product could be used for up to 6 h after reconstitution. All preparations used in the study had a radiochemical purity of 90% or higher, tested using instant thin-layer chromatography.

2–7 days before their planned operation, participants were scheduled to have a SPECT-CT scan on a Veriton-CT scanner (figure 1). The first five participants were included in cohort 1, in which participants had scans at several timepoints (30 min [n=5], 90 min [n=4], 180 min [n=4], and 21 h [n=2]) after intravenous bolus injection—followed by 5 mL saline flush—of 740 MBq (±10%) ^{99m}Tc-maraciclatide to determine the optimal imaging timepoint after injection. Cohort 2 was recruited once it was determined that earlier imaging was preferred. Compared with later timepoints, imaging at 30 min showed fewer dynamic artefacts (eg, bladder filling or gut peristalsis signals produced by gastrointestinal activity). Moreover, earlier imaging was more acceptable for the participant and the scanning department, as the injection and scan could be done within a single appointment. Within cohort 2, participants were imaged between 10 min and 30 min after injection (for operational flexibility), with a preference for earlier imaging due to reduced dynamic artefacts from bladder filling. The SPECT-CT procedure contained a localisation CT and SPECT acquisition for 20 min (as either a single 20-min scan or two contiguous 10-min image sets). Where two 10-min image sets were acquired, the first set was used

See Online for appendix

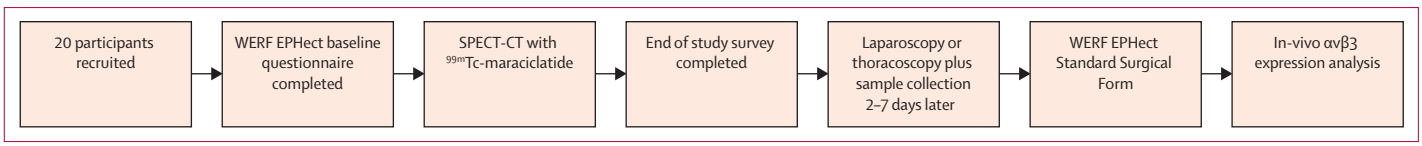

Figure 1: **Timeline of study procedures**
One of the 20 recruited patients did not have surgery. SPECT-CT=single-photon-emission CT-CT. WERF EPHect=World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project.

in the data analysis due to reduced dynamic artefacts. The second 10-min scan was used to validate any uncertainties surrounding the disease signal. Digital Imaging and Communications in Medicine files were analysed using Hermia imaging software (version 7.0.2; Hermes Medical; Stockholm, Sweden). Regions of interest (ROIs) were visually identified after surgery by a radiologist (MG) with more than 25 years of experience in nuclear imaging. The extent and characteristics of ^{99m}Tc-maraciclatide uptake in endometriosis lesions were unknown before this study, so iterative learning was required. As such, MG was not masked to the results of surgery during interpretation of images.

Endometriosis specialists (including CB) performed the laparoscopies in a British Society for Gynaecological Endoscopy-accredited endometriosis centre (EndoCaRe; Oxford University Hospitals, Oxford, UK). The thoracoscopic procedures were done by a consultant thoracic surgeon (FDC) with 18 years of experience who specialises in thoracic endometriosis. As per routine practice, samples were sent to a histopathologist for confirmation of endometriosis. During surgery, images and videos of the surgeon-defined ROIs were captured and matched against lesion categorisation according to the completed WERF EPHect standard surgical forms, which classified lesions by region, subtype, size, and colour (ie, red and black).[21] If data were missing on the forms, efforts were made to retrieve the information from the operating surgeon; otherwise, the chief investigator (CB) was asked to review surgical videos to make an assessment. Initially, surgeons did not see the images before surgery; as the study progressed and key features were understood, initial findings were shared before surgery, for information purposes. Images were not used to guide surgery.

After the study, participants were asked to complete an anonymous electronic survey to assess the acceptability of the test as a diagnostic and disease monitoring tool, and to compare with existing diagnostic methods. Responses were captured on REDCap software version 15.5.36.[22]

Outcomes

Study outcomes were assessed after completion of all the SPECT-CT imaging and the final surgical report. The prespecified primary outcome was agreement between the surgeon and the primary radiologist diagnosis of endometriosis, as determined by the presence of αvβ3 expression in ectopic lesions. Lesion definitions, including the distinction between superficial peritoneal endometriosis and deep endometriosis, were guided by the International Terminology on Endometriosis[23] and categorised by the assessing surgeon's visual assessment and experience.

Secondary outcomes were optimising the imaging window after injection, participant diagnostic preference, and participant experiences when undergoing this novel test. No data were obtained for the secondary outcomes to assess the feasibility of machine learning to improve the detection capabilities of the scans and to combine ultrasound and SPECT-CT images. Moreover, no saline flush samples were collected, so the planned secondary outcomes assessing the difference of αvβ3 in saline flush samples were not assessed.

Adverse event reporting began from the time of administering ^{99m}Tc-maraciclatide and was evaluated on a case-by-case basis. Participants who had adverse events were followed up until the event resolved.

Statistical analysis

The study sample size was determined to balance safety and to determine likely utility. The sample size was not powered to provide sensitivity and specificity calculations. Based on the expectation that 50% of women undergoing diagnostic laparoscopy are found to have disease,[24] a sample size of 20 was deemed acceptable for ruling out the utility of ^{99m}Tc-maraciclatide, should it show a minimum of ten false negatives. Only participants who completed both SPECT-CT imaging and surgery could be assessed against the planned outcomes. The primary outcome of radiologist and surgeon agreement at the participant level was defined as concordance, specificity, and sensitivity. The statistical analysis plan included the calculation of Cohen's κ to assess the level of agreement between diagnostic methods. Endometriosis ROIs were categorised by regions defined by the WERF EPHect surgical form[21] (right pelvic side wall, uterovesical fold, etc). Primary and secondary outcomes were assessed per protocol, and safety outcomes were assessed in all participants who underwent the SPECT-CT scan.[25] Sensitivity was calculated as number of occasions where imaging and surgery agreed disease was present divided by the number of participants positive by surgery. Specificity was calculated as the number of occasions where imaging and surgery agreed disease was not present divided by the number of participants negative by surgery. 95% CIs (Clopper–Pearson exact) were calculated using an online calculator.[25] Given the current

	Participants (n=20)
Age, years	
Mean (SD)	34·2 (8·9)
Range	20–59
Ethnicity	
White	18 (90%)
Asian (Indian)	2 (10%)
Previous surgical diagnosis	9 (45%)
Previous non-invasive imaging in the 12 months before participation in the study	
Ultrasound	14 (70%)
MRI	7 (35%)
Concurrent exogenous hormones at the time of the scan	
Progesterone-only pill	4 (20%)
Mirena intrauterine device	4 (20%)
Gonadotropin-releasing hormone agonist	1 (5%)
Hormone replacement therapy	1 (5%)
None	10 (50%)
Menstrual phase of the endometrium	
Proliferative	4 (20%)
Secretory	4 (20%)
Menstrual	1 (5%)
Unable to comment	10 (50%)
Missing questionnaire data	1 (5%)
American Society for Reproductive Medicine staging	
I	8 (40%)
II	2 (10%)
III	3 (15%)
IV	2 (10%)
Endometriosis subtypes	
Superficial peritoneal endometriosis	12 (60%)
Deep endometriosis	9 (45%)
Ovarian endometriomas	3 (15%)
Thoracic endometriosis	2 (10%)
Additional pelvic pathology	
Adenomyosis	6 (30%)
Salpingosis	1 (5%)
Fibroids	1 (5%)

Data are n (%), unless otherwise indicated.

Table 1: **Participant characteristics**

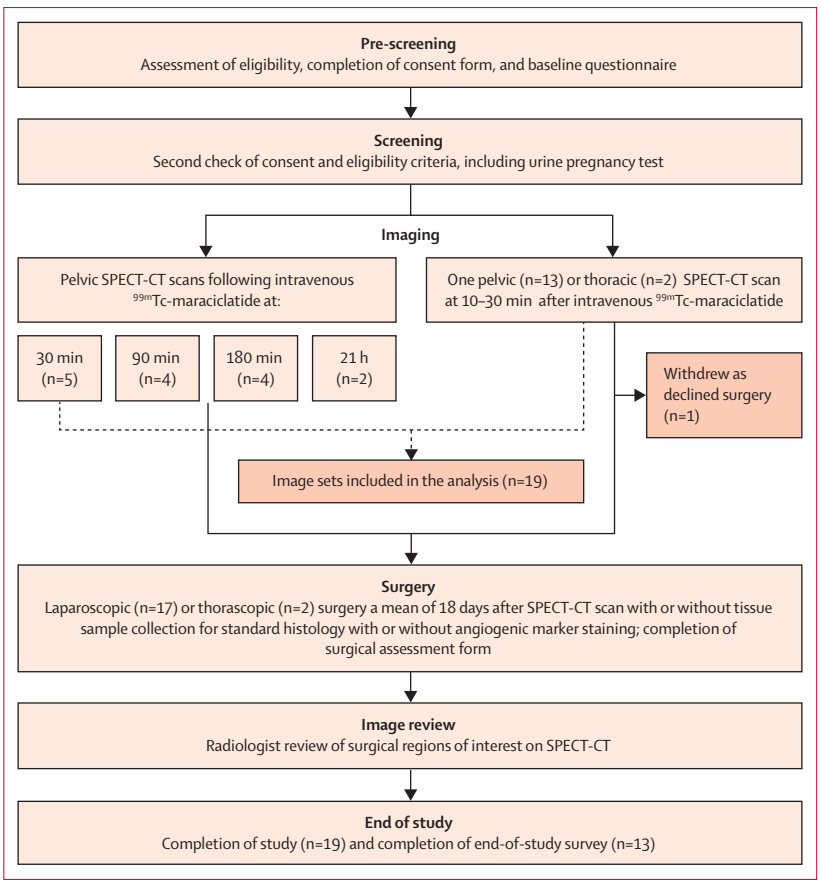

Figure 2: **Schematic of study events and patient flow**
In cohort 1, participants were imaged across various time points (30 min, 90 min, 180 min, and 21 h after injection). In cohort 2, participants were imaged once at 10–30 min after injection. SPECT-CT=single-photon-emission CT-CT.

diagnostic limitations in detecting superficial endometriosis, a post-hoc analysis on the agreement between radiologist and surgeon in detecting superficial disease was done.

Participant experiences on undergoing a SPECT-CT were assessed in a mixed-methods survey that included obtaining participants' level of satisfaction with the SPECT-CT scan and other diagnostic methods they had undergone (ultrasound, MRI, or laparoscopy), measured on a 0–10 numerical rating scale, along with selection of their preferred diagnostic test. Data were analysed with REDCap.[22]

For completeness and transparency, the Standards for Reporting Diagnostic Accuracy studies checklist was followed (appendix pp 2–4).

Role of the funding source

The National Institute for Health and Care Research Oxford Biomedical Research Centre had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Serac Healthcare provided project management support for the study set-up, co-ordinated between the surgical team and the radiologists on image reads, hosted the images and workstation as a central resource for the study, reviewed the manuscript, and supported comment resolution.

Results

Between March 6, 2023, and Sept 16, 2024, 20 participants were recruited and imaged (table 1). 18 (90%) of 20 participants had pelvic scans, 17 (94%) of whom underwent subsequent laparoscopy (figure 2). One (5%) participant decided against surgery, and her data were excluded from the study. Two (10%) participants had

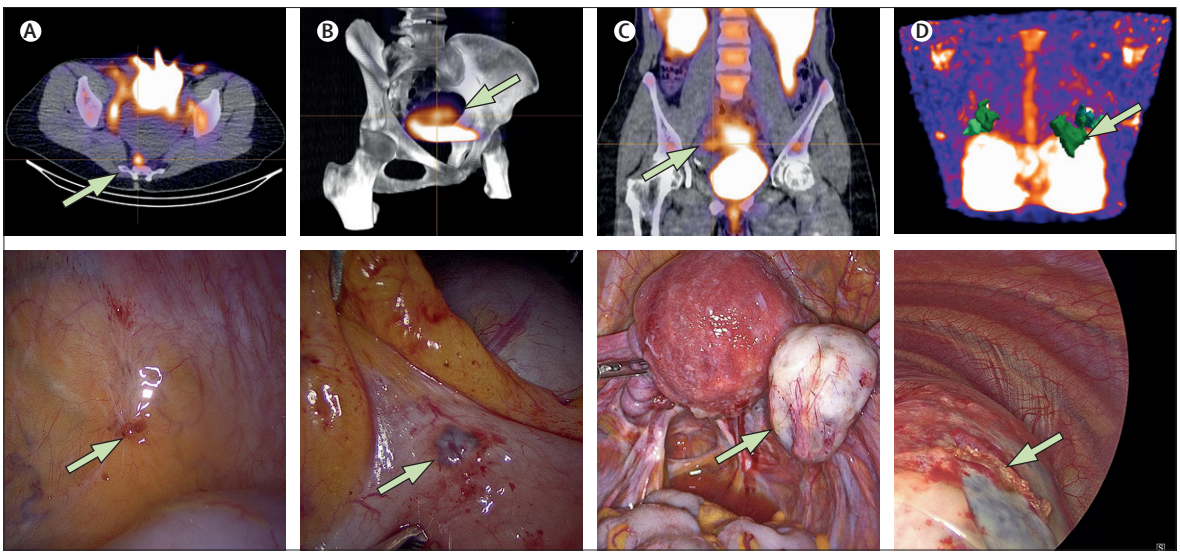

Figure 3: **Representative single-photon-emission CT-CT detection and matching surgical images of superficial peritoneal endometriosis (A), deep endometriosis (B), ovarian endometrioma (C), and thoracic endometriosis (D) from four different participants**
Arrows indicate region of interest. Thorax images were taken using only single-photon-emission CT imaging.

	Surgery positive for endometriosis (N=17)	Surgery negative for endometriosis (N=2)	Total (N=19)
^{99m}Tc-maraciclatide positive for endometriosis	14	0	14
^{99m}Tc-maraciclatide negative for endometriosis	3*	2	5
Agreement	14/17 (82%, 95% CI 56–96)	2/2 (100%, 95% CI 16–100)	16/19 (84%, 95% CI 60–97)

19 of 20 participants underwent pelvic or thoracic surgery after imaging with ^{99m}Tc-maraciclatide (one participant withdrew from surgery after scanning). *One participant with a fibrotic rectovaginal nodule; one participant receiving gonadotropin-releasing hormone agonists with an inactive superficial lesion on their bladder that was histologically negative for endometriosis; and one participant with superficial peritoneal endometriosis in the uterovesicular fold that was obscured by background signal in the bladder—however, uptake was seen in the left fallopian tube, where endosalpingiosis was seen during surgery.

Table 2: **Agreement between surgery and single-photon-emission CT-CT imaging for all endometriosis lesion types**

thoracic scans with subsequent thoracoscopic surgery. Endometriosis was detected surgically and supported by histology where feasible in 17 (84%, 95% CI 60–97) of the 19 participants who completed the study. 18 (95%) of 19 participants who had surgery had it within the protocolled time of under 3 months, with a mean of 19 days (SD 15) after SPECT-CT. One participant had surgery outside the protocolled time, at 154 days, due to surgical cancellations. Data regarding additional pelvic pathology were obtained from surgical reports, by reviewing the participants' most recent MRI or ultrasound, or both. Five of the transvaginal ultrasounds completed were advanced specialist scans, and a radiologist with a special interest in endometriosis interpreted all seven MRIs. The main protocol deviation was not completing all secondary outcomes; these outcomes and the justification for not completing them are in the appendix (pp 48–50).

This exploratory study identified all three pelvic endometriosis subtypes—superficial peritoneal endometriosis, ovarian endometrioma, and deep endometriosis—and thoracic endometriosis (figure 3). ^{99m}Tc-maraciclatide signal (ie, localisation outside of physiological uptake and aligned with anatomical landmarks) agreed with the intraoperative diagnosis or exclusion of endometriosis in 16 (84%, 95% CI 60–97) of 19 participants (prespecified primary outcome). Although the study was not powered for definitive diagnostic accuracy, participant-level sensitivity was calculated to be 82% (95% CI 57–96) and specificity to be 100% (16–100). In the two (10%) participants in whom endometriosis was not seen during diagnostic laparoscopic surgery (negative cases), the ^{99m}Tc-maraciclatide images did not show any areas beyond physiological uptake. ^{99m}Tc-maraciclatide-positive pelvic endometriosis was intraoperatively visually confirmed in 14 (82%, 95% CI 57–96) of 17 participants (the primary outcome; table 2). Despite high observed agreement between surgeon and radiologist, the pre-statistical plan to use Cohen's κ was omitted due to an imbalance in participants with (17 [89%] participants) and without (two [11%] participants) endometriosis, leading to the kappa paradox. This paradox arises when low prevalence in one category, for example, participants without endometriosis, distorts the kappa coefficient, misrepresenting the true level of methodological agreement.[26]

For each participant with pelvic endometriosis undergoing a laparoscopy, the completed WERF EPHect standard surgical form[21] was assessed in terms of the lesion's anatomical region (eg, pelvic side wall), subtype, size, and colour. The forms categorised lesions into three sizes: less than 1 cm (eight [20%] lesions), 1–3 cm (26 [63%] lesions), and more than 3 cm (seven [17%] lesions)

diameter. The ^{99m}Tc-maraciclatide scan detected superficial peritoneal endometriosis and deep endometriosis lesions estimated to be less than 1 cm in diameter, and an endometrioma estimated to be 2 cm in diameter.

Subcategorisation of the 26 superficial peritoneal endometriosis lesions seen during surgery with available WERF EPHect questionnaire data, found that clear or clear-red lesions were the most common (seven [27%] lesions); followed by blue, blue-black, or blue-black-white (six [23%] lesions); white or yellow-white (six [23%] lesions); red, red-white, red-brown-white, red-blue-white (three [12%] lesions); and brown (one [4%] lesion). ^{99m}Tc-maraciclatide identified three clear lesions (assessment of the remaining clear-red lesions was obstructed by background bladder or uterus activity). Additionally, ^{99m}Tc-maraciclatide detected superficial peritoneal endometriosis lesions classified as filmy blue pseudocyst (one lesion), red (one lesion), red-white or red-brown-white (two lesions), yellow-white (one lesion), and white (one lesion). Although ^{99m}Tc-maraciclatide unexpectedly detected fibrotic (white) disease, the right ovarian fossa and uterosacral ligament of this participant was found to have fibrotic superficial and deep endometriosis surrounded by highly vascularised tissue. In this case, ^{99m}Tc-maraciclatide likely detected the surrounding vascularity and inflammation, rather than the fibrotic superficial peritoneal endometriosis lesion.

Beyond the primary outcome, the agreement of imaging with superficial peritoneal endometriosis was assessed as an important exploratory outcome. In addition to analysing for all endometriosis-related disease, analysis for superficial peritoneal endometriosis was also done due to the substantial diagnostic gap for this lesion type. As previously discussed, detection of superficial peritoneal endometriosis remains a crucial limitation of existing imaging techniques. ^{99m}Tc-maraciclatide imaging was successful in identifying superficial peritoneal endometriosis in nine (75%; 95% CI 43–95) of 12 participants with superficial peritoneal endometriosis (table 3). Ten (83%) participants with superficial peritoneal endometriosis had previous imaging with traditional modalities (transvaginal ultrasound, MRI, or both) in the past 12 months, none of which had detected superficial peritoneal endometriosis. In the three (25%) participants in whom the ^{99m}Tc-maraciclatide scan missed superficial peritoneal endometriosis, two (17%) had bladder or uterovesical fold superficial peritoneal endometriosis, for which the reporting radiologist noted that bladder accumulation would have masked any possible marker uptake, and one (8%) had pelvic side wall superficial peritoneal endometriosis, for which the radiologist reported that activity in the ureter would have masked any possible marker uptake. Future studies should explore actions to reduce bladder activity. Thoracic endometriosis was visualised using ^{99m}Tc-maraciclatide in both cases in which thoracic disease was seen during surgery.

	Laparoscopy positive for superficial peritoneal endometriosis (N=12)	Laparoscopy negative for superficial peritoneal endometriosis (N=5)	Total (N=17)
^{99m}Tc-maraciclatide positive	9	0	9
^{99m}Tc-maraciclatide negative	3*	5	8
Agreement	9/12 (75%, 95% CI 43–95)	5/5 (100%, 95% CI 47–100)	14/17 (82%, 95% CI 52–96)

There is no established classification system for identifying extra-pelvic endometriosis so only the 17 participants who had pelvic laparoscopy were included within this subgroup. *One participant receiving a gonadotropin-releasing hormone agonist with an inactive (fibrotic) superficial lesion on her bladder that was histologically negative for endometriosis; one participant with superficial peritoneal endometriosis on the uterovesical fold which was obscured by bladder background. However, uptake was seen in the left fallopian tube where endosalpingiosis was seen during surgery; one participant with superficial peritoneal endometriosis on the left pelvic side wall and left ovary, with uptake seen in a deep endometriosis lesion in the pouch of Douglas.

Table 3: **Agreement between pelvic laparoscopy and single-photon-emission CT-CT imaging for superficial peritoneal endometriosis**

Completed surveys were retrieved from 13 (65%) of 20 participants. The acceptability of the scan as a diagnostic test (mean 97·4, SD 5·7; visual analogue scale 0–100) and a disease monitoring tool (97·7, 7·1) was high. Compared with other diagnostic tests, SPECT-CT was rated the highest in terms of satisfaction, as most scores on a numerical rating scale were clustered between 8 and 10 (appendix p 65). This finding was supported by SPECT-CT being rated as the top choice for diagnostic test in nine (69%) of 13 participants, if an accurate diagnosis could be made (appendix pp 51–64).

One (5%) participant reported abdominal pain, diarrhoea, and nausea within the first 3 h after injection of the marker. The participant was followed up until the symptoms resolved within 24 h. Another participant reported arm pain after the scan due to the position in which the arms were held during the scan and the repeated scans. No other adverse events related to the study were noted.

Discussion

There is an urgent need for advancement in non-invasive or minimally invasive imaging of endometriosis, particularly superficial peritoneal endometriosis, given the current reliance on invasive procedures for an accurate diagnosis. The DETECT study describes, for the first time to our knowledge, a minimally invasive diagnostic technique using the detection of angiogenic integrins to visualise endometriosis in humans, including superficial peritoneal endometriosis, which, despite being the most common subtype, cannot be reliably visualised with existing imaging modalities. ^{99m}Tc-maraciclatide identified examples of all endometriosis subtypes. The scan was well tolerated, with only one participant reporting transient, minor side-effects. Participant acceptability was high, highlighting the potential of nuclear imaging to advance minimally invasive diagnostics in endometriosis. SPECT-CT cameras typically available in North America and Europe

would be capable of using this technique, which will be explored in subsequent studies.

A strength of the study was the recruitment of a representative group of people with endometriosis, including those with extrapelvic endometriosis, and a range of ages and various exogenous hormonal exposures. Half of the study participants were taking exogenous hormones, which reflects the findings of larger studies assessing hormonal treatment use in people with endometriosis.[27] Despite hormone use, the SPECT-CT scan was able to detect lesions of each endometriosis subtype, supporting the applicability of the scan to various patient groups. SPECT-CT scanning also showed that despite the use of exogenous hormones, angiogenic pathways continue to propagate. The oestrogen-driven specificity protein 1 pathway, believed to regulate VEGF expression, which is involved in the cause and maintenance of peritoneal endometriosis, still exists in endometriotic lesions of those on gonadotropin-releasing hormone analogue therapy.[28] The angiogenic potential of lesions is likely to play a role in lesion detection, as the majority of detected superficial peritoneal endometriosis lesions were clear, red, or mixed red. Red lesions are known to express higher levels of VEGF than do black lesions, and a higher fraction of immature vessels.[15,29] This finding supports the hypothesis that black lesions represent a later stage in the lesion life cycle, whereby lower levels of neo-angiogenesis are present. Blue-black lesions are frequently encountered during laparoscopy; the scan only showed one of 11 regions of interest identified with blue-black or blue-black-white superficial or deep lesions Similarly, ^{99m}Tc-maraciclatide uptake was observed in two of 16 regions of interest identified with white-fibrotic endometriosis (detection in the single-photon-emission lesion was attributed to surrounding vascularity). That ^{99m}Tc-maraciclatide identifies inflammatory lesions, but not fibrotic ones, is consistent with its mechanism of action and performance in other, non-endometriosis-related studies.[30,31] In the setting of endometriosis, this factor is likely to be a strength rather than a limitation of the agent, as it might allow for therapeutic approaches to be tailored to individual people.

The study was done in a small number of participants, as this was a phase 2 study to generate preliminary evidence of imaging performance characteristics. The number of participants imaged without endometriosis was substantially lower than expected, which limits confidence in the detection of false-positive imaging. The radiology reads were completed unmasked to the surgical reports as the imaging characteristics of lesions needed to be understood. However, phase 3 studies, powered to provide accurate performance characteristics with masked image evaluation, are planned by the maraciclatide product owner Serac Healthcare.

Urinary tract endometriosis has been estimated to affect between 0·3% and 12% of those with endometriosis, with bladder endometriosis being the most common site.[32] Detection of endometriosis in close proximity to the bladder, where the signal is masked by tracer accumulation in the bladder, currently limits the usefulness of the scan in those with isolated bladder endometriosis. However, as most of those with bladder endometriosis also have at least one other site affected,[33] which can be visualised, this suggests utility in the majority of patients. Bladder accumulation is a common concern with nuclear imaging markers, for example, in prostate scans. Imaging software advances are aiding in mitigating this issue; however, in future studies of those with high suspicion of bladder endometriosis, use of a urinary catheter to improve bladder-focused visualisation could be considered. The imaging window in our study was chosen to minimise the effect of physiological uptake. The main area of physiological uptake that can affect visualisation of disease is urinary excretion. Uterine or endometrium uptake of maraciclatide was not observed across all imaged participants, supporting the hypothesis that visible uptake is associated with underlying abnormality. Other physiological uptake associated with the bowel is a slower process and has no effect during the 10–30-min imaging window.

Other disease processes that would be expected to show tracer uptake are malignancies, inflammation or immune disorders, and wound healing. In the likely age group that this technique would be most useful malignancies would be rare. Inflammation or immune disorders of the bowel might affect visualisation but there are no data to assess this issue. If this test was to be used in routine practice, it would provide a minimally invasive diagnostic technique using widely available nuclear medicine equipment and techniques. The benefits of minimally invasive and earlier diagnosis would need to be weighed against radiation exposure (which is similar to other existing SPECT-CT imaging agents).

SPECT-CT imaging with ^{99m}Tc-maraciclatide shows promise as a novel diagnostic test providing functional information in addition to the anatomical data provided by ultrasound and MRI. Developing a method to characterise disease processes could extend beyond diagnostics and aid in reducing uncertainties surrounding disease recurrence, thereby eliminating the need for second-look laparoscopies in disease monitoring or clinical trials. This approach could also potentially provide a marker of treatment response for novel anti-angiogenesis and other treatment development.

In conclusion, the DETECT study shows that imaging with ^{99m}Tc-maraciclatide reliably visualises endometriosis, accurately detecting endometriotic lesions missed by conventional imaging methods. These results indicate that ^{99m}Tc-maraciclatide offers a promising and acceptable diagnostic and monitoring tool, particularly for superficial peritoneal endometriosis. A planned phase 3 study aims to validate these findings in a larger group of participants.

Contributors

TG, DB, JB, KZ, and CB contributed to the conceptualisation, project methodology—including protocol development and amendments—and

the conduct of the study. CB served as the study principal investigator. TG, CB, and FDC were responsible for recruitment of participants. TG was responsible for arranging the study events, leading participant discussions, collecting data, and other administrative tasks. CB, FDC, and other surgeons at Oxford University Hospital were responsible for operating on participants according to standard practice, in addition to completing data collection forms and taking tissue samples. SC and RG were responsible for tasks related to planning, methodology, and conduct of the scans within the Royal United Hospital (Bath, UK). Images were primarily interpreted by MG. However, data analysis and interpretation were done by TG, MG, DB, JB, NP, FDC, CB, and KZ. The original draft was written by TG, DB, JB, KZ, and CB, with visualisation, review, and editing contributions from all authors. TG and CB verified the underlying data reported in this manuscript. All authors take responsibility for the decision to submit for publication. All authors had access to the data.

Declaration of interests

TG received funding from Serac Healthcare and the National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre to conduct the study. Additionally, Serac Healthcare provided financial support for TG's presentation of the DETECT study at two international conferences. TG received a consultancy payment from Cala Lilly. TG reports non-remunerated work as an early career ambassador for the World Endometriosis Society. MG declares consultancy work for Serac Life Sciences, Siemens, Telix, Lantheus, ITM, Novartis, Blue Earth, and Bayer. DB is Chief Scientific Officer for and shareholder in Serac Healthcare and has received funding from Serac Healthcare to attend meetings and for travel. RG is a board member for Ingenium AI and LEAP Digital Health Hub. RG is also the Bone and Joint Chair for European Association of Nuclear Medicine (EANM), a Confederation of Medical Reserve Officers Scientific Committee member, an European Society of Musculoskeletal Radiology Arthritis Committee member, an Administration of Radioactive Substances Advisory Committee member, Medical Advisor for Parathyroid UK, Director of Research and Innovation at Royal United Hospitals Bath NHS Foundation Trust, Clinical Society of Bath President, EANM Innovation Editorial Board member, Royal College of Radiologists iRefer Nuclear Medicine Panel Chair, and Director of Sulis Imaging at Medical and Medicolegal Private Practice. Additionally, RG delivered a paid talk for GE Healthcare. RG is a radiology medicolegal expert witness. JB is an employee of Serac Healthcare and holds employee stock options. KZ reports research funding from Serac Healthcare, Gates Foundation, US Department of National Defence, US National Institute of Health, EU Horizon 2020, Bayer, Aspira, Exeltis, and Proteomics. KZ reports consulting fees from Gedeon Richter, Roche, and LIDEA. KZ also reports financial support for meeting attendance as an invited speaker for ESHRE 2025, SEUD 2024, EEC 2024, and LIDEA 2023. KZ reports non-remunerated board membership with WERF. CB did consultancy work for Serac Healthcare, Myovant, ObsEva, Theramex, Gedeon Richter, and Gesynta. All funding for CB and KZ went to the University of Oxford. All other authors declare no competing interests.

Data sharing

Data supporting this study are available from the authors upon request and with permission from Serac Healthcare for maraciclatide imaging data. JB (jonbarnett@seraclifesciences.com) should be contacted to request the data.

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