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Somatostatin receptor-targeted DOTATATE PET/CT in breast cancer and breast lesions: a systematic review of detection, incidental findings and theranostic potential

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Abstract

Background

Somatostatin receptor 2 (SSTR2) is expressed by a subset of breast cancers, particularly oestrogen receptor (ER)-positive tumours. DOTATATE PET/CT, the reference standard for neuroendocrine tumour (NET) imaging, is increasingly relevant to breast cancer staging, incidental findings and theranostic selection. We systematically reviewed its clinical performance.

Methods

Following PRISMA 2020 (PROSPERO CRD420261508548), Embase, Scopus and PubMed were searched to 16 September 2026, supplemented by citation searching. Studies reporting DOTATATE PET findings in breast cancer or breast lesions were included. Risk of bias was assessed with QUADAS-2 and Joanna Briggs Institute tools, certainty with GRADE, and findings were synthesised narratively.

Results

Nineteen studies (four prospective, two retrospective cohorts, three case series, ten case reports) including 107 patients with breast carcinoma were analysed. In head-to-head comparisons (n = 56), DOTATATE detected disease in most patients and matched ^{18}F-FDG for skeletal (252 vs 255 lesions) and nodal metastases, but identified half as many visceral metastases (134 vs 262), particularly in the liver. Uptake favoured ER-positive, lobular and neuroendocrine tumours. Focal breast uptake occurred on 1.1% of scans performed for other indications; 21.4% of characterised lesions were malignant and SUVmax did not discriminate benign from malignant lesions. Krenning scores ≥ 3 were found in 15/76 (19.7%) patients across three prospective studies. Certainty of evidence was very low.

Conclusions

DOTATATE PET/CT complements, but cannot replace, ^{18}F-FDG for breast cancer staging, and is less established than ^{18}F-FES. Incidental breast uptake warrants standard breast work-up regardless of intensity. Around one-fifth of patients with ER-positive metastatic disease show high SSTR expression, although whether this has therapeutic relevance remains uncertain.

Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide [1]. Most tumours express the oestrogen receptor (ER), and their imaging is shaped by that biology. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT is now widely used for systemic staging of locally advanced and metastatic disease [2–4]. However, glucose avidity is lower in ER-positive, low-proliferation and lobular tumours, and sclerotic bone metastases may be FDG-negative [5–7]. These are the same phenotypes in which conventional and metabolic imaging most often underperform, and a receptor-based tracer that complements FDG in these patients has obvious appeal.

Somatostatin receptors (SSTRs), particularly SSTR2, have been described in breast cancer for more than three decades. Autoradiography and mRNA studies have shown SSTR expression in a substantial proportion of primary tumours, with higher levels in ER-positive and well-differentiated cancers [8–11]. Oestrogen up-regulates SSTR2 transcription in breast cancer cells [12], and SSTR2 expression is retained in a proportion of metastases [13, 14]. Early in vivo work with ^{111}In-pentetreotide scintigraphy visualised many primary breast cancers, but sensitivity was limited by resolution and lesion size [15, 16].

Positron-emitting gallium-68-labelled somatostatin analogues have since transformed SSTR imaging. ^{68}Ga-DOTATATE binds SSTR2 with high affinity [17] and is now the reference tracer for neuroendocrine tumours (NETs) [18, 19]. Its therapeutic counterpart, ^{177}Lu-DOTATATE, prolongs progression-free survival in midgut NETs [20]. Following the success of prostate-specific membrane antigen theranostics [21], interest has grown in whether other SSTR-expressing cancers might be imaged and treated in the same way. For breast cancer, this question arises in three distinct settings: deliberate imaging of known breast cancer, interpretation of incidental breast or breast-cancer-related uptake on scans performed for NETs, and selection of patients for SSTR-directed radioligand therapy.

Evidence in each setting is scattered across case reports, conference abstracts and small prospective studies. Existing systematic reviews have addressed SSTR imaging in breast cancer only as one target among many in breast theranostics [22], within SSTR PET applications beyond NETs [23], or as a small subgroup of a multi-tracer analysis of incidental breast uptake [24]. No review has yet focused on DOTATATE PET across the full range of breast cancer settings. We therefore systematically reviewed the published clinical experience of ^{68}Ga-DOTATATE PET/CT in breast cancer, focusing on lesion detection relative to ^{18}F-FDG, the relationship between tracer uptake and tumour biology, the frequency and differential diagnosis of incidental findings, and the theranostic potential of SSTR targeting.

Materials and methods

Protocol and reporting

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [25]. The review was prospectively registered with PROSPERO (CRD420261508548) on 16 September 2026.

Search strategy

MEDLINE (via PubMed), Embase (via Embase.com) and Scopus were searched from inception to 16 September 2026. Strategies combined three concepts: DOTATATE and DOTATATE-based radiotracer terminology (including gallium-68 and copper-64 labelled forms), PET or hybrid PET imaging, and breast lesion, breast cancer and mammary terminology. Controlled vocabulary (MeSH and Emtree) and free-text terms were used. No date, language, human or study-design limits were applied, so that conference abstracts and case reports could be identified. Full search strategies are provided in Supplementary Methods S1. Reference lists of included studies were screened (backward citation searching), and articles citing included studies were identified (forward citation searching).

Eligibility criteria

Eligible studies reported DOTATATE PET, PET/CT or PET/MRI findings (with ^{68}Ga-DOTATATE or another radionuclide-labelled DOTATATE, such as ^{64}Cu-DOTATATE) in adults in one of three settings. These were known, suspected, recurrent or metastatic breast cancer of any histological type, including breast neuroendocrine neoplasms; an incidental focal breast lesion identified on DOTATATE PET performed for another indication; or assessment of SSTR expression before SSTR-targeted therapy. All study designs reporting original patient data were eligible, including case reports, case series and conference abstracts. No comparator was required. Studies using only non-DOTATATE SSTR tracers (for example ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC or ^{111}In-pentetreotide), animal or in-vitro studies, studies of DOTATATE therapy without pre-therapy PET data, and reviews or editorials without original data were excluded, as were reports of non-breast malignancies without separately extractable breast data. Reports in which the only breast finding was a metastasis from an extramammary NET, with no primary breast lesion, were considered an ineligible population. Throughout this review, DOTATATE PET refers to ^{68}Ga-DOTATATE unless otherwise stated.

Study selection and data extraction

Records were imported into Covidence (Veritas Health Innovation, Melbourne, Australia), where duplicates were removed automatically and manually. Two reviewers (CM and EF) independently screened titles and abstracts and then full texts, and disagreements were resolved by discussion. Where an abstract had since been published in full, the full report was used. Data were extracted independently by two reviewers using a piloted form and included study design, country, setting, number of patients, indication for imaging, histology and receptor status, comparator imaging, semi-quantitative uptake (maximum standardised uptake value, SUVmax), Krenning score, reference standard and clinical consequence.

Risk of bias and synthesis

As registered, comparative and cohort imaging studies were appraised with the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [26]. Because QUADAS-2 is not designed for single-patient reports, case series and case reports were additionally appraised with the corresponding Joanna Briggs Institute (JBI) checklists, interpreted with the domains proposed by Murad et al. [27, 28]; this was a deviation from the registered protocol. Appraisal was performed independently by two reviewers. Certainty of evidence for the main outcomes was rated using the GRADE approach and summarised in a summary-of-findings table. The protocol specified bivariate meta-analysis if at least four sufficiently homogeneous studies reported diagnostic 2 × 2 data against comparable reference standards. No study provided such data, so findings were synthesised narratively across the prespecified clinical scenarios. Simple aggregate counts are presented descriptively where outcomes were defined comparably.

Results

Study selection and characteristics

The database search identified 505 records (Embase 256, Scopus 180, PubMed 69). After removal of 223 duplicates, 282 records were screened and 49 reports were sought for retrieval. Seven could not be retrieved in full text, and the remaining 42 were assessed for eligibility. Twenty-five were excluded, most commonly for an ineligible population (n = 19), leaving 17 studies. Citation searching identified three further eligible reports (two by backward and one by forward citation searching). One could not be retrieved in full text and two were included [29, 30], giving 19 included studies (Fig. 1).

The included studies were published between 2009 and 2026 and originated from Turkey (n = 5), the United States (n = 3), Australia, India and Poland (n = 2 each), and Belgium, Chile, China, Switzerland and the United Kingdom (n = 1 each) (Table 1). There were four prospective studies [29, 31–33], two retrospective cohorts [34, 35], three case series [36–38] and ten case reports [30, 39–47]. Three were available only as conference abstracts [37, 38, 46]; a fourth had since been published in full [41]. In the prespecified sensitivity analysis, excluding the abstracts (five patients) altered no conclusion: they contributed no comparative, receptor or Krenning data, and all lobular (7 of 7) and neuroendocrine (6 of 6) tumours remained avid. In total, 107 patients with breast carcinoma underwent ^{68}Ga-DOTATATE PET, 86 of them in the four prospective studies. A further 14 patients with SSTR-positive breast lesions of other aetiologies (11 benign lesions and 2 NET metastases from one cohort, and 1 fibroadenoma from another) contributed data on specificity [34, 35].

Table 1
Characteristics of the 19 included studies

Study	Country	Design	Breast-relevant patients	Indication for ^{68}Ga-DOTATATE PET	Breast histology / receptor status	Comparator	Principal finding
Ambinder 2020 [39]	USA	Case report	1	Surveillance of metastatic small-bowel NET	Invasive mammary carcinoma; ER+/PR+/HER2−	Mammography, US	New avid breast mass (SUV 3.8) and axillary node during NET response; subtle on baseline scan
Barahona 2022 [40]	Chile	Case report	1	Characterisation of FDG-negative ileal nodule	ILC (HR+) and contralateral HER2 + ductal carcinoma	^{18}F-FDG	FDG-negative osteolytic bone metastases avid on DOTATATE; initially attributed to NET, biopsy showed ILC
Batty 2023 [36]	Australia	Retrospective case series	7 (6 imaged)	Staging/treatment selection, metastatic breast NEN	Breast NEN (WHO 2019); mostly ER+; Ki-67 20–90%	^{18}F-FDG	All 6 avid; FDG+/DOTATATE− discordance in 5/6; 1 treated with ^{177}Lu-DOTATATE
Beydağı 2025 [41]	Turkey	Case report	1	Staging of pancreatic lesion in patient with breast cancer	ILC	^{18}F-FDG, ^{68}Ga-Trivehexin	Breast ILC and pancreatic G2 NET both intensely DOTATATE-avid; ILC also integrin-avid on ^{68}Ga-Trivehexin
Chandekar 2025 [31]	India	Prospective phase II	30	Theranostic screening, ER+ metastatic breast cancer	IBC-NST; ER + 100%, HER2 + 27%	^{18}F-FDG	Per-patient 96.7% vs 100%; fewer visceral lesions (128 vs 235); Krenning ≥ 3 in 10%
Deleu 2021 [42]	Belgium	Case report	1	Suspected progression on atezolizumab	Triple-negative	^{18}F-FDG	Recurrence DOTATATE-negative; avid nodes confirmed sarcoid-like reaction
Desai 2009 [37]	UK	Case series (abstract)	3 breast cancers (15 breast masses)	NET clinic, uncommon metastatic sites	Not reported	Mammography	Of 15 breast masses, 12 NET metastases and 3 breast cancers; all 3 cancers avid
Filizoglu 2024 [43]	Turkey	Case report	1	Adrenal mass, suspected primary adrenal malignancy	IDC (treated 8 years earlier)	MRI	Avid solitary adrenal metastasis (SUVmax 24.5)
Has Simsek 2021 [34]	Turkey	Retrospective cohort	14 (of 1573 scans)	NET, MTC or suspected NET	IDC 1; NET metastases 2; benign 11	Mammography, US, histology	SSTR+ breast lesions in 1.1%; 21.4% malignant; SUVmax non-discriminatory
Hu 2023 [44]	China	Case report	1	Unknown primary after rectal polypectomy	Occult ILC; ER+/PR+/GATA3+	^{18}F-FDG, MRI, US	Nodal metastases SUVmax 8.4 vs 2.1 on ^{18}F-FDG; breasts negative
Kalshetty 2020 [45]	India	Case report	1	Dual-tracer PET during PRRT for jejunal NET	Triple-negative IDC, grade 3	^{18}F-FDG, mammography	New FDG+/DOTATATE− subcentimetre breast lesion = second primary
Kemle 2026 [30]	Switzerland	Case report	1	Staging of typical pulmonary carcinoid	ILC; ER 100%, HER2−, Ki-67 20%	^{18}F-FDG	Two FDG-negative sclerotic bone lesions (SUVmax 10.2) proved to be ILC metastases; partial response on

CT computed tomography; DCIS ductal carcinoma in situ; ER oestrogen receptor; HER2 human epidermal growth factor receptor 2; HR hormone receptor; IBC-NST invasive breast carcinoma of no special type; IDC invasive ductal carcinoma; ILC invasive lobular carcinoma; LCIS lobular carcinoma in situ; MRI magnetic resonance imaging; MTC medullary thyroid carcinoma; NEC neuroendocrine carcinoma; NEN neuroendocrine neoplasm; NET neuroendocrine tumour; PR progesterone receptor; PRRT peptide receptor radionuclide therapy; SSTR somatostatin receptor; SUV standardised uptake value; US ultrasound

Study	Country	Design	Breast-relevant patients	Indication for ^{68}Ga-DOTATATE PET	Breast histology / receptor status	Comparator	Principal finding
							follow-up DOTATATE
Kuyumcu 2013 [35]	Turkey	Retrospective cohort	1 (of 120 scans)	Known or suspected NET	Fibroadenoma	Clinical follow-up	Mild fibroadenoma uptake (SUVmax 3.76) as benign mimic
Lapinska 2016 [38]	Poland	Case series (abstract)	1 (of 9)	Esthesioneuroblastoma	Breast cancer (subtype not reported)	Not reported	Small breast lesion with moderate uptake diagnosed as breast cancer
Loughner 2025 [46]	USA	Case report (abstract)	1	Staging of phaeochromocytoma	Invasive neuroendocrine carcinoma; ER/PR+	CT	Avid retroareolar mass; synchronous primary breast NEC
Nguyen 2022 [32]	Australia	Prospective pilot	10	Restaging, progressive ER+/PR+/HER2 – metastatic disease	IDC 8, ILC 1, unknown 1	^{18}F-FDG, bone scan, CT	Similar per-patient detection; visceral 6 vs 27 lesions; uptake tracked metastatic ER/PR
Sezgin 2025 [33]	Turkey	Prospective observational	16	Initial staging, therapy-naïve	NST 13, ILC 1, mixed 1, DCIS 1; luminal 13	^{18}F-FDG	No significant SUV difference; axillary specificity 100% vs 87.5%; Krenning ≥ 3 in 18.8%
Ulaner 2024 [29]	USA	Prospective phase II	30	Theranostic screening, ER+ metastatic breast cancer (^{68}Ga- or ^{64}Cu-DOTATATE)	IDC 25, ILC 5; ER+	^{18}F-FDG (not formally compared)	Krenning 3–4 in 30%; ^{225}Ac-DOTATATE in 1 patient: complete metabolic response, then SSTR2-negative recurrence
Zemczak 2024 [47]	Poland	Case report	1	Follow-up of pancreatic NET	ILC grade 2 with LCIS; pT2N0	Contrast-enhanced mammography, MRI	Faint breast uptake (SUVmax 1.0) rising to 2.1 over 11 months; ILC on biopsy

CT computed tomography; DCIS ductal carcinoma in situ; ER oestrogen receptor; HER2 human epidermal growth factor receptor 2; HR hormone receptor; IBC-NST invasive breast carcinoma of no special type; IDC invasive ductal carcinoma; ILC invasive lobular carcinoma; LCIS lobular carcinoma in situ; MRI magnetic resonance imaging; MTC medullary thyroid carcinoma; NEC neuroendocrine carcinoma; NEN neuroendocrine neoplasm; NET neuroendocrine tumour; PR progesterone receptor; PRRT peptide receptor radionuclide therapy; SSTR somatostatin receptor; SUV standardised uptake value; US ultrasound

Risk of bias

Overall methodological quality was low to moderate (Table 3; Supplementary Tables S1–S3). Among the imaging cohorts, the reference standard was the most frequent source of high risk of bias: histopathological verification of discordant lesions was not performed in the prospective comparisons, and lesion-level "truth" was largely inferred from the comparator tracer or from follow-up [31–33]. Patient selection was at high risk of bias in the retrospective cohort that analysed only SSTR-positive breast lesions [34]. In the study by Ulaner et al., a single unblinded reader with access to prior ^{18}F-FDG PET/CT assigned Krenning scores, two DOTATATE radionuclides were used, and the work was industry-supported [29]. The case reports generally described the patient, imaging and histological confirmation clearly, but conference abstracts provided limited detail on receptor status, semi-quantitative uptake and follow-up. Using GRADE, certainty of evidence was very low for all outcomes, reflecting risk of bias, imprecision and indirectness (Table 4). Publication bias favouring positive or unusual cases is also likely, given the predominance of case reports.

Table 3

Risk-of-bias assessment *a. Imaging cohort studies (QUADAS-2)*

Study	Patient selection	Index test	Reference standard	Flow and timing	Applicability concerns	Main limitation
Chandekar 2025	Unclear	Low	High	Low	Low	Discordant lesions not biopsied; ^{18}F-FDG effectively the reference
Nguyen 2022	Unclear	Unclear	High	Low	Low	Pilot (n = 10); same reader for both tracers; limited biopsy
Sezgin 2025	High	Unclear	High	Unclear	Low	Convenience subset; pathology only after neoadjuvant therapy; internal inconsistencies
Ulaner 2024	Low	High	Not applicable	Low	Low	Single unblinded reader with access to ^{18}F-FDG; two radionuclides; industry-supported
Has Simsek 2021	High	Unclear	Unclear	High	Low	Only SSTR-positive lesions analysed; 4/18 without final diagnosis
Kuyumcu 2013	Low	Unclear	High	Low	High	Not breast-focused; fibroadenoma diagnosed on history and follow-up
b. Case series (JBI, 10 items) and case reports (JBI, 8 items)						

Table 4
GRADE summary of findings for DOTATATE PET/CT in breast cancer and breast lesions

Outcome	Studies (design)	Patients	Findings	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
Per-patient detection of breast cancer vs ^{18}F-FDG	3 (prospective) [31–33]	56	Metastatic cohorts: 37/40 vs 38/40 patients positive; primary tumour visualised in 14/16 vs 15/16	Serious[a]	Not serious	Serious[b]	Serious[c]	Undetected	⊕●●● Very low
Lesion detection by site vs ^{18}F-FDG	2 (prospective) [31, 32]	40 (> 750 lesions)	Skeletal 252 vs 255; nodal 205 vs 208; visceral 134 vs 262 lesions	Serious[a]	Not serious	Serious[b]	Serious[c]	Undetected	⊕●●● Very low
Correlation of uptake with ER/PR status	4 (prospective) [29, 31–33]	86	Concordant at biopsy level in 1 study; no correlation with primary-tumour scores in 2; SSTR2 enrichment ER + 51% vs ER − 18% in tissue	Serious[a]	Serious[d]	Serious[e]	Serious[c]	Undetected	⊕●●● Very low
Krenning score ≥ 3 (potential theranostic eligibility)	3 (prospective) [29, 31, 33]	76	15/76 (19.7%); range 10–30% across studies	Serious[a]	Serious[f]	Not serious	Serious[c]	Undetected	⊕●●● Very low
Malignancy among incidental SSTR-positive breast lesions	1 (retrospective cohort) [34]; case reports and series	14 (+ case-level reports)	3/14 (21.4%) malignant; benign lesions mainly fibroadenoma	Serious[g]	Not applicable	Not serious	Very serious[h]	Strongly suspected[i]	⊕●●● Very low
SUVmax discrimination of benign vs malignant breast lesions	1 (retrospective cohort) [34]	14	Median SUVmax 5.1 (malignant) vs 5.4 (benign); no discrimination	Serious[g]	Not applicable	Not serious	Very serious[h]	Undetected	⊕●●● Very low
Response to SSTR-directed radioligand therapy	2 (prospective cohort, case series) [29, 36]	2	Complete metabolic response to ^{225}Ac-DOTATATE; partial response to ^{177}Lu-DOTATATE; both later progressed	Very serious[j]	Not applicable	Serious[k]	Very serious[h]	Strongly suspected[i]	⊕●●● Very low

Certainty of evidence was rated with the GRADE approach. [a] Discordant lesions not verified histologically; unblinded or single-reader interpretation in some studies. [b] ^{18}F-FDG used as a de facto reference standard; heavily pre-treated metastatic populations. [c] Small samples with wide confidence intervals. [d] Conflicting direction of association between studies. [e] Receptor status from archival primary tissue rather than imaged metastases; tissue microarray data not linked to imaging. [f] Results ranged from 10% to 30% with differing Krenning definitions (patient-level majority vs most avid lesion). [g] Only SSTR-positive lesions analysed; mixed reference standard of histology and imaging follow-up. [h] Very few events or patients. [i] Evidence dominated by case reports, which are prone to selective publication of positive findings. [j] Single-patient observations without a control group. [k] Different tracers (α vs β emitter) and tumour types (luminal vs neuroendocrine carcinoma). ER oestrogen receptor; PR progesterone receptor; SSTR somatostatin receptor; SUVmax maximum standardised uptake value

Detection relative to ^{18}F-FDG

Three prospective studies imaged the same patients with both tracers (n = 56; Table 2) [31–33], and they gave a consistent picture. At patient level, the two tracers performed almost identically. In the two metastatic cohorts, 37 of 40 patients were DOTATATE-positive and 38 of 40 were FDG-positive, and no patient was positive on DOTATATE alone [31, 32]. At initial staging, 14 of 16 primary tumours were visualised by DOTATATE and 15 of 16 by ^{18}F-FDG [33]. Agreement was closest for skeletal and nodal disease, with an aggregate of 252 vs 255 skeletal and 205 vs 208 nodal lesions across the two metastatic cohorts [31, 32]. All four patients with bone metastases at initial staging were detected by both tracers [33]. Where DOTATATE did detect additional disease, it was almost always skeletal. Five bone lesions were seen only on DOTATATE in one study [32], and in five patients with Krenning 4 disease illustrated in a fourth prospective study, more DOTATATE-avid than FDG-avid sites were visible, although no formal comparison was made [29].

Table 2
Prospective studies of DOTATATE PET/CT in breast cancer

Outcome	Chandekar 2025 [31]	Nguyen 2022 [32]	Sezgin 2025 [33]	Ulaner 2024 [29]
Population	30 (29 F); ER+ metastatic; median 3 prior lines	10 F; progressive ER+/PR+/HER2 − metastatic	16 F; newly diagnosed, therapy-naïve; mixed subtypes	30 F (consecutive); ER+ metastatic; IDC 25, ILC 5; mean age 66 years
Interval to ^{18}F-FDG	Median 4.5 days	Median 3 days (all scans within 3 weeks)	1 week	Recent ^{18}F-FDG required; no formal comparison
Reading	Two blinded readers; third for disagreement	Same physician read both PET studies	Not stated	Single unblinded reader with access to ^{18}F-FDG
Per-patient detection (DOTATATE vs FDG)	29/30 (96.7%) vs 30/30 (100%); P = 1.0	8/10 vs 8/10; 2 negative on both (treated sclerotic bone disease)	Primary tumour 14/16 vs 15/16	—
Skeletal lesions	174 vs 181	78 vs 74 (5 DOTATATE-only)	4/4 vs 4/4 patients	—
Nodal lesions	196 vs 199	9 vs 9	Axilla sensitivity 87.5% vs 87.5%; specificity 100% vs 87.5%	—
Visceral lesions	128 vs 235 (P = 0.003)	6 vs 27	Liver 0/1 vs 1/1 patients	—
Uptake	Skeletal SUVmax 8.0 vs 8.6 (P = 0.573); FDG higher at other sites	Mean SUVmax 10.9 vs 6.6 (P = 0.08)	Primary median SUVmax 5.7 vs 8.3 (NS)	Lesional SUVmax 2.0–48.4
Receptor correlation	No correlation with ER/PR Allred; HER2− > HER2+ (9.0 vs 3.8; P = 0.078)	High ER/PR metastases intensely avid; ER-low metastasis SUVmax 3.1	No correlation with ER, PR, HER2 or Ki-67	SSTR2 enrichment ER + 51% vs ER − 18% (tissue)
Krenning score ≥ 3	3/30 (10%); patient-level, majority of lesions	Not reported	3/16 (18.8%); most avid lesion	9/30 (30%); patient-level, majority of lesions (Krenning 4 in 6)
Therapy	None	None	None	^{225}Ac-DOTATATE in 1 patient: complete metabolic response after 2 cycles; SSTR2-negative peritoneal recurrence after cycle 3

Values are DOTATATE vs ^{18}F-FDG unless stated. Ulaner et al. used ^{68}Ga-DOTATATE or ^{64}Cu-DOTATATE; the other studies used ^{68}Ga-DOTATATE. ER oestrogen receptor; F female; HER2 human epidermal growth factor receptor 2; NS not significant; PR progesterone receptor; SSTR2 somatostatin receptor 2; SUVmax maximum standardised uptake value

The one weakness common to all three comparative studies was visceral, and particularly hepatic, disease. Aggregate visceral detection was roughly half that of ^{18}F-FDG (134 vs 262 lesions) [31, 32]. Liver metastases were frequently photopenic relative to background liver [31], 16 hepatic and 5 pleural metastases were FDG-positive but DOTATATE-negative [32], and the only patient with liver metastases at initial staging was detected by ^{18}F-FDG alone [33]. The clinical consequence was under-staging of M-category disease in 10% of patients [31].

Where the studies differed, the differences tracked case mix. Semi-quantitative uptake was higher with DOTATATE in the cohort restricted to ER-positive/PR-positive/HER2-negative disease (mean SUVmax 10.9 vs 6.6; P = 0.08) [32]. It was lower or no different where HER2-positive (27%) or triple-negative tumours were included (median primary SUVmax 5.7 vs 8.3; not significant) [31, 33]. Skeletal uptake was the exception and was comparable even in the more heterogeneous cohort (mean SUVmax 8.0 vs 8.6) [31]. The only study of treatment-naïve patients was also the only one to examine the axilla against pathology. It found equal sensitivity (87.5%) but higher specificity for DOTATATE (100% vs 87.5%), because a reactive post-vaccination node was FDG-avid only [33].

Relationship with tumour biology

The relationship between receptor status and uptake was consistent at tissue level but not at imaging level. In tissue microarrays, SSTR2 enrichment was nearly three times as frequent in ER-positive as in ER-negative tumours (51% vs 18%; P < 0.001) [29]. The only study that biopsied imaged metastases

found the same pattern in vivo: three metastases with ≥ 95% ER expression were intensely avid (SUVmax 5.8–13.5), whereas a pleural metastasis that had lost ER and PR expression showed low uptake (SUVmax 3.1) [32]. In contrast, the two studies that compared uptake with archival primary-tumour ER and PR scores found no correlation [31, 33]. One of them did observe a trend towards higher uptake in HER2-negative than HER2-positive disease (median SUVmax 9.0 vs 3.8; P = 0.078) [31]. Contemporaneous metastatic tissue therefore aligned with DOTATATE uptake, whereas archival primary tissue did not.

Across the case-level reports, uptake followed tumour phenotype. All seven individually described invasive lobular carcinomas (ILC) had DOTATATE-avid disease [29, 30, 33, 40, 41, 44, 47], and three of these were FDG-negative or only faintly FDG-avid. Two had FDG-negative bone metastases: osteolytic in one [40] and mildly sclerotic in the other (DOTATATE SUVmax 10.2) [30]. The third had occult-primary nodal metastases (DOTATATE SUVmax 8.4 vs ^{18}F-FDG 2.1) [44]. The only partial exception was a lobular primary and axillary node that were negative on both tracers, although a bone metastasis in the same patient was visible on both [33]. Primary breast neuroendocrine neoplasms were likewise uniformly avid (7 of 7) [36, 46]. However, five of six patients with metastatic disease also had FDG-positive, DOTATATE-negative lesions, a dual-tracer discordance that the authors interpreted, as in gastroenteropancreatic NETs, as a marker of high-grade biology [36]. At the other end of the spectrum, both triple-negative cancers described in case reports were DOTATATE-negative [42, 45]. The two triple-negative primary tumours in a prospective cohort showed moderate uptake (mean SUVmax 6.3), but still less than with ^{18}F-FDG (14.0) [33]. Uptake was therefore most consistent in lobular, neuroendocrine and ER-positive/HER2-negative tumours and least consistent in receptor-negative disease.

Incidental breast findings on scans performed for other indications

Eleven studies described breast malignancy on DOTATATE PET performed for another indication (Table 1). In most, this was a known or suspected NET [30, 34, 37, 39–41, 45, 47]; the remainder were for esthesioneuroblastoma [38], phaeochromocytoma [46] and an indeterminate adrenal mass [43]. Four recurring observations emerged.

First, the differential diagnosis of a SSTR-positive breast lesion is broad, and its composition depends on the population. In a single-centre series of 1573 scans, SSTR-positive breast lesions occurred in 1.1% of patients (median age 35 years). Of the 14 with a final diagnosis, 11 (78.6%) were benign (nine fibroadenomas and two fibrocystic changes), two were NET metastases and one was a recurrent breast carcinoma (malignant overall, 21.4%) [34]. A fibroadenoma with mild uptake (SUVmax 3.76) was likewise the only breast finding in a second cohort [35]. In a NET clinic population, by contrast, 12 of 15 breast masses were NET metastases and three were primary breast cancers, all of which were DOTATATE-avid [37].

Second, uptake intensity did not distinguish benign from malignant lesions. Median SUVmax was 5.4 in benign and 5.1 in malignant lesions, and several benign lesions were classified as BI-RADS 4 or 5 [34]. In both reports that compared them, primary breast cancers were less avid than the concurrent NET (SUV 3.8 vs 8.0 in one report; trace uptake vs Krenning 3 in another) and could be very faint (SUVmax 1.0) [39, 47].

Third, change over time was more informative than intensity. In both reports with serial imaging, a subtle breast focus became more conspicuous on surveillance scans: over 9 months while the NET was responding to lanreotide [39], and over 11 months (SUVmax 1.0 to 2.1) in a patient later found to have a 31-mm lobular carcinoma [47].

Fourth, DOTATATE-avid breast-cancer metastases outside the breast were readily misattributed. Bone metastases were initially ascribed to an ileal NET [40], sclerotic bone lesions were found while staging a pulmonary carcinoid that was itself only faintly avid [30], and an intensely avid adrenal mass (SUVmax 24.5) was suspected to be a primary adrenal tumour [43]. In each case, only biopsy established breast origin. Conversely, a lack of uptake was also diagnostically useful. An FDG-positive, DOTATATE-negative breast lesion in a patient with a NET identified a triple-negative second primary [45]. In another patient, DOTATATE-avid mediastinal nodes with a DOTATATE-negative triple-negative recurrence identified an immunotherapy-related sarcoid-like reaction rather than progression [42]. Uptake in a synchronous lobular cancer was also indistinguishable from that in the patient's pancreatic NET [41].

Theranostic potential

The proportion of patients with receptor density sufficient to consider radioligand therapy (Krenning score ≥ 3, uptake greater than liver) varied threefold across the three prospective studies that reported it: 10% (3 of 30) [31], 18.8% (3 of 16) [33] and 30% (9 of 30) [29]. Overall, 15 of 76 patients (19.7%) met this threshold. Methodological and clinical differences may explain the spread:

- Definition: the scoring was based on the majority of lesions in two studies [29, 31], but on the single most avid lesion in the third [33]. - Disease burden: visceral metastases, which were frequently SSTR-negative, were present in 76.7% of the cohort with the lowest positivity [31]. - Case mix: one cohort included treatment-naïve patients and receptor-negative subtypes [33]. - Tracer: one study used both ^{68}Ga-DOTATATE and ^{64}Cu-DOTATATE [29].

All three studies highlighted marked inter-lesion heterogeneity in uptake.

That heterogeneity also defined the course of the only two patients who received SSTR-directed radioligand therapy. A 59-year-old woman with Krenning 4 lobular cancer and 11 prior lines of therapy had a complete metabolic and partial anatomical response after two cycles of ^{225}Ac-DOTATATE. Her pleural effusions resolved, and CA 27–29 fell from 1907 to 292 U/mL; no treatment-related adverse events were reported. After the third cycle, however, she developed SSTR2-negative peritoneal recurrence [29]. A patient with breast neuroendocrine carcinoma had a partial response to ^{177}Lu-DOTATATE, followed by discordant hepatic progression [36]. In the same series, the other five patients were judged unsuitable for peptide receptor radionuclide therapy (PRRT) because of FDG-positive, DOTATATE-negative disease or rapid progression [36]. Across studies, therefore, initial responses were limited by expansion of SSTR-negative clones, the same heterogeneity seen at imaging.

Discussion

Across 19 studies, ^{68}Ga-DOTATATE matched ^{18}F-FDG for skeletal and nodal disease but was consistently inferior for visceral metastases. Uptake was heterogeneous, favouring ER-positive, lobular and neuroendocrine phenotypes. Incidental breast uptake on NET imaging was uncommon but malignant in about one in five cases, and about one in five patients with ER-positive metastatic disease showed high receptor density.

The pattern of concordant bone and nodal detection but discordant visceral detection was reproduced in every study that examined it [31–33]. Several factors probably contribute. High physiological SSTR2 expression in the liver lowers the tumour-to-background ratio [18, 35], and SSTR2 expression is lower in hepatic than in other breast cancer metastases [14]. Receptor expression also evolves under treatment [48, 49], and visceral metastases were the commonest source of under-staging. ^{68}Ga-DOTATATE therefore cannot replace ^{18}F-FDG or contrast-enhanced CT for staging, which is consistent with current guideline recommendations [3, 4].

Its potential value lies elsewhere. In the prospective studies it occasionally identified bone lesions not seen on ^{18}F-FDG [32], it showed higher specificity in the axilla [33], and in individual lobular cancers it outperformed ^{18}F-FDG [30, 40, 44]. ILC is a recognised blind spot for ^{18}F-FDG [6].

Any role for DOTATATE in staging must, however, be judged against 16α-^{18}F-fluoro-17β-fluoroestradiol (^{18}F-FES) PET, which images ER directly and addresses the same weakness of ^{18}F-FDG. ^{18}F-FES is approved in the United States as an adjunct to biopsy in recurrent or metastatic breast cancer. Appropriate use criteria endorse it for assessing ER status when endocrine therapy is being considered, for lesions that are difficult to biopsy and when other tests are inconclusive [50]. In a meta-analysis of head-to-head studies in ER-positive disease, ^{18}F-FES had higher lesion-level sensitivity than ^{18}F-FDG (95% vs 85%), particularly at restaging [51]. In lobular cancer, ^{18}F-FES was avid at 88% of histologically confirmed sites [52] and showed more metastases than ^{18}F-FDG in 12 of 26 patients with metastatic disease [53]. ^{18}F-FES is increasingly used clinically for problem solving, and its evidence base is considerably more mature than that for DOTATATE. No included study compared the two receptor-targeted tracers directly. The case for DOTATATE therefore rests less on detection than on what ^{18}F-FES cannot offer: an established therapeutic counterpart, and characterisation of breast lesions found during NET imaging.

Experimental data predict that ER signalling up-regulates SSTR2 [9, 12], and the tissue analysis by Ulaner et al. confirmed SSTR2 enrichment in about half of ER-positive tumours [29]. The clinical correlation, however, was inconsistent. Biopsy-level concordance between ER loss and low uptake was striking in one study [32], but primary-tumour receptor scores did not predict lesional SUVmax in two others [31, 33]. This discrepancy is unsurprising, because receptor status was usually taken from archival primary tissue in patients with multiply treated metastatic disease, in whom discordance between primary and metastasis is common [48]. DOTATATE uptake may therefore act as an indirect, whole-body read-out of contemporaneous receptor expression, although ^{18}F-FES provides this for ER directly [50]. The absence of uptake in triple-negative recurrences [42, 45] supports this interpretation. In clinical practice, FDG-avid but DOTATATE-negative breast lesions in a patient with a NET should prompt consideration of a second primary rather than NET progression [45].

For breast surgeons and radiologists, the most immediately relevant finding concerns patients referred because of incidental breast uptake on a NET scan. Second primary malignancies are more frequent in patients with gastroenteropancreatic NETs [54], and these patients undergo repeated SSTR imaging. The included evidence suggests that focal breast uptake is found in about 1% of scans and is usually benign, with fibroadenoma the most frequent cause [34, 35, 55]. Nevertheless, about one in five such lesions is malignant, either a primary breast carcinoma or, less often, a NET metastasis [34, 56]. SUVmax did not discriminate benign from malignant lesions [34], and malignant lesions could be faint (SUVmax 1.0) [47]. A recent multi-tracer meta-analysis reported a much higher malignancy risk (86.4% in women) for incidental breast uptake on somatostatin-analogue PET [24]. However, that estimate was based on three small studies, one using ^{68}Ga-DOTATOC, and did not include the largest DOTATATE series, in which most lesions were benign [34]. The divergence shows how sensitive these estimates are to a few small series, although both analyses agree that SUV is unreliable and that tissue diagnosis is needed. Two practical points follow. Any focal breast uptake should be assessed with standard breast imaging and, where suspicious, biopsy, regardless of its intensity [39, 47]. In addition, uptake that is new or increasing while the NET is stable or responding should raise particular suspicion of a separate primary [39]. Standardised frameworks such as SSTR-RADS, which explicitly classify non-NET findings, may help communicate this uncertainty [57]. Conversely, avid bone or adrenal lesions in a patient with both NET and breast cancer should not be assumed to be neuroendocrine without tissue confirmation [30, 40, 43].

The proportion of patients with Krenning 3–4 disease (10–30%) resembles the minority of breast cancers with high-density SSTR expression on autoradiography [11]. The near-complete response to ^{225}Ac-DOTATATE [29] and the transient response to ^{177}Lu-DOTATATE in neuroendocrine breast carcinoma [36, 58] are encouraging, but they are single-patient observations. They also illustrate the central obstacle. Heterogeneous expression, including SSTR-negative hepatic disease, is likely to allow non-expressing clones to escape, as shown by the subsequent progression in both treated patients, including SSTR2-negative peritoneal recurrence after ^{225}Ac-DOTATATE [29, 36]. If SSTR-directed therapy is explored further in breast cancer, patient selection would probably need to require both a high Krenning score and the absence of FDG-positive, SSTR-negative disease, a principle already established in NETs [59]. SSTR antagonists, which bind more receptor sites than agonists in breast cancer tissue [60], may widen eligibility.

To our knowledge, this is the first systematic review dedicated to DOTATATE PET in breast cancer and breast lesions across the diagnostic, incidental and theranostic settings. It was registered prospectively, used a sensitive search with citation searching, and included conference abstracts to limit publication bias. Its limitations reflect the evidence base: most studies were case reports or small series, which are vulnerable to selective reporting. The four prospective studies included only 86 patients, lacked a histological reference standard for discordant lesions, and used different definitions of

Krenning score. Heterogeneous populations precluded meta-analysis. One retrospective cohort included an adolescent among its 14 patients [34]. We restricted inclusion to DOTATATE, so experience with other SSTR ligands was excluded [61, 62]. Results may not transfer to tracers with different SSTR subtype affinity [17]. Finally, prior therapy, which may modulate receptor expression, was variably reported.

Future prospective studies should stratify by histological subtype, receptor status and treatment exposure, biopsy discordant lesions, and compare DOTATATE with ^{18}F-FES as well as ^{18}F-FDG. Registries of incidental SSTR-positive breast lesions on NET imaging would clarify the true malignancy rate and inform a pragmatic work-up pathway.

Conclusions

^{68}Ga-DOTATATE PET/CT visualises most ER-positive breast cancers and performs comparably to ^{18}F-FDG for skeletal and nodal disease, but it misses a substantial proportion of visceral, particularly hepatic, metastases and is not a substitute for standard staging or ^{18}F-FES PET. Uptake favours ER-positive, lobular and neuroendocrine phenotypes and is less consistent in triple-negative disease. Incidental breast uptake on scans performed for NETs is malignant in about one in five cases and should be investigated with standard breast imaging and biopsy regardless of intensity. Around one-fifth of patients with ER-positive metastatic disease show receptor density that may be compatible with radioligand therapy. However, the evidence is of very low certainty, and further well-designed studies are needed to clarify whether this has any therapeutic relevance.

Declarations

Compliance with ethical standards

Conflict of interest

Ethical approval

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

Informed consent

Not applicable.

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CM conceived the review, designed the search strategy and drafted the manuscript. CM and EF independently screened studies, extracted data and appraised study quality. HT, DS, ZQN and SC critically revised the work. All authors read and approved the final manuscript.

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None.

Data availability

All data analysed in this review are available in the included published studies. The data extraction form is available from the corresponding author on reasonable request.

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Figures

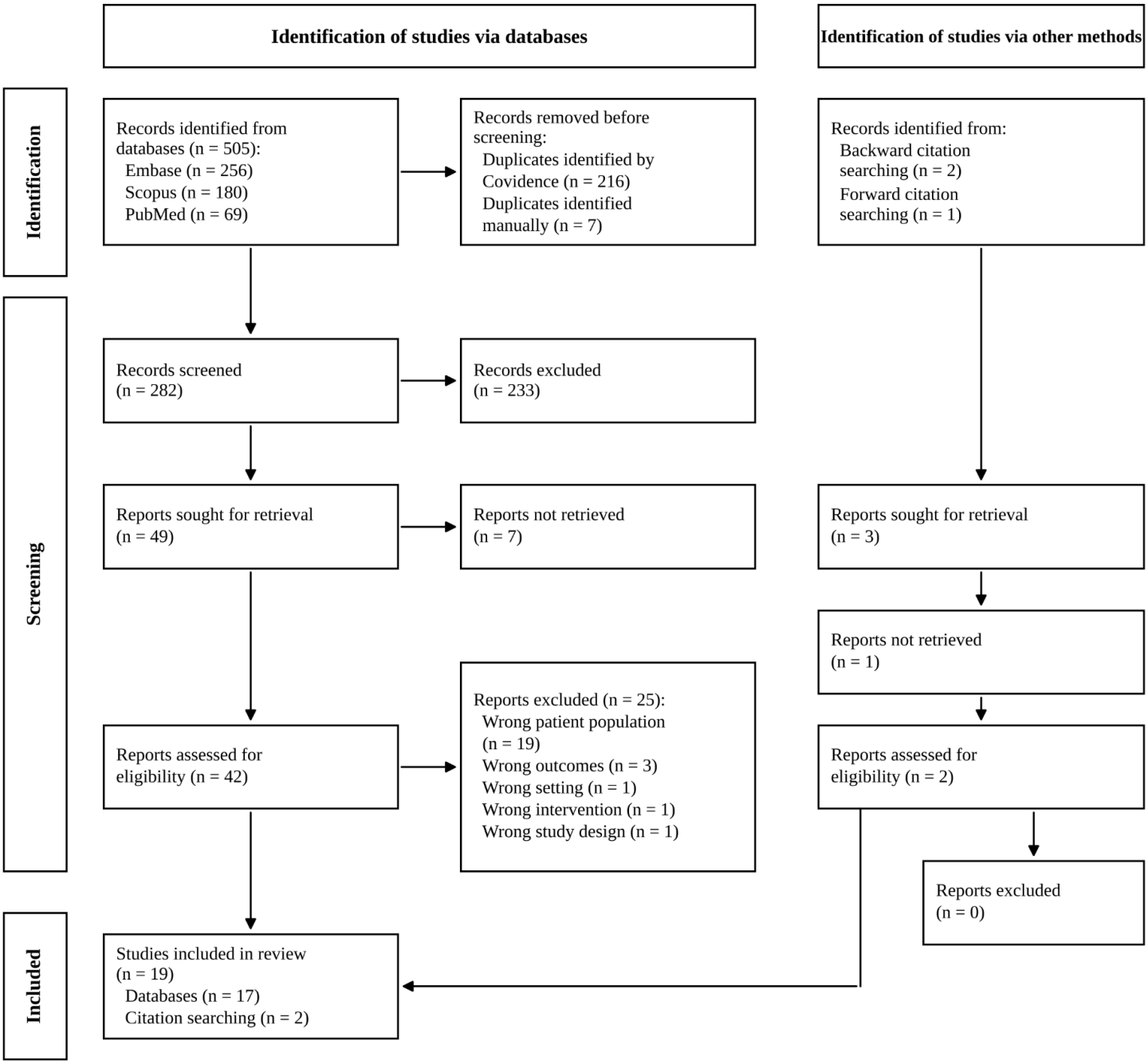


Figure 1

PRISMA 2020 flow diagram of study selection. Three further reports were identified by citation searching of included studies (two backward, one forward); one could not be retrieved in full text.

Supplementary Files

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