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Value of ^{18}F-FES-PET to solve clinical dilemmas in breast cancer patients: a retrospective study

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ABSTRACT

Background: Breast cancer (BC) is a heterogeneous disease, in which estrogen receptor (ER) expression plays an important role in the majority of breast tumors. A clinical dilemma may arise when a metastasis biopsy to determine the ER status cannot be performed safely or when ER heterogeneity is suspected between tumor lesions. Whole-body ER imaging, such as 16α-^{18}F-fluoro-17β-estradiol (^{18}F-FES) positron emission tomography (PET), may have added value in these situations. However, the role of this imaging technique in routine clinical practice remains to be further determined. Therefore, we assessed the value of ^{18}F-FES-PET by evaluating if the physician's clinical dilemma that remained after standard workup was solved by the ^{18}F-FES-PET scan.

Methods: In this retrospective study, ^{18}F-FES-PET scans, performed in patients with (suspected) ER+ metastatic BC with remaining clinical dilemma after standard workup, at the University Medical Center of Groningen between November 2009 and January 2019, were included. We investigated whether the physician's clinical dilemma was solved, defined as 1) ^{18}F-FES-PET provided a solution for the clinical dilemma, and/or 2) a treatment decision was based directly on the ^{18}F-FES-PET. In addition, category of clinical dilemma, and rate of ^{18}F-FES positive or negative PET scans were reported, and related to frequency of solved dilemmas.

Results: One hundred ^{18}F-FES-PET scans were performed in 83 patients. Clinical dilemma categories were: 1) inability to determine extent of (suspected) metastatic disease with standard workup (*n*=52), 2) unclear ER status of the tumor (*n*=31),

and 3) inability to determine which primary tumor caused metastases (*n*=17). Dilemmas were solved by ^{18}F-FES-PET in 87/100 cases (87%). In 81/87 cases a treatment decision was made based directly on the ^{18}F-FES-PET (treatment change: *n*=51 cases; continuance: *n*=30 cases). The frequency of solved dilemmas was not related to the clinical dilemma category (*p*=0.334). However, the frequency of solved dilemmas was related to whether scans were ^{18}F-FES positive (*n*=63) or negative (*n*=37; *p*<0.001).

Conclusion: For various indications, the ^{18}F-FES-PET scan can help to solve the vast majority of clinical dilemmas that may remain after standard workup. Therefore, the ^{18}F-FES-PET scan has added value in BC patients presenting with a clinical dilemma.

Key words: FES-PET; breast cancer; clinical dilemma; conventional imaging.

INTRODUCTION

Breast cancer (BC) is the most common malignant disease among women worldwide (*1*). In the Netherlands it is estimated that 1 out of 7 women will be diagnosed with BC at some point in their life (*2*). Of all BC patients, roughly 10% develop distant metastases in the first 5 years following primary diagnosis (*3*). A clinically relevant characteristic of BC is the estrogen receptor (ER), which is expressed by the majority (79%) of breast tumors (*4*). The ER is an important predictive and prognostic marker and used as target for treatment. ER-positive breast tumors are likely to respond to hormonal therapy (*5*).

Currently, ER expression in BC is determined by immunohistochemistry (*5*,*6*). However, this golden standard has some limitations. A (metastasis) biopsy may lead to sampling errors, and can be infeasible due to its invasive nature or due to the location of the lesion. Also, heterogeneity of ER expression between tumor lesions within patients can be a clinical challenge for clinicians (*7*,*8*). Discrepancy of ER expression between the primary tumor and the metastasis is observed in 16% to 40% of the patients (*5*,*8*). Furthermore, ER expression of tumors may change in time. These factors may cause a clinical dilemma, both for correct diagnosis and best therapy choice, and therefore regular evaluation of the ER status is important. According to the guidelines of the European Society for Medical Oncology, repeated histological biopsies are recommended to re-evaluate the ER status of metastatic BC (*9*).

However, since it is impossible to evaluate the ER status of every lesion in the body by biopsy, a non-invasive imaging method to measure ER expression of

all tumor lesions in the body would be a useful and valuable tool. Positron emission tomography (PET) with 16α-^{18}F-fluoro-17β-estradiol (^{18}F-FES) could be such a tool (*10*). ^{18}F-FES-PET has the potential to visualize the ER expression of all tumor lesions, to estimate the heterogeneity of ER expression in metastatic lesions across the body, and can therefore be used for individualized therapy decision-making (*11*,*12*). A high correlation has been found between ^{18}F-FES uptake and immunohistochemistry findings for the determination of the ER status (*13*–*15*).

^{18}F-FES-PET, recently approved for human use in France and the United States, is an evolving imaging technique and may play an increasingly important role in clinical practice in the near future. Small studies have shown that ^{18}F-FES-PEThas added value for BC patients presenting with a clinical dilemma (*16*–*18*). To confirm these initial findings, evaluation of the role of ^{18}F-FES-PET in a larger patient sample size is needed, and the role of this imaging technique in routine clinical practice remains to be further determined. Therefore, the aim of this study was to assess the value of ^{18}F-FES-PET in a large retrospective patient cohort, by 1) evaluating if the physician's clinical dilemma that remained after standard workup could be solved by the ^{18}F-FES-PET scan, and 2) if this imaging technique supportedBC management.

METHODS

Study Design and Patients

This is a retrospective study of all consecutive patients who received a clinical ^{18}F-FES-PET at the University Medical Center of Groningen (UMCG) between November 2009 and January 2019. ^{18}F-FES-PET scans were eligible for analysis if they were performed in patients with (suspected) ER-positive metastatic BC, of whom pathology assessment of primary tumor and/or suspected metastasis was available, with a remaining clinical dilemma after standard workup. For each patient, a ^{18}F-FES-PET scan was requested by a medical oncologist in the context of the clinical dilemma and the validity of the request was confirmed by a nuclear medicine physician. We used only scans that were acquired on a combined PET/computed tomography (CT) scanner; scans that were acquired with a PET-only scanner were excluded. In case of technical imaging problems, the scan was excluded. ^{18}F-FES- PET scans performed as part of a clinical trial were also excluded. In addition, requests for ^{18}F-FES-PET only related to the detection of liver metastases were excluded due to unreliable image interpretation (*19*). In this study, all procedures were performed as part of routine care. The Medical Ethics Committee of the UMCG has reviewed the protocol and decided that this type of research was beyond the scope of the Medical Research Involving Human Subjects Act (METc 2018/418). All data were pseudonymized before data analysis.

^{18}F-FES-PET Imaging

^{18}F-FES was produced as described previously (*20*). To prevent false-negative results, ER antagonists had to be discontinued at least 5 weeks before ^{18}F-FES-PET, while aromatase inhibitors could be continued (*19*). The tracer (~200 MBq) was intravenously injected 60 min before performing a whole-body ^{18}F-FES-PET, and patients did not have to fast. A 40- or 64-slice mCT (PET/CT) camera (Siemens CTI) was used with a 2-mm spatial reconstructed resolution with an acquisition time of 3 min per bed position. A low-dose CT was acquired for attenuation and scatter correction. Some patients received a ^{18}F-FES-PET in combination with a diagnostic CT-scan. ^{18}F-FES-PET scans were evaluated qualitatively by nuclear medicine physicians and a standard clinical report was documented in the patient file. The scans were divided into 2 categories: showing ER-positive disease (i.e. at least one lesion showed visually increased ^{18}F-FES uptake above background), and ER- negative disease (i.e. no lesion showed visually increased ^{18}F-FES uptake above background). In case of ambiguous lesions upon qualitative analysis of the ^{18}F-FES- PET scan, tracer uptake in the lesion was quantified, using the maximum standardized uptake value 1.5 as cut-off value (*19*). In patients who had also receivedan ^{18}F-FDG-PET scan in the standard workup, a secondary (quantitative) analysis was performed. For both PET scans (^{18}F-FDG and ^{18}F-FES), patient preparation, tracer administration, and reconstruction were performed according to European Association of Nuclear Medicine (EANM) protocols. Quantitative analysis was performed on reconstructed images according to EANM Research Ltd.

Standard Workup

We used electronic patients' records to assess standard workup prior to requesting a ^{18}F-FES-PET: which conventional imaging such as bone scintigraphy (with single-photon emission computed tomography if necessary), CT-scan, ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET scan, magnetic resonance imaging (MRI) was performed; whether a (cytological or histological) biopsy was performed and at which site. To ensure that the previous imaging techniques and the biopsy were used to solve the same dilemma as the ^{18}F-FES-PET, a timeframe of maximum 3 months was set between the standard workup and ^{18}F-FES-PET scan.

Data Collection

The following patient data were retrieved from the electronic patient records: patient and tumor characteristics (including age, sex, BC stage, histology and tumor receptor status), treatment before (within a timeframe of maximum 4 weeks) and after ^{18}F-FES-PET (treatment decisions made within a timeframe of maximum 4 weeks), previous standard workup, category of clinical dilemma, and visual interpretation of ^{18}F-FES-PET results (positive or negative).

Outcomes

Primary endpoint was the percentage of cases in which the referring

physician's clinical dilemma was solved based on the ^{18}F-FES-PET. The dilemma was considered solved if 1) the ^{18}F-FES-PET provided a solution for the clinical dilemma, and/or 2) a treatment decision (to change or continue) was based directlyon the ^{18}F-FES-PET result. If the physician had doubts about the diagnosis after the ^{18}F-FES-PET examination, and additional workup was necessary for treatment decision-making, the dilemma was considered not solved. Secondary endpoints were: 1) the type of clinical dilemma according to three categories: (i) to determine the extent of (suspected) metastatic disease in case of equivocal lesions on standard workup or symptoms for which no abnormality could be found on conventional imaging, (ii) to determine ER status of the disease, and (iii) to determine which primary tumor caused metastases, and the frequency of solved dilemmas per category; 2) the type of treatment before and after ^{18}F-FES-PET; and 3) the ^{18}F-FES- PET scan results (ER-positive or negative) in relation to how frequently the dilemma was solved.

Statistical Analysis

Descriptive statistics (categorical data) were used to report whether the physician's clinical dilemma was solved, and are presented as percentages. Descriptive statistics were also used to depict the secondary outcomes. Continuous variables were expressed as mean ± standard deviation (SD) or median and range, depending on data distribution. A chi-square (χ^2) test was performed to evaluate whether the number of ^{18}F-FES-PET scans that solved the

dilemma was dependent on the category of clinical dilemma and to assess whether the result of the ^{18}F-FES- PET scan (positive or negative) affected the success rate for solving the dilemma. Statistical analysis was performed for the qualitative assessment, descriptive analysis for the quantitative data. A probability value (*p*) inferior to 0.05 was considered as statistically significant. All statistical tests were done using SPSS version 23.

RESULTS

Patients

In total, 100 consecutive ^{18}F-FES-PET scans, performed in 83 patients, were included in the final database (see CONSORT diagram Figure 1). Of the 12 patients with multiple ^{18}F-FES-PET scans, nine patients had two scans, and three patients had three or more scans. Scan characteristics are summarized in Table 1. All patients had ER-positive BC, based on primary tumor or metastasis biopsy, except for 2 patients: a patient with an ER-negative primary breast tumor and a new palpable breast mass with metastases, in which a biopsy was not possible; it was unclear whether this mass was a second primary breast tumor (and possibly ER- positive) or recurrence (*n*=1), and a patient with suspected primary BC with a histological breast biopsy that indicated a gastric carcinoma with breast metastases (instead of primary BC) (*n*=1). In 10 cases, full standard workup prior to ^{18}F-FES-PET was not feasible (see description in Table 1). These cases were included in the analysis, because they do present real life dilemmas occurring in clinical practice.

Value of ^{18}F-FES-PET

The physician's clinical dilemma was solved in 87% of the cases, in which a ^{18}F-FES-PET scan was performed (87/100). In most cases (81/87), a treatment decision was made based directly on the ^{18}F-FES-PET result. In 6/87 cases, ^{18}F-FES-PET provided a solution for the clinical dilemma (an extra site to biopsy and additional imaging based on new ^{18}F-FES-PET findings). In 13/100 cases, the dilemma was not solved due to the following reasons: there were still doubts

about the diagnosis and an additional biopsy was considered (*n*=5); the physician started treatment contradicting the ^{18}F-FES-PET result (*n*=2); origin of the lesions remained unclear (*n*=2); an additional biopsy to confirm a negative ^{18}F-FES-PET scan in fact showed ER expression and thus treatment was based on ER-positive disease (*n*=2; one patient had lack of response to endocrine treatment); there was doubt whether the metastatic disease was in remission or ER underwent positive to negative conversion due to ^{18}F-FES negative PET scan, and therefore an ^{18}F-FDG-PET was performed to detect metabolically active bone metastases (*n*=1); and discrepancy between conventional imaging and ^{18}F-FES-PET (*n*=1). Examples of cases in which the physician regarded the results of the ^{18}F-FES-PET as conclusive, as well as an example of an inconclusive ^{18}F-FES-PET scan are shown in Figure 2, 3 and 4.

In 14 patients, ^{18}F-FDG and ^{18}F-FES-PET could be compared for secondary quantitative analysis (see CONSORT diagram Figure 1). As shown in Supplemental Table 1, we did not observe negative or minimally positive ^{18}F-FDG-PET scans.

Category of Clinical Dilemma

Fifty-two of 100 ^{18}F-FES-PET scans were requested because lesions were equivocal on standard workup. Thirty-one of 100 ^{18}F-FES-PET scans were requested to investigate the ER status. Seventeen of 100 ^{18}F-FES-PET scans were requested to determine the origin of metastases. Examples of a ^{18}F-FES-PET scan for each indication are shown in Figure 2, 3, and 4. The success rate of ^{18}F-FES-PET to solve the physician's clinical dilemma was not significantly different

between the different categories of clinical dilemmas (p=0.334). Out of the 52 ^{18}F-FES-PET scans requested after equivocal conventional workup, the clinical dilemma was solved in 47 cases (90%). ^{18}F-FES-PET requested to determine the ER status solved the clinical dilemma of the physician in 27 cases (87%). ^{18}F-FES-PET requested to predict the origin of a metastasis solved the dilemma in 13 cases (76%; see Figure 5).

Type of Treatment after ^{18}F-FES-PET

Of the 81 cases in which a treatment decision was made based directly on the ^{18}F-FES-PET result, 51 cases received a new treatment (25/51 endocrine therapy ± radiotherapy) and 30 cases continued their treatment. The type of treatment changeis shown in Supplemental Table 2.

^{18}F-FES Negative or Positive PET Results

Sixty-three of 100 ^{18}F-FES-PET scans showed ER-positive disease, while 37 showed ER-negative disease. Out of the 63 scans showing ER-positive disease, the physician's clinical dilemma was solved in 61 cases (97%), but in 26 out of the 37 scans (70%) showing ER-negative disease, the dilemma was solved. As a result, the success rate for solving the dilemma differed significantly between the two groups (p<0.001). Figure 4 shows an example of a ^{18}F-FES-PET scan showing ER-negative disease that was not directly helpful for the clinician.

DISCUSSION

In this retrospective study, we aimed to investigate the value of ^{18}F-FES-PET in the management of BC patients facing a clinical dilemma that could not be solved after standard workup. This is of clinical importance since a persistent clinical dilemma might lead to decreased survival (*21*) and unnecessary therapy, due to over- and undertreatment (*17*).

To our knowledge, this is the largest study evaluating the value of ^{18}F-FES-PET in this target group. We showed that ^{18}F-FES-PET can be clinically meaningful and can support clinical decision-making in the large majority of BC patients presenting with a persisting clinical dilemma, despite standard workup. This study also provides more insight into the clinical indications for the examination and the physician's diagnostic concerns. These findings can potentially support clinical implementation of ^{18}F-FES-PET.

The 87% solved clinical dilemmas by ^{18}F-FES-PET is consistent with previous smaller studies (*16*,*18*). One study reported improved diagnostic understanding in 88% of cases based on the ^{18}F-FES-PET scan (*16*). Another study found that ^{18}F- FES-PET had added value (89%) in the diagnosis of newly diagnosed BC patients (*18*). The present study shows that ^{18}F-FES-PET can support BC management with both a changed and continued treatment plan, which is of added value to the previous studies.

This study identified clinical dilemmas associated with BC in which ^{18}F-FES-PET may play a role in guiding treatment selection, including, but not limited to, determination of ER status of the disease. An accurate request for a ^{18}F-FES-PET

is necessary for clinical interpretation by the nuclear medicine physician, and improves the ^{18}F-FES-PET report (*22*). In the present study, the physician's clinical dilemma was equally solved for all three indication categories, which is in line with a previous study (*16*). One third of the ^{18}F-FES-PET scans were requested to determine ER status in known or suspected metastatic lesions, which is in agreement with the results of van Kruchten et al. (*16*). The potential indications for ^{18}F-FES-PET in the literature included: assessment of ER status of disease, ER heterogeneity in metastatic disease, (re)staging, therapeutic options for hormonal treatment, and predicting response to hormonal therapy (*13*,*15*,*19*,*23*). However, the role of ^{18}F- FES-PET is limited in detecting ER-positive lesions in the liver, because of high physiological ^{18}F-FES uptake due to its metabolism.

The percentage of lobular tumors in the present study was slightly higher than the general population (*24*,*25*). This supports the previously described hypothesisthat metastatic lesions in lobular BC are difficult to detect with standard imaging (*26*,*27*), and that this disease presents relatively frequently with a clinical dilemma. For this setting, we found that clinical dilemmas in lobular BC were equally well solved by ^{18}F-FES-PET as clinical dilemmas in ductal BC (86% vs. 88%) in the present study.

Recently, a high specificity of 98% and sensitivity of 78% for the assessment of ER status by ^{18}F-FES-PET were reported, using biopsy as gold standard (*23*). Thismeans that there are few false-positive findings. Therefore, ^{18}F-FES-PET can be a good alternative tool if a biopsy is not possible or does not

solve the dilemma, both cases occurred in our study. In the present study, the clinical dilemma was solved more frequently if the ^{18}F-FES-PET showed ER-positive disease compared to ER- negative disease, which can be related to its higher specificity than sensitivity. Our results are comparable with the study by van Kruchten et al (*16*). However, caution is necessary in scans showing ER-negative disease. In our study, 9 out of 14 ^{18}F-FES-PET scans of patients with known metastatic BC showed ER-negative disease,despite an ER-positive primary tumor. This could be explained by the dynamics of BC in time (such as receptor status conversion), good response to endocrine treatment, or false-negative findings.

This study has limitations. Our study was retrospective, and data were retrieved from electronic patient charts. Therefore, interpretation bias may play a role.Furthermore, our retrospective design did not allow us to grade how helpful the ^{18}F- FES-PET was with questionnaires (*16*). Also, the intended therapy before ^{18}F-FES- PET could not be compared with the therapy that was chosen after the scan. The strengths of this study are its large sample size, heterogeneous population, inclusion of all consecutive eligible patients over a period of more than nine years, and a structured and detailed analysis of a ‘real daily clinical practice’ setting.

CONCLUSION

In conclusion, we found that for various indications, the ^{18}F-FES-PET scan canhelp to solve the vast majority of clinical dilemmas that remained after standard workup. ^{18}F-FES-PET improves the physician’s understanding of the disease statusin BC patients and provides information for personalized treatment decision-

making. Therefore, the ^{18}F-FES-PET scan has added value in BC patients presenting with a clinical dilemma.

DISCLOSURE

Funding: Not applicable

Conflicts of Interest: No potential conflict of interest relevant to this article was reported.

KEY POINTS

Question: Does ^{18}F-FES-PET have added value for solving clinical dilemmas in breast cancer patients?

Pertinent findings: In this retrospective study in a 'real daily clinical practice' setting, clinical dilemmas were solved by ^{18}F-FES-PET in the large majority of breast cancer patients.

Implications for patient care: Our findings support the use of ^{18}F-FES-PET as a clinically meaningful diagnostic tool and ^{18}F-FES-PET can support clinical decision-making in breast cancer patients presenting with a persisting clinical dilemma despitestandard workup.

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Table 1. Patients and scan characteristics (*n*=100 ^{18}F-FES-PET scans in 83 patients)

Characteristics	**Result**
Age, mean ± SD	59 ± 11 year
Sex (female)	99 (99%)
BC stage at the time of ^{18}F-FES-PET	
• Metastatic disease *	51 (51%)
• Suspected metastatic disease	49 (49%)
Time between primary tumor diagnosis and ^{18}F-FES-PET, median [range] †	6 year [0-34]
BC primary tumor ER expression	*n*=94 ‡
• Positive	92 (98%)
• Negative §	2 (2%)
Histology of the primary tumor †	*n*=87
• Ductal	64 (74%)
• Lobular	21 (24%)
• Ductolobular	1 (1%)
• Micropapillary	1 (1%)
ER expression in BC metastases	*n*=31 ¶
• Positive	28 (90%)
• Negative **	3 (10%)
Standard workup before ^{18}F-FES-PET	
• At least one conventional technique ††	90 (90%)
• CT-scan	59 (59%)
• Bone scintigraphy	36 (36%)
• MRI	23 (23%)
• ^{18}F-FDG-PET	21 (21%)
• Biopsy	29 (29%)
Breast lesion ‡‡	12/29 (41%)
Non-breast lesion	17/29 (59%)

* Ultimately diagnosed with metastatic gastric carcinoma with breast metastases, instead of newly diagnosed metastatic BC (*n*=1); † If >1 primary BC, the first diagnosis and histological type of BC was included; ‡ In 5/6 unknown cases, metastatic lesion or secondary primary BC ER+; § Primary tumor ER- and presenting with a new palpable breast mass with metastases, it was unclear whether it was secondary primary BC or recurrence, and a biopsy was not possible (*n*=1), and primary tumor with mixed ER- and ER+, treated as triple-negative BC (*n*=1); ¶ Metastasis biopsy was not always possible, not performed, not representative, only cytology was available, or data were not available from medical records; ** (secondary) Primary BC ER+; †† In 10 cases, standard workup could/was not performed: priority to determine whole-body ER status for subsequent endocrine treatment (*n*=4), previous tumor progression only detected by ^{18}F-FES-PET, not on conventional imaging, so conventional imaging was deemed non-informative in present

setting (*n*=3), clinical and biochemical suspicion of tumor progression and the presence of two different tumor types (*n*=1), a biopsy was not possible to determine ER status (*n*=1), and after completion of chemotherapy further diagnostic workup was required to clarify the origin of cancer metastases (*n*=1); ‡‡ With(out) axillary dissection.

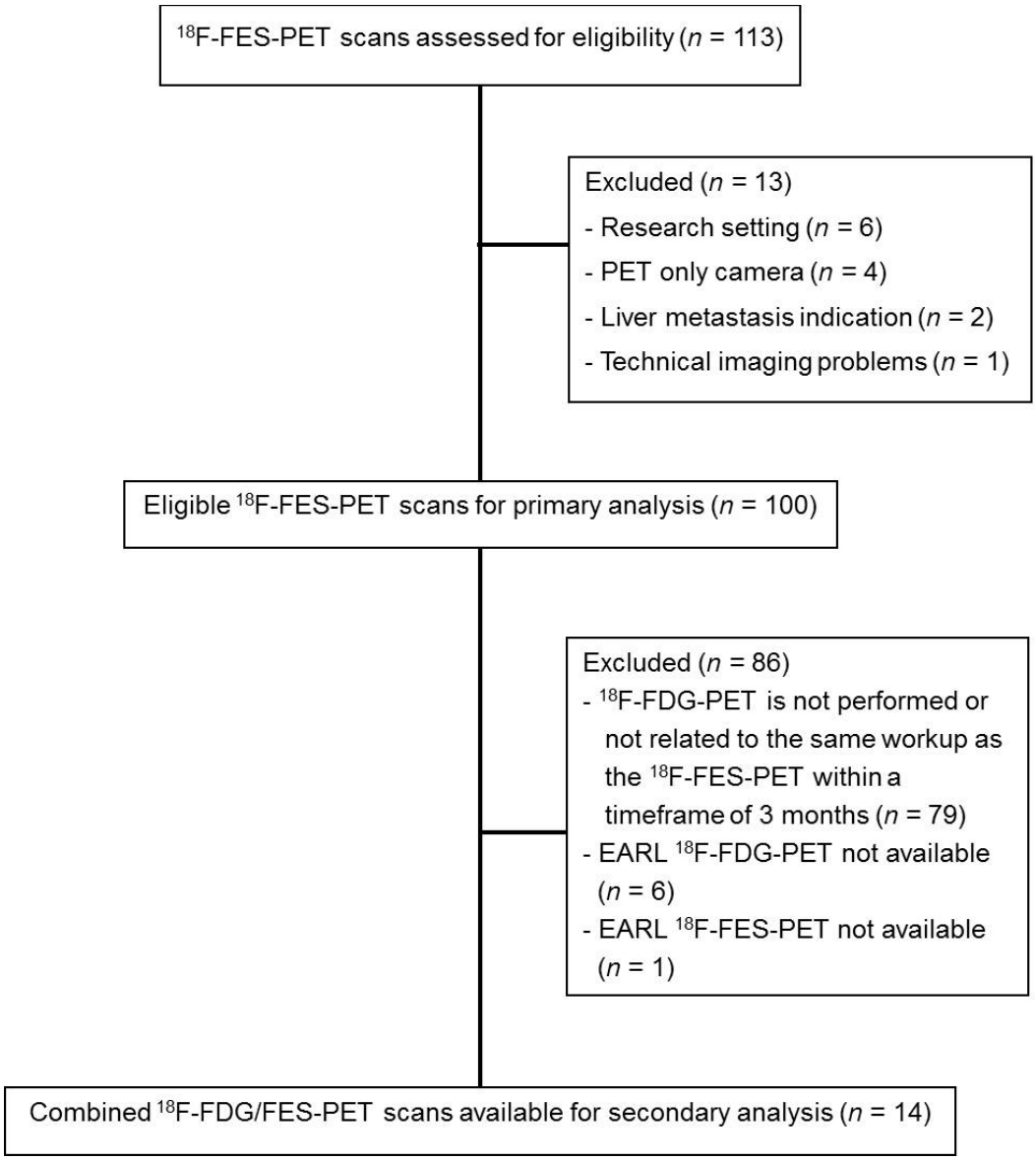


Figure 1. CONSORT diagram.

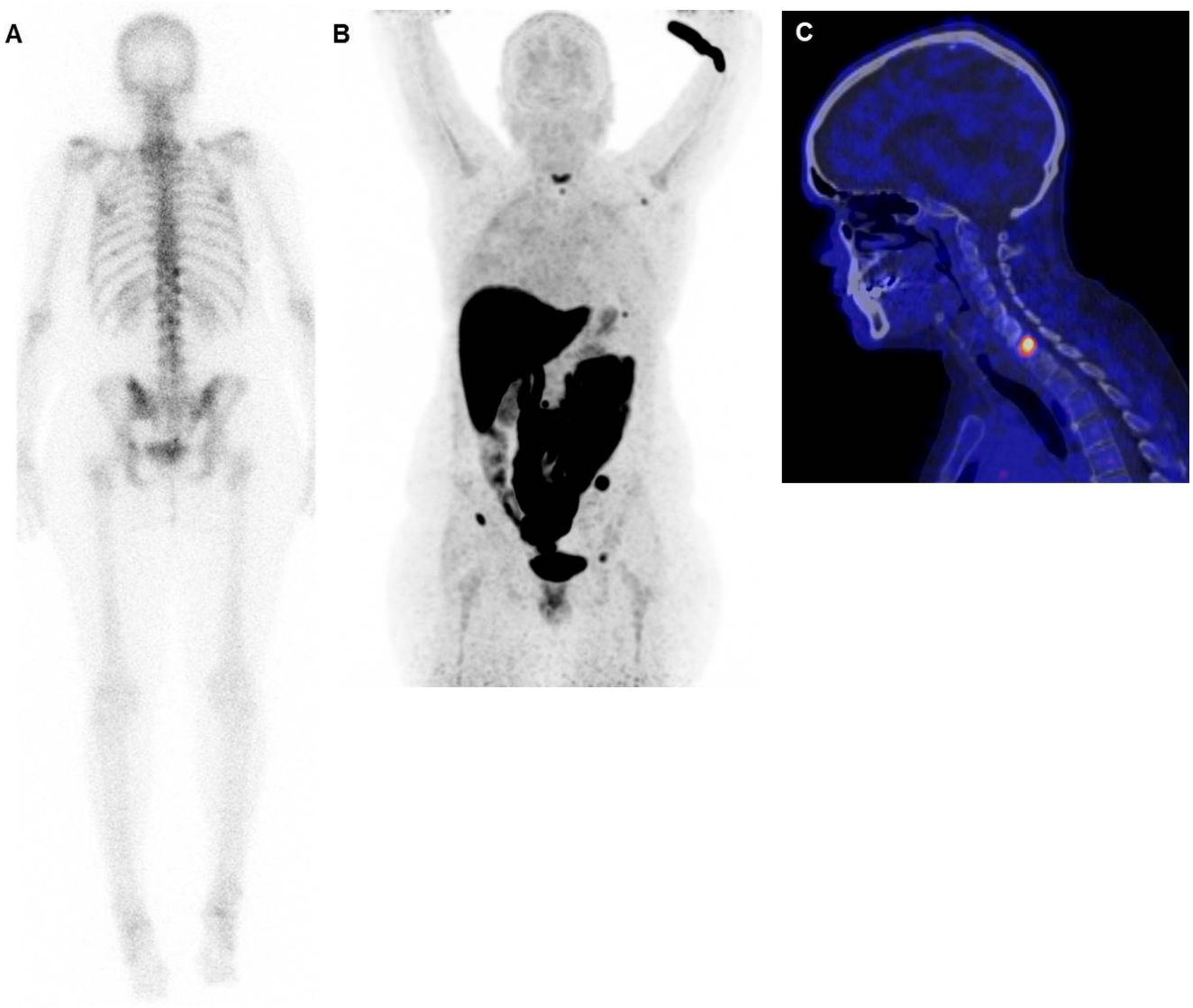


Figure 2. Equivocal lesions on standard workup.

A 41-year-old female known with Bechterew's disease, was diagnosed with primary ER+ BC 2 years ago. Due to pain complaints in the neck region a conventional bone scan was performed, which showed heterogeneous uptake in the spine and pelvis (image A, static image posterior view). To differentiate between the presence of bonemetastases or lesions associated with Bechterew a ^{18}F-FES-PET scan was performed. Increased ^{18}F-FES uptake was seen in multiple skeletal lesions: rib, left scapula, spine, and pelvis (image B: MIP view, and image

C: fused PET/CT sagittal view of the cervical spine). Based on these findings, the diagnosis was settled on metastatic BC, the clinical dilemma was solved and first-line endocrine treatment was started. In addition, the patient received radiation to the cervical spine.

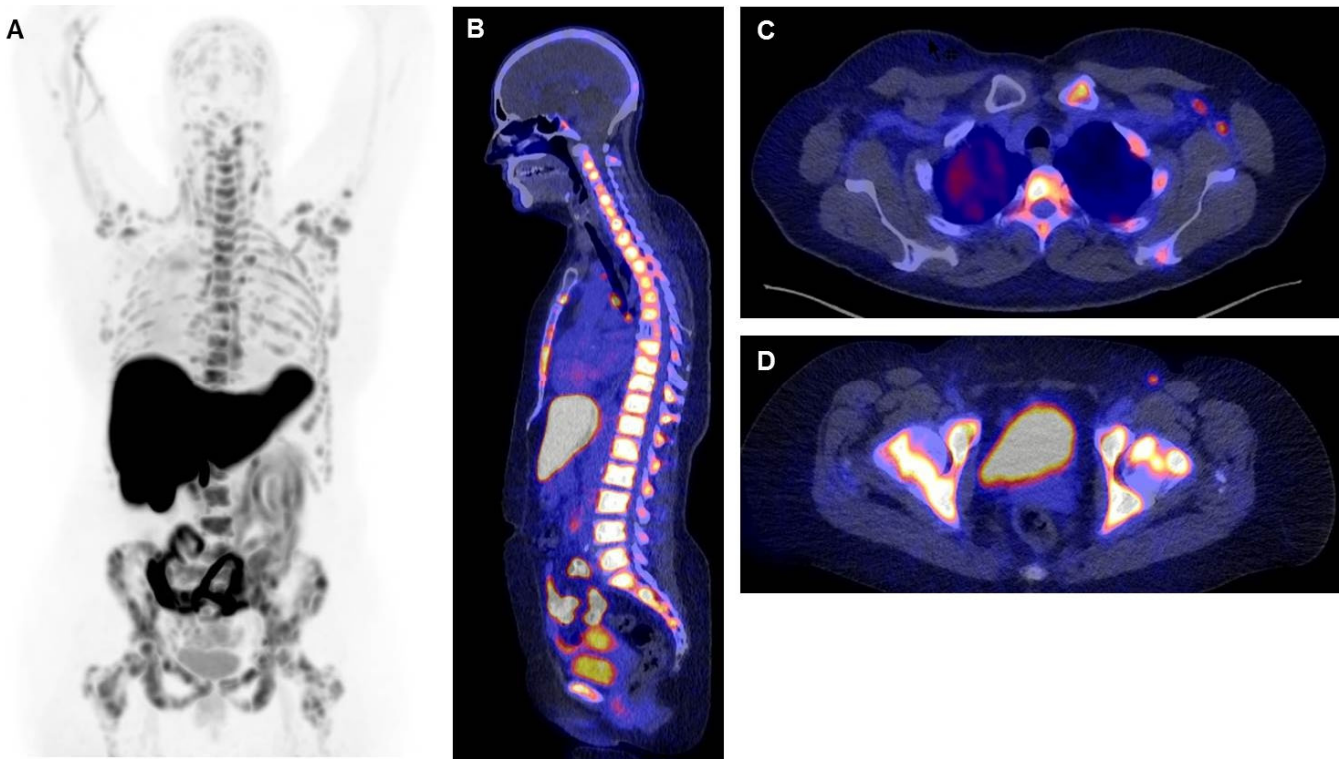


Figure 3. Determination of ER status of the disease.

In a 59-year-old female diagnosed with ER+ lobular BC 2 years ago and treated with tamoxifen, ER+ bone metastases were identified one year after the initial diagnosis. She was first treated with first-line endocrine therapy in palliative setting. Thereafter, the disease became progressive and palbociclib was added. However, after 2 weeks of treatment, she presented with pancytopenia. ^{18}F-FES-PET was performed to determine if bone metastases were still expressing ER, whether there was a rationale for another line of endocrine therapy. Increased ^{18}F-FES uptake could be seen in lymph nodes above and below the diaphragm, and in multiple bone lesions (for example spine, costae, scapulae, sternum and pelvis). Image A: MIP image, image B: fused PET/CT sagittal view, image C: fused PET/CT transversal view of the left axillary region, and image D: fused PET/CT transversal view of the pelvic region with a positive inguinal lymph node). In addition, also bone marrow involvement was visible. The diagnosis was settled on ER+ metastatic disease. The clinical dilemma was solved and another line of endocrine therapy could be considered. However, due to bone marrow involvement, chemotherapy was indicated to achieve a therapeutic effect more rapidly.

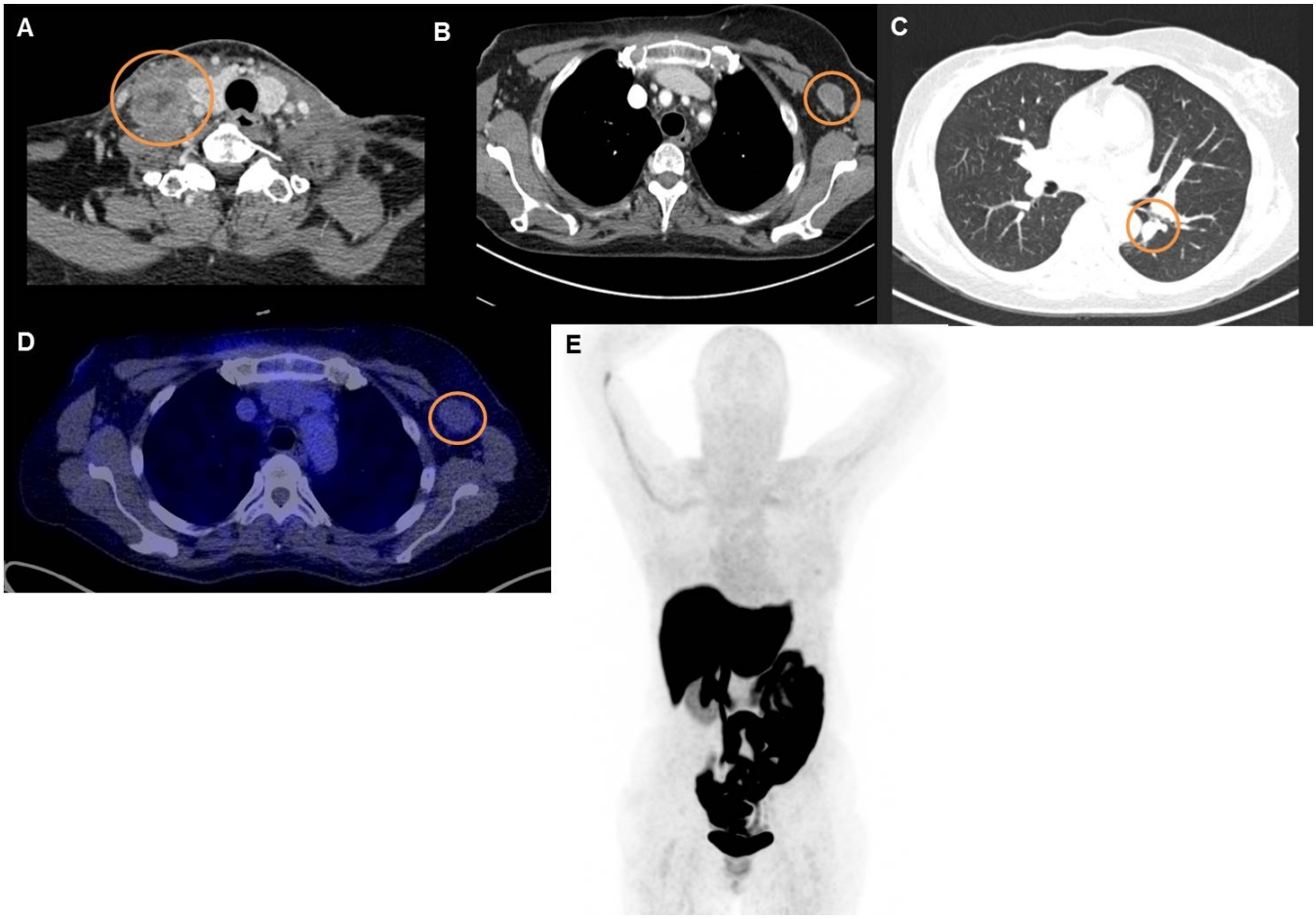


Figure 4. Inability to determine which primary tumor caused metastases.

A 63 year-old female, known with oral squamous cell carcinoma, was recently diagnosed with ER+ BC. At physical examination a palpable mass was found in the right neck region (level IV), which was also visible on CT (image A). In addition, an enlarged lymph node was visible in the left axilla (image B), and an abnormality in the left lung (image C). The dilemma was whether these metastases were associated with ER+ BC or oral squamous cell carcinoma. ^{18}F-FES-PET was performed to evaluate if these lesions were metastasis from the BC (in case of ^{18}F-FES positive findings). However, ^{18}F-FES-PET did not show any significant tracer uptake in metastatic lesions (image D and E). The ^{18}F-FES-PET result did not solve the dilemma, because there could be conversion from ER+ to ER- status, therefore a biopsy of the left axillary area was performed, and confirmed the presence of squamous cell carcinoma.

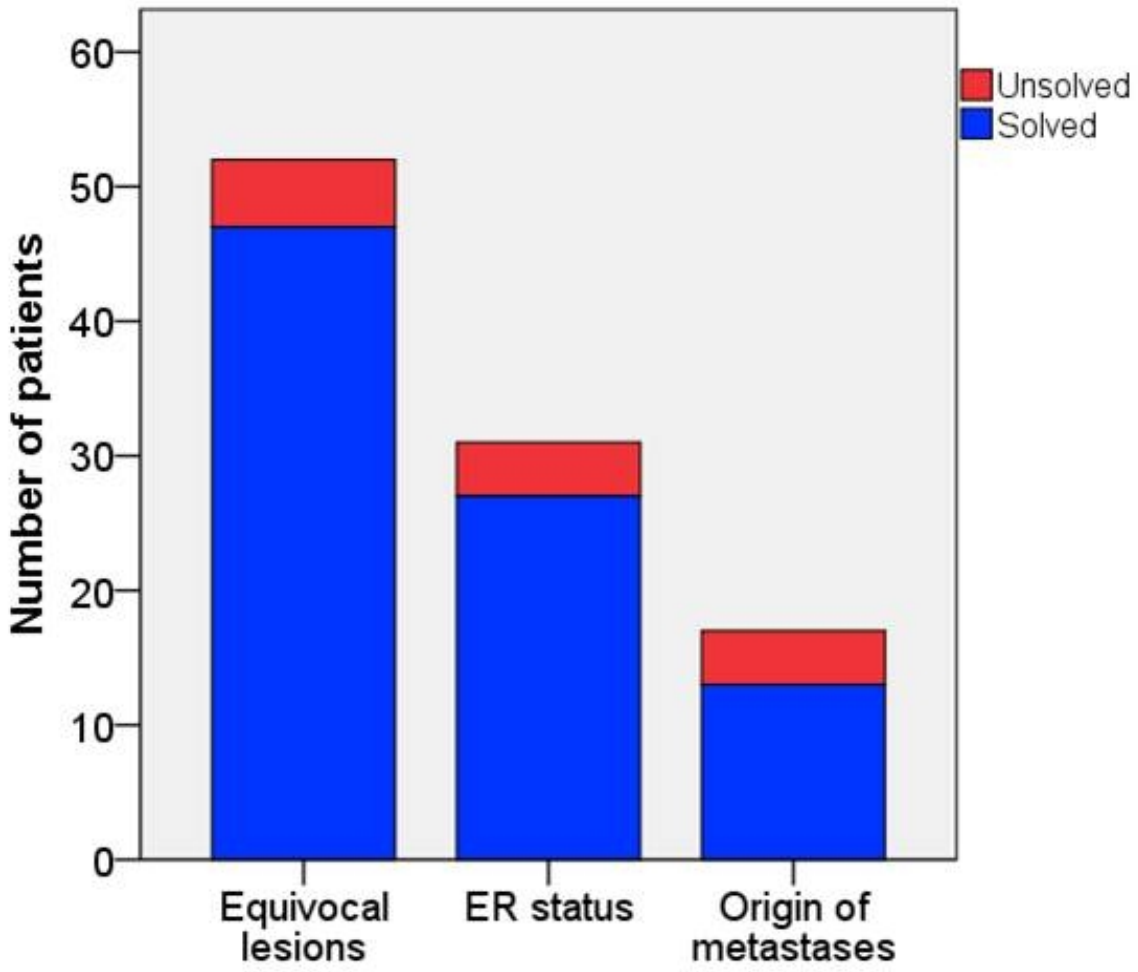
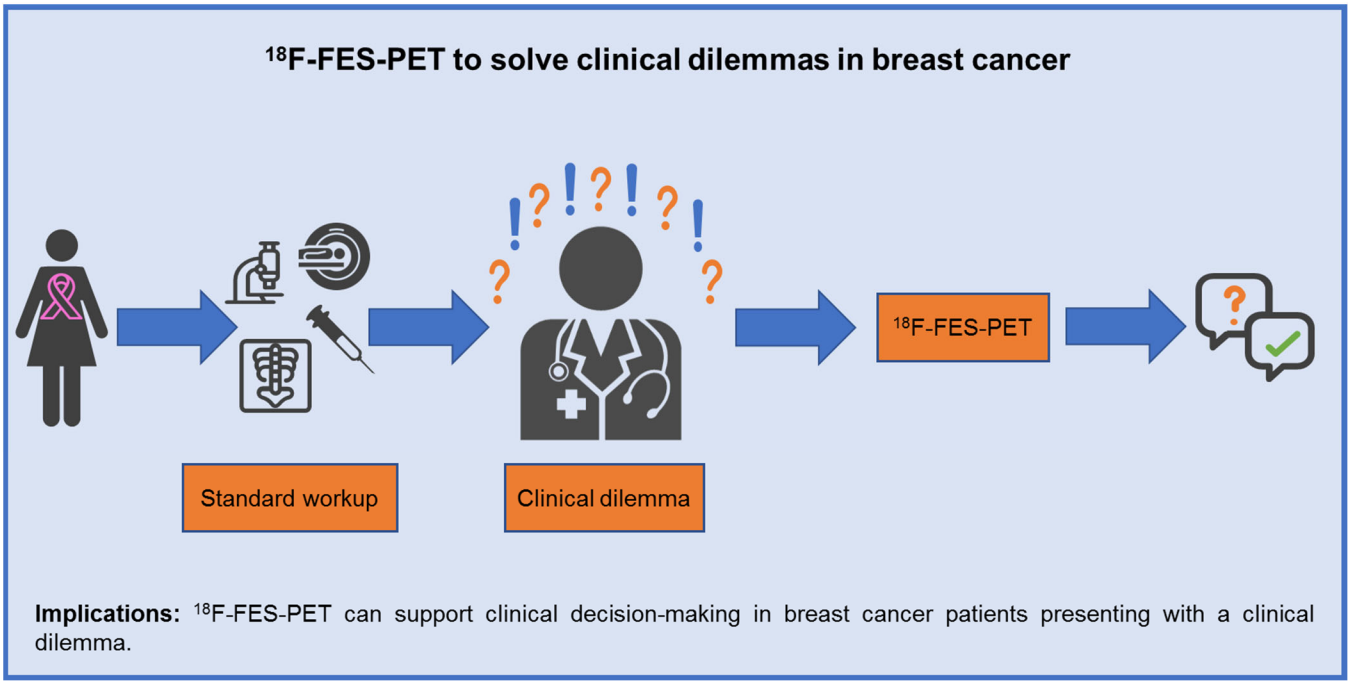


Figure 5. Value of ^{18}F-FES-PET to solve clinical dilemmas per category.

Graphical Abstract



SUPPLEMENTAL DATA

Supplemental Table 1. Quantitative analysis of ^{18}F-FDG/FES-PET*

Case	Primary tumor histology	Mean ^{18}F-FDG SUV_{max}	Mean ^{18}F-FES SUV_{max}
1	Lobular	3.8	1.9
2	Ductal	4.3	2.5
3	Lobular	4.5	1.0
4	Lobular	4.9	5.1
5	Ductal	5.1	5.1
6	Unknown	6.0	3.3
7	Lobular	6.2	1.3
8	Unknown	6.4	3.2
9	Unknown	6.7	1.3
10	Ductal	7.2	3.6
11	Ductolobular	7.3	2.2
12	Ductal	8.4	7.5
13	Ductal	13.8	1.4
14	Ductal	14.1	3.0

*A volume of interest was manually drawn at three metastatic lesions (or less if no other lesions were detected on ^{18}F-FDG-PET) with the highest visual ^{18}F-FDG uptake. These lesions were quantified on ^{18}F-FDG-PET and ^{18}F-FES-PET, using the maximum standardized uptake value (SUV_{max}). The mean ^{18}F-FDG SUV_{max} of these 3 lesions (or less) was reported, and also the mean ^{18}F-FES SUV_{max}.

Supplemental Table 2. Type of treatment before and after ^{18}F-FES-PET in 51 cases, in which the treatment was changed

Therapy before ^{18}F-FES-PET	**Therapy after ^{18}F-FES-PET**	**Cases (*n*)**
Chemotherapy *	Another chemotherapy *	4
	Another chemotherapy + radiotherapy	1
	Endocrine therapy	1
Endocrine therapy	Another endocrine therapy	8
	Another endocrine therapy + radiotherapy	2
	+ Radiotherapy	7
	Chemotherapy	3
	Chemotherapy + radiotherapy	1
	No treatment	1
Endocrine therapy + radiotherapy	Another endocrine therapy	1
	Another endocrine therapy + radiotherapy §	1
	Switch to another local treatment with continuation of endocrine therapy ‡	1
Local treatment ‡	Endocrine therapy	3
	+ Chemotherapy	2
	+ Endocrine therapy	3
	Switch to another local treatment ‡	1
No treatment	Chemotherapy	2
	Chemotherapy + radiotherapy	1
	Endocrine therapy †	4
	Endocrine therapy + radiotherapy	2
	Local treatment ‡	2

* Chemotherapy in combination with anti-HER2 treatment (*n*=1); § AR-antagonist in combination with radiotherapy (*n*=1); ‡ Local treatment is defined as: radiotherapy, surgery, or samarium therapy; † AR-antagonist (*n*=1).