

# Tumor Marker–Guided PET in Breast Cancer Patients—A Recipe for a Perfect Wedding

## *A Systematic Literature Review and Meta-Analysis*

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**Introduction:** Early detection of breast cancer (BC) recurrence is a fundamental issue during follow-up. Although the utilization of new therapeutic protocols aimed at reducing the recurrence risk is defined, the diagnostic approach for early detection remains to be clarified. We aim to provide a critical overview of recently published reports and perform a meta-analysis on the use of tumor markers in BC patients as a guide for fluorodeoxyglucose positron emission tomography (PET) imaging.

**Methods:** Medline and Google Scholar were used for searching English and non-English articles that evaluate the role of PET in BC recurrence when an increase in tumor markers is found. All complete studies were reviewed; thus, quantitative and qualitative analyses were performed.

**Results:** From 2001 to May 2011, we found 19 complete articles that critically evaluated the role of PET in BC recurrence detection in the presence of elevated tumor markers. The meta-analysis of the 13 studies provided the following results: pooled sensitivity 0.878 (95% CI: 0.838–0.909), pooled specificity 0.693 (95% CI: 0.553–0.805), and pooled accuracy 0.828 (95% CI: 0.762–0.878).

**Conclusions:** The current experience confirms the potential of fluorodeoxyglucose PET, and in particular of PET/CT, in detecting occult soft tissue and bone metastases in the presence of a progressive increase of serum tumor markers in BC patients, but this should be better defined in the current practical recommendations.

**Key Words:** breast cancer, tumor markers, cancer recurrence, PET, PET/CT

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Elevated tumor marker levels (carcinoembryogenic antigen [CEA] and cancer antigen 15.3 [CA 15.3]) are associated with an increased risk of recurrence,<sup>1</sup> but localization of metastases or recurrent disease remains a challenge often requiring an extensive diagnostic workup. Tumor cells have an increased metabolism of glucose,<sup>2</sup> which has been shown to be true for breast cancer (BC) cells.<sup>3–6</sup> Evaluation of glucose metabolism is now a routine metabolic imaging procedure using <sup>18</sup>F-fluorodeoxyglucose (FDG) positron emission tomography (PET). Several studies have shown the

high value of FDG PET in the staging and restaging of BC and in therapy monitoring.<sup>7–12</sup> Furthermore, it has been shown that the introduction of FDG PET in the past decades has improved the management of cancer patients as reported by Zangheri et al.<sup>13</sup> The role of tumor markers as a gatekeeper for further exploration by multimodality imaging is controversial because a large number of patients present with negative marker profiles in association with clinical evidence of tumor recurrence or metastases.

### TUMOR MARKERS IN BREAST CANCER

The definition of tumor markers is extremely broad; tumor cells may express certain molecules at a different rate from that of normal cells, and these substances are released in the bloodstream or in other biologic fluids. The most common serum markers used for postoperative monitoring of BC are CEA and CA 15.3, although several other markers can be used. CEA levels are less commonly elevated than are levels of mucin 1 glycoprotein (MUC-1) assays, CA 27.29, or CA 15.3. Only 50% to 60% of patients with metastatic disease will have elevated CEA levels (sensitivity varies from 30% to 70% for visceral and skeletal metastases, with a positive predictive value ranging from 18% to 26%) compared with 75% to 90% in patients who have elevated levels of the MUC-1 antigens. For this reason, CA 15.3 is considered more specific than CEA in monitoring BC evolution, with the latter marker being considered a poor predictor of BC recurrence. Unfortunately, nonspecific elevation of both CEA and CA 15.3 may be found also in patients with inflammatory (eg, diverticulitis, bronchitis), autoimmune (eg, sarcoidosis), and other benign disease (eg, hepatitis, cirrhosis, hypothyroidism) in lung, gastrointestinal, or neuroendocrine tumors, as well as in smokers and in the elderly population.<sup>14,15</sup>

In some studies in patients with disease relapse, the CA 15.3 value was high in two-thirds of cases, whereas in the remaining one-third, the value was normal or became elevated later, thus showing both low specificity and positive predictive value.<sup>15,16</sup> Therefore, in patients suspected of having BC relapse, low levels of markers do not exclude the presence of malignancy, whereas high levels of marker indicate, almost certainly, the presence of metastatic disease.<sup>17,18</sup>

### CURRENT RECOMMENDATION

Several international guidelines were designed to provide practical recommendations for the appropriate interpretation of circulating tumor markers. The current American Society of Clinical Oncology recommendation<sup>19</sup> considered 13 categories of BC tumor markers (CA 15.3, CA 27.29, CEA, estrogen receptors [ERs], progesterone receptors, human epidermal growth factor receptor 2, urokinase plasminogen activator, plasminogen activator inhibitor 1, and certain multiparameter gene expression), 6 of which were introduced recently. Many of these markers did not demonstrate sufficient evidence to support their use in clinical practice. However, present data in the literature are insufficient to recommend CA 15.3

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or CA 27.29 for screening, diagnosis, and staging. For monitoring patients with metastatic disease during active therapy, CA 15.3 and CA 27.29 can be used in conjunction with diagnostic imaging, history, and physical examination. Failure of therapy is indicated when an increase of tumor markers is noted in the absence of readily measurable disease.

Currently, according to American Society of Clinical Oncology guidelines,<sup>20</sup> the follow-up of BC patients should involve only physical examination and conventional annual mammography. In the presence of new symptoms, it is recommended to proceed to tumor markers' evaluation and conventional imaging, such as chest x-ray, CT, MRI, and PET scan. The European Group on Tumor Marker<sup>21</sup> panel suggests the following approach during the follow-up of asymptomatic women: tumor markers should be determined every 2 to 4 months (according to the risk of recurrence) during the initial 5 years after diagnosis and at yearly intervals thereafter. The "biochemical evidence" of a possible cancer relapse suggested by increased tumor markers should lead the oncologists to locate the sites of these lesions through conventional radiologic imaging techniques or nuclear medicine modalities.<sup>22,23</sup> These practices are based on the assumption that the earlier detection of recurrent or metastatic disease enhances the chances of cures (ie, start or change therapies) or improves survival.

## TUMOR MARKERS AND NUCLEAR MEDICINE

The early detection of disease relapse could improve the prognosis and allows better management such as starting a new treatment or changing an ongoing therapy. Polychemotherapy, including anthracyclines, and newer agents like monoclonal antibodies directed against the Her2/neu oncoprotein (eg, trastuzumab) result in a significant survival gain in BC patients.<sup>24,25</sup> Additionally, and because of the combination of immunotherapy and new chemotherapy agents, prognosis of these patients for long-term survival can probably be improved, leading to a higher probability of 5-year survival.

In clinical practice, suspicion for disease relapse is related to positive clinical findings, the appearance of new lesions on imaging examinations, and/or unclear and persistent elevation of tumor markers. The imaging modalities are not only important at cancer presentation to visualize the tumor lesions but also in evaluating the tumor extent (staging and restaging), in follow-up, and in the assessment of therapy responses.<sup>26</sup> A link between imaging and CA 15.3 could be envisaged by considering the work of Tampellini et al,<sup>27</sup> who demonstrated that the high values of CA 15.3 were more frequently positive in patients with liver metastases (74.6%) and with pleural effusion (75.7%), ER-positive tumors, and with a larger extent of the disease than in patients with cancer recurrence in bone (65%), lung (61.8%), or soft tissue (47.1%). At multivariable logistic regression, the pleural effusion, ER status, and disease extent were confirmed as independent variables in determining CA 15.3 positivity. Considering as end point the overall survival, the multivariable survival analysis calculated with the Cox regression model showed that ER status, disease extent, and liver metastases were independent variables, and when the disease extent variable was removed, the CA 15.3 values became an independent variable associated with poor prognosis.<sup>27</sup> Therefore, the extent of disease represents a marker of poor prognosis and may benefit from quantitation by an imaging tool. FDG PET permits a complete tumor staging with a single whole-body investigation, allowing the diagnosis of a significant number of metastases that would be missed or incorrectly diagnosed by CT, MRI, or bone scintigraphy. Thus, there is mounting evidence that whole-body PET can become fundamental in the search for metastases, especially when the recurrences are suspected because of progressive increase in circulating tumor

markers.<sup>28</sup> The indications for PET are constantly changing and require updating with time. In addition to staging and restaging by PET, the recommendations of the European Association of Nuclear Medicine<sup>29</sup> include establishing and localizing disease sites as a cause for elevated serum markers in some tumors, including colorectal, thyroid, ovarian, cervix, melanoma, breast, and germ cell tumors. In the present article, we first qualitatively described (1) the use of tumor marker value as an indicator of performing PET; (2) the diagnostic accuracy of tumor markers, PET, and their combination; and (3) the clinical and therapeutic impacts of tumor markers and nuclear medicine imaging. Second, we performed a meta-analysis of the performances of FDG PET to detect BC recurrence when tumor markers' value was rising.

## METHODOLOGY AND STATISTICAL ANALYSIS

Articles containing information on the results of FDG PET or FDG PET/CT for BC relapse when the tumor markers are increasing, and published in the English and other language literature before June 2011, were reviewed. In non-English editing text, if a complete English abstract was available, it was used for the final analysis. The references of articles and reviews found in the literature search were also examined to find additional reports that met the inclusion criteria. Studies with potentially overlapping study populations were excluded. Articles were included if the absolute numbers of true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) test results were available or derivable from the article, which allowed us to construct  $2 \times 2$  contingency tables. The reference standard was pathology, follow-up with conventional imaging, and/or clinical follow-up. Two independent reviewers evaluated the methodology of the selected studies by using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS).<sup>30</sup> The evaluation was based on a 14-point scale: (1) Was the spectrum of patients representative of the patients who will receive the test in practice? (2) Were selection criteria clearly described? (3) Is the reference standard likely to correctly classify the target condition? (4) Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests? (5) Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis? (6) Did patients receive the same reference standard regardless of the index test result? (7) Was the reference standard independent of the index test? (8) Was the execution of the index test described in sufficient detail to permit replication of the test? (9) Was the execution of the reference standard described in sufficient detail to permit its replication? (10) Were the index test results interpreted without knowledge of the results of the reference standard? (11) Were the reference standard results interpreted without knowledge of the results of the index test? (12) Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (13) Were uninterpretable/intermediate test results reported? and (14) Were withdrawals from the study explained? Each item was answered as "yes," "no," or "unclear." Inconsistent findings between the 2 readers were discussed and agreed on by consensus. The number of TP, TN, FP, and FN was extracted or computed from each selected study based on the FDG PET as the index test. The pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value, likelihood ratio (LR), accuracy, and diagnostic odds ratio (DOR) were calculated. A random effects model was used. The between-study heterogeneity was assessed using the tau-squared and I-squared tests. The tau-squared test provided an estimate of the between-study variance, and the I-squared test measured the proportion of inconsistency in individual studies that cannot be explained by chance. According to Higgins et al,<sup>31</sup> the values of 25%, 50%, and 75% for

heterogeneity were considered low, moderate, and high, respectively. All statistical analyses were performed using Meta-Analyst software (version Beta 3.13, SPSS Inc, Chicago, IL).<sup>32</sup> Additionally, we used Duval and Tweedie's "trim and fill" method developed to estimate potential publication bias (available in CMA, version 2).

### RESULTS

The Medline and Google Scholar research generated 63 publications: 33 original articles on the use of FDG PET or PET/CT for BC recurrence detection, 11 original articles on the use of PET or PET/CT in BC, and 19 reviews on BC and PET or PET/CT and about the role of PET or PET/CT in comparison with other imaging techniques in BC relapse. Some of these articles (n = 19) were focused on the value of PET or PET/CT in detection of BC recurrence when tumor markers' levels are progressively increased (Table 1). For the meta-analysis assessment, we analyzed the performance of FDG PET in 13 original articles (Fig. 1).

### Qualitative Analysis

Circulating tumor markers are biochemical product changes that are commonly detected by nuclear medicine techniques such as overexpression and production of tumor-associated antigens on surface membrane and in the bloodstream. They can also result from completely different physiopathological pathways (such as old age) or lifestyle choices (such as smoking) that cannot be predicted by imaging modalities. Recent data suggest that FDG PET is a useful technique for detecting recurrent BC suspected on the basis of an asymptotically elevated tumor marker level and negative conventional imaging results.<sup>33,34</sup> Suarez et al<sup>11</sup> reported that values of CA 15.3 >60 UI/mL were always associated with positive PET results, and values <50 UI/mL were associated with negative PET results. Patients with symptoms or with clinical suspicion of disease relapse may present with negative markers and conventional imaging but nevertheless have disease recurrence. As described by some authors,<sup>26,33,35</sup> whole-body PET may become the method of choice for the assessment of asymptomatic patients with elevated tumor marker levels. Lonneux et al<sup>10</sup> were the first authors who evaluated whole-body FDG PET in women presenting with a suspicion of recurrence, with a special focus on patients with isolated increase in tumor

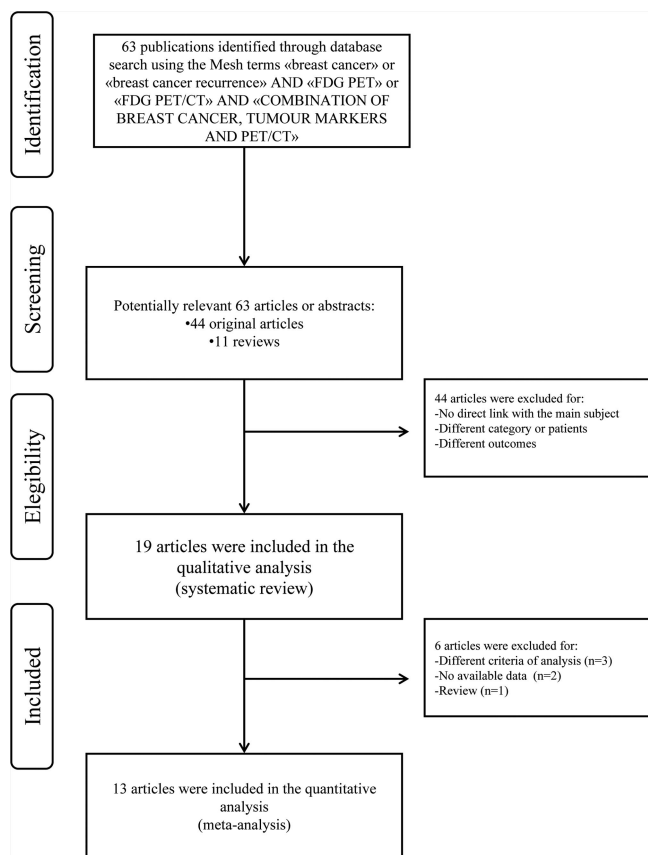


FIGURE 1. Flowchart for the selection of studies.

TABLE 1. Summary of Some Studies for PET–PET/CT and Tumour Markers (Patient Based Analysis)

Study	No. Patients	Sensitivity (%)	Specificity (%)	Accuracy (%)
Gallowitsch et al <sup>8</sup>	31	95.6	75	90.3
Lonneux et al <sup>10</sup>	39	94	50	87
Suarez et al <sup>11</sup>	45	92	75	87
Liu et al <sup>34</sup>	30	96	90	90
Trampal et al <sup>35</sup>	72	96.4	75.6	—
Siggelkow et al <sup>36</sup>	35	80.6	97.6	—
Pecking et al <sup>37</sup>	119	92.9	60	82.3
Kamel et al <sup>38</sup>	70	89	84	87
Grassetto et al <sup>43</sup>	89	90.9	100	91.8
Evangelista et al <sup>44</sup>	111	81.2	51.8	60.3
Radan et al <sup>45</sup>	47	90	71	83
Champion et al <sup>45</sup>	368	93.6	85.4	92.1
Filippi et al <sup>47</sup>	46	86.8	87.5	86.9
Aide et al <sup>51</sup>	35	75	71.4	74.2
Evangelista et al <sup>54</sup>	60	84	91.4	88.3

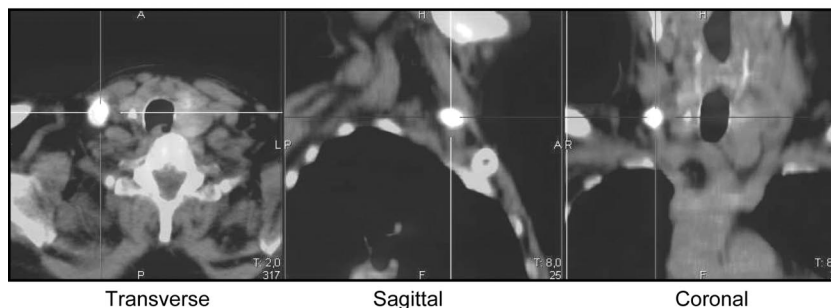
CT indicates computed tomography; PET, positron emission tomography.

markers. They demonstrated that FDG PET is useful in the evaluation of women suspected of distant recurrence of BC, and that PET allowed earlier diagnosis of recurrence, which can lead to earlier therapy. As far as patient management is concerned, their results suggested that, as a noninvasive and highly sensitive imaging procedure, whole-body FDG PET should be performed as first-line imaging when a recurrence of BC is suspected on the basis of clinical or biologic signs. Following that, and only when patient management could be affected, dedicated and oriented CT or MRI could confirm precisely the anatomic localization of the sites with increased FDG uptake. There is clearly no need for additional imaging procedures if PET shows disseminated bone disease or multiple lymph node metastases. However, cases of equivocal PET findings should be checked using appropriate procedures. Gallowitsch et al,<sup>8</sup> Trampal et al,<sup>35</sup> Siggelkow et al,<sup>36</sup> and Liu et al<sup>34</sup> reported that FDG PET in a subset of BC patients with an increase in tumor markers showed a higher diagnostic accuracy than conventional imaging. Furthermore, Gallowitsch et al<sup>8</sup> concluded that FDG PET demonstrated apparent advantages in the diagnosis of metastases in patients with BC compared with conventional imaging on a patient-based analysis. In particular, concerning bone metastases, sclerotic lesions are predominantly detected by bone scan, even though there were several patients with more FDG-positive bone lesions and also mixed FDG-positive/<sup>99m</sup>Tc methylenediphosphonate (MDP)-negative and FDG-negative/<sup>99m</sup>Tc MDP-positive metastases.

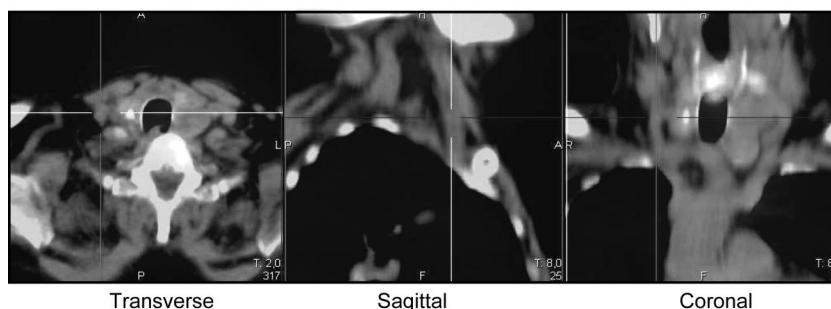
Pecking et al<sup>37</sup> reported that the PPVs of PET increased with the rise in serum CA 15.3 levels, being higher when the CA 15.3 value is >75 U/mL than when the CA 15.3 value is <30 U/mL and ≤50 U/mL (accuracy: 90.3% vs. 64%). On the contrary, Kamel

**FIGURE 2.** A 76-year-old woman with right BC treated with quadrantectomy and radiotherapy in 2006 (invasive ductal cancer, pT1<sub>c</sub>No, G1). In 2009, she underwent conventional imaging examinations (mammography and chest x-ray) for a suspicion of disease recurrence at clinical examination. Conventional imaging findings were negative; thus, she underwent FDG PET/CT. At the time of PET evaluation, CA 15.3 value was normal (6.5 U/mL obtained 2 weeks before PET/CT). FDG PET/CT showed a right supraclavicular lymph node with increased FDG uptake. Biopsy and histology evaluations confirmed the BC recurrence; thus, selective radiotherapy was planned. Twelve months after first PET/CT, a second scan was performed, with negative results in the presence of a higher CA 15.3 value (24.2 U/mL).

#### Baseline PET/CT (Ca15.3 value=24.2 U/ml)



#### Post-therapy PET/CT (Ca15.3 value=3.5 U/ml)

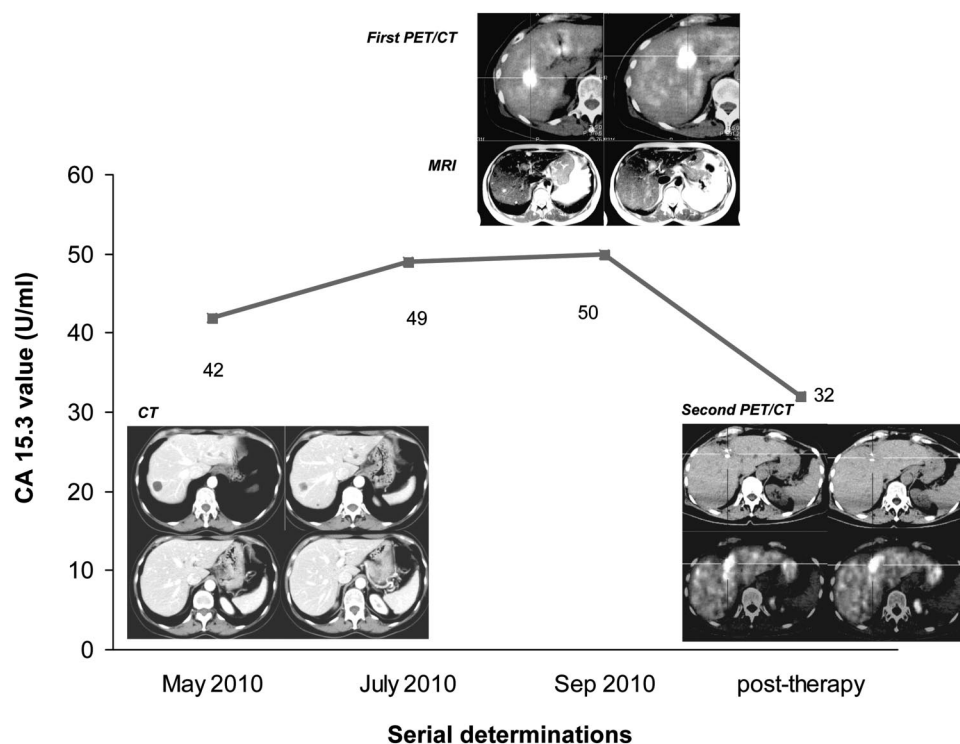


et al<sup>38</sup> reported that FDG PET was more sensitive than serum marker CA 15.3 in detecting relapsed BC because its value was normal in 42% patients with true positive PET findings. Although both FDG PET and tumor marker status are biologic tools that characterize the functional state of existing tumor tissue, the tumor markers were previously reported to be insensitive for identifying the existence of tumor tissue with a relatively smaller burden. However, FDG PET is not sensitive for the detection of micrometastases, but it showed a high predictive value for disease recurrence detection. This suggested that in patients with clinical suspicion but negative tumor marker profiles, FDG PET was a reliable imaging tool for the detection of tumor recurrence or metastases.

Suarez et al,<sup>11</sup> supported by the results from Eubank et al,<sup>39</sup> concluded that tumor marker-guided PET in the follow-up of BC patients is of clinical utility. PET can identify other sites of disease or a new neoplasm, thus allowing for modification of the clinical management in many patients in whom a tumor relapse or unexpected primary neoplasm was discovered, and addressing an adequate therapeutic decision.

Present data indicate that use of FDG PET is rational in patients with asymptotically elevated tumor marker levels and equivocal or negative findings on conventional imaging. Although FDG PET cannot rule out microscopic disease, it nevertheless has a particular value in providing a reliable assessment of the true extent of the disease in a single examination.<sup>40,41</sup> However, it is doubtful whether FDG PET will replace conventional imaging in cases of suspected recurrence in the near future. Some authors<sup>13,33</sup> reported that the combination of FDG PET and tumor marker assay (ie, use of FDG PET when warranted by tumor marker levels) is sufficient for the early detection of BC recurrence, although the impact of therapeutic interventions on survival before clinical symptoms become obvious has not yet been established. Because both tests are based on metabolic changes caused by tumor activity, they provide information on disease progression in a different way than conventional imaging;<sup>41</sup> nevertheless, PET alone has certain limitations including the inability to anatomically localize focal lesions. The

combination of morphologic and functional imaging technologies in a single scanner has provided the additional advantage of simultaneous data acquisition, obviating the need for patient repositioning. Haug et al<sup>41</sup> studied patients with isolated increase of tumor markers who were either asymptomatic or suspected to have disease recurrence. Thirty-four patients were studied; 5 were symptomatic and 29 asymptomatic. They compared PET, CT, and PET/CT in a subset of patients with high levels of tumor markers (both CEA and CA 15.3) and showed that the combined modality is associated with a higher diagnostic accuracy than considered alone. PET/CT was able to identify 149 malignant foci in 24 patients (71%); CT identified 96 foci in 18 patients; and PET, 124 foci in 17 patients. PET was not different from CT, but both were significantly different from PET/CT results (sensitivity: 88% vs. 96% vs. 96% and specificity: 78% vs. 78% vs. 89% for PET alone, CT, and PET/CT, respectively; all  $P < 0.01$ ). Saad et al<sup>42</sup> found a correlation between PET/CT, CA 27.29, and circulating tumor cells, although PET/CT demonstrated a poor sensitivity (59% and 55%, respectively) and negative predictive value (24% and 33%, respectively) to detect metastatic disease. Grassetto et al<sup>43</sup> found that PET/CT may be able to detect occult metastatic and recurrent disease in post-therapy BC patients with rising CA 15.3 level and negative conventional imaging. In a study performed in our nuclear medicine unit,<sup>44</sup> we found that PET/CT was able to recognize the majority of patients with disease relapse, irrespective of the value of CA 15.3 and CT findings, identifying 81% of cancer recurrence and missing 19% with better performance compared with tumor markers and CT. Similar results were reported by Radan et al,<sup>45</sup> who concluded that PET/CT had high performance indices and was superior to CT for diagnosis of tumor recurrence in patients with BC and rising tumor markers. Finally, Champion et al<sup>46</sup> and Filippi et al<sup>47</sup> reported that FDG PET/CT enabled the adjustment of further treatment (the change in patient management was 54% and 50%, respectively), proving a high performance “one stop-shop” procedure.



**FIGURE 3.** A 55-year-old woman with left BC (invasive ductal cancer, pT1<sub>c</sub>No, triple negative) was treated with quadrantectomy plus adjuvant chemotherapy and radiotherapy in 2009. A progressive increase in tumor markers was noted within few months from last therapy (CA 15.3 value ranged from 42 to 44.8 to 49.9 U/mL) without evidence of disease recurrence at conventional imaging (CT). A PET/CT scan showed 2 areas of high FDG uptake in the liver. MRI confirmed the liver lesions; thus, the patient underwent liver metastasectomy. After 4 months from surgical treatment, PET/CT examination demonstrated the persistence of disease, although CA 15.3 value was weakly high (32.6 U/mL).

A strong concordance among the analyzed studies was found: PET and PET/CT are indicated in the presence of abnormally elevated tumor markers and suspicious of BC recurrence, with no reports in literature stating otherwise. In Figure 2 is reported an example of low specificity of CA 15.3 value, whereas PET/CT showed high PPV. As reported by Yasasever et al and Hayes et al,<sup>48,49</sup> an increase of tumor markers can be detected even when the tumor has been responding to treatment; this phenomenon is known as a “tumor marker spike” and represents a transient increase in serum CA 15.3 levels following the initiation of effective therapy for metastatic disease. The peak usually occurs 15 to 30 days after the initiation of treatment, although spikes may last as long as 90 days. The return to a normal value, or to below baseline level, is consistent with response to therapy. In the case of Figure 2, the increase of CA 15.3 value was associated with no specific causes, for example, inflammation or others, as previously mentioned (see Introduction).

### PET and Serial Determination of Tumor Markers

The tumor marker assay is limited when a dichotomous positive/negative cutoff point is used. These criteria are easy to use and well accepted in clinical practice, but are not powerful enough for the early detection of biologic relapse: a relevant quantity of tumor tissue is necessary to produce a sufficient quantity of tumor markers to exceed the cutoff point. Dynamic interpretation, based on serial samples, might provide earlier diagnostic information; thus, a significant increase could be detected before exceeding the cutoff level. The criteria to evaluate the increases as significant are based not only on the cutoff levels but also on the difference between the values in 3 consecutive determinations that should be at least 2-fold the interassay coefficient of variation

(20%). The interval between the serial tests has to be at least 1 month.<sup>50</sup> In the literature, there is a general consensus that steadily rising levels of CEA and CA 15.3 values have to be considered a relevant sign in tumor cell growth; this means that tumor markers' determination during follow-up in patients who are radically operated could anticipate the clinical diagnosis of cancer relapse. In our opinion, the use of PET/CT in patients with BC might improve the accuracy in determination of disease extension in case of tumor markers' increase, but it is important to evaluate the trend of successive increase of marker and not its single value. As is well known, several noncancerous conditions (benign breast or ovarian disease, endometriosis, pelvic inflammatory disease, and hepatitis) can bring up levels of CA 15.3, thus reducing the specificity of biochemical relapse, and PET/CT could identify the disease activity before it becomes clinically manifest, even when the value of tumor markers is within the normal range. Suarez et al,<sup>11</sup> Aide et al,<sup>51</sup> and Molina et al<sup>21</sup> reported that a CA 15.3 blood level >60 UI/mL was correlated with a positive FDG PET. This latter inclusion criterion underlines the low sensitivity of tumor markers and thus the utility of serial determinations. Mariani et al<sup>52</sup> advised that the tumor marker be considered an indicator of disease presence, not only a tumor marker value above the normal limit (dichotomous criteria) but also a difference between 2 consecutive measurements greater than a critical value (dynamic criteria). Serial CA 15.3 measurements may be an efficient and cost-effective method of monitoring disease progression and might be a powerful tool for obtaining information about BC while causing minimal morbidity, inconvenience, and cost.<sup>53</sup> The advantage of adding PET/CT in combination with constant elevation of CA 15.3<sup>54</sup> could be translated in a more valuable method to identify earlier

TABLE 2. Studies Included in Meta-Analysis

Author (Reference)	Year of Publication	Design	Country	Technique	FDG Diagnostic Criteria	QUADAS Score
Lonneux et al. <sup>10</sup>	2000	Prospective	Belgium	PET	Visual	8
Pecking et al. <sup>37</sup>	2001	Retrospective	France	PET	Visual and T/B ratio	12
Liu et al. <sup>34</sup>	2002	Prospective	Taiwan	PET	Visual	10
Suarez et al. <sup>11</sup>	2002	Prospective	Spain	PET	Visual/semiquantitative (SUV)	11
Kamel et al. <sup>38</sup>	2003	Retrospective	Switzerland	PET	Visual	9
Gallowitch et al. <sup>8</sup>	2003	Retrospective	Austria	PET	Visual	9
Radan et al. <sup>45</sup>	2006	Retrospective	United Kingdom	PET/CT	Visual	8
Aide et al. <sup>51*</sup>	2007	Retrospective	France	PET	Visual	11
Champion et al. <sup>46</sup>	2010	Retrospective	France	PET/CT	Visual	10
Grassetto et al. <sup>43</sup>	2010	Retrospective	Italy	PET/CT	Visual/semiquantitative (SUV)	9
Filippi et al. <sup>47</sup>	2011	Retrospective	Greece	PET/CT	Visual	10
Evangelista et al. <sup>44</sup>	2011	Retrospective	Italy	PET/CT	Visual/semiquantitative (SUV)	11
Evangelista et al. <sup>54</sup>	2011	Retrospective	Italy	PET/CT	Visual/semiquantitative (SUV)	11

\*Thirty-five PET scan in 32 patients.

metabolic changes (which is the basic principle of PET imaging), even before the morphologic changes (noticeable with ultrasound and CT) can occur. Aide et al.<sup>51</sup> retrospectively evaluated 35 FDG PET examinations in 32 patients with CA 15.3 blood level above the normal range and negative conventional imaging within 3 months before PET examination. CA 15.3 assays were performed before the PET examinations using the same technique; all tests were collected and used for doubling time calculation if (1) no therapeutic modification occurred in the meantime, and (2) the delay between assays was <6 months. Median CA 15.3 blood levels were higher in the positive PET group (100 U/mL) than in the negative group (65 U/mL) ( $P = 0.04$ ). The likelihood of depicting recurrence was higher in patients with a short doubling time (<180 days) ( $P = 0.05$ ), a CA 15.3 blood level >60 U/mL ( $P = 0.05$ ), and when a short doubling time was associated with a CA 15.3 blood level >60 U/mL ( $P = 0.03$ ). The authors concluded that the likelihood of depicting recurrence was influenced by CA 15.3 blood level and doubling time. In our recent report,<sup>54</sup> we assessed the relationship between serial measures of CA 15.3 and FDG PET/CT findings in patients with treated BC during follow-up. In 60 patients, 3 serial measures of CA 15.3 were collected within 1 year before PET/CT examination. Coefficient of variation of the CA 15.3 serial determinations was significantly higher in patients with positive than negative PET/CT (39% vs. 24%,  $P < 0.05$ ). Receiver operating curve (ROC) analyses showed that an increase of CA 15.3 between the second and third measurements has an increased likelihood of a positive PET/CT and disease relapse (area under curve [AUC] 0.65 and 0.64, respectively;  $P < 0.05$ ). Thus, we concluded that an increase of CA 15.3 could be considered optimal to address FDG PET/CT examination during follow-up of BC patients. PET/CT performed in the appropriate time frame might allow higher diagnostic accuracy in the early detection of disease relapse in BC patients (Fig. 3).

### Quantitative Analysis (Meta-Analysis)

Based on the QUADAS, the studies were considered to be good quality ( $n = 8$ ; score: 7–10) and high quality ( $n = 5$ ; score: 11–14). Among all the articles selected, a total of 894 patients were recorded and included in the meta-analysis. The characteristics of each study and the QUADAS score are reported in Table 2. The age range of the entire population studied was 49 to 62 years, with a mean age of  $57 \pm 5$  years. The trim and fill procedure showed no publication bias.

The pooled sensitivity of the <sup>18</sup>F-FDG PET in the 13 studies included in the meta-analysis was 0.878 (95% confidence interval

[CI]: 0.838–0.909) with a range between 0.750 and 0.957. The pooled specificity was 0.693 (95% CI: 0.553–0.805) with a range between 0.300 and 0.914. While evaluating the heterogeneity, both for the sensitivity and the specificity of the different studies, the I-squared test was 41% ( $P = 0.098$ ) for the sensitivity and 78% ( $P < 0.001$ ) for the specificity. Therefore, if we consider that there is heterogeneity <50%, this implies that, regarding sensitivity, there was global low-moderate homogeneity among the studies; therefore, the results could be used to reach a global sensitivity estimation. This was different with the specificity, where  $P < 0.05$ ; therefore, it showed that there was heterogeneity among the studies. A DOR was calculated as a diagnostic test performance measurement tool. A pooled value of 17.125 (95% CI: 8.405–34.889) was obtained. The positive LR was 2.775 (95% CI: 1.943–3.963) and shows that a positive <sup>18</sup>F-FDG PET result leads to small changes in the pretest probability. However, the negative LR was 0.189 (95% CI: 0.133–0.267) and shows that when the <sup>18</sup>F-FDG PET was negative, it led to moderate changes in the pretest probability. The I-squared test results were statistically significant for all values except sensitivity. In Table 3 are reported the pooled results for diagnostic accuracy and the results of heterogeneity measure.

TABLE 3. Pooled Results: Meta-Analysis of the Controlled Studies

Pooled Performances	Value	95% Confidence Interval		Tau-Squared*	I-Squared†
		Lower	Upper		
Sensitivity	0.878	0.838	0.909	0.123	0.409
Specificity	0.693	0.553	0.805	0.852	0.781
PPV	0.872	0.773	0.932	1.340	0.878
NPV	0.718	0.613	0.804	0.425	0.627
Accuracy	0.828	0.762	0.878	0.420	0.816
Positive LR	2.775	1.943	3.963	0.263	0.764
Negative LR	0.189	0.133	0.267	0.172	0.501
DOR	17.125	8.405	34.889	1.052	0.816

\*Estimation of the between-study variance.

†Quantification of the extent of heterogeneity, using a percentage value.

PPV indicates positive predictive value; NPV, negative predictive value; LR, likelihood ratio; DOR, diagnostic odds ratio.

## DISCUSSION

## Quantitative Analysis

To our knowledge, this meta-analysis is the first to evaluate global FDG PET diagnostic performance in cases of an increase in tumor markers in BC patients with suspicious of recurrence. Considering PET and PET/CT separately, sensitivity was similar (range: 0.828–0.957 and 0.750–0.936, respectively), whereas specificity was higher for PET/CT as compared with PET alone (range: 0.688–0.914 and 0.300–0.750, respectively); this latter finding underlined how the introduction of hybrid scan has reduced the FP rate. The DOR (DOR = 17.125) showed that there is a significant positive link between tumor recurrence and a positive  $^{18}\text{F}$ -FDG PET result, versus a negative result, which means that its contribution to diagnosis was significant. DOR depends significantly on the sensitivity and specificity of a test. A test with high specificity and sensitivity with low rate of FPs and FNs has high DOR. The positive LR showed small probability changes from pretest to post-test, whereas a negative LR showed moderate changes. The positive LR was 2.775 (a good diagnostic test has a positive LR >10), and  $^{18}\text{F}$ -FDG PET in patients with an increase in tumor markers showed a moderate contribution to the diagnosis. On the contrary, the negative LR was 0.189, indicating a significant contribution of the test in lowering the posterior probability of the subject having the disease. The results obtained mean that an  $^{18}\text{F}$ -FDG PET and, in particular PET/CT, may be useful in patients who are suspected of having a BC tumor recurrence based on the increase of tumor markers. The  $^{18}\text{F}$ -FDG PET presented an intermediate-high specificity (0.693) and a high sensitivity (0.878), which shows that there are very few FNs and FPs. This finding is important in managing oncology patients and may point to its usefulness in the restaging phase of the diagnostic process.

## CONCLUSION

In general, the diagnostic sensitivity (related to the size of tumor) is better assessed with imaging than with tumor markers. However, there are a large number of patients in whom tumor marker levels are high, or are progressively increasing, and in whom physical examination and conventional imaging are unable to detect the tumor. In these cases, the tumor markers' levels (biochemical occult disease) act as a guide for further studying the patients, with more powerful instruments (tumor marker-guided imaging) such as metabolic imaging with PET. Tumor markers are metabolic measures of tumor growth and tumor viability, and therefore are better integrated with metabolic imaging information. The association of tumor markers and PET/CT seems to be a perfect union, together providing qualitative and semiquantitative metabolic information. In particular, marker concentrations expressing the serum measure of tumor products are integrated with the metabolic images expressing pixel content as a measure of tumor uptake.

In conclusion, even if tumor marker-guided PET has still to be extensively evaluated, the current experience confirms the potential of FDG PET, and in particular of PET/CT, in detecting occult soft tissue and bone metastases in the presence of a progressive increase of serum tumor markers. We look forward to specifically designed prospective studies in which PET/CT will be used as first-line imaging in combination with serial increase of tumor markers, and the accuracy and the impact on overall survival of this additional procedure compared with conventional follow-up.

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