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REVIEW ARTICLE

Is there a place for F18-FDG PET/CT in the diagnosis of primary breast cancer?

Dragos Stefan Morariu[1,2], Catalin Vlad[1,2]*, Marius Emil Puscas[1,2]*, Vlad Gata[1,2]*, Doina Piciu[1,3]

[1]University of Medicine and Pharmacy "Iuliu Hațieganu", Cluj-Napoca, Romania; [2]The Oncology Institute "Prof. Dr. Ion Chiricuta", Department of Surgical Oncology, Cluj-Napoca, Romania; [3]The Oncology Institute "Prof. Dr. Ion Chiricuta", Department of Nuclear Medicine, Cluj-Napoca, Romania.

*These authors contributed equally to this article.

Summary

Purpose: *With the improvement of techniques and the update of diagnostic protocols in breast cancer, modern imaging proves to be effective in the diagnosis of this pathology, as well as in its prognosis. This study aimed to evaluate the effectiveness of these modern imaging techniques through a systematic assessment of the most recent studies.*

Methods: *A PUBMED search, using certain key combinations ("breast cancer", "F18 FDG PET-CT", "MRI", "staging", "diagnosis") and some inclusion and exclusion criteria, yielded 24 articles published during 2014-2018.*

Results: *Using these 24 articles, the various statistical tests showed a significant difference between modern imaging techniques, with respect to prognosis (p<0.05), in close correlation with the immunohistochemical profile of the tumor.*

Conclusions: *Modern imaging techniques (F18-FDG/PET-CT, F18-FDG/PET-MRI) were validated to formulate a better prognostic value than conventional imaging, presenting a sustainable higher sensitivity and specificity in evidencing the locoregional invasion and the recurrence of this pathology.*

Key words: *breast cancer, F18 FDG, imaging technique, MRI, PET-CT*

Introduction

Breast cancer is the most common oncologic pathology in women around the world and the leading cause of mortality, with 1.38 million newly diagnosed cases and 458,000 annual deaths worldwide [1]. Having a recurrence rate of about 0.5-1% per year in breast-conservative treatment and a 5-10% recurrence risk 10 years after the first treatment, careful follow-up of patients and certain breast imaging methods are required [2,3]. Risk factors such as history of familial disease, BRCA 1,2 and p53 mutations have a major role in the diagnosis and breast cancer recurrences [2,4]. Earlier detection with a higher accuracy is essential in controlling and establishing an oncologic therapy, as well as in the prognosis and survival of patients with this pathology [2,5].

The most common imaging investigations that are currently used in breast cancer pathology worldwide are breast ultrasound and mammography (the current gold standard in diagnosis for women >40 years); other imaging methods in breast cancer, include CT, MRI, scintigraphy which are commonly used to establish staging and to monitor patients during oncologic treatment, as well as for detecting possible recurrences, all these being associated with using a tracer [2-8].

Corresponding author: Catalin Vlad, MD, PhD. The Oncology Institute "Prof. Dr. Ion Chiricuta" 34-36 Republicii Street, 400015 Cluj-Napoca, Cluj, Romania.
Tel: +40 740 256 076, E-mail: catalinvlad@yahoo.it
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In recent years, improvements in these investigations have taken place, the combination of CT and MRI techniques with single photon emission tomography (SPECT) and positron emission tomography (PET) provides molecular information about the anatomy as well as about the metabolic and functional features of the tumor, metabolic and anatomical features [2,4,5,8]. Generally, cancer cells have higher metabolic activity compared to normal cells due to glucose-carrying proteins which increase their glycolytic activity [2,4,8].

This increased glucose metabolic activity has made it possible to use FDG, a tracer that is not specific for cancer, as it is increased in inflammatory processes, infections and plays a significant role in physiological processes in the muscles and the brain. Most studies on breast cancer were performed with care, as FDG is an analogue of glucose transported to the cell and phosphorylated by hexokinase [4-11].

The combined PET and CT system was designed for visualizing the body and allows a better resolution compared to PEM (positron emission mammography) [10].

Currently, there is no generalized imaging protocol neither in the diagnosis of breast cancer or in the prognosis of locoregional recurrences nor in the evaluation of chemotherapeutic response due to the fact that there are no studies reporting a well-defined therapeutic response [12]. Although many comparative studies between the two imaging techniques have been conducted, there is a high heterogeneity regarding these studies, as the results vary according to the technique, center, or imaging experience.

The purpose of this systematic review was to evaluate the effectiveness of modern imaging techniques both with an aim of diagnosing breast cancer and for demonstrating the prognostic response as compared to standard techniques, using a systematic evaluation of recent studies while looking at their cost-benefit ratio. Moreover, this review takes into account the influence of the immunohistochemical profile on the imaging results, and also highlights various associations of imaging techniques and their influence on patients' diagnosis and prognosis [8,12].

Methods

A literature search on PUBMED was conducted and we selected the articles that reported modern imaging in breast cancer as a potential diagnostic tool, studies that reported sensitivity, specificity and sufficient information in order to evaluate modern imaging for diagnosis, prognosis and response to treatment in breast cancer.

In order to be able to perform this systematic analysis, we used PRISMA software (Preferred Reporting Items for Systematic Review and Meta-Analyses) to select the appropriate items.

To search for articles, we used the PUBMED database with the following keywords:

a. "imaging, breast cancer, axilla, FDG, PET CT, response, specificity, sensitivity";
b. "imaging, MRI, breast cancer, prognosis, response, specificity, sensitivity";
c. "comparison, MRI, PET CT, diagnosis, breast cancer, specificity, sensitivity";
d. "diagnosis, prognosis, imaging, breast cancer, specificity, sensitivity".

The articles were reviewed based on eligibility criteria:

a. Presence of a certain number of candidates, showing specificity and sensitivity;
b. A comparison of all physical imaging methods, or a comparison between imaging and tumor markers;
c. Evaluation of evolution of the locoregional disease and the presence of metastasis.

Statistics

For statistical analysis, we used contingency tables, as well as various tests to interpret specificity and sensitivity. Data were interpreted using IBM SPSS v20.0 and REVMAN software. The exclusion criteria were: letters, editorials, case reports and studies with incomplete data, studies unrelated to modern imaging for breast cancer.

Results

Based on the inclusion and exclusion criteria, the abstracts of 35 studies were selected, which were subsequently evaluated. To verify the eligibility of these studies, full text was retrieved. Thus, after a rigorous review, 24 studies were finally selected.

Of the 24 studies, 20 were retrospective and 4 prospective. Most studies assessed the sensitivity and specificity of PET-CT compared to MRI or conventional imaging in breast cancer. Three studies focused on the financial aspect as well as on the cost-benefit ratio of these modern imaging techniques. The number of patients, clinical particularities, as well as the sensitivity, specificity and accuracy of the diagnostic techniques were evaluated. Many studies focused on the immunohistochemical profile of the tumors, as well as on a comparison of imaging in post-neoadjuvant chemotherapy [13-17].

Below are described a few of the most researched imaging methods in breast cancer:

Guo et al discuss not only the diagnostic performance of mammography, MRI, PET and computed tomography for patients with breast cancer, but they also compare the quality of the imaging techniques and their accuracy in initial diagnosis, diagnosis of recurrence, as well as patient follow-up (Table 1) [18].

Table 1. Diagnostic performance of multimodality imaging in breast cancer (sensitivity and specificity)

First author and year [Ref. no.]	*Interval period*	*No. of subjects*	*Mammography*	*Ultrasound*	*MRI*	*PET*
Kolb et al, 2002 [26]	1995-2000	11,130 asymptomatic, Mean age 63.7 y	Total SE=77.6% ≤49 y: SE=58% ≥50 y: SE=82.7%	Total SE=75.3% ≤49 y SE=78.6% ≥50 y SE=74%	-	-
BCSC data through 2009 (BCSC 2014a) [27,28]	2004-2008	363,048 mammography examinations	SE=84.4% SP=91.3%	-	-	-
Saarenmaa et al, 2001 [29]	1996-1997	572 breast cancer cases, age groups 26-49, 50-59 and 60-92	Total SP=98.8% SE=0.93% Increased by age, fattiness of breast OR=0.2-0.	Total SP=96.8% SE=0.86% Decreased by age OR=2.3	-	-
Hussami et al, 2003 [30]	1994-1996	480, 25-55 y, 240 with breast cancer, 240 age matched without cancer	Total SE=75.8% 45 y: SE=71.7% 46-55 y: SE=79.1% Total SP=87.6%	Total SE=81.7% 45 y: SE=84.9% 46-55 y: SE=79.1% Total SP=88.0%	-	-
Shen et al, 2015 [31]	2008-2010	13,339 high-risk women, 30-65 y	SE=57.1% SP=100% Diagnostic accuracy=76.6% PPV=72.7%	SE=100% SP=99.9% Diagnostic accuracy=99.9% PPV=70.0%	-	-
Berg et al, 2004 [32]	1999- 2002	177 malignant foci in 121 cancerous breasts	SE=67.8% SP=75%	SE=83.0% SP=34%	SE=94.4% SP=26%	-
Kuhl et al, 2005 [33]	1996-2002 mean follow-up of 5.3	529 asymptomatic women suspected or proven to have BRCA	SE=32.6% SP=96.8%	SE=39.5% SP=90.5%		
Kuhl et al, 2000 [34]	1996-1998	192 asymptomatic women proven or suspected to be carriers of a breast cancer susceptibility gene	SE=33% PPV=30%	SE=33% PPV=12%		-
Leach et al, 2005 [35]	1997-2004	649 patients with a strong family history of breast cancer or high probability of BRCA1, BRCA2 or TP53 mutation	SE=40% SP=93%	-		-
Sardanelli et al, 2011 [36]	2000-2007	501 women with high genetic risk	SE=50% SP=99%	SE=52% SP=98.4%		-
Warner et al, 2008 [37]	Databases 1995-2007	11 studies screening women at very high risk for breast cancer	SE=32% SP=94.7%	-		-
Zhang et al, 2014 [38]	2006-2012	164 patients with invasive breast cancer	-	-		SE=86%

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First author and year [Ref. no.]	*Interval period*	*No. of subjects*	*Mammography*	*Ultrasound*	*MRI*	*PET*
Song et al, 2015 [39]	2008-2012	86 patients with invasive breast cancer	SE=66.7% SP=89.5%	SE=83.3% SP=71.1%		SE=33.3 % SP=93.4 %
Berg et al, 2011 [40]	2006-2008	388 women with invasive and/or intraductal breast cancer	-	-		For PEM SE=80.5% SP=91.2% PPV=66%
Berg et al, 2006 [41]		94 consecutive women with known breast cancer	-	-		For PEM SE=90 SP=86 PPV=88 NPV=88 Accuracy=88

BRCA=breast cancer susceptibility gene; MRI=magnetic resonance imaging; NPV=negative predictive value; OR=odds ratio; PEM=positron emission mammography; PET=positron emission tomography; PPV=positive predictive value; SE=sensitivity; SP=specificity.
Adapted from [18] with permission.

According to Tozaki et al, 18FDG-PET is not recommended as a routine investigation after surgery. However, 18FDG-PET is commonly performed as a tool to find possible distant metastasis and to establish a treatment policy in patients who are suspected of disease recurrence, 18FDG-PET being considered feasible for this group of patients [19].

Moreover, Sawicki et al studied 21 patients that were suspected to have breast cancer recurrence. According with the standard observation, and the National Comprehensive Cancer Network (NCCN) breast cancer guideline, 17 patients were detected with recurrence. F18FDG combined with PET-MRI and PET/CT identified all 17 patients. Instead, PET/CT without tracer (18FFDG) identified only 15 patients with recurrence, having a low specificity and sensitivity without a tracer [4].

Ulaner et al conducted a study on 232 patients with triple negative breast cancer trying to reveal occult distant that were not detected by conventional imaging technique metastasis, this conclusion revealed that18 F-FDG PET/CT can and should be used for initial diagnosis [5].

In addition, Conejero et al in a study conducted in Spain, demonstrated that 18F-FDG and FDG-PET/CT have limited capacity in diagnosing metastatic lesions of breast cancer which are smaller than 1cm and also have limitations regarding the surveillance of treatment; though, adding a tracer to this investigation (18FFDG and FDG-PET/CT) may have a potential of inclusion in the breast cancer follow-up algorithm [2].

As reported by Cho et al, in their review, the performance of PET/CT mammography and PET/MR mammography combined with radiotracer (18FFDG) can be highly effective in diagnosing the local lesion of breast cancer and axilla for the future surgical management. Instead, FDG-PET/MRI associated with PET/MR mammography in a single session, can also detect distant metastatic lesions [10].

Additional studies also discuss about breast cancer detection using imaging by elastography and contrast-enhanced ultrasound, which provides additional information on breast lesions based on duplex sonography. Elastography imaging is a qualitative and quantitative technique based on structural characteristics (consistency and elasticity), and less on anatomy. If the tissues have a linear elasticity degree, elaborating the diagnosis can be difficult, and this could make ultrasound elastography a limited examination [20-23].

In the studies shown in Table 1, the pooled sensitivity of PET-CT in detecting the primary lesions was 0.78 (95% CI 0.63-0.91), in contrast with the MRI sensitivity in primary lesion detection, which was 0.76 (95% CI 0.63-0.88). Regarding specificity, MRI had a higher value, 0.82 (95% CI 0.78-0.85), versus the specificity of 0.67 (95% CI 0.61-0.73) of the CT. In addition, in the evaluation of nodal metastases, CT sensitivity was 0.51 (95% CI 0.39-0.63) and MRI sensitivity was 0.69 (95% CI 0.65-0.72). In some cases, other conventional imaging techniques with lower sensitivity and specificity (sensitivity: 0.62, 95% CI 0.49-0.79, specificity: 0.54, 95% CI 0.50-0.61) were compared. However, for PET lesions, the sensitivity of PET-CT was higher in comparison to the sensitivity of MRI (0.81, 95% CI 0.74-0.90

vs. 0.72, 95% CI 0.67-0.78), FDG techniques demonstrating a significant increase in the sensitivity and specificity in both cases (FDG PET-CT: 0.84, 95% CI 0.77-0.91, FDG NMR: 0.81, 95% CI 0.78-0.84). At the same time, a statistically significant difference was observed between certain imaging techniques using different markings ($p<0.05$). The cost-effectiveness ratio between the imaging techniques was also evaluated, and the average cost of conventional imaging was lower than the average cost of MRI/CT for the tested patients ($p=0.0021$) [18].

Discussion

These techniques are of particular importance in diagnosing mammary lesions as benign or malignant and may further improve the detection of early breast cancer. This review may be beneficial for young doctors who want to perform in the field of breast cancer. One of the limitations of this review is that it does not address in detail all aspects of ultrasound imaging in breast cancer. Based on the reviewed studies, a difference in the predictive values between the imaging techniques was observed. Thus, many studies support a much higher sensitivity of CT in locoregional diagnosis compared to conventional MRI imaging techniques. Studies also show that CT has a higher sensitivity in remote assessment, and would be also indicated for a reevaluation in order to upstage and re-evaluate treatments in breast cancer. Taking into account these aspects, MRI also plays a crucial role in the evaluation of nodal metastases, with both higher sensitivity and specificity. Although some studies support a higher sensitivity of MRI in both locoregional disease and the evaluation of nodal metastasis, most studies attempt to differentiate between these two imaging techniques from the point of view of their use.

This analysis also included studies regarding the effectiveness of imaging techniques in combination with various tracers to obtain imaging results according to the immunohistochemical profile. These studies suggest that parenchymal activity may influence the specificity of the imaging results, with fluorodeoxyglucose uptake occurring at different rates (moderate to good correlation, $p<0.05$).

Some of the studies have also looked at the effectiveness of modern imaging in patients with neoadjuvant chemotherapy. Based on the results, PET-CT has been shown to have a much higher value regarding the diagnosis than conventional imaging techniques. However, MRI plays a key role in the evaluation of nodal metastases. Some studies focus on the combined positive predictive value of these two imaging techniques, allowing to achieve promising results (PPV=100%, $p<0.05$) [2-10,13-16,20,22-25].

To evaluate the cost-benefit ratio, some studies have taken into account the average cost per patient, summing up all investigations. The costs were much higher with more advanced imaging techniques, being approximately 60% higher. However, there has been no general consensus on an improvement in technique compared to an equivalent cost, this being one of the limitations of the study. Another limitation of the study was the concrete assessment of different values of sensitivity and specificity, as well as the lack of a clear delimitation of the inclusion criteria. Some items showed lower ranges, but with a high diagnostic value [2-7,9-16,20,25].

In conclusion, the fight against breast cancer continuously evolves and the results are getting better every year. 18-FDG PET-CT is an increasingly used technique in the staging of breast cancer, with a potential role in disease prognosis and with a better accuracy than the rest of the imaging investigations, but involving higher costs [2-7,9,10,12-15,22-25].

18-FDG PET-CT provides images of the entire body, allowing better staging of the initial or recurrent disease, being useful in personalizing the treatment, competitive with 18-FDG PET-MRI, but probably not as good in resolution. Modern imaging techniques (18-FDG/PET-CT, 18FDG/PET-MRI) have been shown to have a better prognostic value than conventional imaging, presenting higher sensitivity and specificity in evidencing the locoregional invasion and recurrence of disease [3,4,11-15,23,25].

Although currently no adequate protocol regarding the use of imaging techniques exists, studies report the effectiveness of certain techniques in assessing the various criteria. Modern techniques (PET-CT, PET-MRI associate with 18 FDG) have shown a much higher efficiency in diagnosis, as well as higher sensitivity and specificity compared to conventional imaging techniques. This results in an improvement or adjustment of the patient-specific treatment scheme, however, there is still no cost-benefit ratio calculated so far. At the same time, the immunohistochemical profile plays an important role, which could lead to a clear delimitation of standardized diagnostic protocols in the near future [2,4,6,7,12-17,20-23].

Conflict of interests

The authors declare no conflict of interests.

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