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Monitoring the Response to Neoadjuvant Chemotherapy in Breast Cancer

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Additional information is available at the end of the chapter

1. Introduction

The World Health Organization (WHO) estimates that more than 1,050,000 new cases of breast cancer occur per year worldwide, making this one of the most common diseases among women. Its mortality/incidence relationship in developed countries is 29.9%, whereas in developing countries it reaches 42.9% [1].

In developing countries, it is still a reality to find a large number of tumors in advanced stages. This is due to age [2], psychological disorders [3], racial and socioeconomic differences, besides the biological behavior of the tumor. In Brazil they are associated with the problems related to limitations in the infrastructure of the health system [4].

Data from the Surveillance Epidemiology and End Results (SEER) show between 1985 and 1995 ratios of stage III and IV tumors (advanced tumors) were respectively 18.3% (11.6% +6.7%) and 11.6% (7.4%+4.2%) [5]. On the other hand, data obtained from the registry of the Barretos Cancer Hospital, evaluated the period from 1985 to 2007, divided into four periods, showed that there was little change in the advanced tumors (III + IV), corresponding to 37.7%, 35.0%, 39.4% and 34.9% respectively, which makes the locally advanced tumors a public health problem this way.

Treatment of breast cancer is less mutilating and more effective when the diagnosis is made early. Currently, the primary systemic treatment for locally advanced tumors is advocated

in order to obtain a better therapeutic response, however there is controversy in respect to this subject.

Locally advanced breast carcinoma (LABC) represent a relatively heterogeneous group, in terms of clinical, biological and pathological. Tumors locally advanced and non-metastatic involve: tumors with a diameter greater than 5 cm, large lymph node involvement (N2 or N3), direct involvement of the chest wall or skin, and inflammatory carcinoma [6].

The staging of patients with LABC suggests care, thus, those with tumors larger than 5 cm associated with more than three compromised axillary lymph nodes it is advisable that the staging be performed with computed tomography of the abdomen, thorax and pelvis, where the presence of metastatic disease, can be observed in up to 23% of cases [7]. However, its applicability in clinical routine is still a matter of controversy.

Currently, the therapeutic approach of LABC is multidisciplinary, consisting of neoadjuvant chemotherapy, surgery, radiotherapy and adjuvant chemotherapy [8-10]. In the past, the treatment of LABC was surgery, followed by chemotherapy. However, 5-year survival was less than 20%. The first reports of the application of neoadjuvant chemotherapy in LABC dating from the 70s, was initially used in inoperable patients to allow the best resection of the neoplastic lesion. In subsequent decades, with a large number of publications, an improvement was demonstrated in survival of patients undergoing this type of treatment, more evident in those with complete pathologic responses [11]. Although preclinical models suggest that neoadjuvant chemotherapy may have an impact on tumor biology and improved survival when compared to adjuvant therapy, this has not been demonstrated by clinical study in meta-analysis [12,13]. However, the primary therapy provides an *in vivo* model to evaluate the effectiveness of specific therapeutic regimen, in contrast with adjuvant therapy.

Neoadjuvant chemotherapy or primary systemic therapy suggests offering diverse advantages in relation to adjuvant, being:

- administration of medications through an intact vascular-lymphatic system;

- early treatment of micro-metastatic disease;

- *in vivo* assessment of response to treatment;

- an opportunity to evaluate the response to chemotherapy in relation to diverse clinical and pathological parameters;

- assessment of response to chemotherapy in the identification of tumor subtypes genotypic;

- reduction of tumor volume, causing in an increase in the percentage of resectability and the rate of conservative surgery;

- opportunity of evaluation of the response to new chemotherapeutic schemes;

- prior knowledge of the patient's prognosis, in function to the clinicopathologic response to chemotherapy.

Unfortunately, some malignant breast tumors show resistance to treatment with the principal chemotherapeutic agents, decreasing the effectiveness of this therapy [14]. The mechanisms responsible for this chemoresistance are multifactorial [15], being a late resistance acquired during treatment of predominant factor, present in over 75% of patients. The intrinsic chemoresistance is also important, being observed in 18-51% of untreated carcinomas [16-18].

In regards to chemotherapy drugs, the taxanes, have been featured in more recent studies, they showed excellent anti-neoplastic activity, then being brought to neoadjuvant chemotherapy.

The chemotherapy schemes with anthracycline and taxane combined in various ways, being concurrent or sequential demonstrate a rate of pathologic complete response (pCR) significantly higher. Based on the Aberdeen study [19] and in GEPAR-TRIO [20] the current trend is the sequential combination of anthracycline with taxane, which shows larger response rate initially obtained with anthracycline (85% vs 64%, p = 0.03).

The pCR is defined as the absence of invasive carcinoma in anatomopathological exam of breast and axillary lymph nodes after neoadjuvant chemotherapy. In most extensive studies, the rate of pCR ranges from 3 to 30%. However, in these same studies the criteria varies for evaluation of pCR [11].

Results showed that the long-term survival is associated to the response to neoadjuvant treatment, in patients with large volume tumors, being the pathologic complete response, the best predictor of survival in these patients [21].

Therefore, the evaluation of the response to chemotherapy treatment is important for conduct, once that the additional time and side effects triggered by this therapy are not negligible.

Reduction in tumor volume has been used as the standard criterion for response evaluation among solid tumors such as breast carcinoma. The clinical and pathological responses are used for imaging methods to define the two classifications the "World Health Organization" (WHO), created in the 70s, and the RECIST (Response Evaluation Criteria in Solid Tumors), created in the 90s [22]. The difference between the two classifications is shown in Table 1. Apparently a diameter seems to be sufficient to predict response, however the number of articles on this subject is limited.

Response	WHO	RECIST
Complete Response (CR)	Without Disease	Without Disease
Partial Response (PR)	50% response	30% Response
Stable Disease	Without PD or PR	Without PD or PR
Progression (PD)	25% increase	20% increase
Measures	2 measures	1 measure

Table 1. Difference between the classifications responses to neoadjuvant chemotherapy WHO and RECIST

2. Clinical evaluation

Feldman e cols. [23] showed significant discrepancy between chemotherapy response as-sessed by clinical exam and pathological study of the surgical specimen. Clinical examina-tion is often unable to differentiate a residual mass representing fibrosis from a mass representing residual tumor [24-28].

3. Mammography

Currently the most effective imaging method for the detection of breast cancer is mammog-raphy. It has an accuracy of around 90% for mass screening. However, the extent of the tu-mor may be underestimated with this technique. Tabar [29] refers to practical explanations of the difficulty in assessing tumor size depending on the type and compliance of the mam-mary tissue represented radiologically. Similar problems to the clinical exam were observed when mammography was used for chemotherapy response evaluation [24-26]. Thus, due to difficulties in the visualization and subsequent measurement of the tumor, other imaging methods are proposed for the evaluation of chemotherapy response.
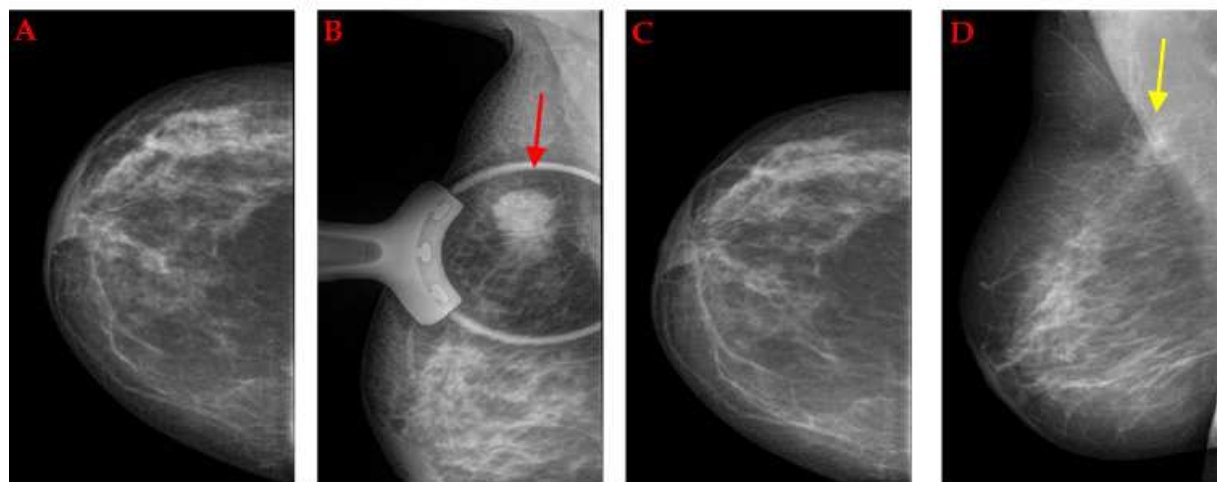

Figure 1. Mammography. Pretreatment. A. Cranial-caudal view (CC): not observed the tumor area. B. Mediolateral-oblique view (MLO) localized compression: nodular oval image, high-density, partially obscured edges with and with-out microcalcifications inside (red arrow). Post-treatment. C. Cranial-caudal view (CC): not observed the tumor area. D. Mediolateral-oblique view (MLO): architectural distortion in the tumor region (yellow arrow).
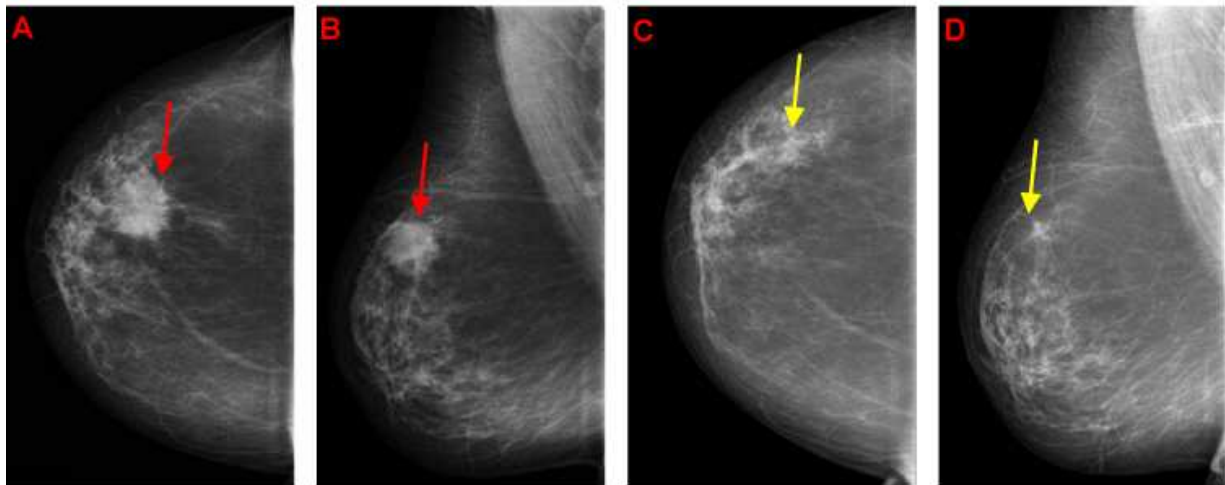
Figure 2. Mammography. Pretreatment. A. Cranial-caudal view (CC). B. Mediolateral-oblique view (MLO): area rounded nodular, spiculated margins, without microcalcifications, high density (red arrow). Post-treatment. C. Cranial-caudal view (CC). D. Mediolateral-oblique view (MLO): nodule with the same characteristics and reduction of dimensions, with partial response (yellow arrow).
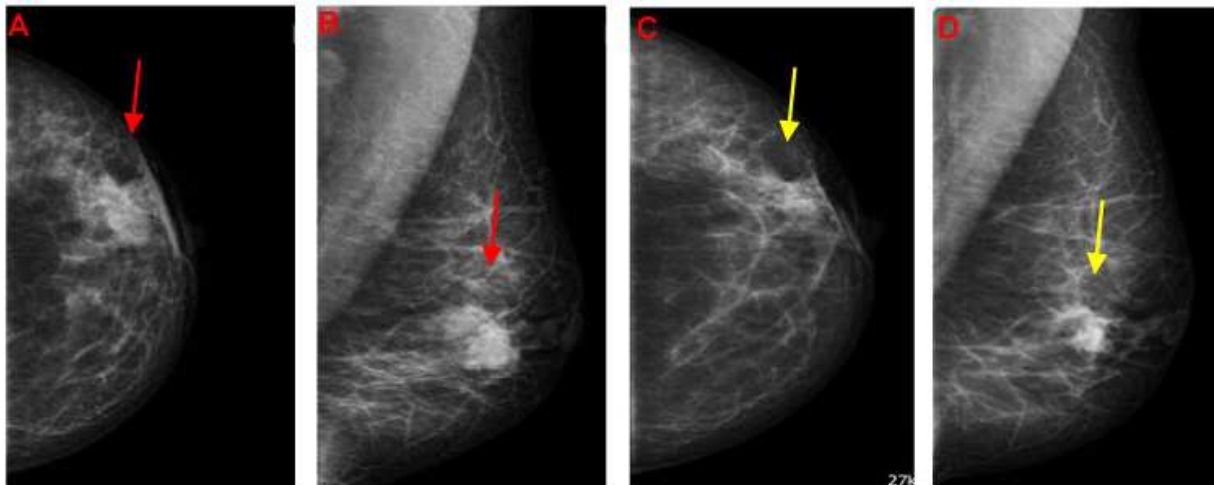

Figure 3. Mammography. Pretreatment. A. Cranial-caudal view (CC). B. Mediolateral-oblique view (MLO): rounded nodule, ill-defined margins, high density (red arrow). Post-treatment. C. Cranial-caudal view (CC). D. Mediolateral-oblique view (MLO): nodule with the same characteristics, with inadequate response (yellow arrow).

4. Breast ultrasound

Breast ultrasound is the method of choice for the determination of solid and cystic lesions. Apparently showing a more effective method in the determination of tumor measurements, however the results were not consistent. [30]

Ultrasound using it as an alternative method for assessing the tumor may predict the response to systemic treatment via the use of primary color Doppler.

Doppler ultrasound vascularization includes evaluation of parameters such as: the number of signs of flow, a peak flow velocity, the resistivity index (RI) and pulsatility index (PI). It also allows the noninvasive evaluation of abnormal vessel architecture in breast tumors, referred to as neoangiogenesis. These changes in vascularization of the tumor correlate to the histopathological response, and therefore, the study of vascularization can be used as a complementary tool to assess the response to chemotherapy, primarily in locally advanced breast cancer.

Kumar et al. [31] registered a reduction of Doppler flux during the neoadjuvant treatment in 77% of patients with partial or complete remission, the residual flux was parameter independent, having sensitivity of 88.88% for predicting pathologic complete response, compared with 44.44% clinical response.

New studies observed changes in vascularization during chemotherapy. In the beginning of chemotherapy there was an increase in vascularity, followed by a reduction thereof. Probably in the beginning of treatment, abundant angiogenic factors, such as vascular endothelial growth factor (VEGF) are released from apoptotic and necrotic tumor cells, resulting in profound increase in vascularity. After the vascularization peak, there is a gradual decrease in the later stage of chemotherapy, due to the smaller number of angiogenic factors. Thus, an increase in velocity greater than 5% was observed during chemotherapy in patients with good response to chemotherapy [32].
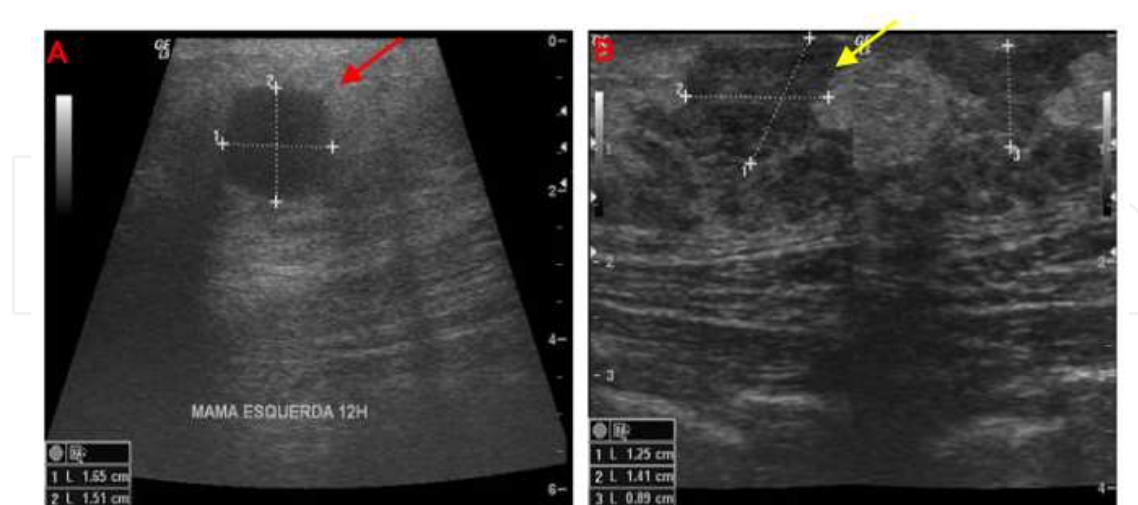

Figure 4. Breast ultrasound. A. Pretreatment: Nodule irregular, margin not circumscribed, hypoechoic, with posterior acoustic enhancement in the left breast (red arrow). B. Post-treatment: not displayed initial tumor, only nodular image of different characteristics of the initial tumor, with good response (yellow arrow).
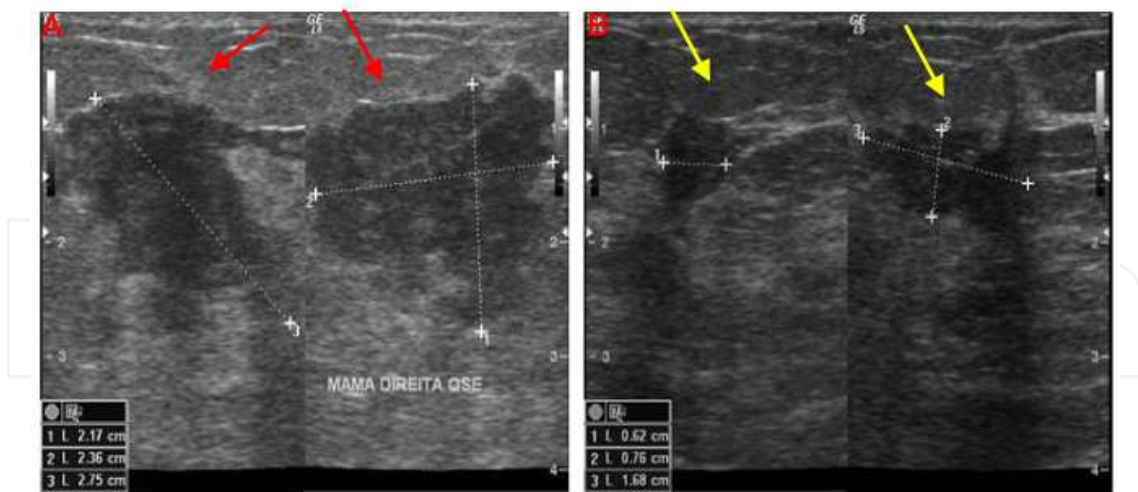
Figure 5. Breast ultrasound. A. Pretreatment: pleomorphic mass, microlobulated margins, abrupt boundary, hypoechogenic, not parallel, without posterior acoustic shadow (red arrow). Post-treatment: mass reduction pleomorphic (yellow arrow), with partial response.
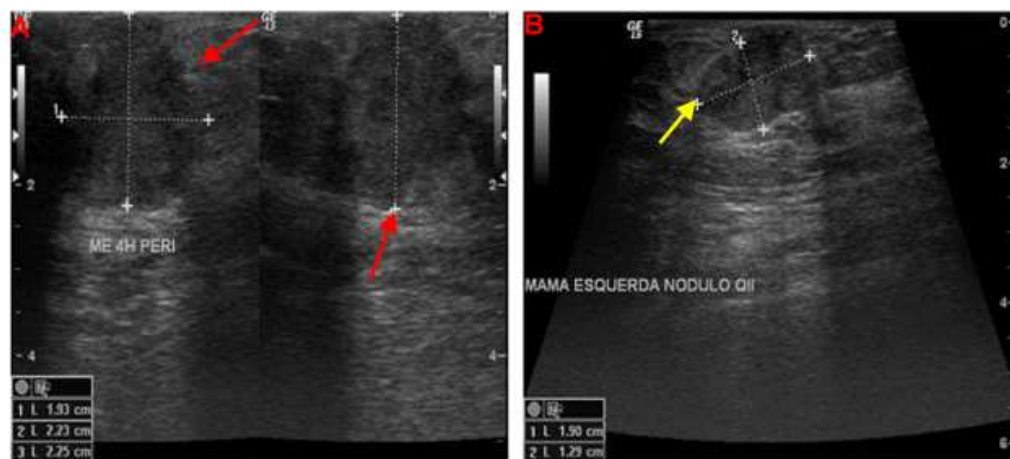

Figure 6. Breast ultrasound. A. Pretreatment: Node irregular, margin not circumscribed, hypoechoic, with posterior acoustic shadow in the left breast (red arrow). B. Post-treatment: Node with the same characteristics (yellow arrow), with inadequate response

5. Magnetic resonance imaging

Recently, magnetic resonance appeared in the list of imaging tests to be ordered, in the treatment of breast cancer. It has low specificity, because it presents difficulties in identification between benign and malignant lesions [33]. However, additional studies are needed to better characterize the resonance as an effective method in the determination of tumor extent. Magnetic resonance imaging has a sensitivity of 95-97% for the evaluation of lesions of less than 1 cm. It is important to detect disease in the contralateral breast (4% to 24% of associat-

ed disease). Magnetic resonance imaging increases the accuracy of radiology evaluated in monitoring response to chemotherapy, therefore it is relevant in the evaluation of a possible conservative surgery [34].

There is a significant disparity in mammography, breast ultrasound and MRI as compared methods in the evaluation of breast tumors. However, to relate them to the anatomopathological study, there is a greater difference between the measurements of ultrasound and mammography and a smaller difference between measurements made by MRI [35]. The accuracy of tumor measurement is fundamental in preoperative assessment when conservative treatment is desired. From a diagnostic point of view, physical examination, mammography, ultrasound and MRI have an accuracy in predicting pathologic response of 75, 89, 82 and 89% respectively [36]. Furthermore, studies comparing the various methods of images show a trend in favor of resonance, with better magnitude of correlation to anatomopathology exam [37].

According to a study of Matthes et al. [38] in 50 patients with locally advanced breast cancer before surgery, mammography and breast ultrasound showed no significant correlation. The MRI showed a moderate and significant correlation, suggesting to be a more reliable exam in relation to referred measurements in clinical examination. Others authors have shown good correlation between the anatomopathological and physical examination (0.68) while mammography and breast ultrasound were not good methods, with weak correlations (r = 0.33 and r = 0.29). However, Weatherall [39] suggests a high correlation for MRI (r = 0.93), moderate for clinical examination (r = 0.72) and moderate, but lower for mammography (0.62). Also noted, that few cases were evaluated with breast ultrasound, not justifying this analysis. According Drew et al a conventional assessment of response to neoadjuvant chemotherapy by clinical or mammographic methods presents many limitations for surgical planning [40].

In general, most studies showed that MRI allows a better assessment of tumors in relation to others tests, varying the index of correlation between r = 0.60 to 0.98 [37,41].

The studies demonstrate a tendency for MRI as an ideal method in the detection of carcinomas reaching the sensitivity of up to 100%. As was demonstrated by Matthes et al. [38], in most cases, MRI demonstrated a better correlation than the other imaging exams in the definition of tumor measurement after neoadjuvant chemotherapy. Yeh [42] conducted a comparison between diagnostic methods and concluded that MRI showed better correlation with pathology in relation to mammography and breast ultrasound. However, this showed that the exam could overestimate measurement of residual tumor in 6% of cases and underestimate them in up to 23%.

We must consider in the literature, that the MRI has a high correlation, but is not able to precisely identify the residual lesion in all cases, which justifies the preoperative marking of the area to be resected, especially in the LABC and when assessing the possibility of conservative treatment, resection of the entire enclosed area, seeing that, there is no data methodologically consistent in literature that ensures the assessment of residual lesion.
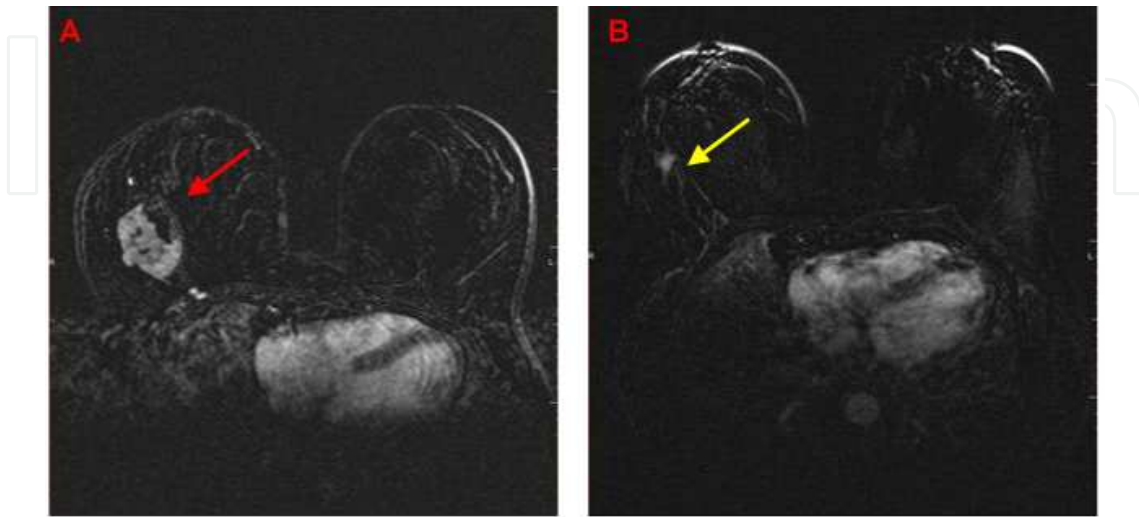
Figure 7. Breast MRI: A. Pretreatment: large tumor mass in the right breast (red arrow). B. Post-treatment: a nodular small area starting at the same topography (yellow arrow), showing a concentric reduction and partial tumor
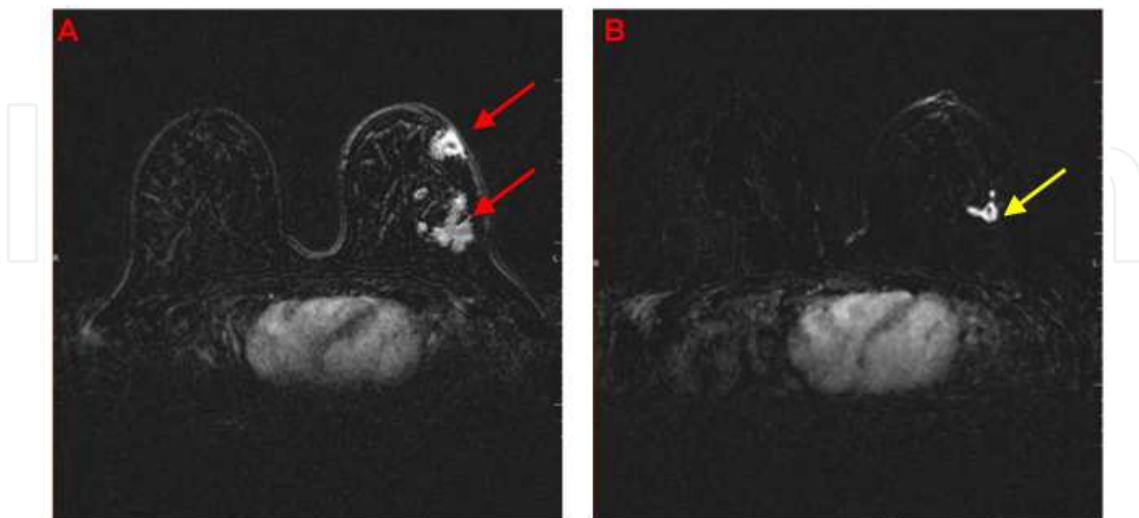

Figure 8. Breast MRI. A. Pretreatment: two masses in left breast (red arrow). B. Post-treatment: single mass in the left breast (yellow arrow), with partial tumor reduction.
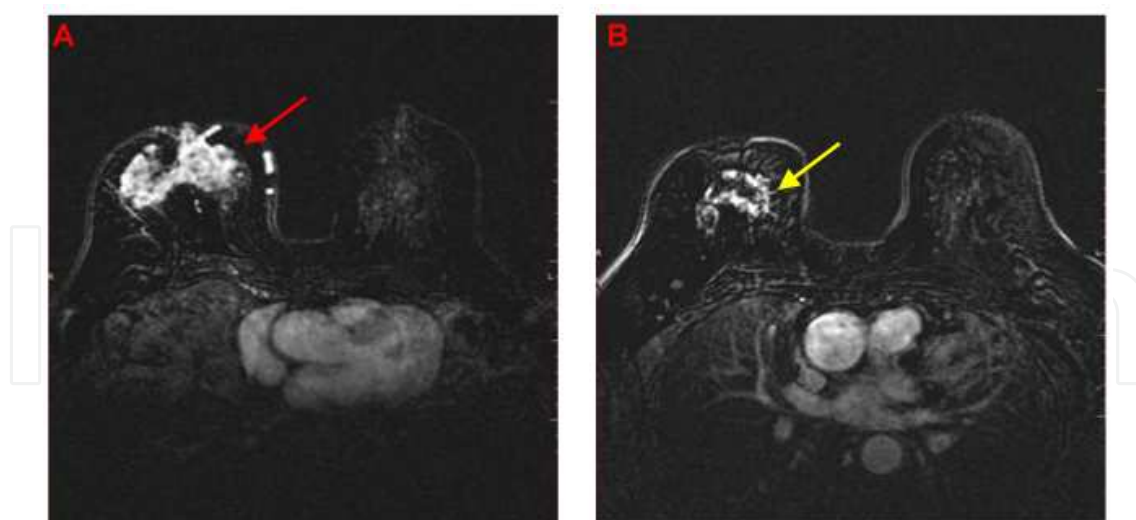
Figure 9. Breast MRI. A. Pretreatment: large mass in the right breast (red arrow). B. Post-treatment: mass in the right breast (yellow arrow), with partial reduction and diffuse tumor.

6. ^{99m}Tc- sestamibi scintigraphy

Nuclear medicine offers a noninvasive detection of histological, molecular and biochemical markers known to tumor aggressiveness and resistance to therapy, which can provide criteria for better therapeutic conduct [43].

Breast scintigraphy is a well-established diagnostic imaging technique [44], of relatively low cost compared with positron emission tomography and magnetic resonance imaging. It can also be used as a method for evaluating the response of breast carcinoma to chemotherapy treatment, thereby providing an *in vivo* indication of the chemosensitivity of the tumor [45]. Tiling et al. [46] showed that PET and breast scintigraphy with ^{99m}Tc-sestamibi are equivalent in monitoring the tumor response to neoadjuvant chemotherapy, with significant advantage of scintigraphy in the availability of the radiopharmaceutical and gamma cameras, besides a low cost.

The mechanism of ^{99m}Tc-sestamibi concentration in tumors is not entirely clear. It is distributed in the tissues in proportion to blood flow and enters cells by passive diffusion. By the transmembrane potential difference it is fixed to the mitochondria, particularly in malignant cells with higher negative potentials [47,48]. The highest accumulation in the lesion depends on mitochondrial activity and density, cellularity, angiogenesis and malformed vessels [49]. Factors of cell proliferation and desmoplastic activity seem to be involved [50].

The characteristics that lead to the accumulation of this radiopharmaceutical are identical to those that promote the inflow of chemotherapeutics, related directly to blood flow and transmembrane potential and negative mitochondrial and inversely with necrosis or fibrosis [47,51], and good correlation was observed between reduced uptake of ^{99m}Tc-sestamibi and the response to chemotherapy in LABC [52].

Mechanisms of accumulation and efflux of [99mTc]-sestamibi in breast carcinomas involve cellular processes that are important in tumor response to treatment. Figure 10 shows the main relationships of accumulation and of the kinetics of [99mTc]-sestamibi in the tumor and mechanisms of related chemoresistance.
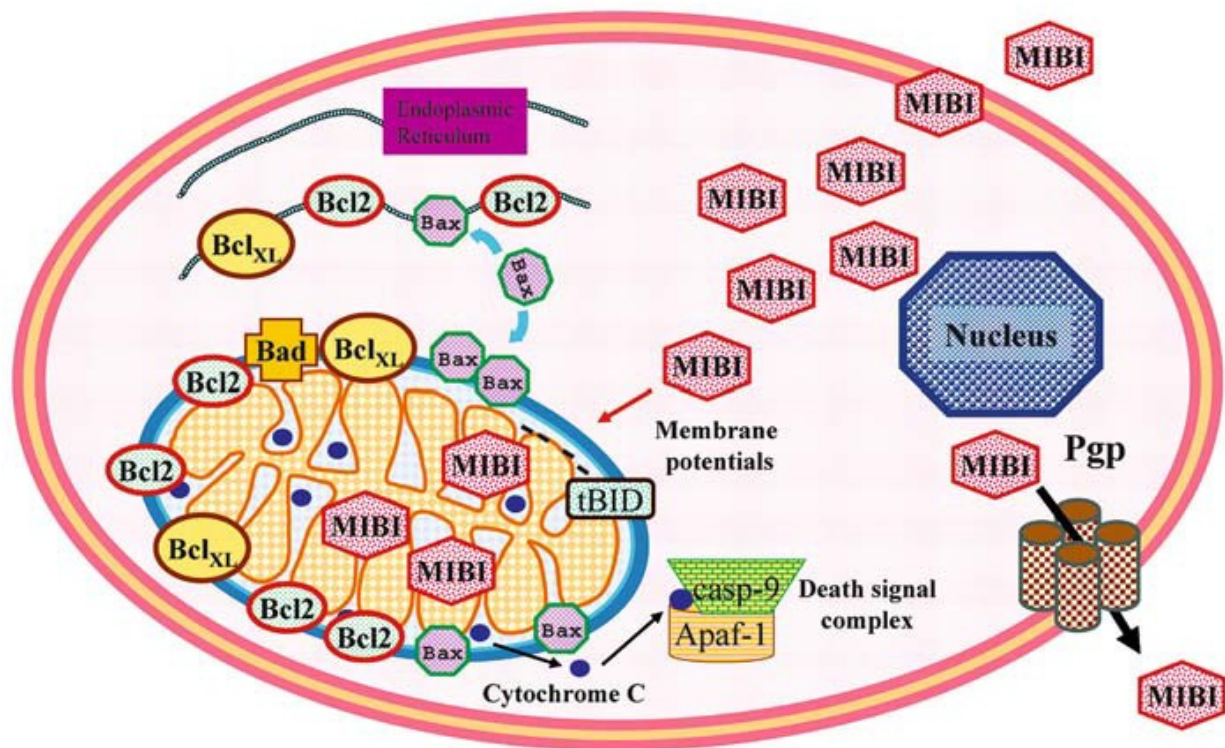

Figure 10. Schematic representation of uptake and efflux of [99mTc]-sestamibi [43].

The mitochondrial membrane permeability is regulated by members of anti and pro-apoptotic of the Bcl-2 family [53]. When a signal of apoptosis converges to the mitochondrion, this causes an early increase in mitochondrial membrane permeability, release of cytochrome-c and other apoptotic factors [54] which trigger the activation of caspases, increasing the breaking of the cell substrate, causing morphological and biochemical changes characteristics of the apoptosis [55].

Due to the characteristics of mitochondrial accumulation of [99mTc]-sestamibi, breast carcinomas that represent reduction of its inflow have high levels of anti-apoptotic protein Bcl-2 [56], which lead to resistance to chemotherapeutic agents and radiation due to the defect in the apoptosis [57]. Levels of Bcl-2 in breast carcinomas range from 32 to 86% [58]. Some studies report that the absence of Bcl-2 in LABCis associated with better chemotherapy response [59-61].

The efflux of [99mTc]-sestamibi and wide variety of drugs of the cytoplasm to the extracellular matrix is related to P-glycoprotein. The over-expression of this protein is inversely related to the accumulation of [99mTc]-sestamibi and with residual tumor in anatomopathological exams

of surgical specimen, indicating inadequate response to neoadjuvant chemotherapy. Takamura et al [62], Alonso et al [63] and Sciuto et al [64] showed that breast scintigraphy with ^{99m}Tc-sestamibi, by analysis of washout of this in delayed images can be used as a predictor of neoadjuvant chemotherapy response. Early and increased concentration of ^{99m}Tc-sestamibi in breast carcinomas is associated with high proliferation rate, indicating more aggressive tumor behavior, and better and faster tumor response [43].

In the study of Koga et al [65], the quantification of ^{99m}Tc-sestamibi uptake is done on the lateral images of the breasts by creating two identical areas of interest: one on the tumor and the other in the mirror position on the contralateral breast. Pixel counting is performed in these areas (Figure 11). The ^{99m}Tc-sestamibi uptake rate caused by the tumor is determined as the pixel count ratio between the area of interest in the tumor and the mirror area in the contralateral breast in pretreatment and post-treatment.
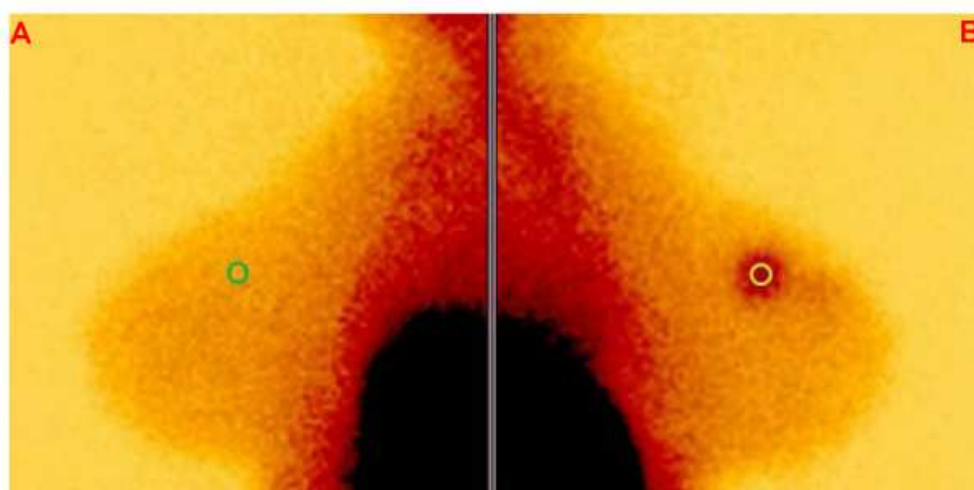

Figure 11. Breast scintigraphy. A. Left lateral: the mirror area in the contralateral breast (green circle). B. Right lateral: the area of interest in the tumor (yellow circle).

A better response to chemotherapy regimen was observed in more aggressive tumors that represent a higher uptake rate reduction. The tumor necrosis resulting from chemotherapy could explain the substantial reduction in tumor size [65]. The invasive ductal carcinoma presents a higher uptake rate reduction compared to those associated to the *in situ* component. Moriguchi et al [66] lower rates were found in ductal carcinomas *in situ* and mucinous probably related to lower cellular proliferation. This findings reflects the routine of oncological therapy, low response, carcinoma *in situ* to chemotherapy, confirming the utility of the rate in the evaluation of chemotherapy response in the different carcinoma groups.

Koga et al [65], Mankoff et al [67], Marshall et al [68] and Cwikla et al [69] reported a reduction of the rate of tumor:background, showing that the concentration of ^{99m}Tc-sestamibi reflects the metabolic activity of the tumor and its reduction resulting from chemotherapy [68]. Koga et al [65], Wilczek et al [70] showed a significant reduction rate of tumor: back-

ground after completion of neoadjuvant chemotherapy, confirmed by tumor regression in histological study of the surgical specimen.

Quantitative analysis on ^{99m}Tc-sestamibi scintigraphy is shown to be an additional tool for evaluating the preoperative chemotherapy response, given that the variation in ^{99m}Tc-sestamibi uptake reflects the biological behavior of the tumor [65].
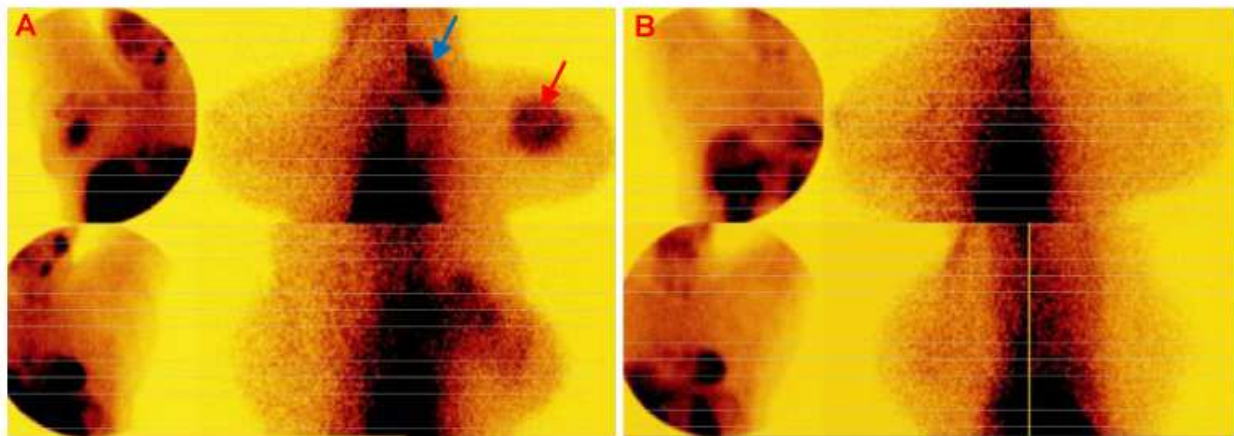

Figure 12. Breast scintigraphy. A. Pretreatment: large nodular area in right breast (red arrow) and ipsilateral axillary lymph node (blue arrow). B. Post-treatment: disappearance of the areas in breast and axillary lymph node, setting good response to neoadjuvant chemotherapy.
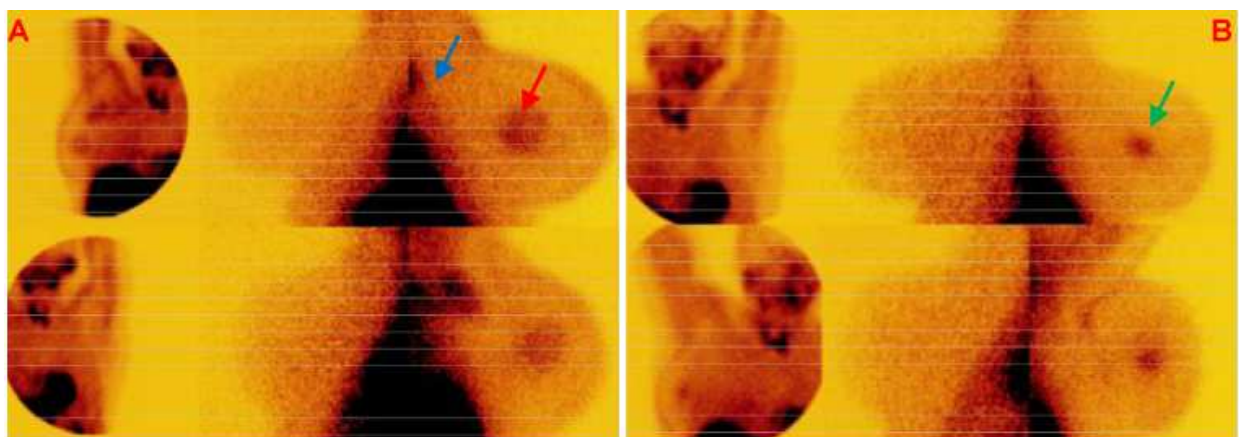

Figure 13. Breast scintigraphy. A. Pretreatment: large nodular area in right breast (red arrow) and ipsilateral axillary lymph node (blue arrow). B. Post-treatment: nodular area reduction in breast (green arrow) and axillary lymph node disappearance, setting partial response to neoadjuvant chemotherapy.
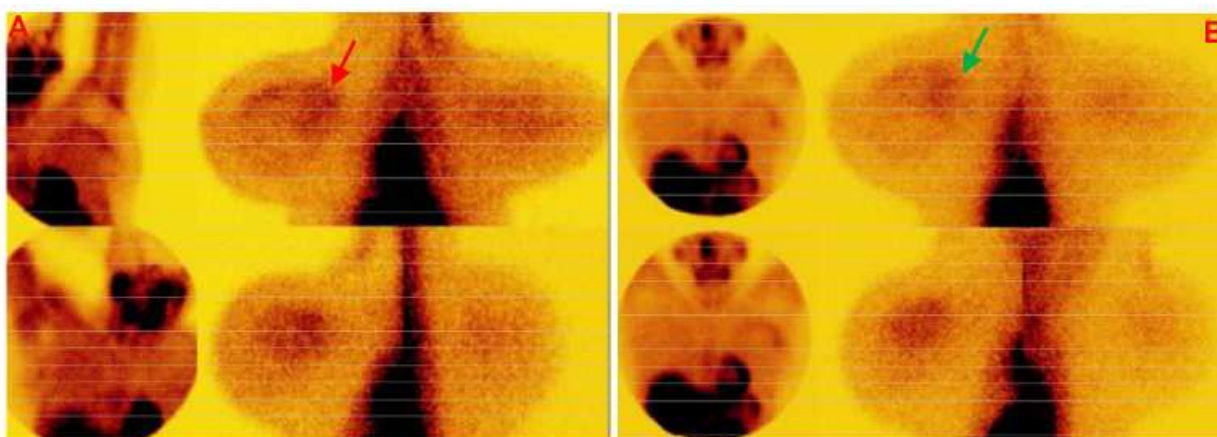
Figure 14. Breast scintigraphy. A. Pretreatment: large nodular area in left breast (red arrow). B. Post-treatment: nodular area unchanged (green arrow), configuring inadequate response to neoadjuvant chemotherapy.

7. Tomography Emission Positron/ Computed Tomography (PET/CT)

Positron Emission Tomography (PET) is a powerful technique to image biochemical or physiological processes within the body. The metabolic and biological activity of disease always precedes any anatomic evidence of the illness. PET is a biological imaging technique does not replace anatomical imaging as X Ray, computed tomography (CT) or magnetic resonance imaging (MRI), but adds the characterization of simple molecular process that are taking place in normal or diseased tissues within the body.

Positron is an antiparticle of the electron. When it is spelled from the nucleous of an atom, it travel only a short distance. During this travel across several millimeters, adjacent atoms are ionized and the positron loses energy and slow down. Positron then pairs up with an electron and undergoing an annihilation interaction, which produces a pair of 511 KeV annihilation photons that travel in opposite directions reaching PET radiation detectors for imaging.

The fusion of PET and CT images is very useful in the correlation of the exact site of anatomical and physiological information.

In PET oncologic imaging, the most widely radiopharmaceutical is 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG). Biochemically ^{18}F-FDG is a nonphysiological compound with a chemical structure very similar to that of naturally occurring glucose; it serves as an external marker of cellular glucose metabolism. The ability no noninvasively image cellular glucose metabolism is important in oncological applications because many cancer cells use glucose at higher rates.

The absolute quantitative radiotracer uptake in tumor can be measured in an effort to differentiate between malignant and benign tissue. Named *Standard Uptake Value* (SUV) it can be useful in measuring tumor metabolic function [71].

Breast tumors have many phenotypical characters, as increase of vascularization and local permeability, increase of glycolitic metabolism and protein production, receptors expression, ADN proliferation index and hypoxia. All these factors can be evaluated by PET scan. The radiopharmaceutical more common for that purpose is ^{18}F-FDG.

^{18}F-FDG has been evaluated for diagnosis, staging (Figure 15) and restaging, monitoring therapy response and prognostication in patients with breast cancer [72].
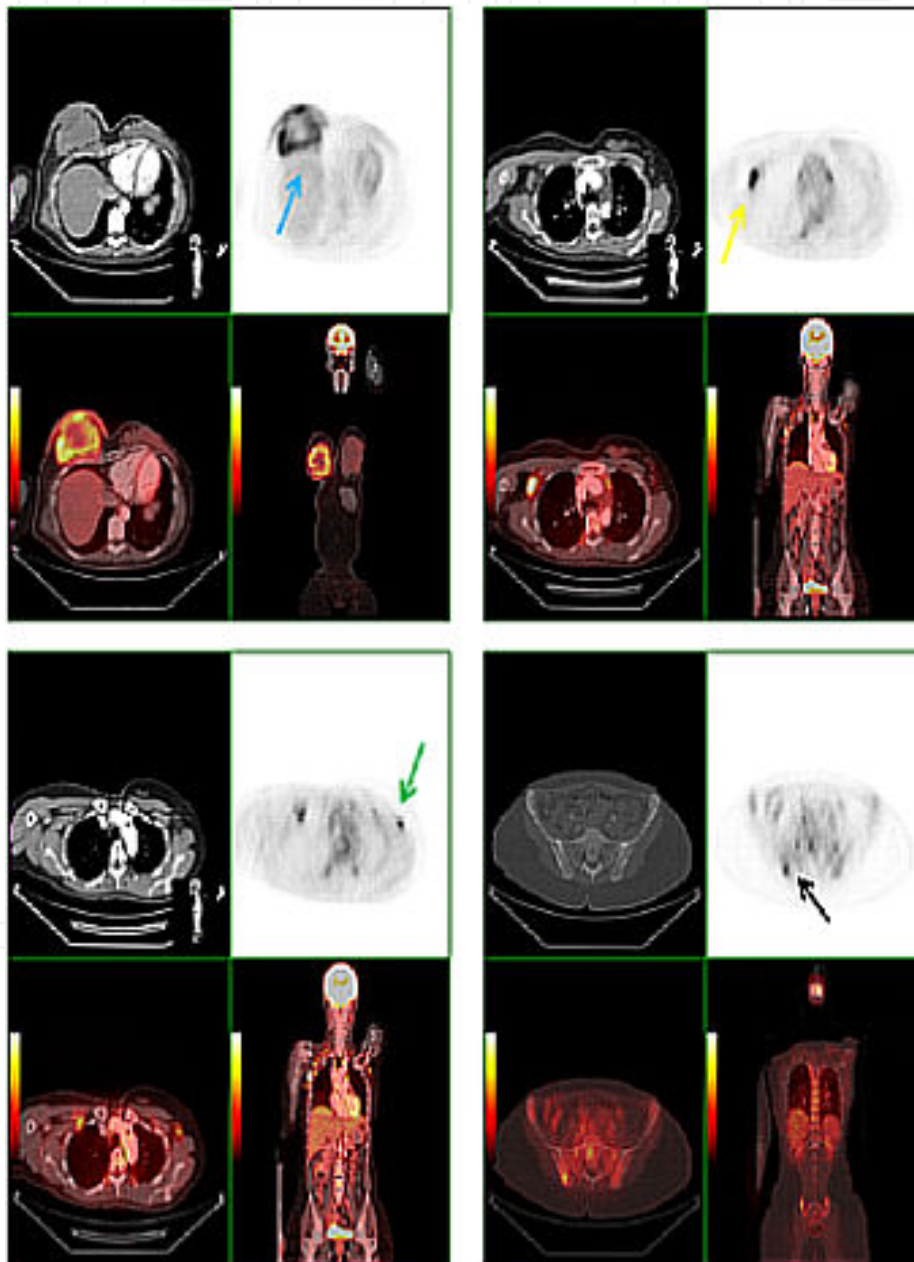

Figure 15. Staging of breast cancer. Female, 30 years old, follow up of right breast nodule for five years. Detected breast carcinoma by recent biopsy. PET/CT for staging identified metabolic hyperactivity in right breast carcinoma (blue arrow), many axillary (yellow arrow) and subpectoral lymph nodes (green arrow), mediastinum and bone lesions (black arrow).

Most studies evaluating ^{18}F-FDG to assess response to neoadjuvant therapy have measured change in ^{18}F-FDG uptake at mid-therapy, compared with at baseline, as a measure of response. Later, many studies found that ^{18}F-FDG uptake declines by aproximately 50% or more was predictive of a good response. Perhaps more important, lesser declines in ^{18}F-FDG uptake predicted poor response [73,74].

For analysis after the completion of chemotherapy, ^{18}F-FDG has shown that although residual ^{18}F-FDG uptake, predicts residual disease, but the absence of ^{18}F-FDG is not a reliable indicator of complete response, specially in lymph node envolvements. The presence of ^{18}F-FDG is highly predictive of relapse, as showed in Figures 16, 17 and 18 [72].
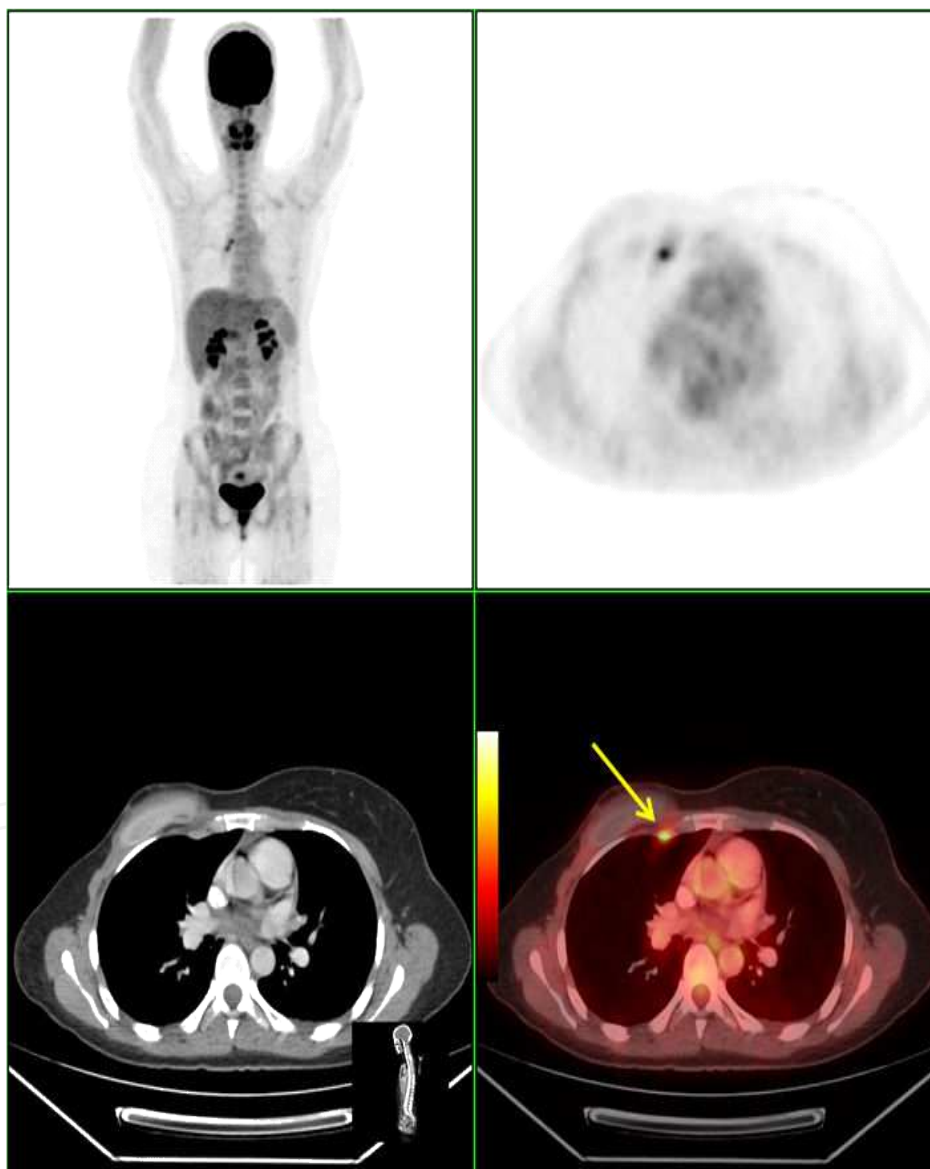

Figure 16. Recurrence of breast cancer. Female, 39 years old, with ductal carcinoma in right breast treated by radical mastectomy, chemotherapy and local radiotherapy two years ago. Follow up identified a nodulation in surgery bed. PET/CT showed metabolic activity in lymph node of internal mammary chair (yellow arrow).
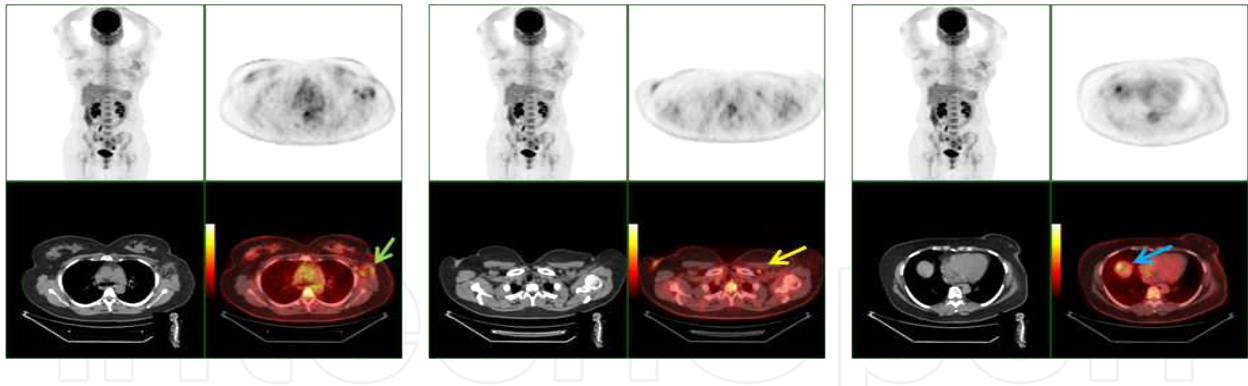
Figure 17. Disease progression. Female, 43 years old, with ductal carcinoma treated by left quadrantectomy and radiotherapy, chemotherapy and hormonetherapy two years ago. Follow up identified a nodule in left axillar region. PET/CT showed metabolic hyperactivity in axillary lymph nodes (green arrow), supraclavicular lymph nodes (yellow arrow) and in liver (blue arrow).
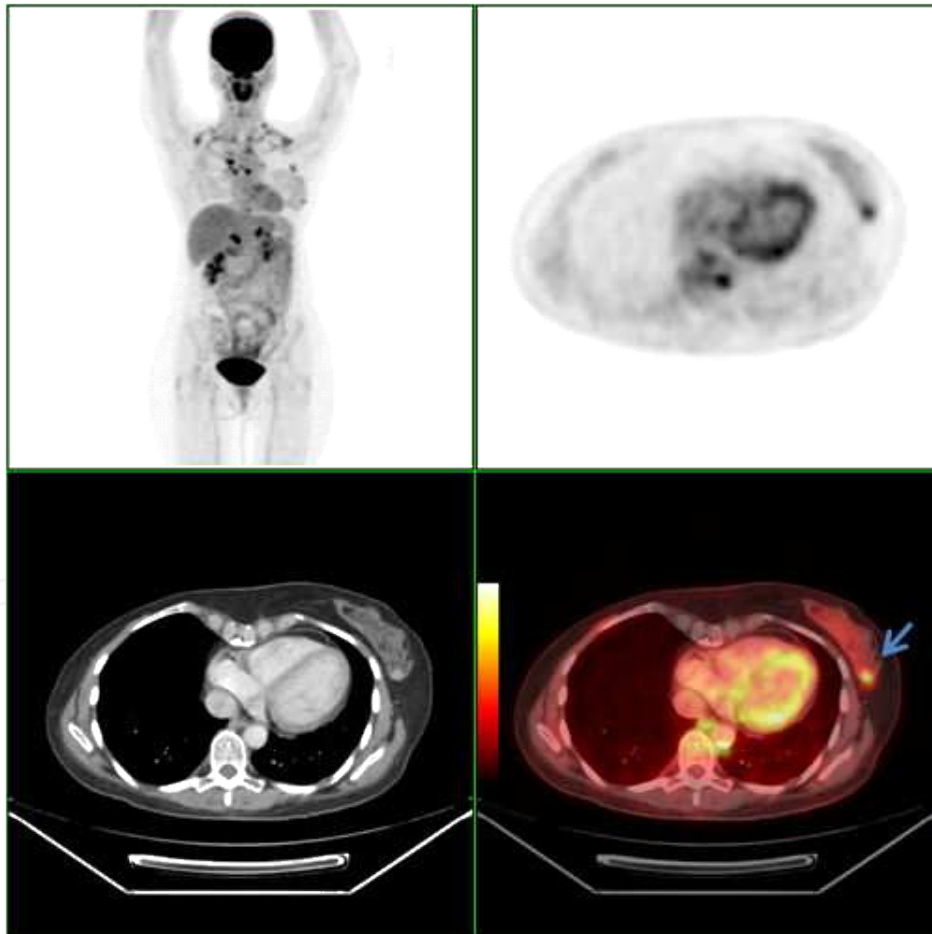

Figure 18. Follow up of breast cancer. Female, 46 years old, with ductal carcinoma in right breast treated by radical mastectomy, chemotherapy and local radiotherapy. Follow up Ca 19,9 levels increased. PET/CT showed metabolic activity in left breast identifying the second tumor (blue arrow).

8. Conclusions

There remains a shortage of information in the literature that confirms the best imaging exam for determining accurate measurements of residual tumor, especially in the case of evaluations related to the primary systemic treatment in locally advanced breast carcinoma.

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