

# Preoperative Clinical, Mammographic and Sonographic Assessment of Neoadjuvant Chemotherapy Response in Breast Cancer

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**Key words:** neoadjuvant chemotherapy, locally advanced breast cancer, clinical and imaging assessment

## Abstract

**Background:** The current methods for pre- and post-chemotherapy examination of the extent of disease in the breast and lymph nodes do not provide sufficiently accurate information and, not infrequently, the surgeon has to re-operate.

**Objectives:** To correlate the findings between three methods of examination (physical examination, ultrasonography, mammography), all performed by the same oncologic and radiologic team, in patients with locally advanced breast cancer or a tumor/breast tissue ratio that precludes breast-conserving surgery.

**Methods:** Forty patients (median age 48 years, range 24–73) with locally advanced breast cancer or with a tumor/breast ratio that precluded breast-conserving surgery were evaluated by the same medical team and received neoadjuvant chemotherapy. Surgery was performed in all, and the pathologic specimen was correlated with the results of the other examinations.

**Results:** In the pre-chemotherapy evaluation, the imaging findings of the breast correlated with the physical findings in 78% of the patients and with the axilla examination in 66.7%. In the post-chemotherapy analysis, imaging agreed with the physical findings of the breast in 62.2% and in 76.3% of the axilla. Sonography best detected occult breast disease and axillary lymph nodes but correlated with pathology in only 58% of the patients in diagnosing breast tumor and in 65.8% in diagnosing axillary lymph nodes. Mammography correlated with breast and lymph node pathology in half the patients.

**Conclusions:** None of the classical methods of post-neoadjuvant chemotherapy evaluations could adequately delineate the actual extent of the disease in the breast and axillary lymph nodes. More exacting techniques of imaging combined with the classical methods are required.

*IMAJ 2006;8:342–346*

Locally advanced breast cancer is defined by a lesion greater than 5 cm with involved lymph nodes, a tumor that involves the vicinity (skin or chest wall), or a tumor of any size in the breast but with the presence of a conglomerate of lymph nodes. The current treatment of LABC is a complex and difficult issue, combining chemotherapy, hormonal/immunotherapy, surgery, and radiation therapy. This therapeutic approach to LABC converts many patients with initially unresectable disease to surgical candidates, and has been extended to an earlier breast cancer

population in which the tumor/breast ratio precluded *a priori* breast-conserving surgery or involvement of axillary lymph nodes only. The goals of a preoperative chemotherapeutic approach are to monitor tumor response *in vivo* and improve the rates of breast-conserving surgery. Induction of a complete pathologic response with the new drugs should be one of the primary goals of neoadjuvant therapy, affording longer disease-free and overall survival. The dramatic evolution of breast cancer treatment over the past two decades, which has brought about a transition from radical local therapy (radical mastectomy or modified radical mastectomy) to breast conservation, has not generally adversely affected overall survival and local recurrence [1,2]. Breast-conservation surgery involves complete excision of the tumor with cancer-free surgical margins and axillary lymph node dissection followed by radiation therapy to the breast. The field of radiation therapy is extended to include regional lymph nodes if there is lymph node involvement. The goal of breast-conservation surgery is to achieve effective local regional control of the tumor as well as good cosmetic results, without deleteriously affecting overall survival [3].

Of all women diagnosed with breast cancer, 20% have LABC. This subset of patients must be treated with chemotherapy upfront [4,5]. The decision regarding the need for neoadjuvant chemotherapy is mostly based on clinical examination and imaging modalities, including mammography and ultrasonography. Pretreatment assessment of tumor size is commonly estimated by palpation. The accuracy of clinical assessment is influenced by the experience of the examiner, which is often controversial, and is not useful for clinically occult tumors. The accuracy of imaging techniques in predicting the size of breast tumors is contradictory. Mammography is the first modality of choice in breast evaluation, providing information complementary to the physical examination, and is essential in the accurate assessment of treatment [6]. Ultrasound is considered as complementary to mammography. It has become superior in the assessment of breast cancer size and for monitoring response to neoadjuvant chemotherapy [7,8]. Physical examination was shown to correlate best with pathologic findings in estimating the size of the primary tumor following neoadjuvant chemotherapy treatment, and was considered the best predictor of tumor size [9].

The purpose of this retrospective study was to compare the ability of physical examination, mammography and ultrasound

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LABC = locally advanced breast cancer

to assess the response to neoadjuvant chemotherapy, compared to the surgical pathology findings, in patients with LABC and in patients with a tumor/breast ratio that does not permit breast-conserving surgery.

## Patients and Methods

Forty consecutive patients were clinically diagnosed with breast cancer (loco-regional disease) and examined by mammography and ultrasound in our medical center between September 1999 and January 2003. Their median age was 48 years (range 24–73). They were diagnosed by physical examination as having stage TX-T4, N0-N2 (according to the Staging Classification of the American Joint Committee on Cancer, 1997, fifth edition).

The patients were divided into two groups for the purpose of this study: the predominant clinical presentation of the patients in group A was palpable axillary lymph nodes with occult non-palpable or T1 tumors, while the patients in group B were clinically diagnosed as having T2, T3, or T4 tumors with or without palpable axillary lymphadenopathy.

Mammography was performed with dedicated mammography equipment (Seno DMR+ unit, GE Medical Systems, France) using standard craniocaudal and mediolateral oblique projections and complemented with 90° lateral and magnification views when necessary. Lesion dimensions were determined from the standard views. Breast ultrasonography was performed with a 7.5–10 MHz linear array transducer (128 x p/10 Acuson, Mountain View, CA, USA) and a 5–12 MHz linear array transducer (HDI 5000 ATL, Bothell, WA, USA). The largest lateral and anteroposterior diameters in the axial and coronal planes of the scan were used for establishing tumor size.

All the study patients had core biopsy histologically proven breast cancer. Clinically or sonographically suspicious axillary lymph nodes were further evaluated by fine-needle aspiration or core biopsy.

The 40 patients received 75 mg/m<sup>2</sup> epirubicin and 175 mg/m<sup>2</sup> taxol on day 1 every 21 days for 5 courses or more when indicated, in a maximum of seven courses. All patients were evaluated at presentation before treatment onset, and after the third and fifth course: in cases in which more than five courses were given the patients were evaluated after the last chemotherapeutic cycle. In this paper, we analyzed the first and last examination. The same oncology team performed the clinical evaluations and the same radiologists performed the mammographic evaluation, tumor size measurements and interpretation of the ultrasound examination. Evaluation of response to treatment was performed 3–4 weeks after the last cycle and the results were correlated with those of surgical pathology.

Metallic markers were implanted under ultrasound guidance, mostly before treatment in the case of earlier disease. Patients with relatively large tumors and/or inflammatory skin changes were marked during the period of chemotherapy treatment.

## Statistics

Agreement between the different diagnostic methods was evaluated using Cohen's Kappa and Kendall's coefficient of concor-

dance. This was done first between each two methods, and then over all methods simultaneously. Significance was set at a *P* level of < 0.05.

## Results

The most common presentation in our study involved 29 patients (72%) in group B (T2, T3, or T4 tumors with or without palpable axillary lymphadenopathy).

Clinical evaluation of the disease at presentation was correlated with mammography and ultrasound: the imaging findings correlated well with the physical examination of the breast in 62.2% of the cases. Ultrasound detected the primary tumor in the breast in two patients with occult disease. The imaging findings were compatible with multifocal or multicentric disease in three patients in whom physical examination revealed only focal disease. The physical examination over-staged the disease relative to the imaging findings in these patients.

In our cohort of 40 patients, 26 (65%) presented with pathologically proven metastatic lymph nodes by fine-needle aspiration or core biopsy of the axilla, all of them diagnosed by ultrasonography. The physical examination of the axilla before starting chemotherapy was well correlated with ultrasound in 81.8% of the cases. Mammography correlated with the ultrasonographic examination of the axilla in only 76.3% of the cases [Table 1].

The ultrasound examination correlated better than mammography with the pathologic measurements of the excised primary breast tumor after chemotherapy: 57.9% for ultrasound and 52.8% for mammography [Table 1]. Physical examination at the time of preoperative staging evaluation correlated with pathologic findings in only 65% of patients: it overestimated the tumor in three and underestimated the tumor in nine. The agreement between the three methods of examination was statistically significant [Table 2].

The sensitivity of the mammography in diagnosing the tumor in the breast was 88.9% with a specificity of 80%, but the sensi-

**Table 1.** Agreement between clinical/imaging examinations to pathologic findings

	Examination 1		Examination 2	
	Agreement %	Kappa	Agreement %	Kappa
<b>Tumor stage</b>				
Physical examination & mammography	76%		47.2%	
Physical examination & ultrasound	75%	0.60	60.5%	
Mammography & ultrasound	78%	0.68	62.2%	0.47
Mammography & pathology			52.8%	
Ultrasound & pathology			57.9%	0.41
Physical examination & pathology			47.4%	
<b>Lymph node stage</b>				
Physical examination & mammography	52.5%	0.36	81.6%	
Physical examination & ultrasound	58.9%	0.43	81.8%	
Mammography & ultrasound	66.7%	0.55	76.3%	0.3
Mammography & pathology			53.8%	0.21
Ultrasound & pathology			65.8%	0.42
Physical examination & pathology			64.1%	

Kappa is not applicable when the groups are not equal

**Table 2.** Agreement between three methods of examination

	Examination I		Examination II	
	Kendal	Kappa	Kendal	Kappa
Tumor stage	0.8	0.57	0.53	0.38
Lymph node stage	0.667	0.34	0.60	0.27

Kappa, but not Kendal, takes into account the possibility of incidental agreement. Therefore, Kappa values can be expected to be relatively smaller.

**Table 3.** Sensitivity and specificity of the clinical/imaging examinations

	Sensitivity	Specificity
<b>Tumor stage</b>		
Mammography	88.9%	80%
Ultrasound	80%	93.3%
Physical examination	75%	93.8%
<b>Lymph node stage</b>		
Mammography	14.3%	100%
Ultrasound	45%	94.4%
Physical examination	38.1%	100%

tivity was only 14.3% with a specificity of 100% in the diagnosis of axillary lymph nodes [Table 3]. The other two methods of examination were quite similar: the sensitivity of the ultrasound was 80% with a specificity of 93.3%, and for clinical examination of the tumor in the breast it was 75% and 93.8%, respectively. For the evaluation of axillary lymph node status following treatment, the sensitivity was only 45% and the specificity 94.4% for ultrasound, and 38.1% and 100%, respectively, for the physical examination [Table 3]. All Kappa and Kendall coefficients were significant,  $P < 0.0001$ .

The agreement between the three methods of examination and the pathology findings was smaller for group B than group A (65% vs. 78%, respectively).

## Discussion

Accurate staging of breast cancer plays a critical role in deciding upon the administration of neoadjuvant chemotherapy and is crucial in the surgical decision-making process [10]. It is essential to precisely assess the size of the tumor and to accurately monitor the response to treatment. Locally advanced breast cancer affects 20% of all women diagnosed with breast cancer, and these patients require neoadjuvant chemotherapy. There has been a trend over recent years to treat even much earlier disease in the same way. The main objectives of this approach are to treat distant metastases earlier and to reduce the size of inoperable tumors and improve the tumor-breast tissue ratio, thereby facilitating the surgical procedure by enabling more breast-conserving operations [10]. Disease-free and overall survival rates were shown to increase when a complete response is achieved pathologically [11].

Preoperative tumor size is commonly estimated by palpation, a method that is influenced by the experience of the

examiner and is not informative for clinically occult tumors, actually yielding an accuracy of 65–75% [12,13]. The accuracy of imaging techniques in predicting the size of breast tumors has also been found lacking [14]. Mammography is the first modality of choice in breast evaluation, providing information complementary to physical examination, and is an essential tool for accurate assessment of treatment efficacy. An ultrasound examination is considered complementary to mammography: it has become superior to it in the assessment of lesion size and for monitoring response to neoadjuvant chemotherapy. Physical examination and ultrasound correlated best with pathologic findings in assessing the size of the primary tumor after neoadjuvant chemotherapy, and the combination of the two methods was considered the best presurgical predictor of tumor size in the breast.

Our findings showed that the following correlations should be borne in mind before assigning a patient to neoadjuvant treatment:

- Physical examination of the primary tumor in the breast and axilla correlated with imaging findings in approximately 80% of our patients.
- Axillary staging was underestimated by physical examination in 20% of our patients.
- Physical examination and ultrasonography of the primary breast tumor correlated better than mammography with the pathologic findings, but the assessment of disease response to chemotherapy by physical examination and ultrasound was inaccurate in 40% of our cases.
- The tumor size was not correctly estimated before operation in approximately one-third of our cases by all three methods. The tumor image in these cases had been considered a single large mass but was found at pathology to be multi-focal disease. This may be due to the effect of chemotherapy.
- The tumor size was overestimated by mammography and ultrasound (6 cases, 15%, and 3 cases, 7.5%, respectively). We believe that the fibrosis due to chemotherapy could be the cause for these findings.
- The combined ultrasonographic and physical examination was the best method for evaluating the presence of lymph node involvement, before and after treatment, but it was still highly inaccurate in the assessment of disease extension.
- Agreement between the methods and the pathologic findings after chemotherapy is less in more advanced local disease. This is because the tumor is sometimes only partially destroyed and impossible to detect by the usual methods of diagnosis due to the effect of the chemotherapy.
- In conclusion, the retrospectively retrieved data on 40 women with loco-regional advanced breast cancer or tumor/breast ratio inadequate for breast conserving surgery who received preoperative neoadjuvant chemotherapy showed that none of the three modalities for detection and assessment (size and stage) of malignancy is satisfactory. Clinical examination and ultrasound were diagnostic for one-half of the patients.

A combination of all three raises the level of size and staging accuracy before treatment to approximately 55% for the primary tumor and 81% for axilla involvement: before surgery the results were about 60% in both sites.

## Other techniques for evaluating patients after neoadjuvant chemotherapy

### Magnetic resonance imaging

MRI has shown better correlation rates, and although negative or benign MRI findings cannot replace a recommendation for biopsy based on traditional methods, MRI does seem to be important in the assessment of disease extent in patients recently diagnosed as having breast cancer. This application was pioneered by Harms et al. [15] and confirmed by multiple reports over the past 15 years [16], all demonstrating that MRI can identify otherwise occult multi-centric and multi-focal disease in women with breast cancer. Harms et al. [15] compared results from *in vivo* MR images with serially sectioned pathologic analyses in 30 mastectomy specimens, and reported that MRI detected additional disease in 37% of the specimens. Several subsequent reports [17] confirmed that MRI changed the management in 23% of patients scheduled for breast-conserving therapy. In the largest multi-center study thus far, the International Breast MRI Consortium reported on 426 women with a current cancer diagnosis: MRI identified additional disease at least 2 cm from the index malignant lesion in 18% of patients [18]. Other studies supported these findings but cautioned that the false negative rate of MRI increases after chemotherapy and that MRI cannot exclude microscopic disease [19,20].

### Positron emission tomography

A meta-analysis of 13 studies, for a total of 606 subjects, found a sensitivity of 89% and specificity of 80% for PET in the diagnosis of breast cancer. The most significant flaws cited were small study sizes, large mean tumor sizes (2–4 cm), and the high prior probability of malignancy in subjects referred to PET. There is, indeed, insufficient literature on the sensitivity of PET to detect breast lesions smaller than 1.5 cm with current state-of-the-art PET technology. A variety of studies have assessed PET for initial staging of axillary lymph nodes. In general, those with a high sensitivity (> 90%) have had a lower specificity (66–89%) [19]. Those studies in which the specificity was maximized to > 90% had a lower sensitivity (79–90%). Smith and colleagues [21] stated that PET is the most accurate non-invasive method for assessing the axilla in breast cancer.

A study of a small group of 203 subjects yielded a pooled sensitivity of 81% (range 40–93%), confirming that the detection of micrometastases and small tumor-infiltrated lymph nodes is limited by current PET resolution (the specificity of the pooled data was higher: 95%, range 87–100%). The available data, however, were too sparse to draw any firm conclusions, and the false negative rate (19%) was too high, which would result

in under-treatment of too many patients with local metastatic disease [22].

PET is not approved for axillary staging *per se*, meaning that axillary node sampling should remain the standard of care. Nevertheless, current data clearly indicate that when PET is performed for overall staging of metastatic disease in patients with breast cancer, it can provide clinically valuable information on axillary nodal stage in many cases [23]. Current standard imaging tests, such as mammography, sonography, computed tomography and MRI are hampered by a prolonged lag time of weeks to several months before anatomic changes are measurable. In contrast, metabolic imaging with FDG-PET is more effective than anatomic imaging in monitoring early treatment response [23]. A rapid decrease in glucose metabolism in responders can be detected on PET as early as after the first cycle of chemotherapy [24,25].

## Conclusion

The classical methods of diagnosis and staging of patients with breast cancer receiving neoadjuvant chemotherapy are inadequate and disappointing. It is our hope that the very intensive work currently being conducted worldwide will soon yield the long-awaited techniques to precisely assess the size of the tumor and accurately monitor the response to treatment for optimal management of patients receiving neoadjuvant chemotherapy.

**Acknowledgment.** Esther Eshkol is thanked for editorial assistance.

## References

1. Fischer B, Redmond C, Poisson R, et al. Eight-year results of a randomized trial comparing total mastectomy and lumpectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1989;32:822–8.
2. Veronesi U, Cascinelli N, Luigi M, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–32.
3. Miller BA, Feuer EJ, Hankey BF. Recent incidence trends for breast cancer in women and the relevance of early detection: an update. *CA Cancer J Clin* 1993;42:27–41.
4. Schwartz GF, Birchansky CA, Komarnicky LT, et al. Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. *Cancer* 1994;73:362–9.
5. Calais G, Berger C, Descamps P, et al. Conservative treatment feasibility with induction chemotherapy, surgery and radiotherapy for patients with breast carcinoma larger than 3 cm. *Cancer* 1994;74:1283–8.
6. Segel MC, Paulus DD, Hotobagyi GN. Advanced primary breast cancer: assessment at mammography of response to induction chemotherapy. *Radiology* 1988;169:49–54.
7. Fornage BD, Toubas O, Morel M. Clinical, mammographic and sonographic determination of preoperative cancer size. *Cancer* 1987;60:765–71.
8. Hieken TJ, Harrison J, Herreros J, Velasco JM. Correlating sonography, mammography and pathology in the assessment of breast cancer size. *Am J Surg* 2001;182:351–4.
9. Gawne-Cain ML, Smith E, Darby M, Given-Wilson R. The use of ultrasound for monitoring breast tumor response in neoadjuvant therapy. *Clin Radiol* 1995;50:681–6.

2 PET = positron emission tomography

10. Loprinzi C, Thome S. Understanding the utility of adjuvant systemic therapy for primary breast cancer. *J Clin Oncol* 2001;19:972–9.
11. Sataloff DM, Mason BA, Prestipino AJ, Seinige UL, Lieber CP, Baloch Z. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: a determinant of outcome. *J Am Coll Surg* 1995;180:297–306
12. Haagensen CD. Diseases of the Breast. Philadelphia: WB Saunders, 1986:502.
13. Harris JR. Diseases of the Breast. 2nd edn. Philadelphia: WB Saunders, 2000:33.
14. Herrada J, Iyer RB, Atkison EN, Sneige N, Buzdar AU, Hortobagyi GN. Relative value of physical examination, mammography and breast sonography in evaluating the size of primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. *Clin Cancer Res* 1997;9:1565–9.
15. Harms SE, Flamig DP, Hesley KL, et al. MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. *Radiology* 1993;187:493–501.
16. Bedrosian I, Mick R, Orel SG, et al. Changes in the surgical management of patients with breast carcinoma based on preoperative magnetic resonance imaging. *Cancer* 2003;98:468–73.
17. Schnall MD, Blume J, Bluemke D, et al., for the International Breast MRI Consortium. MRI detection of multi-focal breast carcinoma: report from the International Breast MRI Consortium. *J Clin Oncol* 2004;22(Suppl):14S.
18. Gilles R, Guinebretiere JM, Toussaint C, et al. Locally advanced breast cancer: contrast-enhanced subtraction MR imaging of response to preoperative chemotherapy. *Radiology* 1994;191:633–8.
19. Rosen EL, Blackwell KL, Baker JA, et al. Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. *Am J Roentgenol* 2003;81:1275–82.
20. Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Sudilovsky D, Hylton NM. Accuracy of MR imaging for revealing residual breast cancer in patients who have undergone neoadjuvant chemotherapy. *Am J Roentgenol* 2002;179:1193–9.
21. Smith IC, Ogston KN, Whitford P, et al. Staging of the axilla in breast cancer: accurate in vivo assessment using positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose. *Ann Surg* 1998;228:220–7.
22. Hubner KF, Smith GT, Thie JA, et al. The potential of F-18-FDG PET in breast cancer: detection of primary lesions, axillary lymph node metastases, or distant metastases. *Clin Pos Imag* 2000;3:197–205.
23. Adler LP, Crowe JP, Al-Kaisi NK, et al. Evaluation of breast masses and axillary lymph nodes with [F-18] 2-deoxy-2-fluoro-d-glucose PET. *Radiology* 1993;187:743–24.
24. Schelling M, Avril N, Nahrig J, et al. Positron emission tomography using [18f] fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. *J Clin Oncol* 2000;18:1689–1695.
25. Schott AF, Roubidoux MA, Helvie MA, et al. Clinical and radiologic assessments to predict breast cancer pathologic complete response to neoadjuvant chemotherapy. *Breast Cancer Res Treat* 2005;92:231–8.

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