Molecular Subtypes of Breast Cancer Are Not Associated with the Clinical Under- or Overstaging of Breast Cancer

Subtipos moleculares de câncer de mama não estão associados ao subestadiamento ou ao superestadiamento do câncer de mama

Juliana Pinho Espinola[1] Raquel Mary Rodrigues Peres[2] Kátia Piton Serra[1] Sophie Françoise Mauricette Derchain[3] Luis Otávio Sarian[2]

[1] Gynecology and Breast Oncology, Department of Tocogynecology, Universidade Estadual de Campinas, Campinas, SP, Brazil
[2] CAISM - Hospital da Mulher "José Aristodemo Pinotti", Universidade Estadual de Campinas, Campinas, SP, Brazil
[3] Department of Tocogynecology, Universidade Estadual de Campinas, Campinas, SP, Brazil

Address for correspondence Luis Otávio Sarian, PhD, Department of Tocogynecology, Universidade Estadual de Campinas, Rua Alexander Flemming 848, 13093-140, Campinas, SP, Brazil (e-mail: sarian@unicamp.br).

Rev Bras Ginecol Obstet 2016;38:239–245.

Abstract

Purpose to evaluate the agreement between the clinical and pathological stagings of breast cancer based on clinical and molecular features.

Methods this was a cross-sectional study, in which clinical, epidemiological and pathological data were collected from 226 patients who underwent surgery at the Prof. Dr. José Aristodemo Pinotti Women's Hospital (CAISM/Unicamp) from January 2008 to September 2010. Patients were staged clinically and pathologically, and were classified as: understaged, when the clinical staging was lower than the pathological staging; correctly staged, when the clinical staging was the same as the pathological one; and overstaged, when the clinical staging was greater than the pathological staging.

Results understaged patients were younger (52.2 years; $p < 0.01$) and more symptomatic at diagnosis ($p = 0.04$) when compared with correctly or overstaged patients. Clinicopathological surrogate subtype, menopausal status, parity, hormone replace therapy and histology were not associated with differences in staging. Women under 57 years of age were clinically understaged mainly due to underestimation of T (tumor staging) ($p < 0.001$), as were the premenopausal women ($p < 0.01$). Patients whose diagnosis was made due to clinical complaints, and not by screening, were clinically understaged due to underestimation of N (lymph nodes staging) ($p < 0.001$).

Conclusion the study shows that the clinicopathological surrogate subtype is not associated with differences in staging, while younger women diagnosed because of clinical complaints tend to have their breast tumors understaged during clinical evaluation.

Keywords
- breast cancer
- cancer staging
- mammography
- neoplasms
- breast

received
February 24, 2016
accepted
April 8, 2016
published online
May 17, 2016

DOI http://dx.doi.org/10.1055/s-0036-1584127.
ISSN 0100-7203.

Resumo

Objetivo avaliar a concordância entre o estadiamento clínico e patológico do câncer de mama em função das características clínicas e moleculares das pacientes.

Métodos estudo de corte transversal, sendo coletados dados clínicos, epidemiológicos e anátomo-patológicos de 226 pacientes operadas no Hospital da Mulher Prof. Dr. José Aristodemo Pinotti (Centro de Atenção Integral à Saúde da Mulher – CAISM/Unicamp), de janeiro de 2008 a setembro de 2010. As pacientes foram estadiadas clínica e patologicamente e classificadas como: subestadiadas, quando o estadiamento clínico foi menor do que o patológico; corretamente estadiadas, quando o estadiamento clínico foi equivalente ao patológico; e superestadiadas, quando o estadiamento clínico foi maior do que o patológico.

Resultados as pacientes subestadiadas eram mais jovens (52,2 anos; $p < 0,01$) e sintomáticas ao diagnóstico ($p = 0,04$) do que as pacientes corretamente estadiadas ou superestadiadas. O subtipo clinico-patológico, o *status* menopausal, a paridade, a terapia de reposição hormonal e a histologia não foram associados com a diferença no estadiamento. Detectamos que as mulheres com menos de 57 anos de idade foram clinicamente subestadiadas principalmente devido à subestimação do T ($p < 0,001$), assim como as mulheres na pré-menopausa ($p < 0,01$). Por outro lado, as pacientes cujo diagnóstico foi realizado por queixa clínica, e não rastreamento, foram clinicamente subestadiadas devido à subestimação do N ($p < 0,001$).

Conclusão o estudo nos mostra que o subtipo clinico-patológico não está associado a diferenças de estadiamento, enquanto mulheres mais jovens, e que tiveram seu diagnóstico por queixa clínica, tendem a ter seus tumores mais frequentemente subestadiados.

Palavras-chave

- câncer de mama
- estadiamento do câncer
- mamografia
- neoplasmas
- mama

Introduction

The staging of breast cancer involves an adequate assessment of the local and distant extensions of the disease. In the age of precision medicine, clinical tumor staging must be very accurate in order to avoid inadequate treatment. For instance, data from the American College of Surgeons Oncology Group (ACOSOG) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) most recent trials, as well as the European Organization for Research and Treatment of Cancer (EORTC) AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) and a few other trials defined very conservative approaches to women with early stage breast cancer[1–3]; it seems sensible, however, that these advantages may not be enjoyed by women whose tumors have been understaged during pretreatment clinical evaluation.

The currently available methods for breast cancer clinical staging rely on physical examination and radiologic assessment of the breast.[4] It is well known that several factors may interfere with clinical breast examination (CBE), such as breast density and volume, and women's menstrual status.[5] The same applies to mammography, since breast density may compromise exam accuracy, for example.[6] Moreover, recent studies have suggested that low-grade luminal A tumors are generally detected with screening, whereas rapidly growing tumors may be detected only when they become symptomatic,[7] which implies that the molecular subtype of breast cancer may be associated with clinical presentation and thence with the sensitivity of the clinical and radiological assessments. Current staging guidelines, however, do not suggest staging procedures tailored according to molecular subtype.

It remains unknown to what extent the characteristics of patients and their tumors may hamper a correct presurgical evaluation of the breast cancer stage. In this study, we examined whether factors such as clinicopathological surrogate subtypes, age, menopause status, and diagnosis by screening or symptoms are associated with the discrepancy between the clinical and pathological stagings of breast tumors in women unaware of the existence of treatment.

Methods

Study Design

We performed a secondary analysis of data collected from other studies linked to our study group.[8–12] The principal investigator (Juliana Pinho Espinola – JPE) conducted a further review of 226 medical records, specifically for the present report, in order to obtain data regarding clinical staging, exams, and pathological staging. Clinical and epidemiological data are from January 2008 to September 2010. Data were collected at Professor Dr. José Aristodemo Pinotti Women's Hospital (CAISM/Unicamp). In this study, data pertaining to the molecular and pathological characteristics of the tumors had already been obtained for the studies cited above.

Inclusion criteria consisted of: women undergoing primary surgical treatment for breast cancer; invasive ductal carcinoma or invasive lobular carcinoma; histological samples that could provide material for the safe and accurate diagnosis of cancer, and the information about its stage for this study. Exclusion criteria consisted of: lack of information about the staging or the molecular features of the tumor (technical inability to perform any of the laboratory procedures); patients undergoing neoadjuvant chemotherapy; patients with metastatic breast cancer; patients already treated for breast cancer before their entry into the study.

Data Collection

Information about the epidemiology, clinical and pathological staging, and surgical treatment performed were reviewed and annotated in a specific form. The review of the medical records was performed only by the main investigator, reducing the potential for bias in the interpretation of the information contained in the medical reports. The data collection form was initially used to evaluate 20 medical records, and the information was entered into the pre-existing database, allowing the adjustment of both the collection record and the database, which was formatted to contain all information relevant to this study.

Information pertaining to the clinical staging was obtained from the patient's initial appointment after the histological diagnosis had been confirmed. All patients were evaluated by a breast surgeon, and the staging of the disease was done according to well-established protocols (such as the American Joint Commission on Cancer –AJCC – protocol).[13] Women underwent two-incidence digital mammographies, craniocaudal (CC) and mediolateral oblique (MLO). Breast ultrasound was used when needed. Clinical lymph nodes status was determined with palpation of the axilla. All pathological reports were reviewed by JPE. Evaluation of the expression of estrogen/progesterone receptors HER2 and Ki67 was performed using immunohistochemistry and fluorescent in situ hybridization (FISH) according to standard protocols. All pathological assessments were performed at the Experimental Pathology Laboratory of CAISM/Unicamp. The surrogate molecular subtypes of breast cancer were determined according to the 13th St. Gallen Consensus.[14]

Classification of Staging Status

Patients were classified as: understaged, when the clinical staging was lower than the pathological staging; correctly staged, when the clinical staging was the same as the pathological staging; and overstaged, when the clinical staging was greater than the pathological staging.

Data Analysis

Data were analyzed using the R statistical package for microcomputers (R Development Core Team, 2015, Aalborg, Denmark). The significance level was 5% ($p \leq 0.05$ and confidence interval of 95%). Bivariate analysis consisted of calculating the kappa value for agreement between the clinical and pathological stagings. Cases were classified as: understaged, if the clinical staging was less than pathological; correctly staged, if both matched; and overstaged, if the clinical staging was higher than pathological (we call these conditions "staging statuses"). A logistic regression model was adjusted to determine possible associations between the congruence of staging and the clinical and pathological features of the tumors. Finally, we separately analyzed whether the molecular subtype of breast cancer was associated with staging status using the Chi-square (χ^2) test.

Results

Eighty-six (38%) patients were understaged, 130 (57.5%) patients were correctly staged, and 10 (4.5%) patients were overstaged. In ►**Table 1**, we compare clinical and pathological characteristics according to staging status (understaged, correctly staged/overstaged). For the statistical analysis, patients who were correctly staged and overstaged were grouped. Patients understaged were younger (mean age at diagnosis = 52.2 years; $p < 0.0001$) and more symptomatic at diagnosis ($p = 0.04$) than their counterparts (mean age at diagnosis = 60.7 years). Menopausal status, parity, family history of breast cancer, post-menopausal hormonal replacement, histology (whether ductal or non-ductal) and body mass index (BMI) were not associated with the staging status. The affected breast quadrant was not related to the discordance of the staging status ($p = 0.18$, data not shown). The mean time between the first appointment at the institution when clinical staging was performed and the surgery was of 65 days for correctly and overstaged patients, and of 62 days for understaged patients ($p = 0.25$; data not shown in table).

►**Table 2** cross-tabulates the clinical and pathological staging of the women according to the 2010 AJCC consensus[13], and further dissects T (tumor) and N (lymph nodes) stagings. Out of all women clinically considered as stage I, 32 were later considered as stage II (24 women) or stage III (8 women). From the group of women in stage II, 54 were later considered as stage III, whereas 8 were downstaged. From the stage III group, 2 were downstaged to stage II pathological. Because all metastatic patients were excluded from the analysis, there are no stage IV patients in this study. The intraclass correlation coefficient (ICC) for AJCC staging agreement was 0.54. While analyzing only T staging, ICC was slightly superior (ICC = 0.62). It is worth noting that the agreement was negatively affected by 27 women who were clinically T1, T2 or T3 and were later found to be pT4, due to dermal involvement not seen in the clinical evaluation. The mean pathological size of the tumor was also relevant in understaged patients (mean 32 mm, range 12 to 80 mm) in comparison to correctly staged and overstaged patients (mean 25 mm, range 1 to 75 mm) ($p < 0.001$).

Restricting the analysis to N staging (ICC = 0.33), agreement was low mainly because of understaging of axillary lymph nodes: out of the 137 N0 patients, 48 were later found to harbor lymph node compromise. Also, patients with a clinically positive axilla were often understaged: 41out of 85 N1 patients were actually pN2 or pN3. It was found that the

Table 1 Clinical and pathological features as related to staging status

	Understaged	Correctly staged/ Overstaged	*p*-value	*p*-value adjusted
Number of Patients (n/%)	86 (38)	140 (62)		
Age (mean/SD)	52.2 (11.5)	60.7 (13.9)	< 0.01	< 0.0001
Menopause (n/%)				
No	34 (39.6)	35 (25)		
Yes	52 (60.5)	105 (75)	0.02	0.06
Parity (n/%)				
Nulliparous	8 (9.3)	23 (16.4)		
1 or more offspring	78 (90.7)	117 (83.6)	0.16	–
Family history of breast cancer (n/%)				
Yes	14 (16.3)	27 (19.3)		
No	72 (83.7)	113 (80.7)	0.59	–
Diagnosis (n/%)				
Screening	21 (24.4)	57 (40.7)		
Symptomatic	65 (75.6)	83 (59.3)	< 0.01	0.04
Hormonal therapy (n/%)				
No	65 (76.5)	120 (85.7)		
Yes	20 (23.5)	20 (14.3)	0.10	–
BMI (n/%)				
< 25	30 (34.9)	46 (32.9)		
25–29.9	28 (32.6)	42 (30.0)		
≥ 30	28 (32.6)	52 (37.1)	0.79	–
Histology (n/%)				
Ductal	83 (96.5)	132 (94.3)		
Lobular	3 (3.5)	8 (5.7)	0.54	–

Abbreviation: BMI, body mass index; n, number; SD, standard deviation;
Note: * multicentric tumors not included ($n = 22$).

understaged patients had a mean of 6.9 lymph node involvement (range 0 to 41), and the correctly staged and overstaged patients had a mean of 2.3 (range 0 to 29) ($p < 0.001$) compromised nodes.

In ►**Table 3** we further analyze the significant associations described in ►**Table 1**, between staging status and age, menopausal status, and whether diagnosis was made during breast cancer screening or triggered by symptoms. We arbitrarily established the cutoff point for this analysis as the median age (57 years) of the patients. We detected that women < 57 years of age were clinically understaged mainly due to underestimation of tumor volume or dermal involvement (T) ($p < 0.001$). The same was true for premenopausal women ($p < 0.01$), although these associations were not significant after multivariate adjustment. On the other hand, patients whose diagnosis was triggered by symptoms were clinically understaged due to underestimation of their N status ($p < 0.001$).

We also analyzed whether the type of surgery performed (conservative or radical) was associated with the staging status ($p = 0.33$) and the rate of re-operation due to compromised surgical margins ($p = 0.45$) (data not shown in tables), but no relation was found.

In ►**Table 4**, we examine the staging status according to the molecular subtype of the tumors ($p = 0.48$). Thirty three (38.4%) of the patients whose tumors were understaged had luminal A tumors; 30 (34.9%) had luminal B; 13 (15.1%) had HER2 positive, and 10 (11.6%) had triple-negative tumors. Out of the patients whose tumors were overstaged, 4 (40%) had luminal A; 3 (30%) luminal B; 1 (10%) HER2 positive; and 2 (20%) had triple-negative tumors. Out of the correctly staged women, 47 (36%) had luminal A; 54 (41.5%) luminal B; 9 (7%) had HER2 positive; and 20 (15.5%) had triple-negative tumors.

Discussion

Our study suggests that the surrogate clinicopathological subtype of breast tumor is not associated with the discrepancies between clinical and pathological stagings, whereas younger women and/or those with palpable tumors are at a significantly higher risk of having their disease clinically

Table 2 Clinical and pathological staging

		Pathological stage			
		I	II	III	
Clinical stage ICC = 0.54	I	46	24	8	
	II	8	60	54	
	III	0	2	24	
Comparison of T staging					
		T Pathological			
		1	2	3	4
T clinical ICC = 0.62	1	64	25	0	4
	2	13	68	4	21
	3	0	5	1	2
	4	0	0	0	18
		Mean (range)		*p*	
Tumor diameter (pathological, millimeters)	Correctly staged overstaged	25 (1 to 75)			
	Understaged	32 (12 to 80)		< 0.001	
Comparison of N staging					
		N Pathological			
		0	1	2	3
N Clinical ICC = 0.33	0	89	31	11	6
	1	17	26	22	19
	2	1	0	2	2
	3	0	0	0	0
		Mean (range)		*p*	
Number of compromised lymph nodes (pathological)	Correctly staged overstaged	2.3 (0 to 29)			
	Understaged	6.9 (0 to 41)		< 0.001	

Abbreviations: ICC, intraclass correlation coefficient; N, lymph node staging; T, tumor staging.
Note: Dark shading, overstaged; light shading, understaged.

Table 4 Clinical and pathological staging according to molecular surrogates

	Luminal A	Luminal B	HER2	Triple-negative
Understaged (n/%)	33 (38.4)	30 (34.9)	13 (15.1)	10 (11.6)
Correctly staged (n/%)	47 (36.0)	54 (41.5)	9 (7.0)	20 (15.5)
Overstaged (n/%)	4 (40.0)	3 (30.0)	1 (10.0)	2 (20.0)

Abbreviation: n, number.
Note: Chi-square (χ^2) $p = 0.48$.

understaged. This may result in significant detrimental effects for treatment planning in younger women, since suboptimal treatments may be prescribed. Interestingly, younger, premenopausal women had their tumors understaged mainly due to T underestimation, whereas women with symptomatic tumors had their disease understaged mainly due to N underestimation.

It is important to notice that CBE workup may vary according to practitioner experience, whereas mammography is performed according to strict technical parameters dictated by BI-RADS® (American College of Radiology, NY School of Medicine, New York, 2014).[15] One possible explanation for our findings is that younger women have faster growing tumors[16] compared with older women, and, in theory, these rapidly growing tumors may be smaller during pretreatment evaluation than they are at the moment surgery is performed.

Our data also revealed that clinical T underestimation was also more common in women with larger tumors, which in turn suggests that the semitechnical strategy for T estimation has sensitivity flaws. It is important to notice that we excluded, as per study protocol, patients with clinical advanced tumors, since these were prescribed neoadjuvant treatments, although 18 patients with cT4 were included, probably because they had small tumors with skin involvement, and they were not sent to neoadjuvant chemotherapy.

Table 3 Staging features as related to age at diagnosis, menopausal status and clinical symptoms

	T staging status				N staging status			
	Under staged	Correctly staged	Over staged	*p*	Under staged	Correctly staged	Over staged	*p*
Age ≥ 57 years	18 (33.3)	89 (59.2)	11 (61.1)		41 (46.2)	67 (57.8)	10 (52.6)	
Age < 57 years	38 (66.7)	61 (40.8)	7 (38.9)	< 0.001	50 (53.8)	49 (42.2)	8 (47.4)	0.18
Menopaused	30 (54.4)	112 (73.9)	15 (83.3)		61 (67.7)	82 (70.1)	14 (73.7)	
Not menopaused	26 (45.6)	39 (26.1)	3 (16.7)	< 0.01	30 (32.3)	35 (29.9)	4 (26.3)	0.65
Diagnosis by screening	16 (29.8)	58 (38.6)	3 (16.7)		19 (22.6)	52 (44.4)	7 (36.8)	
Diagnosis triggered by symptoms	40 (70.2)	93 (61.4)	15 (83.1)	0.11	72 (77.4)	65 (55.6)	11 (63.2)	< 0.001

Abbreviations: N, lymph node staging; T, tumor staging.
Note: Dark shading, overstaged; Light shading, understaged.

We found that out of 93 patients with clinical T1 tumors, 25 were further diagnosed with pT2 tumors, and another 4, with pT4 tumors. However, out of the 106 women with clinical T2 tumors, 21 were later diagnosed with pT4 disease. These figures suggest that the clinical evaluation of the breast, especially in women with larger tumors, may be flawed by the underestimation of skin and chest wall involvement, which may pose serious implications for the success of the primary surgical treatment.

The failure to clinically detect lymph node involvement was the main responsible reason for the clinical underestimation of the local extension of the disease. The implication of this must be analyzed with caution, since women with clinical N0 tumors who were later diagnosed with pN1 or pN2 do not represent a technical problem, since it is expected that a percentage of patients, depending on tumor characteristics, will be in this situation, and sentinel lymph node biopsy can be used to overcome this situation. The clinical challenge resides in women who are clinically deemed N1 and are later found to be N2 or N3. For these patients, suboptimal dissection of the axillary nodes may occur due to unexpected technical difficulties during surgery. In many cases, prognosis may be affected, since neoadjuvant treatment might have been a better option, although studies have shown that treatment order does not seem to be associated with mortality due to breast cancer.[17,18] Recent evidence from the ACOSOG Z011[1] and EORTC AMAROS[3] studies have shown that women with early stage disease may benefit from less aggressive treatment protocols; however, the benefits of these less aggressive treatment protocols have not been demonstrated in women who were clinically understaged.[1,3] For instance, in the ACOSOG Z011 trial, women who were found to have tumors $\geq$ 5 cm on histology were excluded from analysis.

Overstaging is characterized by the overestimation of tumor size and spread, and may result in overtreatment. In our study, 8 women (3.5%) were thought to be clinically stage II but were pathologically stage I, and 2 women (0.9%) were clinically stage III and were pathologically stage II. We were unable to determine whether patients who were overstaged were also overtreated.

Eighty-six (38%) out of 226 women had their breast cancer understaged. However, the number of women who had to undergo re-operation did not differ between women correctly staged or overstaged and those understaged. This finding reveals that clinical understaging of breast tumors was not associated with suboptimal first-line surgical treatment, and there was no association of clinical understaging with the rate of re-operations or compromised surgical margins. It is worth mentioning that there was no significant difference in the time elapsed from diagnosis to treatment between patients clinically understaged and those correctly staged or overstaged. This is an important finding, because significantly higher intervals between diagnosis and treatment in women understaged could have been interpreted as delayed treatment.

It was our hypothesis that triple-negative, luminal B and HER2 tumors would be more frequently understaged than luminal A tumors due to the rapid growth of the former. However, this hypothesis was not confirmed, and we were surprised by the fact that younger women, and those who had their diagnosis triggered by clinical complaints and not by screening tended to have their tumors understaged more often. Unfortunately, we do not have annotated follow-up data for this cohort of patients, and thus it was impossible for us to evaluate the survival implications of clinical understaging, since there were very significant imbalances in tumor volume and lymph node compromise between groups.

Conflict of Interest
The authors have no conflicts of interest to disclose. This study has not been sponsored.

References

1 Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 305(6):569–575
2 Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010;11(10):927–933
3 Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15-(12):1303–1310
4 Meissner HI, Klabunde CN, Han PK, Benard VB, Breen N. Breast cancer screening beliefs, recommendations and practices: primary care physicians in the United States. Cancer 2011;117(14): 3101–3111
5 Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002;137(5 Part 1): 347–360
6 Pisano ED, Hendrick RE, Yaffe MJ, et al; DMIST Investigators Group. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. Radiology 2008;246(2):376–383
7 Crispo A, Barba M, D'Aiuto G, et al. Molecular profiles of screen detected vs. symptomatic breast cancer and their impact on survival: results from a clinical series. BMC Cancer 2013; 13:15
8 Serra KP, Ramalho S, Torresan R, et al. [The new classification of breast cancers: finding the luminal A]. Rev Bras Ginecol Obstet 2014;36(12):575–580 Portuguese
9 Rodrigues-Peres RM, Cadore S, Febraio S, et al. Tissue aluminum concentration does not affect the genomic stability of ERBB2, C-MYC, and CCND1 genes in breast cancer. Biol Trace Elem Res 2013; 154(3):345–351
10 Rodrigues-Peres RM, Cadore S, Febraio S, et al. Aluminum concentrations in central and peripheral areas of malignant breast lesions do not differ from those in normal breast tissues. BMC Cancer 2013;13:104
11 Serra KP, Sarian LO, Rodrigues-Peres RM, et al. Expression of cyclooxygenase-2 (COX-2) and p53 in neighboring invasive and in situ components of breast tumors. Acta Histochem 2012;114(3): 226–231

12 Ramalho S, Serra KP, Vassallo J, et al. HER2 expression in Brazilian patients with estrogen and progesterone receptor-negative breast carcinoma. Acta Histochem 2013;115(2):120–127
13 American Joint Committee on Cancer (AJCC) [Internet]. Quick references: cancer staging posters. 2015 [cited 2015 May 25]. Available from: http://cancerstaging.org/references-tools/quickreferences/Pages/default.aspx
14 Goldhirsch A, Winer EP, Coates AS, et al; Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013; 24(9):2206–2223
15 Mercado CL. BI-RADS update. Radiol Clin North Am 2014;52(3): 481–487
16 Buist DS, Porter PL, Lehman C, Taplin SH, White E. Factors contributing to mammography failure in women aged 40-49 years. J Natl Cancer Inst 2004;96(19):1432–1440
17 Gralow JR, Burstein HJ, Wood W, et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol 2008;26(5):814–819
18 Kaufmann M, von Minckwitz G, Bear HD, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007;18(12):1927–1934