The Journal of Global Radiology
Ensuring Medical Imaging Access for All

RESEARCH ARTICLE

Pilot Study of a Resource-Appropriate Strategy for Downstaging Breast Cancer in Rural Uganda

Alphonsus Matovu[1,2], John R. Scheel*[3,4,5], Picho Alli Shadrack[2], Renny Ssembatya[2], Angela Njeri[6], Moses Galukande[7], Kristen DeStigter[8]

[1] Mubende Regional Referral Hospital, Kampala, Uganda
[2] Imaging the World Africa, Kampala, Uganda
[3] University of Washington School of Medicine, Department of Radiology, Seattle, WA, USA
[4] Seattle Cancer Care Alliance, Seattle, WA, USA
[5] Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[6] Nawanyago Health Center III, Kamuli District, Uganda
[7] Makerere University, Kampala, Uganda
[8] University of Vermont Medical Center, Burlington, VT, USA

***Corresponding author. Current address:** University of Washington, Seattle Cancer Care Alliance, 825 Eastlake Avenue East, G3-200 Seattle, WA 98109-1023; jrs4yg@uw.edu

DOI: 10.7191/jgr.2016.1021

Received: 12/11/2015

Accepted: 1/28/2016

Published: 5/12/2016

Citation: Matovu A, Scheel JR, Shadrack PA, Ssembatya R, Njeri A, Galukande M, et al. Pilot study of a resource-appropriate strategy for downstaging breast cancer in rural Uganda. J Glob Radiol. 2016;2(1):Article 1.

Keywords: low- and middle-income countries (LMICs), breast cancer downstaging, breast ultrasound

Word count: 3,750

ISSN 2372-8418

Abstract

Breast cancer incidence and mortality are rapidly increasing in low- and middle-income countries like Uganda. Shifting the proportion of women presenting with late-stage breast cancer to early-stage breast cancer (downstaging) at the time of diagnosis would substantially improve survival and efficient use of available resources. Imaging The World (ITW) conducted a pilot study in Uganda where trained village health teams (VHTs) promoted breast cancer awareness in the Kamuli District (Uganda). As a result, 212 women with self-detected lumps presented to the community health center level III (Nawanyago HCIII) for a clinical breast examination (CBE). Patients with masses on CBE were examined with breast ultrasound by a certified sonographer trained in breast imaging. Women with ultrasound-detected masses were referred to a regional health center for further evaluation. Of the 212 women, 44 (21%) had a palpable mass by CBE, 11 (28%) examined by ultrasound were recommended for biopsy, and four breast cancers were diagnosed. Providing ultrasound scanning at Nawanyago HCIII reduced the number of women travelling to the referral hospital by 75%. As a result of breast cancer awareness and ultrasound studies, we were able to diagnose breast cancer at an earlier stage than would be otherwise possible. This pilot project supports locally available breast ultrasound as a resource-appropriate strategy to downstage breast cancer in a low-income country.

Introduction

BREAST cancer is the most common cancer and an important cause of cancer-related mortality among women worldwide (1). The World Health Organization (WHO) estimates that by the year 2020, 70% of newly diagnosed breast cancer cases will occur in low- and middle-income countries (LMICs) (2). In Uganda, for example, the incidence of breast cancer is 32.3 per 100,000, and has increased by 5.2% per year over the past 15 years (1). Many Ugandan women with breast cancer are diagnosed in their thirties, an age when many are taking care of young children and managing their careers and households (3). For this and other reasons, breast cancer has become a major global health problem and has prompted the WHO to intervene (4).

Low breast cancer awareness and absence of a screening program results in detection of 89% of all breast cancers in Uganda at later stages (stages III and IV) (5). Management of late-stage breast cancer is more expensive, technically demanding, and results in more morbidity and mortality (M&M) than that of early-stage breast cancer (3,5-8). This is true even in high-income countries (HIC). Thus, early detection is pivotal to cure and reduce M&M, irrespective of economical factors.

The term "downstaging" may be used for shifting a population with late-stage breast cancers to early-stage cancers over a period of time through screening, or for an individual case where reduction in tumor size (stage) may be affected by neoadjuvant chemotherapy before curative surgery. Screening may be in the form of breast self-examination (BSE), clinical breast examination (CBE), mammography or ultrasound. In Uganda, breast cancer treatment is free through the Ugandan Cancer Institute (UCI), but neoadjuvant chemotherapy is not a viable option

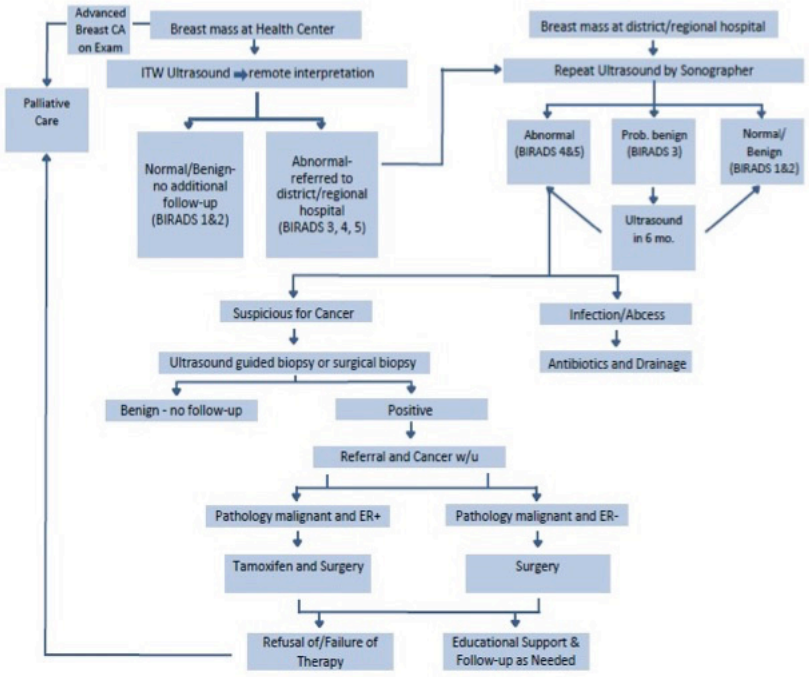

Figure 1. Imaging The World breast cancer downstaging strategy.

in large numbers of patients. Therefore, given the resources, the most resource-appropriate strategy seems to be downstaging through health awareness leading to increased rates of BSE and CBE.

According to the Breast Health Global Initiative (BHGI) guidelines, resource-appropriate strategies to downstage breast cancer in Uganda should include increased breast health awareness, so women begin to practice BSE and present early to their providers after self-detecting a lump (9, 10). It is also important to train the providers in breast health to obtain appropriate history and physical examination including a proper CBE. Both BSE and CBE have the potential for a high false-positive rate and are, therefore, no longer recommended in countries where screening mammography is available (11-13). But, with one publically available mammography unit in the country, screening mammography is not a feasible option for most Ugandan women, particularly rural women. Ultrasound is more widely available, even in rural areas, and has the ability to characterize palpable masses detected by CBE as those requiring biopsy versus those that can safely be managed by imaging or clinical follow-up (14).

In accordance with the World Health Organization's recommendations to reduce the global burden of breast cancer (15), Imaging The World (ITW) developed a resource-appropriate strategy to downstage breast cancer. ITW is a non-profit organization with a global team of volunteers who provide ultrasound training, equipment and technology in LMICs to improve and sustain health outcomes (16). For this pilot study, we determined the feasibility of this breast cancer downstaging strategy in a rural, low-resource setting (Kamuli District, Uganda), specifically in terms of: (1) training village health teams (VHTs) to provide breast cancer awareness, and (2) training sonographers to perform and interpret breast ultrasound.

Materials and methods

Study team and settings

Imaging the World Africa (ITWA) is a registered non-governmental organization (NGO) in Uganda, and locally executes ITW's mission with a team of physicians, midwives, sonographers and support staff. This pilot project was conducted in the Kamuli District, at the Nawanyago Clinic Health Centre III (Nawanyago HCIII) and Kamuli Mission Hospital (Referral Hospital), between March and August 2013.

Intervention

Study overview

This IRB-approved prospective study evaluated the feasibility of the ITW breast cancer downstaging strategy (Figure 1). Women <18 years, pregnant or acutely ill were excluded. ITW trained VHTs to educate women on breast cancer and the importance of presenting early after self-detecting a breast lump. Women with a self-detected lump presented to Nawanyago HCIII for evaluation, which included a CBE by a trained provider. Women with a positive CBE received a triaging breast ultrasound by an ITWA-trained sonographer, and referred those women with a suspicious mass to the referral hospital for further evaluation and potential biopsy by an ITWA-trained surgeon.

Patients receiving a breast cancer diagnosis were referred to the UCI for treatment. Patients travelled to the UCI by bus and were met at the bus stop in Kampala by an ITWA patient navigator. The UCI provided standard-of-care treatment (17) at no cost to the patient, and the patient navigator helped arrange necessary medical tests, doctor's appointments, and treatment.

Breast ultrasound training

ITWA held a three-day workshop and five days of apprenticeship to teach a certified sonographer with prior breast imaging experience to perform and interpret breast ultrasound (Figure 2) using the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) (18).

VHT training

ITWA trained VHTs to promote breast cancer awareness at events advertised through the local radio and television. VHTs educated women at these events on breast cancer and the importance of presenting early after self-detecting a lump.

Breast ultrasound imaging equipment and peer review

Ultrasound imaging at the Nawanyago HC III was performed on a Philips (Royal Philips, Amsterdam, Netherlands) ClearVue 350

Figure 2. Ugandan sonographer undergoing ultrasound training on a breast phantom.

with a L12-4 MHz transducer. The sonographer used a standardized volumetric scanning protocol performed by sweeping the transducer over the entire palpable area, as described previously. Ultrasound data was managed via a PACS-compatible electronic medical records system, which enabled site data entry and remote database access. An American board-certified radiologist reviewed all images remotely in the United States and signed off on their interpretations using peerVue (peerVue, Inc., Sarastoa, FL, USA), a commercial Web-based system, for quality assurance. The sonographer communicated any changes in the interpretation to the patient.

Data analysis

For this study, we collected the data at each point of care and their outcomes, including contacting women with negative and benign results one year after the examination. Performance measures for CBE and ultrasound included cancer detection rate (CDR; per 1,000 CBEs); abnormal CBE interpretation rate; positive predictive value (PPV) 2 (recommendation for tissue diagnosis); PPV3 (biopsy performed); sensitivity, specificity, and percent minimal cancers, according to the ACR BI-RADS manual, 5th edition (18). The percent of women managed locally with BI-RADS 1, 2, or 3 ultrasound findings that obviated the need for travelling to the referral hospital and concordance between the sonographer and the American board-certified radiologist were also calculated. Calculations were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA).

Results

Breast cancer downstaging strategy performance

The 212 women consenting to participate in this study averaged 33 years of age. (median: 29 years; range: 17-70). The observed and calculated performance of the ITW breast cancer downstaging strategy is depicted in Table 1. Forty-four women (21%) presenting for evaluation at the Nawanyago HCIII had a positive CBE and received a breast ultrasound. Eleven (25%) were interpreted as BI-RADS 1 or 2, 22 (50%) as BI-RADS 3, and 11 (25%) as BI-RADS 4 or 5. No breast ultrasound was interpreted as BI-RADS 0 or 6.

Four women (36%) with a biopsy recommendation (BI-RADS 4 or 5) traveled to the referral hospital and received a biopsy, and all were diagnosed with breast cancer (Figure 3). Of the seven women with a biopsy recommendation who did not receive a biopsy, three declined, one died prior to biopsy, two converted to BI-RADS 1 after antibiotic therapy or lactation ended, and one was lost to follow-up.

The breast cancer detection strategy performed as follows: CDR: 19 per 1,000 CBEs, abnormal interpretation rate: 21% (44/212), PPV2: 36% (4/11), and PPV3: 100% (4/4), sensitivity: 100% (4/4) and specificity: 28% (11/40). Ultrasound used as a triage test at the Nawanyago HCIII reduced the number of women travelling to the referral hospital after a positive CBE by 75% (33/44).

Breast cancer outcomes

Of the four cancers detected during the trial period, two represented early-stage and two late-stage breast cancer. Of the two women with late-stage breast cancer, one died prior to treatment at 11 months post-diagnosis, and one died during treatment at nine months post-treatment. The two women with early-stage breast cancer have completed treatment (chemotherapy, radiation, and surgery) at the UCI, are taking Tamoxifen and are being monitored for recurrence at the Nawanyago HC III.

Performance of front-line sonographers at Nawanyago HCIII

Interpretation by the sonographer at the Nawanyago HCIII showed 91% (40/44) concordance with the American board-certified radiologist. Three of the discordant examinations upgraded from BI-RADS 3 to BI-RADS 4 and one upgraded from BI-RADS 2 to BI-RADS 3. One of these discordant examinations (upgraded from BI-RADS 3 to BI-RADS 4) was biopsied and represented breast cancer.

Discussion

Currently, women presenting to the Nawanyago HCIII with

Figure 3. Ultrasound images of a mass from a woman presenting with a palpable lump to Nawanyago HCIII. Biopsy of this mass showed breast cancer.

Table 1. Performance Measures of Breast Ultrasound.

Variable	
Observed Outcomes - Health Center III	***Number***
Screened with CBE	212
Positive CBE	44
Screened with US	44
BR 1 or 2	11
BR 3	22
BR 4 or 5	11
Cancers Diagnosed	4
Performance Measures	***% (Number)***
Cancer Detection Rate (per 1,000 CBE)	19 (4/212)
Abnormal Interpretation Rate (CBE)	21 (44/212)
PPV2 (Recommendation for Biopsy)	36 (4/11)
PPV3 (Biopsy Performed)	100 (4/4)
Sensitivity	100 (4/4)
Specificity	28 (11/40)
Prevented from Referral (BR 1,2,3)	75 (33/44)
% Early Stage Cancer	50% (2/4)

CBE: Clinical Breast Examination
US: Ultrasound
BR: BI-RADS
PPV: Positive Predictive Value

symptoms receive a CBE, and those with a positive CBE are referred to a regional hospital located a long distance away for further evaluation and potential biopsy. The costs associated with travel and time away from work and family responsibilities represent a significant barrier to breast cancer detection services. This is partially responsible for delayed diagnosis and high mortality (19). For this pilot project, we trained certified sonographers with previous breast ultrasound experience to perform and interpret breast ultrasound using BI-RADS following a positive CBE at the Nawanyago HCIII.

Using the data from this pilot study, we demonstrate the feasibility of the ITW breast cancer downstaging strategy in rural Uganda. ITW leveraged existing VHTs to promote breast cancer awareness in the community and trained a sonographer with breast imaging experience to perform and interpret breast ultrasound using BI-RADS at the Nawanyago HCIII. We further demonstrate how this strategy reduced by 75 percent the number of women travelling to the referral hospital, in many cases long distances, just for diagnostic breast ultrasound. Through ITWA's health awareness program and ultrasound we detected breast cancers in stages earlier than they would have been detected without our interventions (i.e. downstaged).

Shortage of regional referral centers in the country limits patient access to centers where women can receive imaging evaluation for palpable lumps. Other NGOs in Uganda are involved in training sonographers to use basic ultrasound techniques at community health centers (HCIIIs) to triage pregnant women with potential obstetric complications to district hospitals (20-22). Similarly, ITWA's efforts to train sonographers to characterize breast masses at the level of HCIIIs would not only help to downstage breast cancer, but also reduce the number of women travelling unnecessarily to referral hospitals for nonmalignant breast lumps.

Aiming to downstage breast cancer using available resources represents an essential starting point for interventions addressing breast cancer mortality in LMICs. While this pilot study was performed to determine feasibility of the ITW strategy, we note that two of the four breast cancers (50%) detected by this strategy represented early-stage disease, which is lower than the proportion of early-stage disease reported in the Ugandan literature (10%)

(5). While there is no evidence for improved survival from our intervention, both women diagnosed with early-stage breast cancer received curative treatment (surgery, chemotherapy, and radiation) at the UCI and have returned to their communities.

CBE performed by ITW-trained providers demonstrated a CDR of 19 breast cancers per 1,000 women evaluated. A previous study from India showed a CDR of 10.4 per 1,000 women (23). We attribute the higher CDR observed in our study to the higher incidence of breast cancer in Uganda (32.3 per 100,000) compared to India (20 per 100,000) and the inclusion of only symptomatic women in our study (23,24). We further demonstrate interpretive performance for PPV2 and 3 that are within the performance ranges published previously (2-96%) (25-28). Our specificity was lower than in these studies (49-97%), which reflects the high proportion of women presenting with masses assessed as BI-RADS 3 (46%), and also the high proportion of young women presenting for evaluation. Since BI-RADS 3 masses were followed by ultrasound locally, these women did not require travel to the referral hospital for further evaluation. The performance of the ITW strategy in this setting highlights the success of the ITW training program and suggests that training sonographers to perform and interpret breast ultrasound at HCIIIs is a resource-appropriate strategy for breast cancer detection in Uganda. The sonographer's 91% concordance rate with an American-trained radiologist was within the expected inter-observer variability observed in other studies (29,30). Future efforts to train sonographers to perform and interpret breast ultrasound at HCIIIs should improve the telemedicine capacity of Ugandan radiologists to provide peer review and ensure sustainability.

There are several potential limitations of this pilot study. First, CBE and BSE as screening strategies are no longer recommended in the United States; however, these recommendations do not apply in Uganda, where screening mammography is not available. Indeed, the National Comprehensive Cancer Network (NCCN) recommends BSE because it is essential for women to first detect abnormalities in their own breasts before they can present for evaluation (31). In addition, seven women recommended for a biopsy did not receive one, which may have reduced performance measures. This low adherence to biopsy recommendations also emphasizes the challenges facing downstaging efforts in Uganda. As this program expands, we will add curricula to VHT training programs that will address barriers to adhering to biopsy recommendations.

In summary, we demonstrate the feasibility of the ITW breast cancer downstaging strategy in rural Uganda. This strategy combines VHTs providing breast cancer awareness in the community to encourage women to present early after self-detecting a lump, and CBE plus breast ultrasound provided at a HCIII to reduce the number of women traveling to the referral hospital. In the future, we will expand this program into other districts, in collaboration with the Ugandan Ministry of Health and local providers, and collect pre-intervention tumor sizes to demonstrate downstaging with this strategy.

Acknowledgments

This work was supported by the Stars in Global Health Grant from Grand Challenges Canada and the citizens of Canada. JRS is supported in part by the American Roentgen Ray Society Scholar award. The authors thank Ms. Catherine O'Donnell and Dr. Gaytri Scheel for their critical review of this manuscript.

Conflict of interest

The authors have no conflicts of interest to report.

References

1. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A. International variation in female breast cancer incidence and mortality rates. Cancer Epidemiol. Biomarkers Prev. 2015 Oct;24(10):1495-506.

2. Lingwood RJ, Boyle P, Milburn A, Ngoma T, Arbuthnott J, McCaffrey R, et al. The challenge of cancer control in Africa. Nat Rev Cancer. 2008 May;8(5):398-403.

3. Gakwaya A, Kigula-Mugambe JB, Kavuma A, Luwaga A, Fualal J, Jombwe J, et al. Cancer of the breast: 5-year survival in a tertiary hospital in Uganda. Br J Cancer. 2008 Jul;99(1):63-7.

4. Beaglehole R, Bonita R, Horton R, Adams C, Alleyne G, Asaria P, et al. Priority actions for the non-communicable disease crisis. Lancet. 2011 Apr;377(9775):1438-47.

5. Galukande M, Wabinga H, Mirembe F. Breast cancer survival experiences at a tertiary hospital in sub-Saharan Africa: a cohort study. World J Surg Oncol. 2015;13:220.

6. American Cancer Society. Breast cancer survival rates, by stage [Internet]. American Cancer Society; 2015 [cited 2015 Oct 24]. Available from: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-survival-by-stage

7. Barlow WE, Taplin SH, Yoshida CK, Buist DS, Seger D, Brown M. Cost comparison of mastectomy versus breast-conserving therapy for early-stage breast cancer. J Natl Cancer Inst. 2001 Mar;93(6):447-55.

8. Groot MT, Baltussen R, Uyl-de Groot CA, Anderson BO, Hortobágyi GN. Costs and health effects of breast cancer interventions in epidemiologically different regions of Africa, North America, and Asia. Breast J. 2006 Jan-Feb;12 Suppl 1:S81-90.

9. Anderson BO, Cazap E, El Saghir NS, Yip CH, Khaled HM, Otero IV, et al. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. Lancet Oncol. 2011 Apr;12(4):387-98.

10. Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, et al. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. Cancer. 2008 Oct;113(8 Suppl):2221-43.

11. McDonald S, Saslow D, Alciati MH. Performance and reporting of clinical breast examination: a review of the literature. CA Cancer J Clin. 2004 Nov-Dec;54(6):345-61.

12. Trapp MA, Kottke TE, Vierkant RA, Kaur JS, Sellers TA. The ability of trained nurses to detect lumps in a test set of silicone breast models. Cancer. 1999 Nov;86(9):1750-6.

13. Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Ya-Chen TS, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA. 2015 Oct;314(15):1599-614.

14. Tsu V, Scheel J, Weigl B, Murray M, Lehman C. Breast ultrasound after palpable findings at clinical breast examination: does it have a role in low- and middle-income countries? J Glob Radiol. 2015 Nov;1(2);Article 1.

15. World Health Organization. Cancer control knowledge into action: WHO guide for effective programes. Switzerland: World Health Organization; 2012.

16. Imaging the World. 2015 [cited 215 Oct 21]. available from: http://imagingtheworld.org.

17. Gakwaya A, Galukande M, Luwaga A, Jombwe J, Fualal J, Kiguli-

Malwadde E, et al. Breast cancer guidelines for Uganda (2nd Edition 2008). Afr Health Sci. 2008 Jun;8(2):126-32.

18. ACR. ACR BI-RADS®. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas. Reston, VA: American College of Radiology; 2013.

19. Odongo J, Makumbi T, Kalungi S, Galukande M. Patient delay factors in women presenting with breast cancer in a low income country. BMC Res Notes. 2015 Sep;8:467.

20. Nathan R, Swanson JO, Marks W, Goldsmith N, Vance C, Sserwanga NB, et al. Screening obstetric ultrasound training for a 5-country cluster randomized controlled trial. Ultrasound Q. 2014 Dec;30(4):262-6.

21. Stolz LA, Muruganandan KM, Bisanzo MC, Sebikali MJ, Dreifuss BA, Hammerstedt HS, et al. Point-of-care ultrasound education for non-physician clinicians in a resource-limited emergency department. Trop Med Int Health. 2015 Aug;20(8):1067-72.

22. Swanson JO, Kawooya MG, Swanson DL, Hippe DS, Dungu-Matovu P, Nathan R. The diagnostic impact of limited, screening obstetric ultrasound when performed by midwives in rural Uganda. J Perinatol. 2014 Jul;34(7):508-12.

23. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Prabhakar J, Augustine P, et al. Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. J Natl Cancer Inst. 2011 Oct;103(19):1476-80.

24. Wabinga HR, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991-2010. Int J Cancer. 2014 Jul;135(2):432-9.

25. Pande AR, Lohani B, Sayami P, Pradhan S. Predictive value of ultrasonography in the diagnosis of palpable breast lump. Kathmandu Univ Med J (KUMJ). 2003 Apr-Jun;1(2):78-84.

26. Yang WT, Mok CO, King W, Tang A, Metreweli C. Role of high frequency ultrasonography in the evaluation of palpable breast masses in Chinese women: alternative to mammography? J Ultrasound Med. 1996 Sep;15(9):637-44.

27. Lehman CD, Lee CI, Loving VA, Portillo MS, Peacock S, DeMartini WB. Accuracy and value of breast ultrasound for primary imaging evaluation of symptomatic women 30-39 years of age. AJR Am J Roentgenol. 2012 Nov;199(5):1169-77.

28. Loving VA, DeMartini WB, Eby PR, Gutierrez RL, Peacock S, Lehman CD. Targeted ultrasound in women younger than 30 years with focal breast signs or symptoms: outcomes analyses and management implications. AJR Am J Roentgenol. 2010 Dec;195(6):1472-7.

29. Baker JA, Kornguth PJ, Soo MS, Walsh R, Mengoni P. Sonography of solid breast lesions: observer variability of lesion description and assessment. AJR Am J Roentgenol. 1999 Jun;172(6):1621-5.

30. Berg WA, Blume JD, Cormack JB, Mendelson EB. Training the ACRIN 6666 Investigators and effects of feedback on breast ultrasound interpretive performance and agreement in BI-RADS ultrasound feature analysis. AJR Amer J Roentgenol. 2012 Jul;199(1):224-35.

31. Bevers TC, Helvie MV-C. Breast Cancer Screening and Diagnosis. NCCN Clinical Practice Guidlelines in Oncology. 2015.