Challenges in Breast Imaging

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Introduction

Breast imaging is fraught with unique challenges in decision making and patient management. The objective of not missing early-stage disease so as to fulfill the prime goal of diagnosing nonpalpable cancers to be balanced with keeping false positives low presents unique practice patterns and challenges. The list of controversies in breast imaging is long; some of the important ones are discussed in this chapter:

- Inappropriate indications for mammography
- Breast intervention
  - Intraductal masses
  - Follow-up after concordant biopsy results
  - Cytology of cyst aspirates
- Dense breast law
- Double reads
- Clinical breast exam during screening
- Imaging the male breast
- Overdiagnosis of breast cancer with screening mammography
- Isolated abnormal axillary nodes

Inappropriate Indications for Mammography

Screening mammography has proven benefits in reducing breast cancer mortality and attention to proper methodology, and appropriate use is critical to optimize these benefits [1]. Some of the controversial indications for use of mammography in asymptomatic women are discussed next.

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Prior to and Following Breast Augmentation

There is no reason for routine use of mammography prior to placement of breast augmentation other than in those who are in the age group where annual screening mammography is recommended by American Cancer Society. It has been suggested that preoperative mammogram will detect abnormalities that could be potentially biopsied during implant placement surgery and to serve as a baseline prior to augmentation. These reasons have not been validated in any published study. Similarly the need for postaugmentation mammogram 6–12 months after surgery has been suggested to serve as a baseline for future follow-up. Although a need for such an examination has also never been validated, there may be some justification since postsurgical changes may be mistaken for signs of malignancy and having a baseline will serve to minimize false positive biopsies [2].

In a series of 1,149 cases of cosmetic surgery of the breast performed from 1973 to 1989, early diagnosis of breast cancer in 34 cases was possible by relying mainly on the use of mammography for the diagnosis. Based on these findings the authors recommended that a policy of mandatory preoperative mammography be implemented so that all patients can be protected from a lethal disease that has a far better prognosis when detected early [3]. This study did not have adequate information on the age group, presence of symptoms, or risk factors in cases of breast cancer that was identified on the mammogram. The findings of this study therefore do not justify routine use of mammography preimplant placement in women under the age of 40 years who are at an average risk.

Imaging Surveillance in the Postmastectomy Patient

There is insufficient evidence for mammographic surveillance in women who have undergone mastectomy or in those who have undergone mastectomy with breast reconstruction or augmentation. The one exception is in women who have

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undergone nipple-sparing subcutaneous mastectomy in whom the nipple-areolar complex and the tissue behind are left behind. The annual recurrence rate of cancer in those who have undergone nipple-sparing mastectomy has been reported to be 6.7 % [4]. The yield of nonpalpable cancers in women who have undergone mastectomy is low. Ultrasound and mammography are indicated in the symptomatic patient postmastectomy and reconstruction, with fat necrosis being the most common benign finding in both the symptomatic and the asymptomatic women. In one series of the 227 patients who had undergone mastectomy with breast reconstruction, one cancer was detected among 116 who underwent mammographic surveillance. The recall rate was 4 %. In the symptomatic group of 54 women on the other hand, there were 4 cancers; the most common cause of a palpable finding was fat necrosis [5]. Others have recommended the routine surveillance of the mastectomy side since it is impossible to know how much of glandular tissue has been left behind. A recurrence rate of as high as 7 % has been reported and has been cited as the rationale behind routine surveillance of the postmastectomy breast [6]. Routine surveillance has also been recommended in those patients who undergo postmastectomy reconstruction with transfer of a musculocutaneous flap; recurrence of cancer after 5 years was found by surveillance in a small group of patients [7, 8].

Mammography for Breast Pain

Women seek attention when afflicted with breast pain due to concern of breast cancer. In our practice mammography is frequently ordered in women who present with breast pain; a majority of these women fall in the nonscreened group most commonly in their 30s. As a means of reassurance in those without clinical findings, we perform ultrasound only particularly in those under 30 years old. In one series breast pain accounted for 32 % of new patient referrals, 60 % were in women under the age of 40 years. There was no increased reassurance in excluding malignancy. Although six cancers were detected in the study group of 916 women during a 1-year study period, none were found in patients not associated with clinical breast abnormalities. There is no rationale in imaging the breast for a complaint of pain in the absence of clinical breast abnormalities [9]. In a primary care setting, 45–70 % of breast complaints are attributed to breast pain. When breast pain is the sole complaint, the risk of breast cancer is very low and reported to be 0–3 % [10–12]. Imaging is not justified although commonly used as a means of patient reassurance. Cyclic pain and or diffuse or bilateral breast pain should not prompt imaging in the absence of a clinical abnormality.

Breast Intervention

Intraductal Masses

Intraductal masses are frequently papillomas that are generally recommended to undergo excisional biopsy due to known association with DCIS, an upgrade to malignancy of 4–14 % has been reported [13, 14]. Mammography shows a tubular density with or without branching usually in a subareolar location; calcifications may be associated. Ultrasound may reveal an intraductal mass with or without calcifications and may reveal vascularity on Doppler imaging (Fig. 14.1a–d). A series of 163 intraductal masses reported a malignancy rate of 8 %, 10 of which were DCIS and three invasive cancers. Malignancy was more often associated with symptoms and personal history of cancer. Distinguishing sonographic features in malignant masses included intraductal masses that filled the lumen, extended outside the duct or extended into a branch. Malignant masses were larger than benign intraductal masses [15]. In our practice all papillomas are recommended to undergo excisional biopsy, and on imaging if a papilloma or a papillary lesion is suspected based on the presence of an intraductal mass particularly in a subareolar location, excisional biopsy is recommended at the outset bypassing the step of percutaneous biopsy. It has been suggested that excision be suggested only in those cases where atypia is associated or when the size of the papilloma is greater than 1.5 cm [13].

Follow-up After Concordant Percutaneous Biopsy

Calcifications

For benign concordant pathologic results, a single 6-month follow-up is adequate with magnification views to ensure that calcifications are stable [16]. In case of a specific diagnosis such as a fibroadenoma, a 12-month follow-up may be sufficient. At follow-up if there is no increase in the number of calcifications or a change to a suspicious morphology, no further follow-up is warranted.

Masses

There is no consensus on follow-up after a benign concordant biopsy. Some advocate that no follow-up is needed, while others recommend a 6-, 12-, and 24-month follow-up;, the latter seems excessive. At our institution a single 6-month follow-up is performed for benign concordant histology. If there is a significant increase in the size of the mass or if there are new morphologic features that are suspicious such as marginal irregularity, excisional biopsy is appropriate [16].

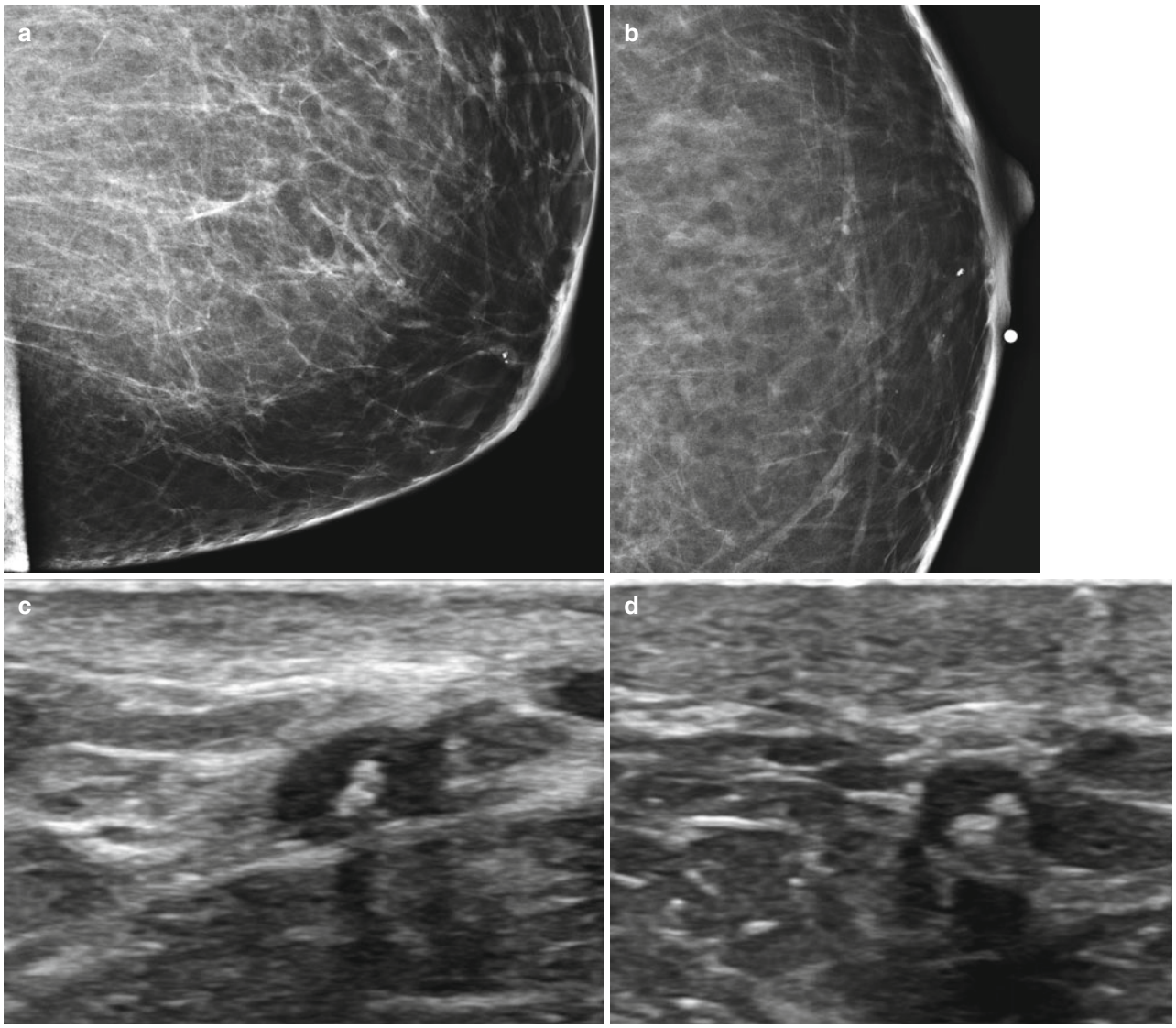

Fig. 14.1 Intraductal papilloma in a 44-year-old female with a spontaneous unilateral serous nipple discharge. (**a**) Mediolateral oblique view of the left breast demonstrates a branching subareolar tubular density with calcifications. (**b**) Craniocaudal view showing a similar finding. (**c**) Ultrasound image of the subareolar region showing a distended duct with an intraductal mass in the radial plane. (**d**) Ultrasound image of the subareolar region showing a distended duct with an intraductal mass in the antiradial plane

Aspiration of Cysts

A simple cyst is a benign finding and requires intervention only for symptomatic relief. Complicated cysts are those which do not fulfill all of the criteria of a simple cyst such as when internal echoes or septations are seen within a cyst or when there is no increased through transmission. These are mostly benign and may not require aspiration. In one series only 1 of 243 lesions (0.4 %) proved malignant; this lesion was 1 of 33 complicated cysts that did not yield fluid [17]. Even when cytology yields atypical cells, the final histology is mostly benign [17]. In a large series of 6,782 cyst aspirations over a 7-year period, the incidence of intracystic papillomas was 5 [0.1 %] [18]. All cases of papilloma showed blood-stained fluid. Overall only 2 % of cyst fluids were blood stained. Cytology of six cases of papilloma was positive in two, negative in two, and falsely positive in two cases [18]. These investigators recommended cytology only when aspirate is blood stained. A cyst that demonstrates thick indistinct walls, thick internal septations, or mixed solid and cystic components requires core biopsy sampling. Clustered microcysts and septate cysts are generally benign [19]. A recently published large series of 5,375 aspirations performed over a 16-year period of noncomplex cysts reported a malignancy rate of 0.3 % [20]. Atypical cytology revealed malignancy in 21 % of cases. All atypical results

should undergo further workup. Malignant cytology revealed malignancy in 91 % of cases and hence all patient with malignant histology need to undergo biopsy [20].

Dense Breast Law

Sensitivity of mammography in women with dense breasts has been reported to be as low as 48 % [21]. About 41 % of women may have dense breasts on a mammogram [22]. Increased breast density is an independent risk factor for breast cancer and increased the risk by a factor of 5 [23]. Supplemental ultrasound has been shown to detect additional cancers in women with dense breasts in those with an elevated risk as well in those with an average risk [24–27].

Recently based on these facts and a public campaign undertaken by a breast cancer survivor, several states have passed a law called the "Henda's law" or the "dense breast law" requiring women with dense breasts to be informed by their clinician about their breast density and discussing the option of undergoing supplemental screening depending on their risk factors.

The ACRIN 6,666 trial showed that 4.2 additional cancers were identified by ultrasound in women with an elevated risk for breast cancer [24]. The dense breast law passed in Connecticut requires notification of women with a greater than 50 % density and recommendation for supplemental screening ultrasound; the law also required insurance to pay for supplemental ultrasound screening. A study from Connecticut looking at such women showed that ultrasound lead to an additional yield of 3.25 cancers per 1,000 in women with dense breasts, normal mammograms, and no additional risk factors [25]. Although the NPV [99.9 %] and sensitivity was very high [96.6 %], the positive predictive value was low at 6.7 % [25]. Yet in another study of 5,519 women with dense breasts who underwent sonographic screening, the supplemental yield was only 1.8 per 1,000 and positive predictive value was low at 5.5 %, and mean tumor size was 9.7 mm [26]. Post enactment of the Connecticut law, a study that looked at women with low risk [614/935], intermediate risk [149/935, 15.9 %], and high risk [87/935, 9.3 %] found one cancer in each of the three groups. All of these three cancers were small solid masses in postmenopausal women for a cancer detection rate of 3.2 per 1,000 women screened again with an expected low positive predictive value of only 6.5 % [27].

Double Reads

About half of the countries that use screening mammography have implemented double reading, although direct evidence of its effectiveness in the context of a national screening program is lacking [28]. Analysis of ten cohort studies showed that overall double reading increases the cancer detection rate by 3–11 per 10,000 women screened and most of the cancers thus found are small cancers. The effect on recall rate depended on the methodology. Double reading with unilateral recall increased the number of women recalled from 38 to 149 per 10,000 women screened. In programs where a consensus or arbitration policy was in place, the recall rate decreased between 61 and 269 per 10,000 women screened [28]. In a large majority of cases, double reads do not lead to disagreement; when there is one mutual consultation, this further diminishes the number of recall. In some facilities cases with disagreement are referred to an arbitration panel. The effectiveness of this methodology of referral to an arbitration panel has been studied. In a series from Netherlands involving screening of 65,779 women, there was concordance in the reads of double readers in 98.7 % of women, and there was agreement on the need for referral in 0.8 % of cases and disagreement on the need for referral in 0.5 % of cases which decreased to 0.3 % after mutual consultation. These 183 studies were referred to the arbitration panel which referred 89 of these for further workup that resulted in a cancer diagnosis in 20/89 [22 %]. Among the 94 cases that were not referred, there were 3 cancers [3 %] at the site of the discrepant mammographic findings [29]. Screening mammograms with discrepant findings form a small but significant subset that may lead to a diagnosis of breast cancer.

Double Reads vs Single Reads With CAD

The effectiveness of double reading has been compared to single reader using a CAD [computerized aided detection] by several investigators [30–32]. In a study of 10,267 mammograms, single reading with CAD led to a cancer detection rate that was higher albeit with a higher recall rate of 8.6 % vs 6.5 % achieved with a double read [30]. The cancer detection rate though increased in the CAD group by 15 %. Others have reported similar results. A meta-analysis of ten studies that looked at efficacy of single readers using CAD vs single readers' found that CAD did not significantly increase the cancer detection rate and increased the recall rate. The same report in a meta-analysis of 17 studies that assessed the value of double reads over single reads found that double reads increased both cancer detection rate and the recall rates; however, double read with arbitration increased cancer detection rate with decreased recall [31]. A literature review of six studies that compared single reads with CAD vs double reads showed that three of these studies did not show any differences in sensitivity or specificity: one showed increased sensitivity with same specificity, one showed higher specificity with the same sensitivity, and one had higher sensitivity with lowered specificity [32].

Cost-Effectiveness of Double Reading

The cost-effectiveness resulting from double reading has also been studied [33, 34]. Double reading followed by consensus involving 33,734 consecutive screening mammograms detected an additional 9 cancers per 10,000 women screened. A nonconsensus double reading policy detected an additional 10 cancers per 10,000 women screened. However, nonconsensus double reading resulted in a recall rate was significantly higher than single read; recall rate in consensus double read was significantly lower than with single reads. From a cost-effectiveness perspective consensus double read costs less than single reading (4,853 £ saved per 10,000 women screened) and nonconsensus double reading costs more than single reading (difference of 19,259 £ per 10,000 women screened) [33]. The cost-effectiveness in terms of the cost per cancer detected has also been studied. Data from 255,000 women from Scotland showed that costs per cancer detected by double reading compared to single reading range from $ 1,859 to $ 3,553 [34].

Clinical Breast Exam with Screening Mammography [35–37]

Clinical breast examination [CBE] in conjunction with screening mammography can be implemented concurrently when administered in a breast center by a registered nurse or when a screening mammogram is done following a well woman exam as is more often the case. The former has been studied to determine the added benefit of increasing cancer detection. There were 232,515 women in the group receiving CBE and 57,715 in the group undergoing screening mammogram without a clinical breast exam. Sensitivity in the CBE group was 94.9 % vs 88.6 % for the screened group without CBE. However, the false positive was also higher for those women who had CBE with screening mammography compared to those who did not receive CBE [12.5 % vs 7.4 %] [35]. Another large study with dual screening in 300,303 women, CBE increased the rate of detection of small invasive cancer by 2–6 %. Without the concurrent use of CBE, three cancers would be missed for every 10,000 screens [36]. The cost-effectiveness of offering CBE in a comprehensive breast center was reported in a cohort of 60,000 women who received CBE by a nurse practitioner. Four hundred and seventy four had a positive exam leading to a diagnostic evaluation. Forty-six cancers were identified, 32 of which would have been identified by mammography alone, and only 14 were not seen on a mammogram. The cost of CBE was 122,598 per cancer detected based solely on CBE findings [37].

Imaging of the Male Breast

A male breast is composed of subcutaneous tissue, atrophic ducts, and stromal elements with preponderance of fat [38]. Conditions that affect the male breast are therefore related to ductal and stromal proliferation and include the most commonly encountered gynecomastia, invasive ductal carcinoma, and papillary neoplasm. Most commonly men are referred for a breast lump, breast enlargement, or tenderness. Mammography is the initial imaging and may be the only modality needed. If abnormality cannot be imaged on mammography or if findings are questionable, sonography is indicated. The most common cause of breast symptoms are due to gynecomastia.

Gynecomastia

Gynecomastia is the most common breast problem in a male patient and has been reported to be between 87 and 90 % of cases [39, 40]. There are three patterns of gynecomastia, nodular, dendritic, and diffuse glandular. The nodular pattern represents the early florid phase of ductal and stromal proliferation and is seen in the first year of onset and accounts for 34–36 % of gynecomastia [39, 40]. At mammography it produces a fan-shaped subareolar density that blends into surrounding parenchyma (Fig. 14.2a–d). Ultrasound is not needed when mammographic appearance is characteristic. Ultrasound may show the area of gynecomastia as an irregular mass prompting a recommendation for a biopsy of a benign abnormality and should be avoided for this reason (Fig. 14.2d). The presentation is in the form of a painful mass and the process is reversible if the inciting factor is withdrawn [38]. The dendritic phase is the fibrotic quiescent phase characterized by stromal fibrosis and ductal proliferation. This accounts for 31–35 % of cases of gynecomastia [39, 40]. This represents irreversible phase of gynecomastia. Diffuse glandular type accounts for 31–33 % of cases and is seen in patients receiving estrogen therapy and represents a combination of dendritic and diffuse nodular types. Gynecomastia tends to be bilateral in 55–65 % of cases [39, 40].

Male Breast Cancer

Breast cancer accounts for 1–8 % of symptomatic breast disease in males [39–41]. About 0.7 % of all breast cancers are diagnosed in men [38]. In 2010 based on cancer statistics, 1,970 new cases of male breast cancers were diagnosed [42]. Mass without calcifications is seen in 86 % of breast cancer cases in men and as calcifications in 7 % [39]. Mean size of the mass is 2.4 cm; prognosis is generally poor due to late

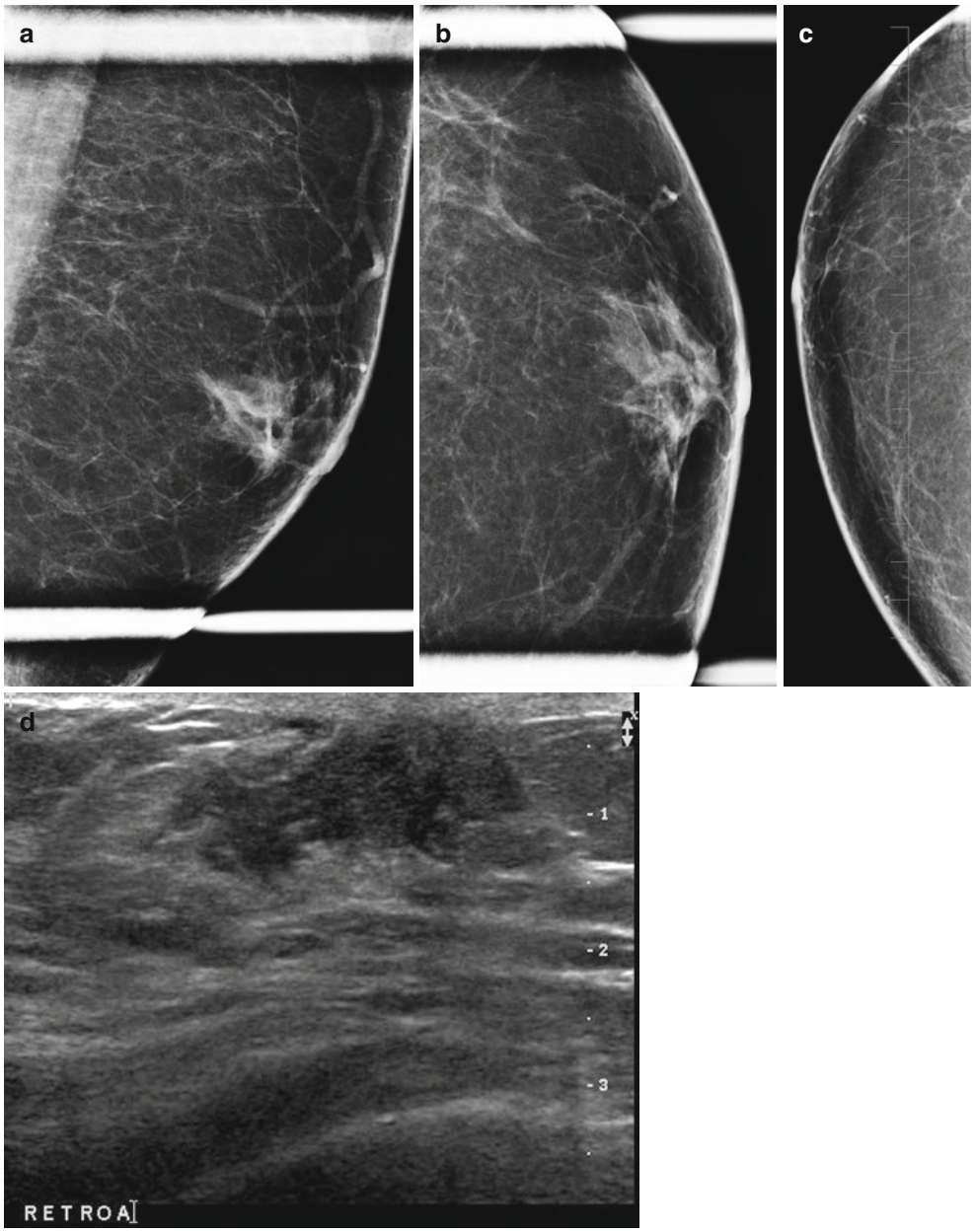

Fig. 14.2 A 65-year-old male with history of liver disease presenting with left breast swelling. (**a**) Mediolateral oblique view of the left breast demonstrates a fan-shaped subareolar density consistent with gynecomastia. (**b**, **c**) Craniocaudal views of the left breast demonstrate a fan-shaped subareolar density consistent with gynecomastia. (**d**) Ultrasound demonstrates an irregular hypoechoic mass-like abnormality representing gynecomastia

stage of presentation. Risk factors for breast cancer in males include Klinefelter syndrome, BRCA1 or BRCA2 mutation, family history of breast cancer in a first-degree male or female relative, hyperestrogenism, exogenous estrogen for feminization purposes, advanced age, and history of chest radiation. Breast cancer typically presents at an age on an average 10 years later than in women, the mean age at diagnosis being 67 years [38]. The disease is often at an advanced stage at diagnosis with axillary node metastasis seen at initial evaluation in 50 % of cases [38]. Secondary signs of breast cancer occur earlier in the male breast because of the smaller size of the breast. These include nipple retraction, skin ulceration and thickening, and axillary adenopathy [41]. Cystic lesions in a male breast have to be worked up as potentially malignant since cystic lesions commonly demonstrate malignant findings. Breast cancer most often presents as a discrete mass with malignant features on a mammogram or ultrasound. The relationship of the mass to the nipple is helpful; an eccentric mass is highly suspicious for cancer [41].

The differential diagnosis of male breast includes gynecomastia, lipoma, epidermal inclusion cyst, pseudoangiomatous hyperplasia, and intraductal papilloma. The most common histological type of breast cancer is the infiltrating ductal cancer accounting for 80 % of all cancers, ductal

carcinoma in situ accounts for 5 % of cancers, and rarer types include papillary cancer [38].

Overdiagnosis of Breast Cancer with Screening Mammography

The term *overdiagnosis* of breast cancer by screening mammography in population-based studies refers to the difference between cancer detection and subsequent treatment of abnormal findings and the corresponding effect on mortality. The percentage of overdiagnosis represents the estimated percentage of cases that were detected and treated but that would not have affected mortality if had been left alone. In other words mammography identifies cancers that are nonlethal and do not lead to mortality [43, 44]. Bleyer and Belch used a model for expectation values and estimated that 31 % of cancers that are diagnosed breast cancer represent overdiagnosis [43]. They then concluded that the reduction in mortality can be attributed to improvements in therapy and not to early diagnosis [43]. In an opinion article in response to this theory, Gur and Sumkin correctly point out that once a decision to screen is made, the role of a breast imager should be to detect disease early and towards this end due diligence is needed to detect and correctly diagnose all abnormalities at the earliest stage possible. It is then the responsibility of other specialties to make the best use of the information provided by the radiologist to decide how best to use the information in the appropriate management of the patient. They state that there can only be a "correct, partially correct or an incorrect diagnosis and there can only be optimally managed, suboptimally managed and mismanaged and over treated disease" [44]. They go on to appropriately state "There should not be any doubt that the overall objective of a screening program is to first and foremost detect, correctly diagnose, and appropriately treat early preclinical cancers that, if left alone, would become life threatening cancers" [44]. This seems to be a reasonable and appropriate response to the criticism of overdiagnosis of breast cancer.

Mammographically Occult Breast Cancer with Axillary Metastasis

Axillary metastatic lymphadenopathy with no primary tumor identified in the breast on physical examination or mammography is rare, and only three such cases of mammographically occult breast cancer were reported in one study over a 10-year period [45]. In another reported series, isolated enlarged axillary nodes were present in 72 of 200,716 women screened [46]. Thirteen patients had no reason for recall, and of the 59 patients recalled, only 13 had malignancy, 4 were metastatic breast cancer, and 9 were lymphoma; the remainder of the cases had a benign etiology for the presence of isolated abnormal axillary lymph nodes [46]. Fine needle aspiration biopsy with definitive cytological diagnosis precludes need for excisional biopsy in most cases. It has been suggested that such cases of axillary metastasis from occult breast cancer can be managed with axillary node clearance and chemotherapy with a possible role for radiation treatment to the ipsilateral breast [45]. Metastatic axillary adenocarcinoma with an occult breast cancer is uncommon type of stage II breast cancers. Prognosis is not as grave as is believed for individual patients. In the largest reported series of 48 patients with an axillary mass proven to be metastatic adenocarcinoma consistent with mammary origin, patients were followed for 5 years. All primary cancers were clinically occult and mammographically occult in 28 women [76 %]. In nine patients metastasis was positive for estrogen and progesterone receptors [ER, PR +] and in 10 patients [ER, PR –]. Mastectomy with axillary dissection was carried out in 38 of 48 patients, 21 received adjuvant chemotherapy [47]. Pathologically a primary breast cancer was found in the mastectomy specimen in 36/48 [75 %] of cases; seven of these cancers were histologically noninvasive. Tumor size ranged from 1 mm to 6.5 cm. In 20 of 48 patients, there were 1–3 positive axillary nodes [47].

An isolated abnormal lymph node in the axilla identified on a screening mammogram is optimally imaged with ultrasound [48]. A size greater than 2 cm, absence of fatty hilum, a rounded shape, and focal or diffuse cortical thickening are recognized abnormal sonographic criteria for classifying a lymph node as abnormal with a recommendation for biopsy (Fig. 14.3a, b). In one series 10 of 17 with such abnormal features were histologically proven to be malignant. Six of these ten cases were metastatic adenocarcinoma and three were lymphoma and one was undifferentiated sarcoma [48]. Apart from metastatic breast cancer and lymphoma most commonly non-Hodgkin's type, metastasis from malignant melanoma, lung carcinoma, stomach carcinoma, or ovarian carcinoma should be considered [49]. Breast MRI is useful in further evaluation of a patient with a biopsy-proven metastatic adenocarcinoma in an axillary lymph node with a mammographically and clinically occult ipsilateral breast cancer [50]. In a review of eight retrospective studies, MRI was able to detect cancers in more than two-thirds of patients; in 80 % of these cases, a second-look ultrasound was able to find the MRI-detected abnormality. MRI provided a possibility of a breast-conserving surgery in one-third of these patients [50]. A finding of an isolated abnormal axillary lymph and a normal mammogram is best managed by a whole breast and axillary ultrasound followed by fine needle or a core needle biopsy under ultrasound guidance. If metastatic adenocarcinoma is found, an MRI is indicated to identify an occult cancer.

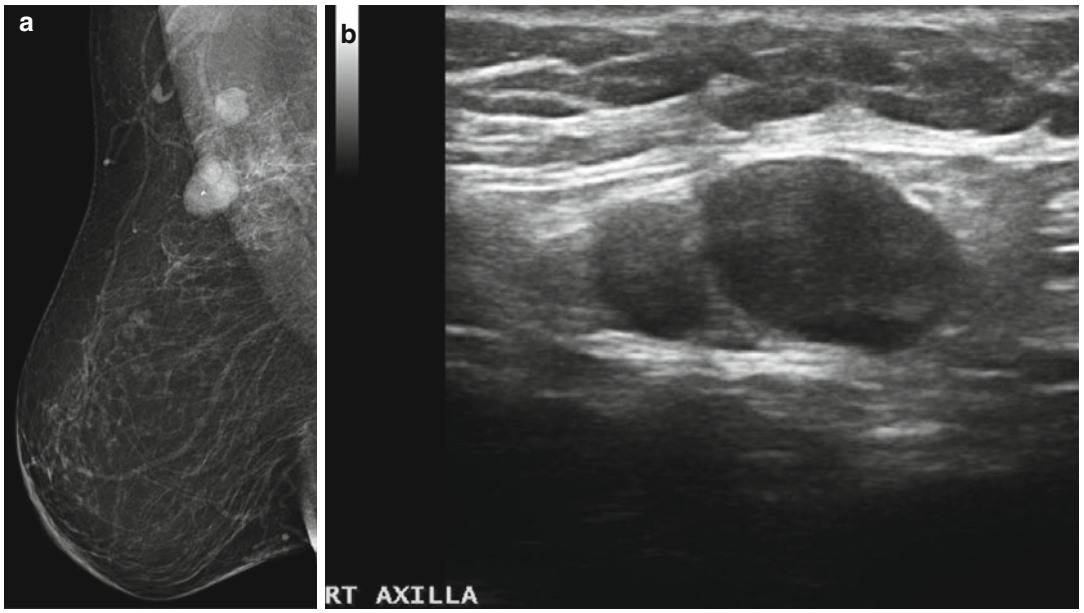

Fig. 14.3 Isolated enlarged right axillary lymph node histologically proven to be benign reactive follicular hyperplasia. (**a**) Right breast mammogram with an enlarged dense fat replaced lymph node with a post-biopsy clip within. There was no mammographic or clinical abnormality in the right breast. (**b**) Ultrasound demonstrates an abnormal enlarged lymph node with absence of fat hilum

Challenges in breast imaging are many, and these challenges often may not have a standardized management protocol; decisions may have to be made based on available resources and expertise as well as the individual patient. Some of the commonly encountered challenges have been discussed previously. Management decisions will continue to evolve as our knowledge in understanding the many facets of breast cancer screening and diagnosis unfolds in the future as technologies and expertise evolves.

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