

Male Breast Cancer: Imaging Considerations for Diagnosis and Surveillance

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Abstract

Male breast cancer accounts for less than 1% of all breast cancer cases. The important risk factors for the development of male breast cancer are family history, genetic mutations, obesity, liver disease, alcoholism, exogenous estrogen administration, and radiation exposure to the chest area. Despite its rarity, numerous studies have investigated the data on imaging considerations (mammogram, ultrasound, and magnetic resonance imaging (MRI)), but have addressed only certain aspects of male breast cancer. A comprehensive approach on the imaging characteristics, timing of imaging, prognostication based on imaging characteristics, and follow-up strategies in male breast cancer are still lacking. The purpose of this review article was to provide a comprehensive overview of the imaging findings, optimal timing to obtain imaging, and the appropriate follow-up strategies in male breast cancer survivors. This article also describes how imaging modalities can aid in determining prognosis. By addressing this knowledge gap, the article provides valuable insights for clinicians managing this uncommon yet clinically significant disease.

Keywords: Male breast cancer; Mammogram; Sonogram; MRI in male breast cancer; Surveillance; Screening

Introduction

Male breast cancer is a rare clinical entity, accounting for less than 1% of all breast cancer cases [1-3]. In 2023, an estimated 2,800 new cases of invasive breast cancer are expected to be diagnosed in men in the United States [4].

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The adult male breast comprises skin, subcutaneous fat, atrophic ducts, and stromal elements [1]. Lobular breast development stimulated by estrogen and progesterone is rare in men. Hence, breast conditions associated with lobular proliferation including invasive lobular cancer (ILC), lobular carcinoma *in situ* (LCIS), fibroadenoma, and phyllodes tumor are uncommon in men [1]. Conditions related to ductal proliferation including gynecomastia, invasive ductal carcinoma (IDC), and ductal carcinoma *in situ* (DCIS) occur in men [1].

Risk Factors and Pathological Characteristics

The risk of male breast cancer increases with age, and cases tend to occur at an older age compared to female breast cancer [5-7]. According to the Surveillance Epidemiology and End Results (SEER) database, the median age at diagnosis of male breast cancer is 67 years, compared to 61 years in women [8]. Approximately 15-20% of men with breast cancer report a family history of breast or ovarian cancer [7]. About 10% of male breast cancers have a genetic predisposition, with *BRC A2* being the most common genetic mutation [9-11]. Other genetic factors predisposing to male breast cancer are *BRC A1*, *PTE N*, *TP53*, *PALB2*, *CHEK2* mutations, and Klinefelter syndrome [12-17]. Klinefelter syndrome is a rare genetic disorder characterized by an additional X chromosome (47, XXY karyotype), resulting in a spectrum of clinical features including behavioral difficulties, azoospermia, small testes, gynecomastia, and androgen deficiency [18]. Apart from genetic risks, the other important risk factors are conditions that alter the estrogen/androgen ratio (obesity, liver disease, testicular conditions, alcoholism, exogenous estrogen administration), and radiation exposure to the chest area [19-21]. Gynecomastia is a benign breast condition affecting approximately 40-65% of males [19]. While some studies have suggested gynecomastia as a potential risk factor for male breast cancer, it is important to note that gynecomastia is usually associated with obesity and high estrogen states, such as alcoholism or liver disease [19]. These associations could potentially confound the results, leading to false positives in determining the true impact of gynecomastia on male breast cancer.

Invasive ductal carcinoma is the most common histological subtype accounting for 85-90% of male breast cancer cases [22, 23], and ductal carcinoma *in situ* (DCIS) accounts for about 5% of the cases [24]. On histopathology, most cases of DCIS demonstrate a solid or cribriform pattern and is less common to see DCIS independent of invasive carcinoma of

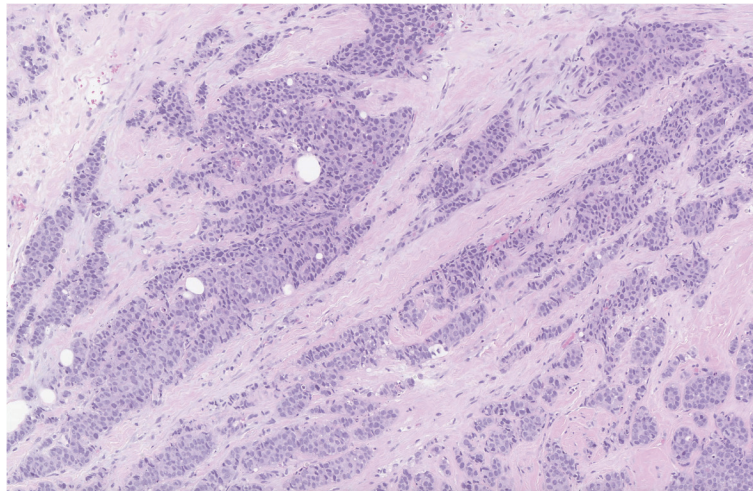


Figure 1. Hematoxylin and eosin stain of the breast biopsy demonstrating IDC with a nuclear grade of 3 at low power. The myoepithelial layer is lost and the tubuloglandular architecture seen in benign breast tissue is not preserved.

no special type [25]. Compared to female breast cancer, male breast cancer has higher rates of estrogen and progesterone receptor expression and lower rates of human epidermal growth factor receptor 2 (HER2)-neu expression [26-28]. Male breast cancer usually presents as a painless unilateral subareolar mass, often eccentric to the nipple [27]. It is also important to exclude the possibility of metastatic tumors affecting the male breast, particularly one originating from prostatic adenocarcinoma or squamous cell carcinoma of the head and neck [29]. The pathological images of IDC are depicted in Figures 1, 2, and DCIS in Figure 3.

Diagnosis

As mentioned above, male breast cancer tends to occur at an

older age compared to female breast cancer [5-7]. The rarity of the disease, coupled with the low index of suspicion and lack of screening techniques, contributes to male breast cancer often being detected at a later stage compared to female breast cancer [8]. History and physical examination play a crucial role in the diagnosis. Increasing awareness among clinicians and utilizing imaging modalities can enhance the early detection of male breast cancer.

Male breast cancer poses diagnostic imaging challenges as benign breast conditions like gynecomastia must be differentiated from breast cancer. On a mammogram, gynecomastia appears as a flame-shaped density (without calcifications), gradually blending into the surrounding fat (Fig. 4) [3]. Other benign breast conditions arising from the skin and subcutaneous tissue like lipoma, epidermal inclusion cyst, pseudo-gynecomastia, and retro-areolar abscess should also be differenti-

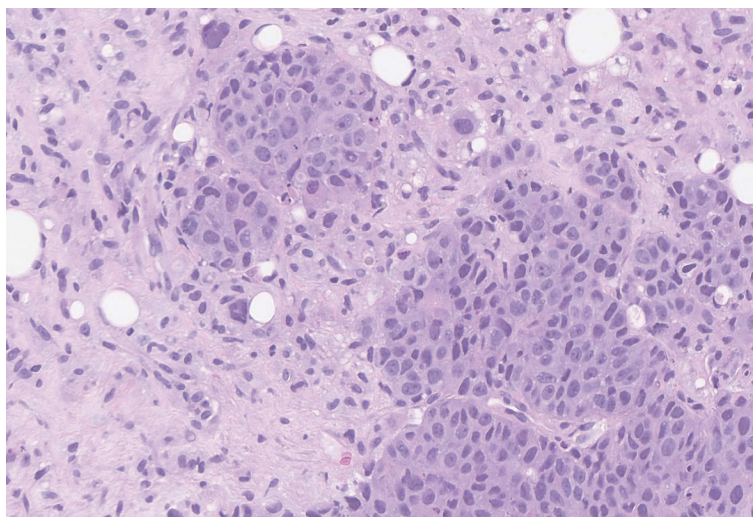


Figure 2. Hematoxylin and eosin stain of the breast biopsy demonstrating invasive carcinoma of no special type, with a nuclear grade of 3 at high power. The cells have bizarre shapes and sizes with prominent nuclei and hyperchromatic chromatin. GATA-3 and mammaglobin stained positively in the tumor cells, consistent with a breast primary.

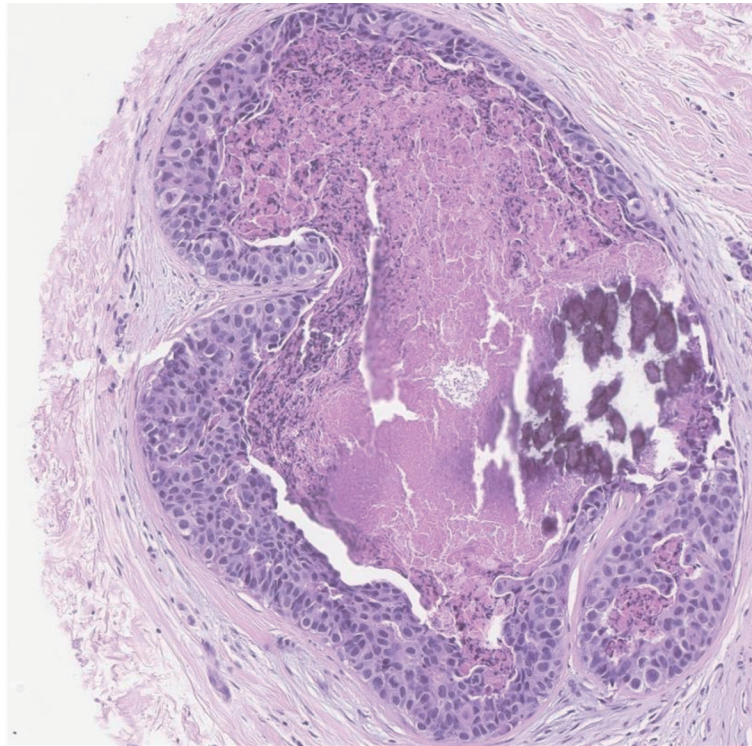


Figure 3. Hematoxylin and eosin stain of the breast biopsy demonstrating ductal carcinoma *in situ* with nuclear grade 3 at medium power. This patient had carcinoma with comedo and solid histological patterns, in addition to comedonecrosis and calcifications. The myoepithelial layer is maintained. The cells themselves are moderately pleomorphic with hyperchromatic chromatin.

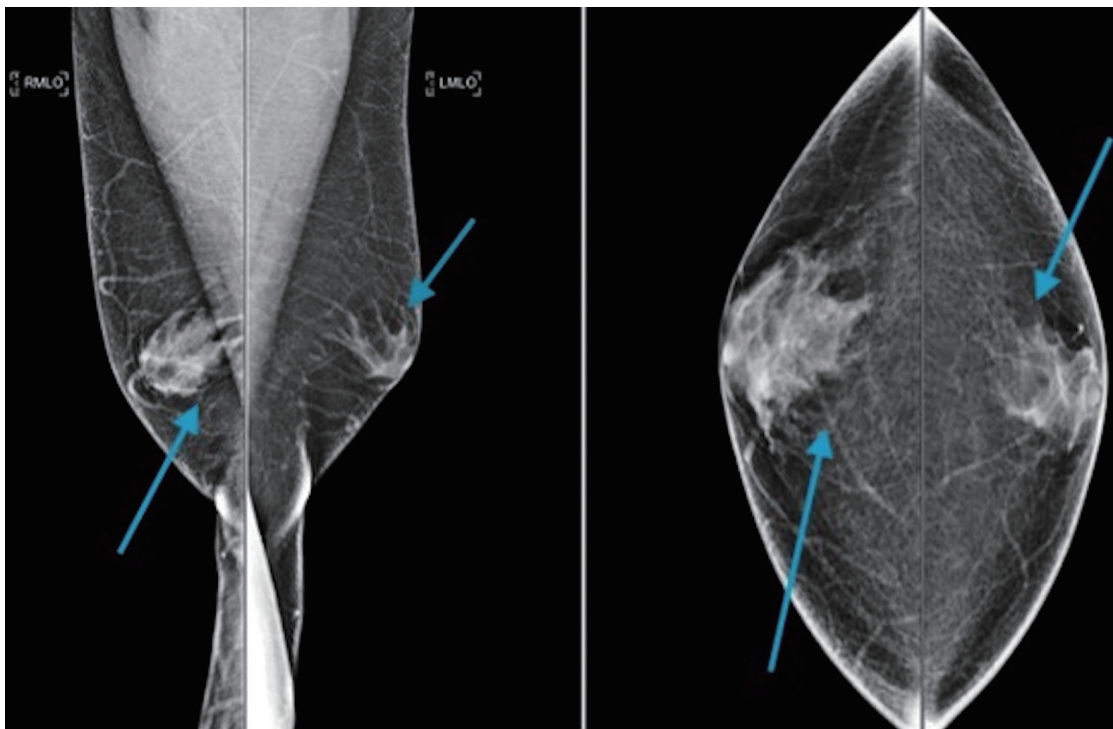


Figure 4. A mediolateral oblique digital mammogram demonstrating irregular flamed shaped structure within the subareolar region of the right breast extending into the adjacent fat, characteristic of gynecomastia (arrow heads). This is greater on the right than on the left side.

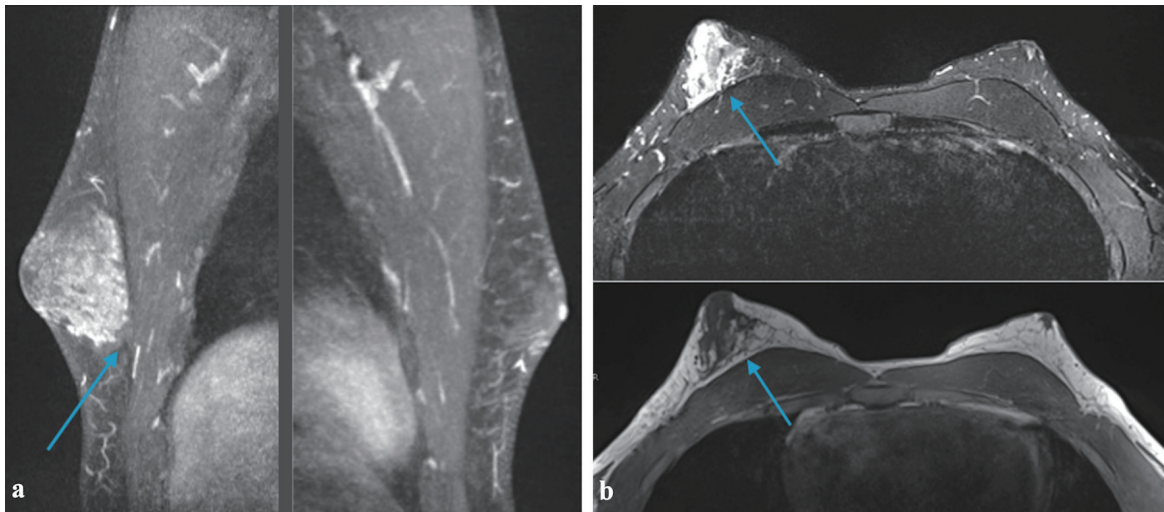


Figure 5. (a) MRI of the breast demonstrating a small area of heterogeneous tissue beneath the left areola. There is an asymmetrically larger amount of heterogeneous tissue within the subareolar region of the right breast extending into the central breast (arrow). These findings are suggestive of gynecomastia (This could be related to an underlying germ cell tumor and/or medications). No suspicious area of mass was identified within either breast. (b) MRI of the breast demonstrating small area of heterogeneous tissue beneath the left areola. There is an asymmetrically larger amount of heterogeneous tissue within the subareolar region of the right breast extending into the central breast (arrow). These findings are suggestive of gynecomastia (This could be related to an underlying germ cell tumor and/or medications). No suspicious area of mass was identified within either breast. MRI: magnetic resonance imaging.

ated from male breast cancer. Data on the utilization of magnetic resonance imaging (MRI) in the evaluation of gynecomastia are limited, but its role in male breast cancer is discussed later. Figure 5a, b represents MRI findings suggestive of gynecomastia.

When to Do a Mammogram in Men?

Mammography screening is highly successful in reducing mortality by early detection of cancer in women, but its role in male breast cancer is less well understood [30]. In general, a screening mammogram is not routinely recommended due to the low incidence of male breast cancer, and hence mammography is used as a diagnostic tool in men.

Symptomatic men above 25 years old should be evaluated with a diagnostic mammogram initially followed by an ultrasound if a mammogram is abnormal or inconclusive. For men less than 25 years, ultrasound followed by a mammogram is preferred [31]. A bilateral mammogram is preferred over a unilateral mammogram, as it can assess the symmetry and can also detect contralateral breast pathologies [31]. The sensitivity and specificity of mammogram in detecting male breast cancer is about 92-95% and 90-95%, respectively [30, 32, 33].

The National Comprehensive Cancer Network (NCCN) guidelines recommend that men with *BRCA* mutations get training for breast self-examination and start receiving yearly clinical breast examinations from 35 years of age [34]. The guidelines do not recommend screening mammography or MRI in male *BRCA* mutation carriers [34]. The 2020 American Society of Clinical Oncology (ASCO) guideline for the management of male breast cancer recommends ipsilateral annual mammogram be offered to men with a history of breast cancer treated with

lumpectomy regardless of the genetic predisposition, and contralateral annual mammogram may be offered to men with a history of breast cancer and a genetic predisposition mutation [35].

A retrospective study conducted by Marino et al [36] investigated the utility of screening mammograms in men at high risk of breast cancer (personal history and/or family history of breast cancer, gynecomastia, etc.). The study included 163 men who underwent 806 screening mammograms. Seventy-seven percent (125/163) of the men had a personal history of breast cancer, and 44% (72/163) had a family history of breast cancer. Fifteen percent (24/163) were known mutation carriers; 17% (4/24) and 83% (20/24) were positive for *BRCA1* and *BRCA2*, respectively. The study yielded a cancer detection rate of 4.9/1,000 mammograms, which is similar to that of screening mammograms in women (5.4/1,000) in population-based screening. This study concluded that screening mammograms can be considered in men at high risk of breast cancer.

Mammographic Appearance

In general, male breast cancer usually occurs in a subareolar location with nipple involvement in 40-50% of cases [37]. It can also occur eccentric to the nipple [3]. The mammogram findings suggestive of cancer include irregular mass with spiculated or indistinct margins [3, 31, 38, 39]. Oval or round masses with well-circumscribed margins are also not uncommon [3, 31, 38, 39]. Calcifications are present in 9-31% of male breast cancer cases but are fewer in number, coarser, and less frequently rod-shaped compared to female breast cancer [3, 40, 41]. Calcifications with typical benign features should be considered suspicious in men [38-40, 42-44]. Secondary signs of breast cancer,

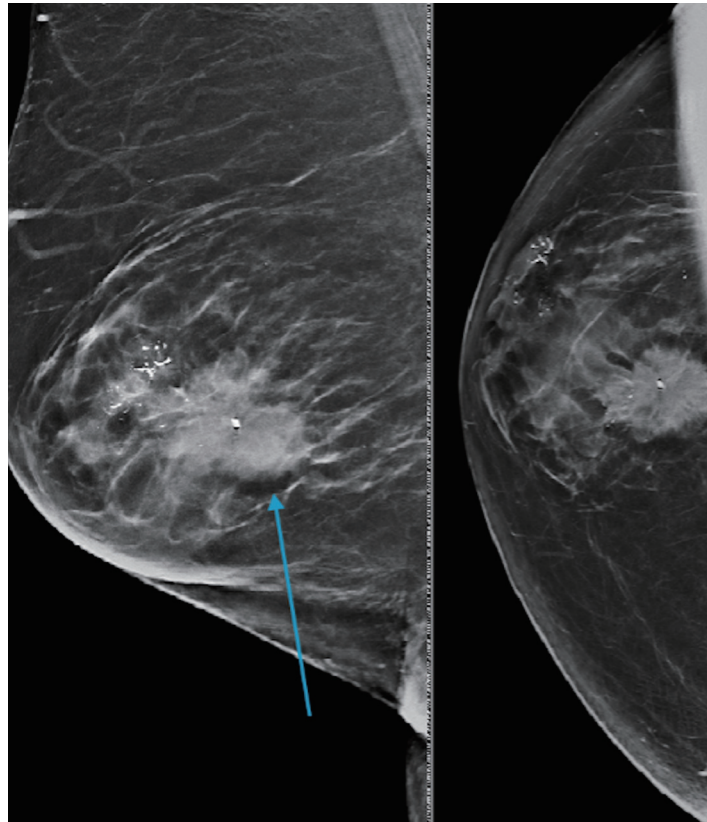


Figure 6. Bilateral diagnostic mammogram demonstrating an irregular mass with pleomorphic calcification in the right breast at 10:00 o'clock position (arrow) and 12:00 o'clock position. Moderate gynecomastia is present in the left breast. Biopsy of the mass at 10:00 o'clock revealed ductal carcinoma *in situ* and 12:00 o'clock revealed invasive ductal carcinoma.

including nipple retraction, skin thickening, and axillary lymphadenopathy can also be detected with a mammogram.

A retrospective single-institution study conducted by Mathew et al investigated the clinical, imaging, and pathological abnormalities in male breast cancer [42]. Two hundred forty-four men with breast cancer were identified, out of which 57 patients underwent either mammogram or ultrasound, 49 patients underwent both mammography and ultrasound, six patients underwent only mammogram, and two patients underwent only ultrasound. The important mammogram findings observed were noncalcified mass alone (69%), a mass with microcalcifications (29%), and microcalcifications without a mass (2%). The masses were either irregular (50%), lobular (20%), oval (11%), or round (17%). Margins were frequently spiculated (33%), indistinct (32%), circumscribed (15%), or microlobulated (6%). Pleomorphic calcifications were present in 47% of the cases.

Dershaw et al conducted a retrospective study to identify the mammographic findings in male breast cancer. The study included 102 male breast cancer patients, out of which a mammogram was performed in 23 patients [44]. The findings observed were mass without calcifications (17 cases (74% of the cases)) and mass with microcalcifications (two cases (9% of the cases)). One case had microcalcifications (punctate, not pleomorphic type) without the presence of an underlying mass. Most of the tumors were subareolar. Secondary signs of

malignancy including nipple inversion and axillary lymphadenopathy were also identified by a mammogram. Benign incidental findings like gynecomastia and skin calcifications were detected in four men.

Appelbaum et al evaluated the mammographic appearances and pathologic features in 97 cases of histologically proven male breast disease [3]. Twelve cases of male breast cancer were detected by mammogram. In 10 cases, the carcinoma manifested as a nodular lesion, with six lesions being eccentric, three central, and one distant relative to the nipple. The lesions were well-defined in six cases and ill-defined in four cases. The lesions were lobulated, round, and ovoid in shape. Primary breast cancer was not visible in one case as it was obscured by concomitant gynecomastia. Calcifications were fewer in number and coarser compared to female breast cancer. Secondary features including skin thickening, nipple retraction, and axillary lymphadenopathy were also detected by mammogram.

From a histopathological perspective, DCIS typically appears as microcalcifications on mammogram, which can present as amorphous, heterogenous, or coarse [45]. DCIS can appear as a mass on mammogram in approximately 10% of the cases and as architectural distortion in approximately 7-13% of the cases [45].

The mammographic appearance in male breast cancer is depicted in Figures 6-8.

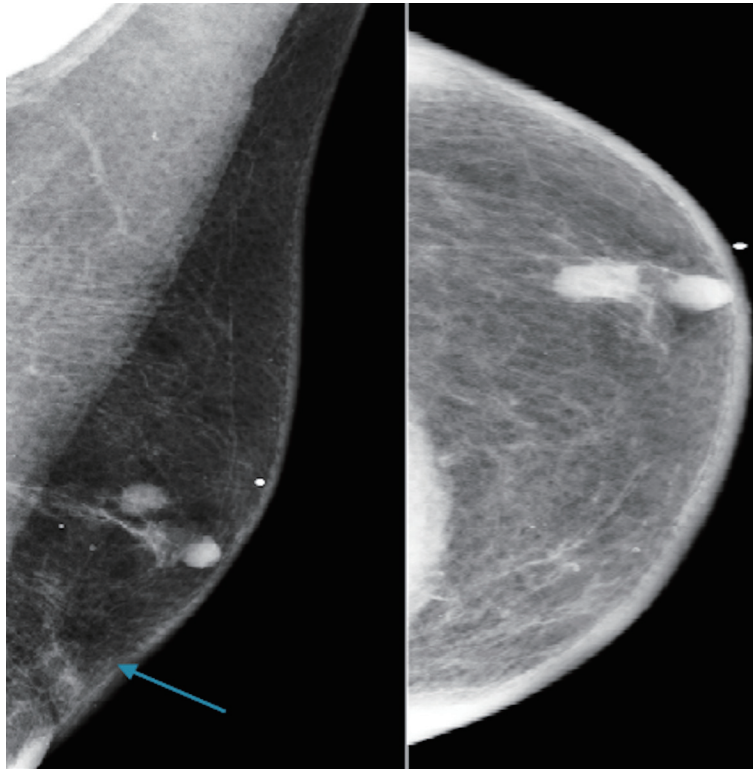


Figure 7. Craniocaudal and mediolateral oblique digital mammogram demonstrating scattered areas of fibro-glandular density and a suspicious mass (blue arrow) at 12:00 o'clock of the left breast according to BI-RADS 4. BIRADS: the Breast Imaging Reporting and Data System.

Ultrasound in Male Breast Cancer

In general, on ultrasound male breast cancer appears as hypo-echoic lesions with angulated, microlobulated, or spiculated margins [46-48]. Ultrasound with Doppler studies can be used to identify the intra-lesional blood flow to assess the posterior extent of the disease. The sensitivity and specificity of ultrasound in detecting male breast cancer are about 88-100% and 95-97%, respectively [33, 49]. Ultrasound is more sensitive in detecting axillary lymphadenopathy than mammography in male breast cancer [33, 47].

As described above, the retrospective single-institution study conducted by Mathew et al also evaluated the sonographic findings in male breast cancer [42]. In this study, a total of 51 patients were evaluated by ultrasound and were able to demonstrate masses in 90% and architectural distortion in 10% of patients with cancer. Of the visible masses, 35 (69%) were solid, and 11 (22%) were complex with mixed solid and cystic components. The masses were irregular and hypoechoic in more than 50% of the patients. The margins were microlobulated, spiculated, circumscribed, or annular in nature. This study also assessed the vascularity of the lesions using power Doppler and demonstrated increased vascularity in 32 (70%) of the cases with cancer.

A retrospective study was conducted by Munoz Carrasco et al to assess the clinical variables useful in differentiating gynecomastia from carcinoma and also to analyze the contribu-

tion of mammography and ultrasound in the evaluation of male breast disease [33]. A total of 628 patients were included in the study, out of which 518 patients underwent mammograms, and 423 patients underwent ultrasounds. The imaging findings were classified according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon [50]. Gynecomastia and pseudo-gynecomastia were placed in BI-RADS category 2. This study was able to detect 19 (2.9%) carcinomas, 526 (80.4%) gynecomastia, 84 other benign conditions, and 25 (3.8%) normal cases. The other benign breast conditions identified included epidermal inclusion cyst, lipoma, fibromatosis, post-surgical changes, and fat necrosis. Of the 423 ultrasound examinations, 388 cases (91.7%) were classified as BI-RADS 1 or 2 (0.5% were false-negative results) and 35 cases (8.3%) were classified as BI-RADS 3, 4, or 5 (54.2% were false-positive results). This study concluded that mammography was the most sensitive (94.7%) and ultrasound was the most specific (95.3%) for the detection of malignancy ($P > 0.05$).

Yang et al [48] evaluated the sonographic appearance in male breast cancer. Eight patients with a mean age of 69 years were included in the study, out of which four (50%) of the study population had complex cystic mass, and the remaining four patients had a solid heterogeneous lesion. In all the patients, masses were identified in the subareolar region eccentric to the nipple. The margins of the lesions were irregular in three patients, indistinct in three, microlobulated in one, and smooth in one patient. Posterior acoustic enhancement was



Figure 8. A mediolateral oblique digital mammogram illustrating a partially circumscribed indistinct mass in the central left breast (blue arrow).

visible in three patients, mild shadowing was visible in three and no acoustic phenomenon was visible in the remaining two patients.

From a histopathological perspective, DCIS is rarely seen on ultrasound [45]. However, it usually appears as a microlobulated mass with mild hypoechogenicity, ductal extension, and normal acoustic transmission [45]. Ultrasound is also used to evaluate the severity of cancer. Historically, malignant breast cancer was thought to show posterior acoustic shadowing on ultrasound [51]. However, it is now accepted that IDC may exhibit variable posterior acoustic appearances ranging from shadowing to enhancement to remaining unchanged. A study conducted by Aho et al [51] demonstrated that the association of posterior acoustic properties was impacted by age. Posterior shadowing was associated with lower histological grade and estrogen receptor (ER)+ status, especially in older adults, while posterior acoustic enhancement was more commonly as-

sociated with ER- status, especially in younger patients [51]. Malignant breast masses were also traditionally considered to exhibit ill-defined or spiculated margins, indicating a poor prognosis. However, subsequent studies have since demonstrated that well-defined margins are more likely to represent high-grade tumors [51].

The sonographic appearance of male breast cancer is described in Figures 9-12.

MRI in Male Breast Cancer

Breast MRI has been shown to have the highest sensitivity in detecting male breast cancer compared to ultrasound and mammogram [52, 53]. However, breast MRI is not routinely recommended for male breast cancer but can be helpful in a subset of patients (Table 1) [52, 54]. MRI to evaluate for the residual

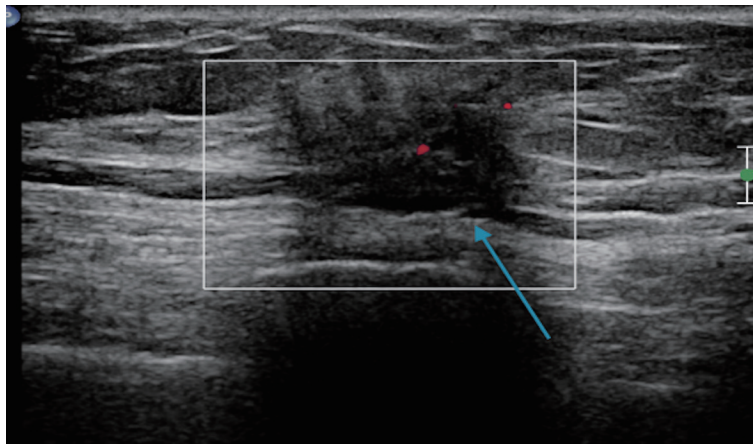


Figure 9. Targeted sonogram of the left breast showing a 1.1 × 0.7 × 0.8 cm irregular nonparallel spiculated hypoechoic mass with posterior shadowing (blue arrow).

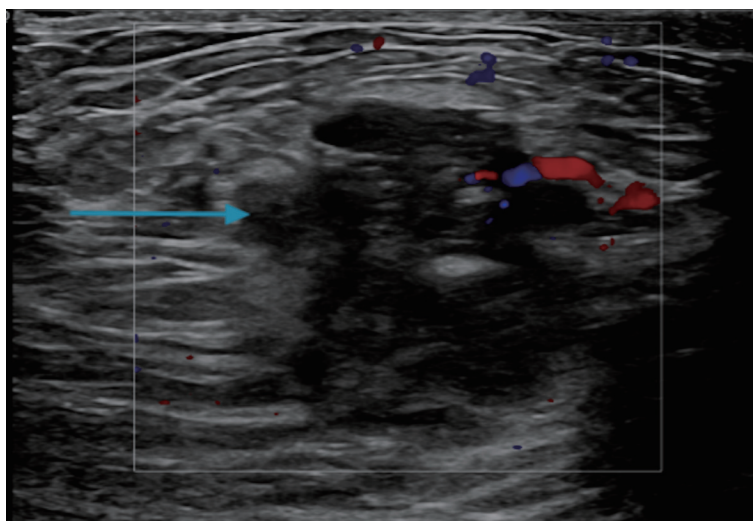


Figure 10. Single transverse image ultrasound of the right breast demonstrating an irregular 2.5 × 1.3 × 3 cm mass at 12:00 o'clock position and a 3.1 × 0.5 × 1.2 cm hypoechoic mass with calcifications at 10:00 o'clock position (blue arrow).

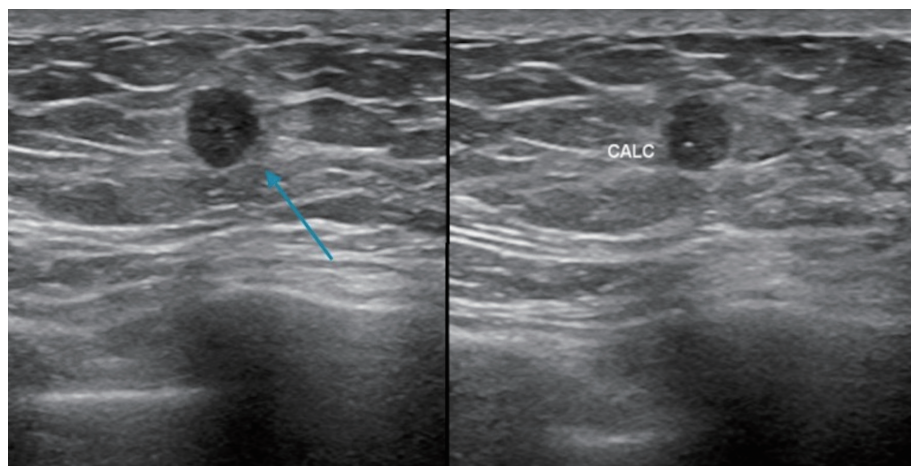


Figure 11. Ultrasound demonstrating a circumscribed mass (blue arrow) in the 12:00 o'clock position with calcifications. CALC: calcification.

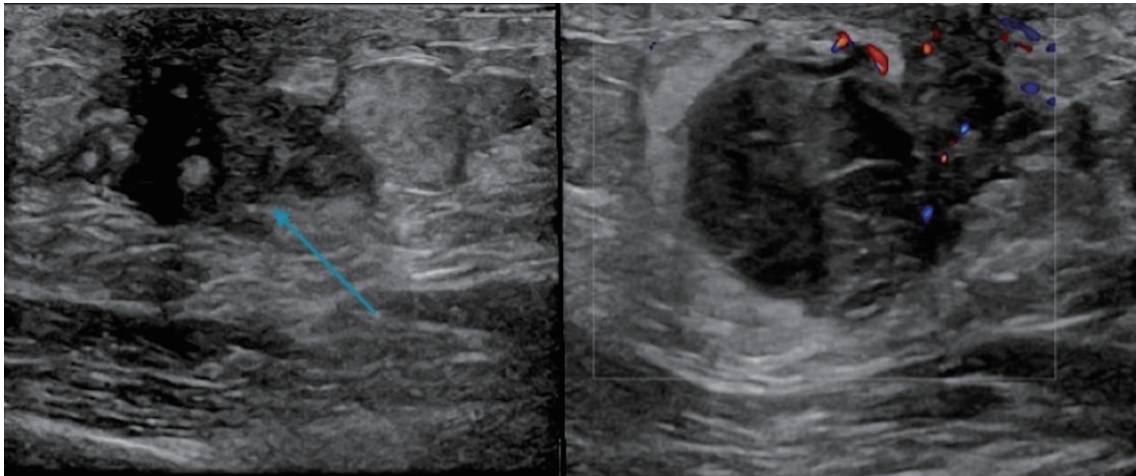


Figure 12. Targeted ultrasound displaying a $3.1 \times 1.8 \times 2.7$ cm hypoechoic mainly circumscribed mass (blue arrow) behind the left nipple with mild surrounding edema (no left axillary lymphadenopathy).

disease has to be done immediately in the post-surgical period before the formation of granulation tissue, which could make the interpretation difficult [52].

Follow-Up Imaging in Breast Cancer Survivors

The absolute risk of second breast cancer in male breast cancer is less than 2%, and hence, in general, a follow-up mammogram is not routinely recommended for the early-stage disease [55].

Conclusions

Male breast cancer is a rare clinical entity and poses unique pathological characteristics compared to female breast cancer. A male breast can be affected by different benign and malignant pathologies, with gynecomastia being the most common pathology. Due to its rarity, screening techniques are not routinely recommended but can be considered in high-risk men. Imaging techniques in the male breast are done as a diagnostic tool. There can be an overlap in the clinical and imaging features of benign and malignant breast pathologies, and hence familiarizing the imaging features helps in the radiological diagnoses. All imaging modalities have their unique advantages and applications in the diagnosis of male breast cancer. According to the literature to date, a routine mammogram is not recommended for follow-up in male

breast cancer survivors due to the absolute low risk of second male breast cancer.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

Mathew Thomas: study conception, design, and drafting the manuscript. Hatem Al Kashroom: data collection (radiology images) and interpretation of the results. Shilpa Reddy and Daniel Zaccarini: data collection (pathology images) and interpretation of the results. Katherine Willer reviewed the manuscript and supervised the project. All authors reviewed the manuscript and approved the final version of the manuscript.

Table 1. Indications for MRI in Male Breast Cancer

- 1) Equivocal imaging findings [54]
- 2) To evaluate the posterior extent of the disease, and skin and chest wall involvement [52]
- 3) To evaluate for a primary breast mass in the setting of axillary metastasis and negative mammography and sonography [52]
- 4) To evaluate for a primary breast mass in the setting of clinical diagnosis of inflammatory breast cancer and evaluation of potential skin involvement in a known malignancy when clinically suspicious [52]
- 5) To evaluate for residual disease post-surgery [52]

Data Availability

The authors declare that the data supporting the findings of this study are available within the article.

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