Trends in Imaging Workup of the Male Breast: Experience from a Single Center

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ABSTRACT: **Background:** Male breast cancer (MBC) is a rare disease representing less than 1% of breast cancers. In the absence of a screening program, such as for females, the diagnostic workup is critical for early detection of MBC.

Objectives: To summarize our institutional experience in the workup of male patients referred for breast imaging, emphasizing the clinical, imaging, and histopathological characteristics of the MBC cohort.

Methods: The case histories of all male patients who underwent breast imaging between 2011 and 2016 in our institution were retrospectively reviewed. Clinical, radiological, and histopathological data were collected and statistically evaluated. All images were reviewed using the American College of Radiology Breast Imaging Reporting and Data System.

Results: In our institution 178 male patients (average age 61 years, median age 64), underwent breast imaging. The most common indication for referral was palpable mass (49%) followed by gynecomastia (16%). Imaging included mostly mammography or ultrasound. Biopsies were performed on 56 patients, 38 (68%) were benign and 18 (32%) were malignant. In all, 13 patients had primary breast cancer and 5 had metastatic disease to the breast. Palpable mass at presentation was strongly associated with malignancy (P = 0.007).

Conclusion: Mammography and ultrasound remain the leading modalities in breast imaging among males for diagnostic workup of palpable mass, with gynecomastia being the predominant diagnosis. However, presentation with palpable mass was also associated with malignancy. Despite a notable MBC rate in our cohort, the likelihood of cancer is low in young patients and in cases of gynecomastia.

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KEY WORDS: breast diagnostic workup, male breast cancer (MBC), mammography, men, ultrasound

Male breast cancer (MBC) is a rare disease, accounting for less than 1% of all breast cancer cases in the United States. About 0.1% of cancer-related mortality in men are connected to breast cancer [1]. In Israel, there are approximately 50 cases of MBC annually [2]. The incidence of MBC is too low to justify screening mammography as in females. Therefore, the vast majority of imaging of the male breast is part of a diagnostic workup, in contrast to the female national screening program [3]. Consequently, MBC typically presents when the patient is symptomatic and is usually diagnosed at a more advanced stage compared to breast cancer in the female population [4]. Several recognized risk factors for MBC are known, including genetic factors such as the BRCA gene mutation and Klinefelter syndrome; lifestyle factors such as obesity, alcohol consumption, and estrogen intake; diseases such as testicular cancer or liver damage; radiotherapy to the chest; work-related factors such as high ambient temperature; and exhaust emission exposure [4,5]. Yet, there are no screening programs in the high-risk populations [6].

The most common presentation of breast cancer in men is a painless, palpable, sub-areolar swelling or mass. Other symptoms may include nipple involvement with retraction and/or ulceration, axillary lymphadenopathy, and gynecomastia [7]. Mammography is the initial imaging modality for a clinically suspicious mass. A palpable mass that is occult or incompletely imaged at mammography mandates targeted ultrasound. Suspicious or indeterminate masses require biopsy, which can usually be performed with ultrasound guidance [8]. The additive diagnostic value of magnetic resonance imaging (MRI) has not been studied extensively, and it is not clear whether MRI is beneficial [9].

In the current study, we summarized the experience of our breast healthcare center in the radiological diagnostic workup of male patients, describing the unique clinical, imaging, and pathological characteristics of the MBC cohort.

PATIENTS AND METHODS

The study was approved by the institutional ethics committee in agreement with the Helsinki Declaration.

Using proprietary software, we searched our institutional radiological information system on a prospectively maintained database for male patients who underwent radiological evaluation between 2011 and 2016. We used the filter of "breast imaging," which includes ultrasound, mammography, MRI, imag-

ing-based biopsy, and an automatic gender filter. Case-by-case confirmation was then performed to exclude misclassified and repeated cases. In addition, transgender patients were excluded since the workup was aesthetic related and not diagnostic. The electronic medical files of the final cohort population were reviewed and were categorized for clinical and demographic characteristics as well as for radiological images and reports. Patients were grouped into two categories: primary and metastatic breast cancer and benign conditions. To determine the specificity and positive predictive value, we defined patients who had biopsies as positive if they were breast imaging-reporting and data system (BI-RADS) categories 4 or 5. Patients who did not have biopsies were categorized as negative with BI-RADS categories 1, 2, or 3. The sensitivity and the negative predictive values were not calculated since the vast majority of the patients did not return for a follow-up examination. In the absence of a long-term follow-up, exclusion of false-negative interpretation was not guaranteed.

Each case was evaluated by a senior breast radiologist. Reports were summarized according to the BI-RADS lexicon [10]. In cases of combined ultrasound and mammography examinations, the higher BI-RADS score was used.

STATISTICAL ANALYSIS

Statistical evaluation included comparison of the mean age between subgroups, using two-tailed unpaired Student's *t*-test. Comparison of the presenting indication between cancer and benign cohorts was determined using Fisher's exact test. The indications were palpable mass, gynecomastia, mastalgia, uptake on positron emission tomography/computer tomography (PET/CT), high-risk follow-up, and nipple discharge retraction or ulcer. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). A P value < 0.05 was considered statistically significant.

RESULTS

COHORT CHARACTERISTICS

We identified 178 consecutive male patients who underwent breast imaging in our institution during the time span of the study. In 160 patients, no malignancy was found. Of the patients with malignancy, 13 were diagnosed with primary breast cancer and 5 with metastatic disease to the breast or axilla from other organs. The most common referral cause was for evaluation of palpable mass (88/178, 49%), followed by gynecomastia (26/178, 15%), and mastalgia (20/178, 11%) [Table 1]. The median age of the patients at the time of the diagnostic workup was 64 years (mean 61.2 ± 16.7, range 18–96 years). The age distribution of the patients as a function of benign and cancer subgroups is presented in Figure 1. Within the cohort, nine were considered high-risk patients (known BRCA carriers) who underwent annual evaluation and they each had normal imaging findings. Additionally, two patients who were diagnosed with MBC were thereafter diagnosed as BRCA mutation carriers.

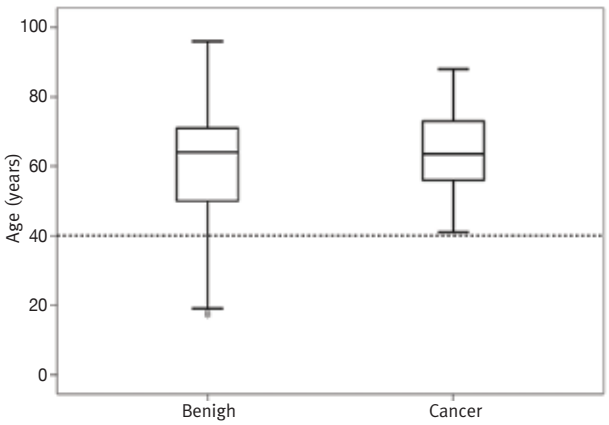
Table 1. Patient characteristics and symptoms

Presenting symptom	Subgroup		
	Breast cancer n=13	Benign n=160	Metastatic breast disease n=5
Palpable mass	9 (69%)	75 (46.9%)	4 (80%)
Gynecomastia	0	26 (16.3%)	0
Uptake on PET	2 (15%)	4 (2.5%)	1 (20%)
Mastalgia	0	20 (12.5%)	0
Follow-up	0	15 (9.4%)	0
High risk screening	0	9 (5.6%)	0
Nipple / skin changes	1 (8%)	3 (1.9%)	0
Ulcer	1 (8%)	0	0
Nipple discharge	0	1 (0.6%)	0
Total	13	160	5

PET = positron emission tomography

Figure 1. Box and whisker plot of age distribution between benign and cancer subgroups

Age is demonstrated in box (median ± interquartile range) and whiskers (± 1.5 interquartile range) plots for patients with benign condition (n=160) and cancer patients (n=18). Despite the lack of statistically significant difference between the groups (P = 0.431), none of the patients with cancer was younger than 40 years old



IMAGING CHARACTERISTICS

An ultrasound examination was performed on 174/178 patients, of them 152 were also examined using mammography (87 %). MRI was performed on 13 patients (7.3%) and of them, 11 patients were also evaluated with ultrasound, mammography, or both. A total of 56 biopsies, all ultrasound guided, were performed during the six-year study period, 38 biopsies (67.9%) were negative for cancer and 18 biopsies were positive. Primary

breast cancer was detected in 13 (23.2%) patients and metastasis to the breast from lymphomas, melanoma or pancreatic cancer was detected in 5 (8.9%) patients. Thus the diagnosis had a specificity of 76.2% and positive predictive value of 32.1%.

All 13 biopsies performed in patients with BI-RADS 3 were benign, with gynecomastia being the predominant diagnosis, whereas all patients in the breast cancer cohort had a BI-RADS score of 4 or 5. In all, 43 BI–RADS 4 and 5 lesions were biopsied, 25 were benign and 18 malignant. All 10 patients with a BI–RADS score of 5 were diagnosed with primary (8/10) or metastatic (2/10) disease, whereas only 8 of the 33 (24%) patients with a BI–RADS score of 4 were eventually diagnosed with cancer. The benign lesions that were biopsied included gynecomastia (n=25), reactive lymph nodes (n=5), lipomas (n=5), abscesses (n=2), and traumatic neuroma (1). In all of the patients younger than 40 years of age, MBC was excluded, both clinically and pathologically.

CANCER GROUP CHARACTERISTICS

Breast cancer incidence was found in 7.3% of our cohort. Cancer typically presented as a palpable mass ($P = 0.007$) and less commonly as a focal hyper-metabolic lesion on PET/CT scans, and nipple retraction or ulcer. None of the cancers presented as clinically apparent gynecomastia or mastalgia. In the breast cancer subgroup of this study, 33.3% of the patients had a body mass index (BMI) > 30. Two patients were found to be BRCA2 carriers. Invasive ductal carcinoma (IDC) was the most common histological type (92%), followed by papillary carcinoma (1/13, 8%). Tumor size was < 2 cm (T1) in 9/13 (69%) patients, 2–5 cm (T2) in 3/13 patients (23%), and > 5 cm in 1/13 patient (8%). Axillary nodal metastasis was diagnosed in 4/13 patients (31%) at presentation. All 13 breast cancers were estrogen receptor (ER) positive, 11/13 (85%) were progesterone receptor (PR) positive, and 5/13 (38%) were human epidermal growth factor receptor 2 (HER2) positive. A high level of Ki–67 was found in 6/13 (46%) of breast cancers. A representative case of the image findings in MBC is shown in Figure 2.

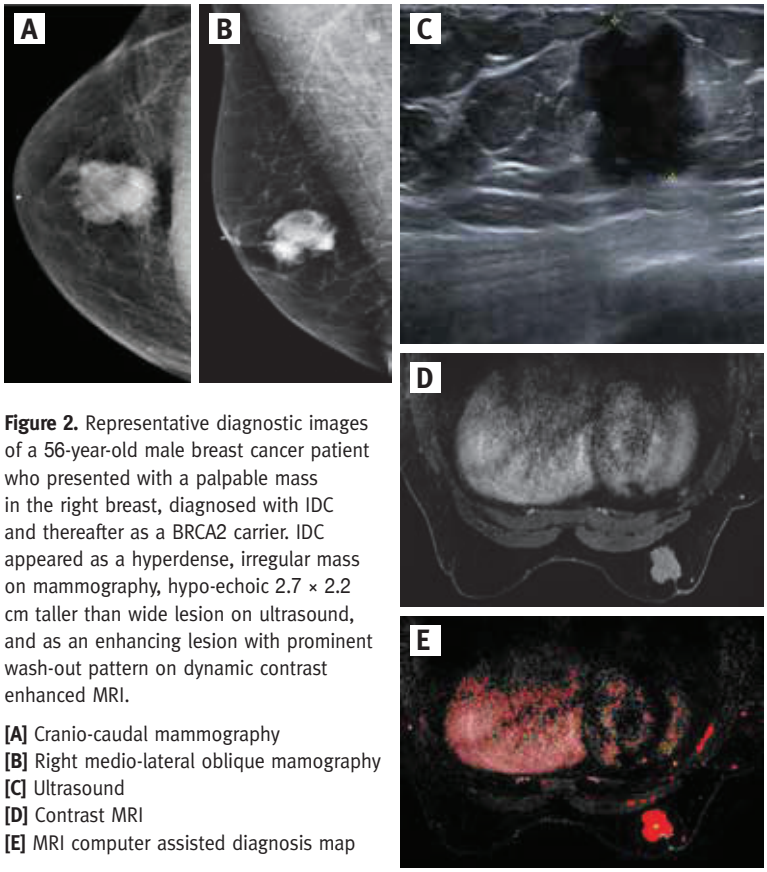


Figure 2. Representative diagnostic images of a 56-year-old male breast cancer patient who presented with a palpable mass in the right breast, diagnosed with IDC and thereafter as a BRCA2 carrier. IDC appeared as a hyperdense, irregular mass on mammography, hypo-echoic 2.7 × 2.2 cm taller than wide lesion on ultrasound, and as an enhancing lesion with prominent wash-out pattern on dynamic contrast enhanced MRI.

[A] Cranio-caudal mammography
[B] Right medio-lateral oblique mamography
[C] Ultrasound
[D] Contrast MRI
[E] MRI computer assisted diagnosis map

IDC = invasive ductal carcinoma, MRI = magnetic resonance imaging

DISCUSSION

Altogether, 178 male patients were examined in our breast care center during a time-frame of 6 years. This low number may represent the rarity of breast symptoms among males. Primary MBC or metastasis to the breast was found in almost 10% of the cases, a relatively high number, reflecting the bias of intrinsic characteristics of the diagnostic workup among a symptomatic population. This number is about tenfold higher than reports of other institutional cohorts [11,12]. However, Günhan-Bilgen and colleagues [13] presented a series of 236 male patients, among whom they diagnosed a carcinoma incidence of 6%.

In a recent summary of male breast examinations in 557 patients, the main referral indication was gynecomastia or breast swelling, accounting for almost 25% of all cases [11]. Gynecomastia accounted for 15% of cases in our cohort, which is in agreement with other reports stating that palpable mass is the main referral indication [14]. A palpable mass was found in 72% of patients in the cancer subgroup, indicating that thorough workup needs to be conducted when encountered. Moreover, in our study the median age at cancer diagnosis was 63 years, similar to that of the general population examined. In addition, no MBC was diagnosed among the 20 patients younger than 40, stressing the trend of lower probability of cancer in this young age group [4]. Interestingly, male carriers of BRCA1 mutation have only slightly higher risk for MBC. However, BRCA2 mutation is a recognized risk factor, occurring in 4% to 40% of MBC [1,15], in accordance with our finding of 20% BRCA2 positive in the MBC cohort.

Obesity has also been implicated as a risk factor for MBC as a result of increased circulating estrogen levels [4]. Likewise, in our cohort 44% of the patients in the breast cancer subgroup were obese with BMI over 30.

In our institution, ultrasound is part of the imaging evaluation investigating breast lesions in men due to the limited breast tissue mass, allowing for a superficial and high-resolution

examination. Ultrasound used in combination with mammography, or more commonly, ultrasound alone, was the most common imagining modality for young men. In general, mammography was avoided in younger patients. Ultrasound was used to guide all biopsies of suspicious findings as this has been shown to accurately establish a pathological diagnosis comparable to excision biopsy [16]. MRI was not performed routinely but rather used in a minority of the cases for BRCA follow-up.

To evaluate the yield of the radiological evaluation we reviewed the cancer probability according to the BI–RADS score and the subsequent biopsy. We found that one-quarter of the BI–RADS 4 cases and all BI–RADS 5 cases were eventually diagnosed with cancer, in accordance with the BI–RADS lexicon estimation of 30% and 95%, respectively. However, the specificity of the biopsies was lower due to inclusion of 13 biopsies performed in patients with BI–RADS 3, which were benign and BI–RADS 4 related false-positive cases. Biopsies of BI–RADS 3 lesions are not routinely performed; however, these 13 cases were conducted because of a physician's request due to strong clinical suspicion.

In this series, all patients younger than 40 years of age had a benign growth, mostly gynecomastia, indicating that biopsies are rarely needed in this population. Mammographic appearances of gynecomastia and breast cancer do not overlap; hence, biopsies should not be performed routinely when gynecomastia is observed but only if a co-existent lesion is suspected clinically or mammographically [17].

In our breast care center during the study period, only 13 breast MRI scans of male patients were performed, usually in known BRCA carriers or high risk patients. In two patients (BI–RADS 4), there was a downgrade to BI–RADS 2 following MRI. These patients nonetheless went on to have biopsies, which revealed gynecomastia. There was no change in the BI–RADS scores after MRI evaluation in the other 11 patients. Typical MRI features in the breast cancer subgroup were tumors with irregular shape and margins, and demonstrated rapid contrast enhancement and washout. Similar findings were observed by Morakkabati-Spitz et al. [18].The role of breast MRI in the evaluation of male breast disease remains unclear [9]. Grimm [19] argued that MRI is generally not indicated in the workup for male breast cancer unless there is concern for chest wall invasion. Shaw and colleagues [20] stated that although it may be technically difficult, MRI can be used successfully in the evaluation of the male breast, and its use should be recommended, particularly in cases where initial imaging is equivocal. Our results advocate for the use of MRI, particularly in cases of BI–RADS 4 in which high likelihood of a false positive biopsy was observed.

Tumor size and lymph node involvement are the two main prognostic factors for breast cancer in men [21]. In our study, 31% of breast cancer patients had ipsilateral nodal metastasis, with one having disseminated disease. This prevalence is similar to that found by Giordano et al. [22]. The predominant histological type of breast cancer is IDC, which represents more than 90% of all male breast tumors. Much rarer tumor types include invasive papilloma and medullary lesions. Lobular carcinomas are extremely rare due to the lack of lobular differentiation of the male breast [4,21]. Almost our entire MBC cohort had IDC while only one had papillary carcinoma. Men are significantly more likely to have ER- or PR-positive disease than women. In this cohort, all patients had ER-positive tumors and the vast majority had PR-positive tumors. Similarly higher rates in men have been demonstrated in previous studies [22,23]. In contrast, the HER2 proto-oncogene is less likely to be overexpressed in cancers of the male breast [24]. However, the 38% HER2 expression in our cohort together with the 37% found by Giordano et al. [22] is significantly higher than that seen in female breast cancers. This disparity could be as a result of the small cohort size. Similar to female breast cancer, receptor positive MBC benefit from hormonal therapy, and has also been shown to improve survival [25].

LIMITATIONS

This is a single-institution data that was retrospectively collected from a prospectively maintained database. Unlike female patients who are annually examined, our patients were not on a follow-up program and therefore in most cases with apparently benign condition, no long term follow-up data was obtained.

CONCLUSIONS

The most common indication for imaging the male breast was palpable mass evaluation. Although this presentation was associated with cancer, the predominant diagnosis in the vast majority of these patients was gynecomastia. Our results also suggest a low likelihood for cancer diagnosis in younger patients and in cases where the presenting symptom was mastalgia or gynecomastia. Therefore, unless clinically and radiologically suspicious, biopsy should not be encouraged.

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Capsule

Escalating responses to DNA

Numerous DNA sensors exist in cells to detect viral and microbial infection, as well as nonphysiological cytosolic DNA. These detection systems activate immune signaling pathways to respond to infection, but why are so many DNA sensors needed? In a perspective, **Emming and Schroder** proposed that DNA sensors, including a newly identified nuclear sensor, function in a tiered system that can adjust the cellular response according to the amount of detected intracellular DNA. Cellular and immune responses can therefore be scaled, from low-level inflammation to immunogenic cell death, according to the threat posed by an infection.

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Eitan Israeli

Capsule

Tumors metabolically paralyze T cells

The cytokine transforming growth factor–β (TGF-β) suppresses both immune and tumor cells. **Dimeloe** and co-authors found that TGF-β from tumor effusions suppressed the antitumor activity of $CD4^+$ T cells by inhibiting their production of the inflammatory cytokine interferon-γ (IFN-γ). The effects of TGF-β were mediated by Smad proteins in the mitochondria and led to decreased mitochondrial respiration. Indeed, IFN-γ production by $CD4^+$ T cells was suppressed by inhibiting a mitochondrial electron transport chain complex. These data suggest that TGF-β suppresses antitumor immunity by metabolically paralyzing T cells.

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Eitan Israeli

Capsule

Targeting cancer transmission in devils

The population of Tasmanian devils has been dropping rapidly, leading to their designation as endangered species. The species has been succumbing to a transmissible cancer called devil facial tumor disease. In a perspective, **Patchett and Woods** discussed the emerging ideas about how this disease has evolved to be transmitted between individuals. Recent findings demonstrate how these tumors evade the host immune system, revealing potential strategies for therapeutic intervention.

Science 2019; 365: 438

Eitan Israeli