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Original Article

Are we on the side of over-diagnosis and treatment in BI-RADS 4A breast lesions?

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Abstract

Aim: In BI-RADS 4A lesions, a malignancy rate of between 2% and 10% has been detected. Many patients avoid biopsy even though biopsy is recommended because of its low malignancy rates. The aim of this study is to investigate the need for biopsy of patients with BI-RADS 4A lesions.

Materials and Methods: 392 patients classified as BI-RADS 4A in our hospital between January 2011 and December 2019 were retrospectively analyzed. Clinical and demographic characteristics of the patients, complaints, physical examination findings, USG (ultrasound), MMG (mammography) and magnetic resonance imaging (MRI) findings, invasive surgical procedure or noninvasive procedure performed, pathology results were analyzed.

Results: The mean age was 44.29 years (range, 15–93 years). The most common complaint was palpable mass (36.5%). While 88.5% of examined pathologies were evaluated as benign lesions, 7.1% were malignant. The rate of malignancy increased with age, and this difference was statistically significant (p = .000). Malignancy increases with lesions size but it was not statistically significant (p = .052). Palpable mass was more common in malignant lesions (55.2%) (p = .014). Comparing the radiological evaluations of BI-RADS 4A lesions with the post-biopsy pathology results, size increase, more than three lobulations, border irregularities, and cystic areas did not make a statistically significant difference in terms of benign, premalignant, and malignant pathologies; however, intraductal localization was observed more frequently in benign and premalignant lesions than in malignant lesions, and this difference was statistically significant (p = .003).

Conclusion: We anticipate that the criteria developed with this study (more than three lobulations, border irregularity, cystic areas, and intraductal locations), applied to a wide range of patients, can be a source for future studies and can be used safely in other clinics. As a result, we strongly recommend biopsy for patients with postmenopausal and palpable masses if the criteria we used for detecting BI-RADS 4A are also present.

Keywords: BI-RADS 4A; breast biopsy; breast cancer

INTRODUCTION

The Breast Imaging Reporting and Data System (BI-RADS®), which was developed to create a standard approach in breast imaging methods and to standardize patient management, to create a common language between disciplines, provides a quality and objective approach for identifying breast diseases. It provides a lexicon of descriptors, a reporting structure that relates assessment categories to management recommendations. In this lexicon, BI-RADS category 4 have been defined as "the findings that do not have the classic appearance of malignancy but are sufficiently suspicious to justify a recommendation for biopsy." Category 4 covers a wide range of likelihood of malignancy (from 2–95%), and the management recommendation in this category is tissue diagnosis. The use of category 4 subdivisions to provide improved stratification of likelihood of malignancy has been suggested in the BI-RADS lexicon. The current definitions of such likelihoods are as follows: 4A > 2% to ≤ 10%, 4B > 10% to ≤ 50%, and 4C > 50% to < 95%. Category 4A may be used for a finding needing intervention but with a low suspicion for malignancy. A malignant pathology result is not expected, and a recommendation for six-month or routine follow-up after a benign percutaneous tissue diagnosis is appropriate. Examples of findings placed in this category may include a partially (< 75%) circumscribed solid mass with US features suggestive of a fibroadenoma, or a circumscribed solid mass with an increase in diameter of more than 20%; palpable solitary complicated

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cyst; and probable abscess (1,2). Furthermore, studies investigating the morphological features and pathological correlations of microcalcifications have indicated that, when amorphous and coarse heterogeneous calcifications that are moderately suspicious are regional, they can be evaluated as BI-RADS 4A. Also, if a change is observed in the follow-up in possibly benign clustered punctate calcifications, the change can be classified as BI-RADS 4A (3). In addition, even though intraductal papillomas without sign of cancer are generally considered benign, radiologists classify these lesions as BI-RADS 4A, because of the likelihood of coincident invasive or in situ malignancy, as well as the long-term risk.

The most problematic category of breast lesions is the BI-RADS 4, as the probability of malignancy varies between 2% and 95 % (4). The wide range of probability of malignancy in this category may cause confusion in patient management. In BI-RADS 4A lesions, a malignancy rate of between 2% and 10% has been detected (5). Many patients avoid surgery even though biopsy is recommended because of its low malignancy rates. There is no consensus among clinicians either, that biopsy should absolutely be performed (6).

The aim of this study is to investigate the need for biopsy of patients with BI-RADS 4A lesions.

MATERIALS and METHODS

Data collected between January 2011 and December 2019 of 465 patients with breast lesions classified as BI-RADS 4A by breast ultrasound (USG) or mammography (MMG) performed in our hospital were retrospectively analyzed. 73 cases excluded whom has refused the biopsy. Other 392 cases were included in this study. Demographics and clinical features of the patients—including age, gender, complaints, physical examination findings, USG, MMG and magnetic resonance imaging (MRI) findings, invasive surgical procedure or noninvasive procedure performed, pathology results, and clinical results—of those followed were analyzed.

Descriptive statistics were reported using mean ± standard deviation or median (minimum-maximum) for categorical variables, depending on the data distribution for number and percentage numeric variables. Data normal distribution was evaluated using a Shapiro Wilks test. Comparison of numerical measurements according to socio-demographic characteristics and research groups was evaluated using a Kruskal-Wallis test for three independent groups, in accordance with the data distribution. Proportion comparisons or correlation studies according to research groups were investigated with either Chi-square or Fisher's exact test. For the level of statistical significance, $p < 0.05$ was accepted. This study was approved by Baskent University Institutional Review Board (Project no: KA20/364) and supported by Baskent University Research Fund.

RESULTS

All our patients were women. The mean age was 44.29 years (range, 15–93 years). The most common complaint of the patients was palpable mass (36.5%); however, 32% of the patients had no complaints. 23% of the patients had mastodynia. While 55.4% of the patients had biopsy with wire-guided excision biopsy, 44.6% of them were diagnosed with a trucut biopsy. When the pathologies were examined, 88.5% of them were benign lesions, malignancy was detected in 7.1%, and lesions that could be premalignant were excised in 4.3%. Fibroadenoma (32.9%), fibrocystic changes (28%), and intraductal papilloma (16.2%) were the most common benign pathologies whereas the least common were myofibroblastoma (0.3%), columnar lesion (1.2%), and hamartoma (1.4%). Other pathology results are shown in Table 1.

Table 1. Distribution of benign, premalignant, and malignant pathologies

Benign pathologies n:346		Premalignant pathologies n:17		Malignant pathologies n:29	
Mammary tissue without significant features	7.2% (n:25)	Atypical ductal hyperplasia	41.2% (n:7)	Lymphoma	3.4% (n:1)
Fibroepithelial lesion	4.3% (n:15)	Ductal carcinoma in situ (DCIS)	52.9% (n:9)	Invasive carcinoma	3.4% (n:1)
Hamartoma	1.4% (n:5)	Lobular carcinoma in situ (LCIS)	5.9% (n:1)	Invasive carcinoma NOS	75.9% (n:22)
Intraductal papilloma	16.2% (n:56)			Invasive lobular carcinoma	3.4% (n:1)
Inflammatory lesion/fat necrosis	6.6% (n:23)			Invasive cribriform carcinoma	3.4% (n:1)
Columnar all lesion	1.2% (n:4)			Invasive carcinoma with neuroendocrine features	3.4% (n:1)
Fibrocystic changes	28.0% (n:97)			Invasive carcinoma with medullary features	3.4% (n:1)
Myofibroblastoma	0.3% (n:1)			Papillary carcinoma	3.4% (n:1)
Fibroadenoma	32.9% (n:114)				
Phillodes tumor (benign)	1.7% (n:6)				

Among the premalignant lesions, ductal carcinoma in situ (DCIS) (52.9%) and atypical ductal hyperplasia (41.2%) were the most common. Among the 7% malignant pathologies, invasive carcinoma not otherwise specified (NOS; 75.9%) was the most common. Considering the relationship between the lesions and the age of the patients, it was found that the rate of malignancy increased with increasing age, and this difference was found to be statistically significant (p = .000). When the relationship between lesion size and malignancy was examined, the data showing that the increase in size increased the probability of malignancy was not found to be statistically significant, but the size of the lesions in patients with malignancy was found to be larger than the size of other patients' lesions (p = .052). When the complaints of the patients were compared with benign, premalignant and malignant lesions, palpable mass was found with a higher rate in malignant lesions with 55.2% compared to other benign (34.7%) and premalignant (41.2%) lesions. This difference was statistically significant (p = .014). Similarly, the higher rate of asymptomatic admission in benign (32.7%) and premalignant (47.1%) lesions, compared to malignant (17.2%) pathologies, was found to be statistically significant (p = .014) (see Table 4).

Table 2. Comparison of parameters used for BI-RADS 4A

US Findings	Histopathological findings			p value
	Benign	Premalignant	Malignant	
Lobulation < 3	88.0%	4.5%	7.5%	0.639*
Lobulation > 3	94.1%	0.0%	5.9%	
Border irregularity (-)	89.9%	3.6%	6.6%	0.054*
Border irregularity (+)	78.9%	8.8%	12.3%	
Cystic area (-)	89.9%	4.1%	6.0%	0.068*
Cystic area (+)	81.1%	5.4%	13.5%	
Size increase (-)	87.2%	4.7%	8.1%	0.395*
Size increase (+)	93.0%	2.8%	4.2%	
Intraductal localization (-)	84.8%	5.1%	10.1%	**0.003***
Intraductal localization (+)	96.6%	2.6%	0.9%	

* Chi square test; p < .05

Comparing the radiological evaluations of BI-RADS 4A lesions with the post-biopsy pathology results, size increase, more than three lobulations, border irregularities, and cystic areas did not make a statistically significant difference in terms of benign, premalignant, and malignant pathologies; however, intraductal localization was observed more frequently in benign and premalignant lesions than in malignant lesions, and this difference was statistically significant (p = .003) (see Table 2).

In addition to the 392 MMG and USG findings, 219 (55.9%) breast MRIs were also performed, for further examination. BI-RADS 4A categorization did not change in 89% of these patients. When this difference was compared in terms of benign, premalignant, and malignant pathologies, benign pathology was detected in 92.8% of the patients who had MRI and reported as BI-RADS 4A, and malignant pathology was detected in only 3.1% (see Table 3).

Table 3. MRI findings for BI-RADS 4A

MRI Findings	Histopathological findings		
	Benign	Premalignant	Malignant
BI-RADS 0	100.0% (n:4)	0.0%	0.0%
BI-RADS 1	0.0%	0.0%	0.0%
BI-RADS 2	100.0% (n:3)	0.0%	0.0%
BI-RADS 3	100.0% (n:3)	0.0%	0.0%
BI-RADS 4A	92.8% (n:181)	4.1% (n:8)	3.1% (n:6)
BI-RADS 4B	80.0% (n:8)	0.0%	20.0% (n:2)
BI-RADS 4C	0.0%	0.0%	100.0% (n:1)
BI-RADS 5	0.0%	50.0% (n:1)	50.0% (n:1)
BI-RADS 6	0.0%	0.0%	100.0% (n:1)

In addition, binary logistic regression analysis was used to determine risk factors for malignant lesions. When malignancy was accepted as the independent factor, the odds ratio (OR) for age was calculated as 1.062 (range; 1.034–1.09; p = .000). No statistical significance was found for size increase, presence of irregular borders, cystic areas, more than three lobulations, breast side, cause of complaint, or location of lesion.

Table 4. Comparison of histopathological findings with demographic status and complaints

US Findings	Histopathological findings			p value
	Benign	Premalignant	Malignant	
Age	43.18 (15–93)	52.76 (29–83)	52.48 (27–88)	**0.000†**
Mass Size	14.975±0.67(0.1–80)	13.247±1.97(3–30)	20.293±2.70(0.1–60)	0.052†
Patients Complaints				
No Complaint	32.7%	47.1%	17.2%	
Nipple Discharge	8.1%	5.9%	0.0%	
Palpable Mass	34.7%	41.2%	55.2%	**0.014***
Mastodynia	24.0%	0.0%	24.1%	
Retraction	0.6%	5.9%	3.4%	

† Kruskal-Wallis test; * Chi square test; p < .05

DISCUSSION

Regarding USG findings in breast lesions, lesions are categorized by evaluating their shape and orientation, border features, echo patterns and posterior acoustic features, and distortion in surrounding structures and edema (7). Oval shape, smooth or sharp border, more than three lobulations, parallel orientation, and homogeneous echo pattern suggest benign lesions whereas irregular shape, microlobulation, indistinct border, spiculated edge, angulation, antiparallel orientation, heterogeneous echo pattern, and posterior shadowing suggest malignancy (8).

BI-RADS 4 does not have the classic appearance of malignancy; however, there are no fixed definitions for determining the categories of the lesions, especially in the BI-RADS 4 subgroups. Biopsy is recommended for all lesions in this category(9). In the present study, the patients designated as BI-RADS 4A were given a straight-through biopsy if there was a palpable mass on examination, and a marked-breast biopsy if there was not. It has been reported in many studies that lesions accepted as BI-RADS 4A are mostly benign pathology in correlation with pathology(10,11). In this study, benign was the most common pathology (88.5%); however, in line with the literature, nearly 7% was malignant. This showed us the importance of biopsy in BI-RADS 4A lesions. Although palpable mass is the only feature considered as BI-RADS 4A, this finding may nevertheless be important, even though it is not correct on its own(10); indeed, the probability of detecting malignancy was high in elderly patients with palpable mass (see Table 4).

In our study, we categorized BI-RADS 4A lesions according to those containing more than three lobulations, border irregularity, cystic areas, and intraductal locations. Although there is no such definition in the literature, categorization is made with similar findings. Costantini et al. and Hong et al. also found that microlobulation and irregular borders favor malignancy (12,13). We could not find a statistically significant difference in favor of malignancy; however, regarding the presence of palpable mass in elderly patients, the radiological findings for BI-RADS 4A can be evaluated in favor of malignancy. When only palpable lesions were examined, we found that border irregularity at the edge of the lesion might be an indicator of premalignant or malignant pathology.

Consistent with the literature, invasive carcinoma was found to be the most common in malignant lesions. Regarding benign pathologies, fibroadenoma and intraductal papilloma were most common in our study (11,14). Furthermore, DCIS is the most common in premalignant lesions (15,16).

Regarding MRI imaging, USG was interrupted, and MRI was performed as an additional examination for suspected patients. In the literature, it is mentioned that, when there is difficulty in determining the nature of BI-RADS 4 lesions, evaluation with MRI can be helpful (17,18); however, in our study, almost 90% of the patients had an MRI, and the lesions categorized by USG did not change. In addition, BI-RADS 4A lesions with benign, premalignant, and malignant pathology did not show a significant change in MRI. Further, when the preoperative risk factors of BI-RADS 4A lesions in terms of malignancy were evaluated as a result of regression analysis, the only statistically significant variable was age—in fact, the increase in the frequency of breast cancer in advanced age harmoniously explains our finding.

LIMITATIONS

Our study has limitations. First, it is a retrospective, single-center study. Also, some of the parameters we used to determine BI-RADS 4A were created based on the experiences of our clinic. This created bias; however, the use of these criteria creates a unique situation for the Başkent University Faculty of Medicine breast clinic in terms of contribution to the literature; when these criteria are combined with clinicians' suspicion, our rate of malignancy detection in patients with BI-RADS 4A lesions is higher than that in the literature. This has shown us how important the parameters and approach used in our center are for detecting breast lesions.

CONCLUSION

For BI-RADS 4A lesions, there are no obvious markers for imaging methods that have been clearly defined in the literature. We anticipate that the criteria developed with this study, applied to a wide range of patients, can be a source for future studies and can be used safely in other clinics. As a result, we strongly recommend biopsy for patients with postmenopausal and palpable masses if the criteria we used for detecting BI-RADS 4A are also present (see Table 4). Additionally, we recommend that clinicians and radiologists work together and make joint decisions regarding treatment for such lesions, especially if there is suspicion.

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