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False negativity rate of ultrasonography with mammography in women with palpable breast lumps

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ABSTRACT

This study was performed to determine the false negativity rates of ultrasonography with mammography in the assessment of women with palpable breast lumps. The relevant data on 202 female patients aged above 14 years of age, who had presented to our institution with a breast lump, had been retrospectively reviewed from our hospital database. Out of these, 155 patients for whom mammography with sonography imaging (MSI) was done were included in the study population. It consisted of tissue-positive cases, tissue-negative cases, and false-negative MSI confirmed on pathology. All cancer cases and false-negative cases using MSI were identified. Cancer rates, false-negative rates, and negative predictive values were calculated based on MSI breast imaging reporting and BI-RADS categories. Among patients who had undergone MSI, 73.55 % (114/155) of patients had BI-RADS 1–2. Despite a benign result, 10.5% (12/114) of them had gone ahead with a tissue diagnosis, whereas BI-RADS 4 and 5 had a 100% biopsy rate (28/28, 4/4, respectively). Out of the seventeen cancers detected in toto, only one belonged to BI-RADS 1–2. The false-negative rate of MSI (i.e., BI-RADS 1–2) was found to be 1.75% (1/114). As none of the remaining cases had progressed into malignancy post-follow-up (Median: 9 months, Range: 2 – 13 months), The negative predictive value (NPV) and cancer rate were estimated to be 99.12% and 0.88% respectively. Therefore, low false negativity and high negative predictive value of mammography with ultrasonography imaging for breast lumps were established.

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INTRODUCTION

Palpable breast lesions are one of the most typical presenting complaints in terms of breast-related disorders, preceded only by pain (Alteri *et al.*, 2013). It puts the patient under a lot of stress and anxiety, despite the majority of lesions being benign (Beyer and Moonka, 2003). To ascertain the status of such a lesion, a complete clinical examination followed by various modalities of investigations are used, including mammography, ultrasonography, fine needle aspiration cytology (FNAC) and a tru-cut biopsy, as indicated (Alteri *et al.*, 2013). Conventionally, a 'Triple Assessment' consisting of a thorough history and clinical examination, mammogra-

phy and FNAC, was followed. This had shown a satisfactory diagnostic accuracy ranging from 95 to 100 per cent (Chan *et al.*, 2015; Coveney *et al.*, 1994; Dietze *et al.*, 2020). In more recent times, ultrasound, in augmentation to mammography, is being recommended to patients who are above 30 years of age, as a preliminary diagnostic modality for breast lumps. (Dixon, 1984). Invasive tests such as FNAC and tru-cut biopsies are only opted for in cases with a high degree of suspicion, either clinically or radiologically.

Besides, mammography as a lone procedure has a high false negativity rate, ranging between 8 and 16 %, generally stated as 15% (Godwins *et al.*, 2011; Graf *et al.*, 2007; Hansell *et al.*, 1988). By combining ultrasound with it, there is a significant decrease in this false negativity rate as it falls to almost 1% (Harvey *et al.*, 2013; Hermansen *et al.*, 1987; Kumar *et al.*, 1999). Similarly, the negative predictive value (NPV) has been seen to improve with this combined approach significantly (Moss *et al.*, 1999).

A high negative predictive value (NPV) would enable the physician to choose the successive steps in treatment, either a tissue diagnosis or simply the follow up of the patient, with better certainty.

Hence, this study aims to ascertain the false negativity rate and negative predictive value by using mammography with sonography imaging (MSI) for palpable breast lumps in a tertiary care setting.

METHODOLOGY

At Saveetha Medical College and Hospital, Thandalam, Chennai, for patients presenting with a breast lump, the choice of imaging modality varies depending on their age. For patients aged 30 and above, mammography is the investigation of choice followed by ultrasound, whereas for those below 30 years of age, ultrasound is preferred. Clinically or radiographically suspicious lesions are further evaluated by tissue diagnosis (fine-needle aspiration, core-needle biopsy) and surgical excision if indicated.

The informed patient consent is waived by obtaining approval from the Institutional Ethical Committee due to the retrospective nature. The relevant data of all female patients, aged 14 and above, who had presented to our institution with a breast lump during the stipulated time frame of study (January 2019 to February 2020) was reviewed retrospectively from the hospital database. The data reviewed includes patients' demographic details, radiology reports, surgical procedures, and cytology/histopathology reports. From the said database, 202 patients

were found to have presented with a palpable breast lump, out of which 155 patients, for whom mammography with sonography imaging (MSI) was done, were included in the study population. It consisted of positive tissue cases, tissue negative cases, and false-negative MSI confirmed on pathology. Radiological assessment was done based on BI-RADS scoring system (1: Negative; 2: Benign finding; 3: Probably benign; 4: Suspicious abnormality; and 5: Highly suggestive of malignancy) - based on which the false negativity rates and negative predictive values were also calculated.

Statistical analysis was done on SPSS v.25., where categorical data was compared using the Chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The data on 202 female patients, aged above 14 years of age, who visited the hospital during the 14 months of study were reviewed retrospectively from the database. Out of the 202 patients, 155 were subjected to combined mammography with sonography imaging (MSI 76.73%) and the remaining 47 patients (23.27%) were subjected to a single modality of investigation, either mammography (7 patients) or ultrasound (40 patients) (Figure 1 and Figure 2). Majority of patients who had undergone an ultrasound alone were relatively younger (mean age: 38 $\pm$ 18.96, range: 14 - 68) when compared to those who had MSI (mean age: 40.99 $\pm$ 11.52, range: 25–71) or those who had mammography alone (mean age: 56.21$\pm$ 12.72, range: 29–63). (p < 0.0001). Older patients who had chosen to undergo an ultrasound alone had done so either because they had already undergone mammography recently or were apprehensive about the radiation exposure associated with it. On the other hand, some patients had opted for lone mammography because they wished to undergo surgical excision of the lump, irrespective of the outcome of further imaging. Few other patients, who had presented with a skin lesion were prescribed mammography alone.

Among patients who had undergone MSI, 73.55 % (114/155) of patients had BI-RADS 1–2, 5.81% (9/155) had BI-RADS 3, 18.06% (28/155) had BI-RADS 4, and 2.58% (4/155) had BI-RADS 5 classification. Out of these 155 patients, 47 had undergone a biopsy (30.32%). This consisted of 10.5% (12/114) of BI-RADS 1-2 and 33% (3/9) of BI-RADS 3, primarily because of the patients' concern or suspicious clinical features. The remaining were 100% (28/28) of patients who were BI-RADS 4 and 100%

(4/4) patients who were BI-RADS 5. Seventeen cancers (36.17%) were detected in the 47 biopsies done.
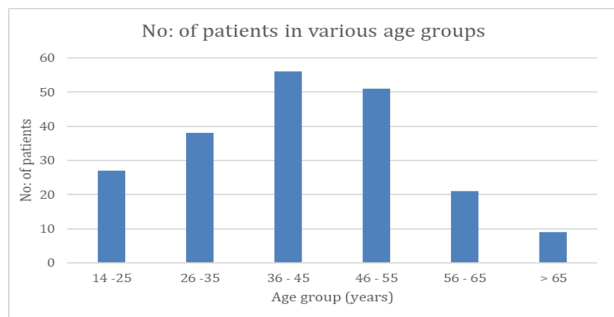

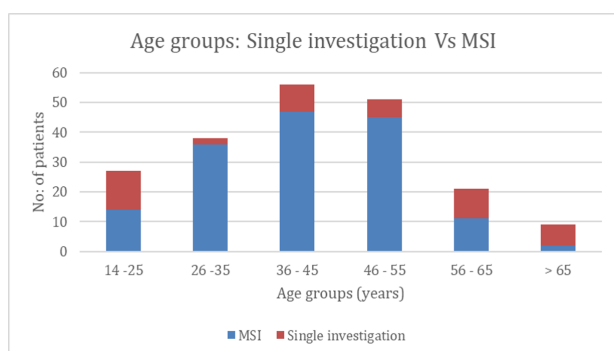**Figure 1: Number of patients across various age groups**

Figure 2: Age group-wise comparison: Single investigation Vs MSI

All clinically palpable breast lumps with BI-RADS 5 (4/4, 100 %) were found to be malignant on biopsy, whereas 42.86 % (12/28) of those with BI-RADS 4 were malignant. Of the nine lesions categorized as BI-RADS 3, 3 clinically suspicious lesions were biopsied. However, none were found to be malignant, resulting in a null cancer rate amongst all BI-RADS 3 lesions (0/9) and (0/3) biopsied BI-RADS 3 lesions. Out of 114 lesions categorized as BI-RADS 1-2, one was found to be malignant from the 12 clinically worrisome lesions that had been biopsied.

From the remaining 102 patients categorized as BI-RADS 1-2 who had not undergone a biopsy, 76 (74.5%) were subjected to a follow-up test; either radiological and physical examination (Median: 9 months, Range: 2 – 13 months) and none had progressed into malignancy. Therefore, the false-negative rate of MSI (i.e., BI-RADS 1–2) was found to be 1.75% (1/114). The negative predictive value (NPV) of BI-RADS 1–2 using MSI was 99.12%, presuming that all the other lesions are, in fact, genuinely benign. Patients who were not subjected to a follow-up examination (Radiological/clinical) were significantly younger (median age of 28 vs 44 years). Notably, 65.38% (17/26) of patients for whom follow-up tests were not done, were below the age of 35, and routine screening mammography was not warranted yet. Few patients were lost to follow-up (10.53%, 3/26).

Majority of the lumps (73.54%, 114/155), were detected by breast self-examination, by the patients themselves, while medical professionals discovered 26.45% (41/155) during the physical examination. Notably, when subjected to MSI, lumps found during self-examination were often found to be BI-RADS 4–5 than those found by medical professionals. (29/114, 25.43% vs 3/41, 9.75%, p < 0.0001). Furthermore, as a higher BI-RADS category, in turn, results in a higher likelihood of a malignancy diagnosis, higher cancer rates were found in masses detected by self-examination (14/114, 12.28% vs 2/41, 4.8%, p < 0.0001). That is, out of the 17 cancers diagnosed, the patients initially detected a vast majority (14/17, 82.35%) of them during self-examination (Table 1).

From Figure 1, it can be inferred from the graph that the ages ranging from 36 to 55 years, were the highest in the occurrence of breast lumps. From Figure 2, out of the 202 patients that had visited our institution, 155 underwent MSI, and 47 underwent a single investigation (either mammography or ultrasonography). It can be inferred from the graph that the ages ranging from 36 to 55 years, not only had the highest occurrence of breast lumps, but the majority of them were subjected to MSI.

DISCUSSION

Radiological evaluation is the prime modality of investigation for palpable breast masses. However, false-negative mammographic results in such cases, roughly range between 8% to 16% (Godwins *et al.*, 2011; Graf *et al.*, 2007; Hansell *et al.*, 1988). As a result of this, a negative mammography result cannot completely rule out a diagnosis of malignancy. Under such circumstances, physicians resort to clinical examination or tissue diagnosis to determine the course of treatment. Combined usage of mammography with sonography imaging (MSI) has been shown to decrease this false negativity rate, thereby improving the reliability of radiological imaging. Hence, knowledge of the false-negative rate and negative predictive value of mammography with sonography imaging (MSI) becomes pivotal in determining the course of clinical treatment.

In this study, 76.73% of patients had undergone mammography with sonography imaging (MSI) while 23.27% had a single modality of treatment, either mammography (3.46%) or ultrasound (19.8) alone.

Table 1: Cancers detected in various MSI BI-RADS categories

BI-RADS	No. of patients	No. of biopsies	No. of cancers	% of cancers*
1 - 2	114	12	1	0.88
3	9	3	0	0
4	28	28	12	42.86
5	4	4	4	100
Total	155	47	17	

*BI-RAD1-3 (all patients), BI-RADS 4–5 (patients with biopsy only)

The mean age of patients who had undergone ultrasound alone was significantly lower than the other two groups as expected; considering that ultrasound alone is sufficient for initial evaluation for patients below 30 years of age without any risk factors (Dixon, 1984). For patients aged between 30 to 40 years, a single modality may suffice as long as there is no abnormal finding (Dixon, 1984).

In this study, 17 cancers were detected in 47 biopsies. Predictably, patients with BI-RADS 4 or 5 had higher rates of cancer, 42.86 and 100 per cent, respectively. Also, cancer rates were found to be higher in older patients (Moy et al., 2002). Majority of the cancers occurred in women aged 50 years and above (Moy et al., 2002). Notably, cancer rates were higher for breast lumps discovered by structured breast self-exams than those detected by medical professionals (12.28% and 4.8%, respectively). Though structured breast self-examination is no longer recommended by the American Cancer Society (Moy et al., 2002), it can be seen that these examinations can be a useful aid for early detection of breast cancers, as seen in various studies (Murphy et al., 2007; Park et al., 2008).

In this study, a vast majority of cases bore a low index of radiological suspicion; BI-RADS 1 - 2, 73.55%. Yet 10.5% of these patients went ahead for a biopsy, either because of the patients' distress or worrisome clinical findings. Out of those 12 biopsies done, only one was found to be malignant, resulting in a cancer rate of 0.88% among the said group. Out of the 17 cancers diagnosed, one case had an MSI of BI-RADS 1–2, thereby resulting in a sensitivity of 94.11% (16/17). Given that 74.5% of these patients had a follow-up assessment, the false-negative rate of MSI (i.e., BI-RADS 1–2) was found to be 1.75% (1/114) assuming that all the other lesions are, in fact, genuinely benign. Our findings are consistent with other studies published in this area of interest (Kumar et al., 1999; Moss et al., 1999). A couple of these studies were also done using retrospectively retrieved data (Secginli et al., 2017; Soo et al., 2001) whereas one study was done using a study population of malignant cases obtained from a cancer registry (Wallis et al., 1991). However, the current study was done by retrospectively retrieving patient data from a prospectively entered database. The patient data consisted of cases who had visited our tertiary care centre with a palpable breast lump during our stipulated period of study, thereby minimizing selection bias. This study has corroborated the findings of existing studies in terms of false-negative rates and negative predictive values; but speaks from a clinical narrative, highlighting the liability of having radiologically negative cancers. The high negative predictive value ascertained by this combined approach is pivotal in providing reassurance to patients.

However, our study had its limitations. Our study had a study population of 202, out of which 155 were subjected to MSI that was obtained during the 14 months of study. A longer time frame and larger sample size can be utilized to emphasize the results. 10.53% of those patients who were BI-RADS 1 - 2 category and had not undergone a biopsy were lost to follow-up. This could have had a repercussion on the actual cancer rates of this category. Also, our study population was confined to a single tertiary care centre; hence our findings may not be generalizable. Nonetheless, our findings have been consistent with previously published studies in this domain, thereby reaffirming the statement that a combined imaging approach has a low false-negative rate and a high negative predictive value. These findings can be used to reassure patients presenting with a palpable breast lump that is negative on MSI and not clinically worrisome.

CONCLUSION

Given the low false negativity and high negative predictive value of mammography with ultrasonography imaging for breast lumps, a patient with a clinically unsuspicious lesion can be reassured with a benign MSI report.

Conflict of Interest

The authors declare that they have no conflict of

interest for this study.

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