ABSTRACT

Introduction: Despite the advances in mammography techniques, it still has a number of limitations. It is estimated that about 10 to 25% of lesions are overlooked in mammograms out of which about two thirds are detected retrospectively by radiologists and oncologists. Causes of missed breast cancer on mammography can be secondary to many factors including those related to the patient (whether inherent or acquired), the nature of the malignant mass itself, poor mammographic techniques, provider factors or interpretive skills of radiologists and oncologists (including perception and interpretation errors).

Aim of Work: The aim of this study is to investigate the aforementioned factors hindering early breast cancer detection and in turn lowering mammographic sensitivity and to outline the major guidelines to overcome these factors aiming to an optimum mammographic examination and interpretation by radiologists and oncologists.

Subject and Methods: We conducted this multicenter study over a two-year interval. We included 152 histopathologically proven breast carcinomas that were initially missed on mammography. The cases were subjected to mammography, complementary US, MRI and digital mammography in some cases and all cases were histopathologically proven either by FNAB, CNB or open biopsy.

Results: Revision of the pathological specimens of these 152 cases revealed 121 infiltrating ductal carcinomas, 2 lobular, 4 mucinous, 14 inflammatory carcinomas, 6 carcinomas in situ (3 of which were intracystic), 2 intraductal papillary carcinomas and 3 cases with Paget’s disease of the nipple. In analyzing the causes responsible for misdiagnosis of these carcinomas we classified them into 4 causative factors; patient, tumor, technical or provider factors. Tumor factors were the most commonly encountered, accounting for 44.1%, while provider factors were the least commonly encountered in 14.5%. Carcinomas were detected using several individual or combined complementary techniques. These techniques mainly included double reading, additional mammography views, ultrasound and MRI examinations. Forty four carcinomas were detected on double and re-reading by more experienced radiologists. Additional mammographic views were recommended in 35 (23%) cases. Complementary ultrasound examination was performed for all 152 cases (100%) and showed a higher sensitivity than mammography in carcinoma detection. It was diagnostic in 138 (90.8%) cases only. In the remaining 14 cases, further MRI and biopsy were performed.

Conclusion: Why can breast carcinoma be missed? Four main factors are responsible for missing a carcinoma: (1) Patient factors (Inherently dense breasts or acquired dense breasts). (2) Tumor factors (subtle carcinoma, masked carcinoma, multifocal carcinoma and multicentric carcinoma). (3) Technical factors (bad exposure factors, malpositioned breasts and bad processing quality). (4) Provider factors (bad perception and misinterpretation).

How to avoid missing a breast carcinoma? Review clinical data and use US and other adjunct techniques as MRI and biopsy to assess a palpable or mammographically detected mass. Be strict about positioning and technical factors. Try to optimize image quality. Be alert to subtle features of breast cancers. Always consider the well defined carcinoma. Compare current images with multiple prior studies to look for subtle increases in lesion size. Look for other lesions when one abnormality is seen. Judge a lesion by its most malignant features. Double reading and the use of computer aided diagnosis (CAD) and finally FFDM (Full Field Digital Mammography). Close cooperation between the oncologist, radiologist and pathologist is essential to avoid missing any case of breast carcinoma.

Key Words: Missed breast carcinoma – Mammography – Ultrasonography – MRI.

INTRODUCTION

The primary role of any breast imaging modality is breast cancer early detection. The standard of care for breast cancer screening of
asymptomatic women is mammography [1]. It is the only available screening method proven to reduce breast cancer mortality [2]. Mammography plays a major role in early detection of breast cancers, detecting about 75% of cancers at least a year before they can be felt. With early detection, intervention and postoperative treatment, breast cancer mortality has decreased [3]. This means that breast cancer can be detected early enough to make a difference in the quality of life, disease progression and mortality rates.

Although mammography is a major weapon in the war against breast cancer; unfortunately it is not perfect. It is a fact that most experts believe it lowers the death rate from cancer by at least 20% [4], but this will not happen if the mammograms are not done and are not interpreted correctly. Despite the advances in mammography techniques, it still has a number of limitations. It is estimated that about 10 to 25% of lesions are overlooked in mammograms, out of which about two thirds are detected retrospectively by radiologists [5].

Causes of missed breast cancer on mammography can be secondary to many factors including those related to the patient (whether inherent or acquired), the nature of the malignant mass itself, poor mammographic techniques, provider factors or interpretive skills of radiologists (including perception and interpretation errors).

Aim of work:

The aim of this study is to investigate the aforementioned factors hindering early breast cancer detection and in turn lowering mammographic sensitivity and to outline the major guidelines to overcome these factors aiming to an optimum mammographic examination and interpretation.

**SUBJECTS AND METHODS**

We conducted this study over a period of two years between December 2004 to December 2006. We included 152 histopathologically proven breast carcinomas that were missed on mammography and detected by double reading and/or complementary imaging modalities including ultrasound and/or MRI examinations.

Symptomatic patients were referred mainly from the Surgical and Oncology Departments and Outpatient Clinics of Kasr El Aini & National Cancer Institute to the "Women Imaging Unit" in the Radiodiagnosis Department of Kasr El Aini Hospital to perform a diagnostic mammogram. Another group of patients were referred from private clinics to the "Mammography Unit" in ALFA Scan Radiology Centre.

Diagnostic Mammograms were performed for all cases under request of their treating physicians after full history taking and complete clinical examination. Mammograms were interpreted by one senior (48 mammograms) or combined junior and senior (104 mammograms) staff radiologists. Ultrasound was performed for all cases as a complementary confirmatory examination tool to exclude or detect any underlying pathologies missed on mammograms. In selected cases, MRI examination was also performed when ultrasound results were still inconclusive.

Inclusion criteria included cases with false negative mammograms for malignancy initially assigned BIRADS 0 to BIRADS 3 score with non concomitant ultrasound, MRI and consequently histopathological results. BIRADS 4 and 5 cases were included only if multifocal, multicentric or contralateral carcinomas were missed on mammograms.

**Mammography examination:**

1- **Mammography machines:**
   - Siemens Mammomat Mammography Unit.
   - ALPHA RT GE Mammography Unit.
   - Full Field Digital Mammography GE 2000 Unit.

2- **Mammographic views:**
   - Conventional views (Craniocaudal (CC) and mediolateral oblique (MLO) views.
   - Additional views (extended CC and MLO, spot compression, magnification Views) whenever indicated.

3- **Exposure factors:**
   - Compression is applied and respiration is suspended on exposure.
   - 25-28KVP.
   - 30-60MAS.
4- Mammography interpretation and report:
- Films were reviewed in a mirror image pattern to compare similar areas.
- Well illuminated view boxes were used.
- Old films when available were reviewed.
- Parenchymal density was assessed.
- Skin thickness, nipple areola complex and associated axillary lymph nodes were assessed and reported.
- Areas of parenchymal distortion and asymmetrical densities were considered.
- Mass lesions and calcifications were analyzed and a BIRADS score was assigned for detected lesions.

Breast imaging reporting and data system (BI-RADS) category [6,7]:
0- Assessment is incomplete. Need to review prior studies and/or complete additional imaging studies.
1- Negative. Continue routine screening.
2- Benign finding. Continue routine screening.
3- Probably benign finding. Short term follow-up mammogram after 6 months, then every 6 to 12 months for 1-2 years.
4- Suspicious abnormality, perform biopsy, preferably needle biopsy.
5- Highly suspicious of malignancy, appropriate action should be taken. Biopsy and treatment are necessary.

Ultrasound examination:
1- Ultrasound machines:
   - Ultramark Philips HDI 5000.
   - Siemens Elegra.
   - General Electric Logic 7.

2- Technique of examination:
   - Patient lied supine with the examined side elevated.
   - Examination extended from the clavicle down to the inframammary fold and from the sternum medially to the mid axillary line laterally.
   - The axillae were carefully scrutinized for lymph nodes enlargement.

MRI examination:
1- MRI machine:
   - Philips Intera (Netherlands) 1.5 tesla Machine.

2- Technique of examination:
   - Patient lies prone.
   - Breasts are placed within special designed breast coils.
   - Both breasts were examined in axial and sagittal planes.
   - T1 and T2 WI and post contrast T1 fat suppressed dynamic sequences were obtained.
   - Time signal intensity curves were plotted for detected enhancing lesions.
   - Morphology and dynamics of detected lesions were assessed.

RESULTS

The study included 152 women with histopathologically proven mammographically missed breast carcinomas diagnosed by double reading, U/S and/or MRI examinations. The mean age of the patients was 53.5 years (range 32 to 75 years).

Ninety-one ladies were referred from the Surgical and Oncology Departments and Outpatient Clinics to the ”Women Imaging Unit” in the Radiodiagnosis Department of Kasr El Aiin Hospital to perform a diagnostic mammogram. Sixty one ladies were referred from private clinics to the ”Mammography Unit” in ALFA Scan Radiology Centre.

Revising the pathological specimens of these 152 cases yielded 121 infiltrating ductal carcinomas, 2 lobular, 4 mucinous, 14 inflammatory carcinomas, 6 carcinomas in situ (3 of which were intracystic), 2 intraductal papillary carcinomas and 3 cases with Paget’s disease of the nipple.

Analyzing the causes responsible for misdiagnosis of these carcinomas, we classified them into 4 causative factors; patient, tumor, technical or provider factors as shown in Table (1). Tumor factors were the most commonly encountered, accounting for 44.1% (67 cases) while provider
factors were the least commonly encountered in 14.5% (22 cases).

An initial BI-RADS score was assigned for these cases as shown in Table (2). BIRADS 0 (71 cases) included 34 inherently or acquired dense breasts (Figs. 1,2), 14 cases with missed subtle areas of asymmetrical densities and parenchymal distortion (Fig. 3), 15 cases with diffuse edema pattern, 3 cases with Paget’s disease (Fig. 11) and 5 cases missed due to technical factors (Figs. 12,15). BIRADS 1 score was assigned for 34 cases including 4 small undetected subtle carcinomas, 21 malpositioned breasts with deeply seated carcinomas (Fig. 13) and 9 missed carcinomas due to bad perception by unskilled radiologists. BIRADS 2 (23 cases) included 14 subtle well defined, 2 masked (Fig. 5) and 7 misinterpreted carcinomas. BIRADS 3 (9 cases) included 6 misinterpreted carcinomas and 3 badly processed mammograms (Figs. 4,14). BIRADS 4 and 5 (15 cases) included 7 multicentric and 3 contralateral carcinomas (Figs. 6,7) and 5 breasts with diffuse edema pattern with pathologically enlarged lymph nodes (Fig. 8).

Carcinomas were detected using several individual or combined complementary techniques in reference to Table (3). These techniques mainly included double reading, additional mammographic views and postprocessing capabilities available on digital mammography like using the magnifying lens and the inverted images (Figs. 9,16,17), ultrasound and MRI examinations. Forty four carcinomas were detected on double and re-reading by more experienced radiologists. Additional mammographic views were recommended in 35 (23%) cases. Complementary ultrasound examination was performed for all 152 cases (100%) and showed a higher sensitivity than mammography in carcinoma detection. It was diagnostic in 138 (90.8%) cases only. In the remaining 14 cases, further MRI and biopsy were performed (Fig. 10). These cases included 2 lobular, 2 mucinous, 2 well defined infiltrating ductal carcinomas, 3 papillary carcinomas and 3 cases with Paget’s disease of the nipple.

The different mammographic and ultrasound features of missed carcinomas are described in Table (4).

<table>
<thead>
<tr>
<th>Cause of missed carcinoma</th>
<th>No. of cases</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inherent dense breast</td>
<td>24</td>
<td>15.8</td>
</tr>
<tr>
<td>• Aquired dense breast</td>
<td>10</td>
<td>6.6</td>
</tr>
<tr>
<td>• Hormonal therapy</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>• Post treatment breasts</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Tumor factors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Subtle carcinomas *</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>• Masked Carcinomas</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>• Multicentric and multifocal carcinomas</td>
<td>7</td>
<td>4.6</td>
</tr>
<tr>
<td>• Contralateral breast carcinoma</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>• Diffuse edema pattern **</td>
<td>20</td>
<td>13.2</td>
</tr>
<tr>
<td>• Paget’s disease</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Technical factors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bad exposure factors</td>
<td>5</td>
<td>3.2</td>
</tr>
<tr>
<td>• Malpositioned breasts</td>
<td>21</td>
<td>13.8</td>
</tr>
<tr>
<td>• Bad processing quality</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Provider factors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bad perception</td>
<td>9</td>
<td>5.9</td>
</tr>
<tr>
<td>• Misinterpretation</td>
<td>13</td>
<td>8.6</td>
</tr>
<tr>
<td>Total</td>
<td>152</td>
<td>100</td>
</tr>
</tbody>
</table>

* Subtle carcinomas include 4 small (<3mm) carcinomas, 14 well defined carcinomas and 10 carcinomas presenting with focal asymmetrical densities and 4 with areas of parenchymal distortion.

** Diffuse edema pattern was detected in 6 cases of infiltrating duct carcinoma and 14 cases of inflammatory carcinomas.

<table>
<thead>
<tr>
<th>Birads score</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-</td>
<td>71</td>
</tr>
<tr>
<td>1-</td>
<td>34</td>
</tr>
<tr>
<td>2-</td>
<td>23</td>
</tr>
<tr>
<td>3-</td>
<td>9</td>
</tr>
<tr>
<td>4-</td>
<td>5</td>
</tr>
<tr>
<td>5-</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>152</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>No. of cases</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double &amp; re-reading</td>
<td>104</td>
<td>68.4</td>
</tr>
<tr>
<td>Addit. mammographic views *</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>152</td>
<td>100</td>
</tr>
<tr>
<td>MRI</td>
<td>18</td>
<td>11.8</td>
</tr>
</tbody>
</table>

* Spot compression views were performed for 13 cases, post processing magnification using the digital machine lens for 7 cases and extended CC and MLO views for 15 cases.
Fig. (1): A 51-year-old female with an inherently dense breast parenchyma showing an area of focal increased density within the left upper outer breast quadrant (A). An underlying small 10x13mm carcinoma was detected on ultrasound examination (B). The message in this case is ‘complementary US is essential in dense breasts’.

Fig. (2): A 41-year-old patient under hormonal replacement therapy with an acquired dense breast parenchyma on mammography (A). A giant left intramammary mass lesion (B) with infiltrated axillary nodes (C) were detected on complementary ultrasound examination.

Table (4): Mammography and ultrasound features of missed carcinomas.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mammography</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical mass *</td>
<td>30</td>
<td>111</td>
</tr>
<tr>
<td>Atypical mass **</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>No mass detected</td>
<td>53</td>
<td>2</td>
</tr>
<tr>
<td>Parenchymal distortion</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Focal asymmetric densities</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Diffuse edema pattern</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Skin thickening</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>**Total</td>
<td>152</td>
<td>152</td>
</tr>
</tbody>
</table>

* Typical malignant mass lesions are considered when masses showed microlobulated or spiculated outlines, with marked surrounding distortion +/- clustered microcalcification and pathologically enlarged lymph node.

** Atypical mass lesions included 9 well defined and 3 intracystic and 2 intraductal carcinomas.
Missed Breast Carcinoma

Fig. (3): Subtle left intra mammary areas of parenchymal distortion (A). On ultrasound examination underlying multifocal, small, few mm carcinomas were detected.

Fig. (4): A 46-year-old female with a well defined right retroareolar mass lesion. Her mammogram (A) was assigned a BI-RADS 3 score. On ultrasound examination an intracystic fungating mass lesion was detected.

Fig. (5): A calcified fibroadenoma masked an adjacent carcinoma (arrow). The message is “one should avoid the satisfaction of search”.
Fig. (6): A young 28-year-old female complaining of mastalgia with multiple palpable left intramammary mass lesions. Her initial mammogram (A) was assigned a BI-RADS 3 score. On ultrasound (B) examination a deeply seated carcinoma was detected. Re-ray of the patient after adequate breast pulling (C) was performed and the US detected carcinoma was detected (arrow). Biopsy proved the malignant nature of the lesions and the case was upgraded to BI-RADS 5 with multicentric carcinoma.

Fig. (7): A large right retroareolar well mass lesion detected on the mammogram (A) of a 70-year-old female. On ultrasound examination (B) a large intra-ductal papillary carcinoma was detected. Clustered microcalcific foci (arrow) were missed on the contralateral left breast mammogram (C) seen only in the post processing magnification view (D). An underlying carcinoma was detected on ultrasound examination (E). Again, the message is the radiologist should avoid the satisfaction of search.
Fig. (8): A case of inflammatory carcinoma showing diffuse edema pattern of the right breast (A). On ultrasound examination, marked underlying interstitial edema was detected with overlying skin thickening (B) associated with right axillary pathological lymphadenopathy (C).

Fig. (9): A 40-year-old female with a palpable left breast mass. Her initial mammogram was assigned a BI-RADS 3 score. The spiculated outline of the mass (missed by a junior radiologist) was more evident on the post processing magnification view of the digital machine unit and complementary ultrasound examination.
Fig. (10): A well defined macrolobulated outlined mass lesion misinterpreted in both mammography and ultrasound as benign. A BI-RADS 3 score was assigned for the patient. Excisional biopsy of this mass revealed an underlying infiltrating ductal carcinoma.

Fig. (11): (A) Negative mammogram in a 44-year-old presented with nipple ulcer. The ulcer was biopsied and proved to be Paget's disease of the nipple. The patient was referred for US (B&C) and a small hypoechoic lesion fixed to the areola is seen. The dermal defect corresponding to the ulcer is appreciated in the spectral high resolution ultrasonography (arrow). The message is complementary US as well as the patient's complaint and clinical findings are very important to reach a correct diagnosis.
Missed Breast Carcinoma

Fig. (12): Right axillary tail irregular mass not seen in the CC views and only projected in the MLO (A&B). The case was missed in the initial mammogram that was done without adequate pulling in the MLO views. Targeted US (C) confirmed the presence of a solid hypoechoic malignant looking mass (BIRADS 5) in the axillary tail of the left breast.

Fig. (13): A 43-year-old lady with a palpable lesion at the right upper outer quadrant (A) multiformat CR film combining the CC & MLO views of the right breast and the associated complementary US images showing negative findings (This was done outside the centers of the study and the case was referred to one of the authors for revision). The author decided to repeat the mammogram because the posterior third of the breast is not shown in the images. Bilateral CC & MLO (B & C) views after good positioning showing two irregular spiculated lesions in the right upper outer quadrant. High resolution superficial complementary US images (D & E) showing one of the two spiculated masses as well as the pathologically enlarged lymph nodes. The case was diagnosed as multifocal invasive duct carcinoma was managed by radical mastectomy.
Fig. (14): A small well defined lesion in the right upper outer quadrant was discovered on screening mammography (A) and confirmed on the targeted US image (B). It was classified as BIRADS 3. Unfortunately, the lesion was diagnosed by histopathology after open biopsy as medullary carcinoma. The message is that "some malignant breast lesions present as a well defined nodule and so biopsy is recommended in all suspicious cases".

Fig. (15): A 37-year-old female with positive family history. Repeated CC mammographic view (A) after adjusting the exposure factors resulting in clear demonstration of an irregular spiculated mass (BIRADS 5) that was masked in the first examination (B) with low exposure factors. Complementary US image (C) revealed the solid hypoechoic nature of the lesion that was pathologically proved to be invasive duct carcinoma.
Fig. (16): CC & MLO digital mammographic views showing such a small malignant looking lesion with pathological microcalcification only appreciated by the use of magnifying lens (A), a post processing advantage available on digital mammography.

Fig. (17): (A) Inverted digital mammographic MLO of both breasts showing a small left breast irregular lesion appreciated in the inverted image (arrow) and in the spot magnified image (B).

DISCUSSION

Since mammography was introduced as a part of preventive care, breast cancer is most often diagnosed at its early asymptomatic stage as a non-palpable suspicious lesion on mammography [8]. Early detection of breast cancer is vital to decrease the mortality and morbidity caused by the disease. Although currently mammography is the best screening modality available, unfortunately it is both underused and over-rated [8].

It is estimated in previous studies that only 40% of high-risk women undergo regular screening in the United States, despite the fact that it reduces mortality by 30% in women 50 years and older [9-11]. Moreover, despite a high sensitivity and specificity, mammography can miss deadly tumors [8]. According to the data from the Breast Cancer Detection Demonstration Project, the false negative rate for screening mammography may be as high as 8-10% [12,13]. Since then, other authors have suggested an even higher rate (up to 25%) of missed breast cancers during screening mammography [14].

Screening mammography is used to detect clinically occult breast carcinomas, while diagnostic mammography is performed to assess symptomatic patients or to further evaluate an abnormality detected on screening mammography [15]. Up to date, there are no validated results to the national screening program in Egypt and thus we conducted this study on diagnostic mammograms of symptomatic ladies.
complaining of palpable breast masses, nipple discharge, mastalgia, skin changes or signs due to distant metastases.

Causes of missed breast cancers can relate to a variety of factors, including those related to the patient, to the nature of the tumor itself, to technical factors and to provider factors. We defined a false negative mammogram as that assigned an initial BI-RADS score of 0 to 3 with non concomitant MRI and ultrasound findings or those assigned as Bi-RADS 4 and 5 with undetected multicentric, multifocal or contralateral carcinomas on mammography. Histopathological examination of these masses was considered as our mark reference.

To improve the detection of breast cancer, various imaging modalities are being used as adjuncts when a mammogram has abnormal or inconclusive results [15]. Complementary ultrasound was performed for all patients (100%) on the same day of mammography examination. We performed MRI examination for 18 ladies (11.8%) with inconclusive ultrasound examination yet highly suspicious clinical complaint. Additional mammographic views were performed for 35 cases (23%). Carcinomas were detected on double or re-reading by more experienced senior staff radiologists in 104 cases (68.4%).

'Patient factors' accounted for 22.4% of cases (34 patients), mainly attributed to increased breast parenchyma density whether inherent or acquired following surgery, hormonal, radio or chemotherapy. A nearly equal percentage (24%) was recorded in previous studies performed by Bird et al. [14] in a screening population. Fajardo, et al. [16] demonstrated that the radiologist's certainty of interpretation of mammograms is inversely proportion to the breast density and complexity of images. Dense breasts may obscure breast tumors and make interpretation more difficult, resulting in decreased sensitivity and specificity of mammography [17,18]. Missed carcinomas in dense breasts are also usually non calcified and non distorting [19]. Malignant lesions could sometimes be missed in dense breasts due to technical factors, including reduced image contrast and unsharpness [20]. For mammographic dense breasts we strongly recommend that examinations are performed on digital machines. Adequate compression should be applied. Thorough comparative examination of both breasts should be done on well illuminated view boxes on which images of both breast are viewed as mirror image. Enough time should be spent looking for subtle areas of architectural distortion and clustered microcalcification. Complementary ultrasound examination being ultimate in carcinoma detection in mammographic dense breasts should be considered a standard complementary technique to rule out any underlying pathology. Contrast enhanced MRI examination may be requested for selected cases. Furthermore, women at risk receiving adjuvant therapy should be made aware of the lower sensitivity of mammography and should be offered alternative procedures for screening as recommended in previous studies [21].

'Tumor factor' was the most common factor responsible for missed breast carcinoma in our study accounting for 44.1% of cases (67 patients). According to Majid et al. [19], the cancers that are most challenging to diagnose are those with subtle or indistinct features of malignancy. These features include areas of architectural distortion, small groups of amorphous or punctate microcalcification, focal asymmetrical densities, dilated ducts and well circumscribed masses. Georgen et al. [22], found that missed cancers were statistically significant of lower density and were seen on only one of two views more often than were detected cancers. We encountered 32 (21%) subtle carcinomas that were missed in mammography including: 4 small (<3mm) infiltrating duct carcinomas and 14 well defined carcinomas (5 infiltrating duct, 4 mucinous, 3 intracystic and 2 intraductal papillary carcinomas). Others included 10 carcinomas presenting with subtle focal areas of asymmetrical densities and 4 cases with areas of parenchymal distortion 2 of which turned out to be infiltrating lobular carcinomas.

Asymmetric breast densities are frequently seen at mammography. According to Majid et al. [19], these findings in isolation have a low positive predictive value for malignancy; however when they are associated with microcalcifications or architectural distortion, the risk of malignancy is increased. They recommended that the workup of areas of asymmetric density should include clinical examination, additional mammography views and ultrasound examina-
tion. In our study, we mainly depended on clinical assessment, ultrasound examination and post processing manipulation (magnification, inversion and density control) when examinations are performed on digital machines. Magnification and spot compression views were performed for mammograms that were performed on conventional machines. FFDM is superior to conventional mammography because of many reasons, FFDM is the system of advantages. It is superior in cancer detection. It leads to reduction in examination time and retakes. It results in improved Image quality and lesion detection, perfect analysis of microcalcification, X-ray dose reduction and improved workflow with centricity solutions [19].

Any worrisome feature detected on ultrasound was respected and further biopsy was resorted to. MRI was also performed and was diagnostic in 5 cases. Spot compression and magnification views were particularly useful to evaluate the margins of masses, areas of asymmetry and characteristics of microcalcification. Comparison of similar breast portions and of previous mammograms is mandatory to detect any newly developed densities. The identification of a focal density on one view should prompt a search in the same arc (measured from the nipple) on the other view as suggested in a previous study [13]. A well circumscribed carcinoma should always be considered in peri or post menopausal women who present with a circumscribed solid mass, since fibroadenomas are not common at this age [19].

The observation of an obvious finding (benign or malignant) may cause the "happy eye syndrome," misleading the radiologist into not looking carefully for other lesions [13]. Two carcinomas were missed due to adjacent striking benign lesions, one of which showed subtle microcalcific cluster seen on inversion images of digital mammography. Multicentric and multifocal carcinomas were missed in 4.6% of cases (7 patients) and contralateral carcinomas in 3 other patients (2% of cases). Multifocal disease is defined as multiple discrete, discontinuous tumor foci within 4cm in one breast while multicentric disease was defined as two or more malignant foci separated by 4 or more cm apart in one breast [20]. The detection of multicentric and multifocal carcinomas has a major impact on patient management. Multicentricity of foci and multiplicity of histologic types may portend a worse prognosis when the clinical and pathologic stage is otherwise specified [20]. Multicentric carcinomas are also a contraindication to breast conservative therapy [13]. Contralateral synchronous breast cancer occurs in 0.19 to 2.0% so careful attention must also be paid to the opposite breast. To avoid this pitfall we recommend that when any striking feature is encountered on mammography, our search should not come to a stop, and we should look carefully in both breasts to exclude any other synchronous lesions. Complementary ultrasound examination has proved itself in this study as well as in a previous study [20] to be particularly useful in identifying additional foci of infiltrating carcinoma.

Diffuse edema pattern found in 20 (13.2%) cases, although hindered the detection of underlying breast masses and although not a specific sign of malignancy, yet it pointed to the presence of an underlying pathological process. Further ultrasound examination detected underlying infiltrating duct carcinoma in 6 cases. Ultrasound together with mammography raised suspicion of inflammatory carcinoma in 14 other cases. Mammograms of these cases showed signs of isolated acute or subacute inflammatory changes in the form of extensive edema, marked skin thickening with stromal coarsening associated with pathological lymph nodes. On ultrasound examination, breasts showed increased parenchymal echogenicity with diffusely edematous fat and intervening interstitial edema, overlying skin thickening with pathologically enlarged lymph nodes. The hallmark of these cases is the detection of dermal lymphatic invasion on pathological revision of biopsy specimens. We reported a higher incidence of inflammatory carcinomas in our study (9.2%), compared to a frequency ranging from 1 to 4% reported in a previous study [23]. We thus stress the fact that any acute inflammatory process in non lactating women should be taken seriously and followed-up. Non resolution is an absolute indication for immediate biopsy.

Patients with mammary Paget's disease (PD) present with a relatively long history of an eczematous skin lesion or persistent dermatitis in the nipple and adjacent areas. By thorough histologic examination, documented intra epidermal extension of malignant ductal epithelial
cells from underlying breast tissue into the epidermis was detected. Only about 50-70% of patients with biopsy-proven mammary PD show positive findings on mammography including subareolar microcalcification which are helpful in evaluating and locating clinically occult, non palpable underlying breast carcinoma, architectural distortion and thickening of the nipple and the areola (reflecting edema) [24,25]. Our study included 3 (2%) cases of Paget’s disease of the nipple that were missed on mammography. These cases were suspected on US examination. MRI was performed for 2 cases showing markedly thickened enhancing areolar skin. Final diagnosis of these patients was mainly based on revision of biopsy specimens.

High quality mammography images enhance a radiologist’s ability to interpret mammograms because they have greater sensitivity and specificity. Images should be free from artifacts and should be performed with adequate exposure, high contrast, high resolution, proper compression and inclusion of the maximum amount of breast tissue [15,26]. ‘Technical factors’ were responsible for 29(19%) missed carcinomas, due to bad exposure factors in 5 (3.2%), malpositioned breasts in 21 (13.8%) and bad processing quality in 3 (2%). Correct positioning of a woman for a mammogram is needed to ensure a high quality image [4]. Technologists today must learn to break away from old habits. They need to apply new techniques with creativity. They should understand that the goal of imaging is to maximize the amount of breast tissue seen on the film [22]. In order to reach perfect performance, special care should be given to technologists’ training and they should work under continuous supervision. Many problems of exclusion can be eliminated if the breast is positioned in a careful and complete way. Traditionally this view calls for placement of the bucky at the neutral inframammary fold but this fails to take advantage of the breast’s natural mobility and results in blind areas [26]. We thus strongly recommend that in craniocaudal views the breasts should be elevated as much as its natural mobility allows and pulled as much as possible until the pectoralis muscle appears. The nipple should be profiled and the medial and lateral fibroglandular tissue should be included. The mediolateral oblique view is the single most useful mammography view as it includes the breast from high up in the axilla down to the inferior mammary fold. The gantry angle ranges from 30 to 60% following the rule proposed by Heinlein [27], “the higher the person, the higher the angle and vice versa”. The pectoral muscle should be convex in shape reaching down to the level of the nipple. In a study performed by Buist et al. [2], they found that what is sometimes interpreted as a mammography dense breast may also be a reflection of poor mammography quality. Therefore technologists should optimize image contrast to avoid over or under penetration. Careful attention to daily processor quality is also necessary [13].

The accuracy of mammography interpretation among individual radiologists varies widely [18,28]. One study showed a 40% disparity among radiologist screening sensitivity and a 45% range in the rates at which women without breast cancer are recommended for biopsy. As indicated by the receiver operating characteristics analyses, the ability of radiologists to detect cancer varies by as much as 11% [29]. The source of radiologist variability has not been completely explained. In our study, as well as in a previous study [30], the experience and training of radiologists were the main contributing factors.

Provider factors were responsible for 22 (14.5%) of missed carcinomas in our study. These cases were considered when carcinomas were detected on double reading by a more experienced senior radiologist. Double reading of mammograms has been proven to increase the detection rate of carcinomas by up to 15%. Radiologists errors were mainly attributed to two major factors, namely, perception and interpretation problems. In perception errors, accounting for 4.5% of cases of missed carcinomas in our study (9 patients), the lesions were included within the field of view and was evident, yet the radiologists failed to interpret it. Subtle, small, non calcified and non distorting carcinomas are responsible for these cases and the same precautions described above to enhance their detection should be followed. Interpretation errors by the radiologists occur when a lesion with suspicious features is mis-interpreted as a benign or probably benign lesion (BI-RADS 2 and 3). Perception and interpretation are caused by several factors including; deficient training, lack of experience, subtle features of malignancy, presence of an obvious finding, fatigue,
inattention, haste, poor view conditions and distractions [15]. We strongly support the results of a previous study [18], that the radiologists’ accuracy of mammography interpretation is strongly related to the years of experience and training. In their study, radiologists’ years of experience had the strongest association with performance, such that radiologists with fewer years in practice had high sensitivity but lower specificity. We thus, in agreement, hypothesize that training prior to starting and during practice is a very important component of accuracy of mammography interpretation. Direct feedback of performance characteristics coupled with training may be more helpful than experience without feedback. Open discussion of misjudged mammograms may be useful [30]. We also recommend that mammography interpretation should be carried out under optimum conditions. Optimum viewing conditions include view boxes with adequate luminance, reduced extraneous light and low ambient room light. Distractions should be minimized. Computer aided diagnosis (CAD System) could increase the sensitivity of mammography interpretation [15].

Conclusion:

Why can a breast carcinoma be missed?

Four main factors are responsible for missing a carcinoma: (1) Patient factors (Inherently dense breasts or acquired dense breasts). (2) Tumor factors (subtle carcinoma, masked carcinoma, multifocal carcinoma and multicentric carcinoma). (3) Technical factors (Bad exposure factors, malpositioned breasts and bad processing quality). (4) Provider factors (bad perception and misinterpretation).

How to avoid missing a breast carcinoma?

Review clinical data and use US and other adjunct techniques as MRI and biopsy to assess a palpable or mammography detected mass. Be strict about positioning and technical factors. Try to optimize image quality. Be alert to subtle features of breast cancers. Always consider the defined carcinoma. Compare current images with multiple prior studies to look for subtle increases in lesion size. Look for other lesions when one abnormality is seen. Judge a lesion by its most malignant features. Double Reading and use of CAD and finally FFDM (full field digital mammography).

REFERENCES


