A Retrospective Comparative Study of Image-Guided Excisional Biopsy in High-Risk Non-Palpable Breast Lesions: Predictive Factors for Malignancy

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ABSTRACT

Objective: The use of mammography (MM) in breast cancer screening programs has been increasing in recent years. Thus, increasing the number of detected nonpalpable breast cancer patients, through early diagnosis and treatment also increased survival rates. In our study, we wanted to share the factors about imaging-guided excisional biopsies for non-palpable breast lesions in postoperative proven breast carcinoma patients.

Materials and Methods: The surgical data were reviewed for 83 patients with non-palpable high-risk breast lesions undergoing imaging-guided surgery in our department between January, 2006 and May, 2011. Histopathologic results and age, ultrasound (US) results, MM image results, BI-RADS categorization, localization of lesion (quadrant) were assessed and factors for predicting malignancy were detected.

Results: Median age was 52 (age range 32-80 years). 29 (34,9%) of patients were malign in histopathologic results. In four patient, re-excision performed because of positive surgical margins. Axillary examination results were normal in 24 (82,7%) of malignant patients. In MM examination; microcalcifications and nodular opacity were diagnosed in 74,6% of patients before surgery. There were no difference about malignancy in these groups after surgery ($p:0,428$). 59% and 32,7% of patients were BI-RADS 4 and 3, respectively. Postoperative diagnosed malignancies in BI-RADS 4 group were significantly higher than BI-RADS 3 group ($p:<0,001$).

Conclusion: In our study; we concluded that, preoperative BI-RADS categorization (US and MM) is correlated with histopathologic findings after surgery and imaging-guided breast surgery is effective for diagnosis of early-stage breast carcinoma.

Keywords: Non-palpable, breast, localization

Introduction

With the widespread use of mammography (MM) in breast cancer screening programs, there has been a significant increase in the incidence of clinically latent and/or early stage breast cancer (1, 2). On the other hand, early diagnosis and treatment of non-palpable breast cancers with multidisciplinary approach, and application of modern imaging methods in diagnosis and treatment of breast cancer has resulted in a significant increase in survival rates (3-6).

The fact that breast cancer survival rates in developed countries are higher as compared to underdeveloped/developing countries can be associated with factors such as widespread use of screening mammography and early diagnosis as well as good treatment possibilities and easy access to treatment (3, 7-9). Some publications report that screening for breast cancer among women above the age of 50 has reduced breast cancer-related mortality rate by approximately 20-40% (4, 6, 10).

Global organizations engage in efforts to demonstrate malignancy risk, based on the radiological characteristics of breast lesions identified in imaging studies as part of screening and to create new diagnostic algorithms in that respect. By this means, attempts on identification of suspicious lesions at higher rates and minimizing false positive or false negative rates are being made. The radiologic classification Breast Imaging Reporting and Data System (BI-RADS) is the most commonly used classification in that regard (11-13).

The study will be presented as an oral paper during the 50th Golden Anniversary Congress of the European Society for Surgical Research, University of Liverpool to be held on 10 - 13, June, 2015.

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Various techniques are used for surgical excision of non-palpable breast lesions that are identified with screening methods and are suspicious for malignancy. The most frequently used techniques among those include skin projection via Ultrasound (US) or US-guided wire localization, mammography-guided wire localization and ROLL (radio-guided occult lesion localization) (14-17).

Our study evaluated a number of factors that aid in predicting the presence of histopathologically proven carcinoma based on excision of non-palpable breast lesions using various techniques. The objective was to calculate and assess the positive predictive values (PPV) of lesion descriptions in radiologic study reports for the identification of malignancies.

Materials and Methods

83 patients who had breast lesions suspicious for malignancy identified with either MM or US and underwent surgical excision with techniques like US-guided skin marking, US-guided wire localization, mammography-guided wire localization and ROLL at our clinic between January 2006 and May 2011 were included. Since the study was conducted using retrospective data, an ethics committee approval was not obtained. However, written informed consents were obtained from each patient for the study.

Histopathological results and age, ultrasound (US) results, MM image results, BI-RADS categorization, localization of the lesion (quadrant) were comparatively assessed and factors for predicting malignancy were detected. In lesions with different evaluation in US and MM in terms of BI-RADS scores, the result that was more suspicious for malignancy was taken into consideration.

Biopsy was performed in all cases with BI-RADS 4 and 5 lesions, as well as other BI-RADS scores requiring definitive diagnoses and not willing to comply with long-term follow-up and cases whose family history had a high risk for cancer. Wire localization was performed directly if the highest BI-RADS score was reported on MM. As for US-guided excisional biopsy, biopsy was initially performed with thick or fine needle, and it was performed in cases with inconclusive results or patients who prefer excision of the mass in a single procedure. An experienced radiologist employed at our hospital carried out the marking procedure. The marking procedure was conducted under US or MM as per lesion characteristic. Before MM-guided marking, cranio-caudal and oblique x-rays were taken, the lesion localization was determined by the radiologist and the lesion was marked by taking the shortest wire distance into account.

To be able to intra-operatively localize the lesion by means of a wire following US- or MM-guided marking, supportive notes such as the distance of the mass to the skin or insertion angle of the wire into the skin were communicated to the surgeon.

The pre-operative study used for imaging the lesion (US/MM) was also used for ROLL marking. All the surgical procedures were performed under general anesthesia. The marking procedure was carried out in the morning before surgery for patients in US-guided skin marking and wire-localization (US/MM) group, and 1 day before surgery for patients in the ROLL group.

In patients that received wire localization, general anesthesia and antisepsis were performed followed by incision at the peri-areolar site closest to the side without moving the wire. After that, skin flaps were mobilized; the wire was reached subcutaneously, shortened and included within the incision. Consequently, the wire was centralized and the suspicious site was excised in such a way that the tip of the wire was invisible. The surgical margins of all the specimens were marked with sutures, and the specimens were evaluated for verification of complete excision using the radiological technique the pre-operative diagnosis was made.

All the materials were fixed in a 10% formaldehyde solution following radiologic control and sent to the pathology laboratory. Pathologists experienced in breast diseases assessed the materials.

Statistical analysis

The data obtained were statistically analyzed using the Minitab 14 version (Pennsylvania, U.S) software program and group comparisons were conducted by using the appropriate tests (Z test, Fisher's exact test). $p < 0.05$ was considered statistically significant.

Results

The median age of 83 patients included in the study (range: 32-80) was determined as 52. The breakdown of patients by age ranges was as follows: 28 patients (33.7%) aged 30-49, 51 patients (61.4%) aged between 50-69 and 4 patients (4.8%) above the age of 70.

The correlation of age range and the probability of identifying malignancy on histopathological examination was evaluated in two groups of 30-49 and ≥ 50 , since there were no patients aged < 30 , and 4 patients aged > 70 . There were no significant differences in malignancy rates for both age groups ($p = 0.916$).

While malignancy was identified in 29 out of 83 patients (34.9%), the excision materials of 54 (65.1%) patients were reported as benign. According to TNM staging (18), 5 patients were classified as T1a, 5 patients T1b, 10 patients T1c and 9 patients T2.

Among benign lesions, 62.9% had fibrocystic condition ($n = 34$), 16.6% ($n = 9$) had fibroadenoma, 9.2% ($n = 5$) had ductal ectasia, and 11.1% ($n = 6$) had other reasons (intra-ductal papilloma ($n = 1$), elastosis ($n = 1$), keratinous cyst ($n = 1$), sclerosing adenosis ($n = 3$)).

In our study, complications were related to wire migration in one patient, hemorrhage in one patient, bent needle in one patient and vasovagal reflex in two patients. The rate of histopathologic incomplete lesion excision in our study was identified as 13.7% ($n = 4$).

The median size in malignancy-positive lesions was calculated as 13 mm (range: 2-40 mm). Re-excision was performed in four patients (13.7%) due to positive surgical margins. No tumors were encountered in re-excision materials. Among patients identified to have malignancy, 82.7% ($n = 24$) were reported not to have axillary involvement on sentinel lymph node biopsy. 17.3% cases who were identified to have axillary involvement ($n = 5$) underwent axillary dissection.

Mammography results showed micro-calcification in 37.3% ($n = 31$, ppd=42%), nodular opacity in 37.3% ($n = 31$, ppd=33%), asymmetrical density in 6% ($n = 5$, ppd=60%), structural distortion in 3.6%

(n=3, ppd=33%), calcification in 3.6% (n=3, ppd=0%), and normal findings in 12.0% (n=10) (Table 1).

There were 6 different group of findings on mammography. The association of these mammographic findings with malignancy is indicated in Table 1. Since enough number of observations could not be reached for the 4 findings apart from micro-calcification and nodular opacity, the correlation with pathology results were only evaluated for these two groups. The rates of malignancy were not different between micro-calcification and nodular opacity findings ($p=0.428$).

The breakdown of US results was as follows: 54.2% normal (n=45), 25.3% hypo-echoic lesions (n=21, ppd=33%), 12% solid lesions (n=12, ppd=20%), 4.8% echogenicity pertaining to micro-calcification (n=4, ppd=75%), 3.6% mass lesion (n=3, ppd=66%).

The breakdown of BI-RADS scores was identified as follows: 1.2% BI-RADS 5 (n=1, ppd=100%), 59% BI-RADS 4 (n=49, ppd=59%), 32.5% BI-RADS 3 (n=27, ppd=11%), 3.6% BI-RADS 2 (n=3, ppd=0%) and 3.6% BI-RADS 0 (n=3, ppd=0%).

Since there were not enough observations corresponding to other scores apart from scores 3 and 4 within BI-RADS scores, a comparison to the pathology results was only performed for these two scores. It was seen that the rate of malignancy was significantly higher in BI-RADS 4 than in BI-RADS 3 ($p=0.00092$) (Table 2).

There were five different situations regarding lesion localization. The localization sites were handled in five different groups as lower inner quadrant, lower outer quadrant, central, upper outer quadrant and upper inner quadrant, and comparisons were made in pairs according to pathology results. Since the result of Fisher's Exact test was found to be 0.607 ($p>0.05$) (Table 3), verification was done using a paired comparative chi-squared test for 5 different quadrants. As a result of the Bonferroni's correction implemented in a way proportional with the number of groups, the p values found as a result of paired comparisons of quadrants was >0.005 . In conclusion, no significant differences were identified among them regarding the possibility of malignancy as per the localization site of the masses in breasts (Table 3).

As for the marking method, MM-guided wire localization was used in 60% of the patients (n=50), US-guided wire localization in 19.2% (n=16), US-guided skin marking in 14.4% (n=12) and ROLL in 6% (n=5).

Grouping was also performed based on whether the MM and US findings were normal or not (Table 4). There were 3 different groups. Initially, the patient group with normal MM (-) and abnormal US (+) findings and the patient group with abnormal MM and US findings (+) were compared, and the p value was found to be 0.059 (Fisher's exact test). This result led to the conclusion that there were no statistically significant differences between the malignancy rates within the two groups. Secondly, the patient group with normal MM (-) and abnormal US findings (+) and the patient group with abnormal MM (+) and normal US findings (-) were compared, and the p value was found to be 0.250 (Fisher's exact test). This result led to the conclusion that there were no significant differences between the malignancy rates within the two groups. Finally, the patient group with abnormal MM and abnormal US findings (+) were compared with the patient group with abnormal MM (+) and normal US findings (-), and the p value

Table 1. Cross-chart comparison of mammography results and pathology results

Mammographic Findings	Pathology Results			
	Benign	Malignant	Total	
Micro-calcification	18	13	31	p=0.428
Nodular opacity	21	10	31	
Normal	9	1	10	
Asymmetrical density	2	3	5	
Calcification	3	0	3	
Structural distortion	1	2	3	
Total	54	29	83	

Table 2. Cross-chart comparison of BI-RADS score and pathology results

BI-RADS	Pathology Result			
	Benign	Malignant	Total	
0	3	0	3	
1	0	0	0	
2	3	0	3	
3	24	3	27	p=0.00092
4	23	26	49	
5	1	0	1	
6	0	0	0	
Total	54	29	83	

Table 3. Histopathological distribution of breast lesions sorted by breast quadrants

	Pathology Result						p
	Benign		Malignant		Total		
Lesion Localization	n	%	n	%	n	%	
Upper Outer Quadrant	26	48.1	19	65.5	45	54.2	0.607*
Upper Inner Quadrant	6	11.1	3	10.3	9	10.8	
Lower Inner Quadrant	6	11.1	3	10.3	9	10.8	
Lower Outer Quadrant	9	16.7	2	6.9	11	13.3	
Central	7	13	2	6.9	9	10.8	
Total	54	100	29	100	83	100	
*Fisher's Exact test							

was found to be 0.265 (Z test). This result led to the conclusion that there were no significant differences between malignancy rates within the two groups. In conclusion, no significant differences were observed among malignancy rates as per the US and MM findings (Table 4).

Table 4. The distribution of histopathological results according to MM and US findings

	Histopathology						p
	Benign		Malignant		Total		
	n	%	n	%	n	%	
MM (-), US(+)	9	16.7	1	3.4	10	12	0.097*
MM(+), US(+)	15	27.8	13	44.8	28	33.7	
MM(+),US (-)-	30	55.6	15	51.7	45	54.2	
Total	54	65.1	29	34.9	83	100	
*Fisher's Exact test							
The status 'normal' was defined in the chart as (-) and 'abnormal' as (+)							

Discussion and Conclusions

A great majority of patients with non-palpable lesions who are diagnosed with malignancy based on biopsy results has a small tumor size and a negative-axilla (5). The facts that the average tumor size of our patients identified to have malignancy was 16 mm, the median value was 13 mm and axilla-negativity was 82.7% are consistent with the literature. Similarly, the fact that 20 lesions (68.9%) were T1, 9 were T2 (31.1%) and there were no T3 or T4 lesions indicates an early stage disease in line with the literature.

The technique that is currently most frequently used in the localization of non-palpable breast lesions is wire-guided localization (19). This technique is limited by certain complications. The complications observed so far include the following: wire migration within the breast, migration to the pleural cavity or pericardium, bent needle, penetration into the pectoral muscle, tumor seeding, wrong placement, vasovagal reflex, dislodgement of wire during surgery, wire severance and contact of the electrocautery with the wire (20, 21). One of the most serious complications is the failure to completely excise the suspicious lesion. This rate is reported as approximately 12% in the literature (22). The complications observed in our study and their rates are similar to those in the literature. Most of these complications can be prevented by the development and standardization of needle system and insertion procedures (21, 23).

The malignancy rate of non-palpable lesions ranges between 19-50% (5, 24-28) in various series. Our malignancy rate of 34.9% in our study was found to be consistent with the literature. In a study conducted at our hospital by Derici et al. (29) between the years 1998-2006, the malignancy rate was found to be 32.8%. This rate shows that the experience of our center in this respect has been similar in the past and the present.

When a slightly suspicious lesion is identified on mammography, the decision for surgical biopsy is influenced by the physician's experience as well as the patient's view of his/her disease, his/her psychic condition and character for follow-up. In our study, some cases underwent biopsy although they had a low BI-RADS category for these reasons. The excision of non-palpable lesions based on marking offers an aesthetic advantage in that it causes minimal trauma, small tissue damage and requires a low lesion volume / breast volume (30). In some of

our patients, problems related to the possibility of excision of more breast tissue should the mass grow on follow-up and cosmetic problems emerged.

For the decision of either surgery or follow-up, the physician considers patient age in addition to radiological findings. According to studies on age and malignancy factors, there is a significant increase in breast cancer above the age of 50 (3, 9). In our study, there were no differences between the group aged 30-49 and the group aged >50 in terms of malignancy rates. This situation might have been due to the fact that the sample size in our study was not large enough to demonstrate statistical significance.

The studies conducted show that mammographic finding is the most important factor in the decision for biopsy. The most important radiomorphological finding leading to the indication for biopsy is reported to be mainly micro-calcification detected in mammography (31-33). Parallel with this finding, the fact that the ultrasound findings were normal in 52.4% of the patients in our study indicates that the decision for biopsy is taken mostly based on mammographic findings. Our most frequent surgical indication criterion was determined as micro-calcification at a rate of 37.3%.

In BI-RADS categorization, a score of 3 is defined as probably benign and of 4 as probably malignant (11-13). The fact that both the malignancy rate and positive predictive value of BI-RADS 4 lesions were significantly higher as compared to BI-RADS 3 lesions is a manifestation of the expected situation. The positive predictive value of BI-RADS 4 lesions was determined as 53%. Accordingly, it is recommended that the lesions in category BI-RADS 4 definitely be assessed via biopsy.

Although it is conventionally reported that breast cancer is identified most often at the upper outer quadrant (34), no associations could be identified between the quadrant site of lesions detected in our study and the identification of cancer.

The fact that as high as 50-80% of biopsies of non-palpable lesions revealed benign results might raise the question that unnecessary biopsies have been performed (5, 24-28, 35). Taking this situation into consideration, from a cosmetic point of view, the decision for surgical excisional biopsy may start to be questioned. This may ensure a trend towards the use or development of alternative diagnostic methods. The rate of benign diseases in our study was identified as 65.1%, parallel with the literature.

The limitations of our study are the limited number of patients and its retrospective nature. The results of a similar study with a prospective design might provide effective data on the importance of radiologic identifications. Furthermore, less invasive diagnostic methods such as stereotactic biopsy, vacuum-assisted breast biopsy or Magnetic Resonance-assisted biopsy, that are alternatives to US-guided fine needle aspiration biopsy and tru-cut biopsy, could not be performed in our hospital due to technical and operational limitations. However, we are of the opinion that the evaluation and close follow-up of non-palpable lesions, independent of the method employed, would contribute to identification of early stage breast cancer and prolong survival. Decision on the appropriate method is based on the knowledge, experience and preferences of a team composed of a radiologist, surgeon, pathologist and the patient.

In conclusion, surgical excision of non-palpable lesions that are suspicious for malignancy via various localization methods is a commonly used and beneficial method. Removal of non-palpable breast lesions (especially those with high BI-RADS scores) may aid in the detection of breast cancer at an early stage before leading to axillary metastasis. Non-palpable breast lesions interpreted as BI-RADS 4 should definitely be evaluated by means of biopsy. We conclude that the increased accuracy rates, widespread use and enhanced experience in the use of image-guided needle biopsies would result in reduction in unnecessary localization-guided surgical excisions.

Ethics Committee Approval: Ethics committee approval was not received due to the retrospective nature of this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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