ORIGINAL ARTICLE

# Follow-up versus tissue diagnosis in BI-RADS category 3 solid breast lesions at US: a cost-consequence analysis

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## PURPOSE

The aim of this study was to compare the economic effect of a proposed follow-up strategy for managing category 3 breast masses. The strategy incorporated direct tissue diagnosis at the patient's discretion for masses that had been assessed only based on ultrasonography (US) and for which mammography made no diagnostic contribution.

## MATERIALS AND METHODS

This prospective cohort study was conducted between 2003 and 2006 and included 174 patients. We used a two-year short-term follow-up protocol composed of five steps. A biopsy was recommended for masses that were increasing in size and changing in nature. The long-term results were available at the end of 2010. The mean and total costs were calculated for the women who preferred our follow-up protocol and for those who preferred direct tissue diagnosis. The cost savings were calculated by comparing the costs of the current study protocol to the costs of two different scenarios.

#### RESULTS

Two malignancies were found among the 18 women who underwent tissue diagnosis on the recommendation of the radiologist during follow-up. Thirteen of these women underwent biopsy at the request of the patient or surgeon, and these biopsies all revealed benign tumors. The overall negative predictive value was 99.2% (95% confidence interval, 98.46%–100%). There was a statistically significant difference between the mean costs for the women who chose our follow-up regimen (147.57±106.7 TL) and those who preferred direct tissue diagnosis (426.89±149.8 TL) (P = 0.0001). The use of our follow-up protocol decreased the cost of diagnosis by 60% compared with the cost of using direct tissue diagnosis as the initial procedure.

#### CONCLUSION

Our long-term results indicate that following-up solid category 3 masses detected only by US for at least two years at short intervals is a cost-effective alternative to direct breast biopsy.

Key words: • breast • biopsy • cost analysis

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Published online 13 October 2011 DOI 10.4261/1305-3825.DIR.4462-11.1 n 2003, the American College of Radiology (ACR) developed a breast imaging reporting and data system (BI-RADS) lexicon for breast ultrasonography (US) to standardize the characterization of lesions in US. Solid masses with circumscribed margins, an oval shape, and parallel orientation are classified as BI-RADS category 3, which indicates a probable benign solid mass in the BI-RADS assessment (1). Some studies have demonstrated that short-interval follow-up of category 3 masses is an acceptable alternative to biopsy (2–5) because these lesions have a low probability of malignancy (less than 2%) (2, 3, 6, 7). Graf et al. (3) have evaluated category 3 masses that are seen on US but that are partially or completely obscured at mammography. They reported that due to the extremely high negative predictive value (99.8%), follow-up with US appears to be an acceptable alternative to biopsy for solid masses with benign morphologic features in US imaging.

If a category 3 lesion observed on US is obscured on mammography, it is logical to follow with US because US is easily accessible and noninvasive. Whether US or mammography is used, radiological follow-up has advantages over the tissue diagnosis of breast lesions. Radiological follow-ups do not cause deformation of the breast or scarring in later mammograms. There is also no risk of postoperative complications. These are important factors that should be considered when determining a diagnostic strategy. However, it is also important to know which approach is more cost-effective prior to choosing one of them. In the literature, there are few reports on cost analyses of managing BI-RADS category 3 breast lesions. The existing studies have compared the costs of different biopsy techniques or analyzed the costs of mammographic follow-ups versus biopsy. Alonso-Bartolome et al. (8) have reported that the economic cost of the 11-G vacuum-assisted percutaneous biopsy approach was 82% lower than that of a surgical biopsy in probably benign breast lesions. In 1997, Brenner and Sickles (9) compared the economic cost of stereotactic core needle biopsy with that of short-term unilateral surveillance mammography in the management of probably benign breast lesions detected during routine screening mammography. They found that core biopsy was more costly than mammographic surveillance and had similar false-negative rates. To our knowledge, there is no study in the literature comparing the economic cost and the benefits of this follow-up strategy with that of breast biopsy in probably benign breast masses observed only on US. We initiated our study to clarify this issue for nonpalpable category 3 masses for which mammography adds no diagnostic value and generated the following research question: is our proposed short-term follow-up regimen more or less costly than breast biopsy for managing category 3 breast masses observed on US?

# Materials and methods

Study design

This was a prospective cohort study conducted between September 2003 and April 2006. We established a shortterm follow-up protocol to monitor BI-RADS category 3 nonpalpable solid breast masses that had been detected only on US. Patients with such masses were the target population of the study. The costs associated with the patients who complied with our protocol were compared to the costs associated with the patients who chose other options, and the differences were tested.

## Follow-up protocol

Our two-year short-term followup protocol consisted of five steps. Each patient was invited for US at three-month intervals for the first six months and six-month intervals for the next 18 months. Mammography was added to the protocol at the 12th and 24th months (Fig. 1). If the lesion was stable at any follow-up step, the patient was invited to continue with the next step. For example, when the lesion was stable at the 3rd month follow-up exam, the patient was asked to return three months later for a second follow-up exam (six months after the initial examination). No further follow-up was conducted for masses that decreased in size or disappeared because these lesions were considered benign. A cyst that appeared as a solid mass due to deep localization or internal echoes at any follow-up step was downgraded to BI-RADS category 2 and excluded from the shortterm follow-up protocol. The patients with such lesions were recommended to have routine screenings. The follow-up protocol was ended when masses disappeared, were biopsied, or stayed stable at least two years. If we observed a new category 3 mass in a patient who was already under follow-up for single or multiple masses, we called this lesion a "newly seen category 3 mass" and monitored it separately, but we kept it out of the study analysis. We performed a lesionto-lesion comparison at follow-up examinations. We scheduled annual screenings, including mammography and US, for the women older than 40 years old after the short-term followup was completed. For the women less than 40 years old, we recommended annual US follow-ups. In our breast

unit, if we observe an irregular shape, indistinct borders, and a non-parallel axis in any BI-RADS category 3 solid mass at follow-up, we classify these new features as a "change in imaging features or change in nature". A biopsy was recommended for the masses showing interval progression by increasing the size (more than 20%–25% of the original diameter in the perpendicular plane) or by changing the other features (1, 10). Biopsies were also performed at the discretion of the patients or the surgeon. The patients underwent either percutaneous US-guided core biopsy (14-Gauge needle, Magnum, C.R. Bard, Murray Hill, New Jersey, USA) or surgical biopsy after guide wire localization with US guidance. A total of 35 masses in 31 women were subject to biopsy.

# Patient selection

Patients were included if they were observed in control examinations at least four times throughout the follow-up period or if the preferred biopsy as the initial procedure even though it was not recommended by the radiologist.

Masses were included if they met one of the following conditions: they were visualized on US but not on mammography; they had obscured borders (more than 25%) on mammography due to scattered and heterogeneously or extremely dense glandular patterns; they were detected in young patients (less than 40 years old) for whom mammography was not appropriate; or if they had a circumscribed margin, an oval or round shape, slight or no lobulation, and a parallel orientation (for oval masses) (1–4, 6, 11).

Patients were excluded if they did not complete their follow-up protocol, did not have required data (such as addresses or correct names), missed at least two control examinations during the follow-up, refused both the shortterm follow-up and biopsy, were treated in private hospitals without any cost information, had a personal or family history of breast cancer or underwent partial or total mastectomy.

Masses were excluded if they met one or more of the following conditions: they were diagnosed as benign or malignant by mammography, US or other techniques, such as spot compression; they were diagnosed as probably benign by mammography (in which case they were followed-up using both mammography and US); they were probably benign based on palpation; they had any additional suspicious mammographic findings, such as microcalcification, or US findings incompatible with category 3 assessment, such as irregular shape, a nonparallel axis, or an indistinct/microlobulated/angular margin; or they had a complex, cystic nature.

# Imaging method

US was performed using a variablefrequency linear transducer set at 12 MHz and 7 MHz (Aplio 80, Tosbee, Toshiba, Tokyo, Japan) by three experienced radiologists. One of the radiologists had nine years of experience in breast radiology. The other two radiologists consulted with the most experienced radiologist for all of the solid masses. All the patients were enrolled for follow-up by the same radiologists. Measurements were made and compared in the longitudinal and transverse planes. The mammograms were obtained by screen-film mammography (Philips Mammo Diagnost 3000, Philips Healthcare, Best, the Netherlands) between 2003 and 2005 and full-field digital mammography (Giotto, IMS, Bologna, Italy) after 2005.

# Study group

Among the 11 373 women referred for breast US, we detected 723 solid, nonpalpable category 3 masses in 605 women. These women were referred by the menopause or surgery units of our university hospital for reasons such as mastalgia, fear of cancer, routine screening with mammography and US, hormonal imbalances, screening prior to or during hormone replacement therapy, increased carcinoembryonic antigen levels, whole body work-up before anti-TNF treatment, and abnormal clinical findings, such as palpable and/or suspicious masses, galactorrhea, palpable lumps, and retraction or erythema of the breast skin.

We included the US reports and images in our digital US archive (Tomtec Imaging Systems, version 2.7, Munich, Germany) between 2003 and 2006. We used radiology/patient information programs (MEDI-RIS 10.18, 1997/2009 and MEDI-HASTA 13.14, 1997/2010, Akdeniz University Hospital Data



**Figure 1.** The diagram depicts a decision tree. A woman with a category 3 mass can choose breast biopsy or our follow-up protocol for her diagnostic work-up options. The woman proceeds with step-by-step follow-up with US unless an interval change during surveillance prompts tissue diagnosis. "©" denotes cost. US, ultrasonography; MG, mamography.

Processing Center, Antalya, Turkey) to access the required personal and medical information. Of the 605 women, 64 were not included in the study because they had not yet completed their follow-up protocol in 2006. We lost information on 154 women in the above-mentioned systems because of programming errors during system upgrades, changes in addresses or misspelled names. Furthermore, 30 women who refused the short-term follow-up protocol or biopsy and 179 who missed at least two control examinations during the follow-up period (209 total) were excluded from the study. Finally, four women who were treated in private hospitals were excluded from the study because we could not obtain exact information on their treatment costs. Consequently, a total of 174 women with 248 masses who were seen under the short-term protocol at least four times and whose follow-up results or biopsy results were available composed our study group. The long-term results for the women who underwent our follow-up protocol between 2003 and 2006 were also accessible in our digital archive or in the above-mentioned data storage systems until the end of 2010.

The study group was divided into three subgroups.

Group I (n=143) included 213 masses that were stable, disappeared, decreased in size, or were observed to be a cyst but were not biopsied during the follow-up.

Group II (n=18) included 20 masses on which biopsy (surgical biopsy after wire localization or core biopsy) was performed based on the recommendation of the radiologist. Such recommendations were made based on interval progression demonstrated by an increase in size (more than 20%–25% of the original diameter in the perpendicular plane) or on changes in features during follow-up. The sum of Groups I and II (n=161) accounts for the total number of patients who adopted our follow-up protocol (the follow-up group).

Group III (n=13) included 15 masses for which a biopsy (surgical biopsy after wire localization or core biopsy) was performed upon the request of the patient or the surgeon. These patients did not adopt our follow-up regimen.

The patients with a personal or family history of breast cancer and those evaluated by unilateral/bilateral breast US due to partial or total mastectomy were not included in the study because our approach to category 3 masses in such patients recommends biopsy rather than follow-up. Ethical approval was obtained from the local ethics committee. The patients were informed about probably benign lesion behavior and the follow-up protocol.

## Decision analysis model

Our study used a decision tree model (Fig. 1). The source of the efficacy data is our prospective cohort study and its long-term results between 2003 and 2010. Therefore, we did not use any assumptions in the study model. Our efficacy measure was the number of cancer cases detected. The time horizon was 80 months.

Two scenarios were generated to determine the cost of the follow-up protocol and the cost of the tissue diagnosis methods, including surgical and core biopsy.

Scenario A: If all of the study population had undergone tissue diagnosis (core or surgical biopsy) without follow-up, what would the cost per case and the overall costs have been?

Scenario B: If the patients in Group III had complied with our follow-up

protocol instead of having biopsies, what would the cost per case and the overall costs have been?

# Calculating the costs

The direct costs were calculated using the national health insurance reimbursement rates for each patient (Table 1). The procedure codes were extracted from the Health Budget Implementation Regulations (BUT) of the Ministry of Health in 2006 (except for complications or comorbidities) (12). The reimbursement rates (except for the hospital stay per day) have not been changed by the Health Department since 2005. In other words, the government fixed most of the health insurance reimbursements. irrespective of inflation, between 2005 and 2010. Thus, there was no need to take incremental rates into account. The hospital stay fee was increased in 2010 and this increase was reflected in the calculations of the total costs for each procedure and of the overall cost savings over surgical biopsy. The cost savings were calculated by subtracting the cost of diagnosis using the followup protocol from the cost that would have been generated if tissue diagnosis had been performed as the initial procedure. In Groups II and III, the health insurance reimbursement rates for the following materials and procedures were obtained to calculate the costs of a surgical biopsy after US-guided wire localization and of a percutaneous USguided core biopsy: local anesthesia, excisional breast biopsy, hospitalization, dressings, specimen viewing, 20-21 gauge 10 cm breast localization wire, US-guided wire localization, histopathological evaluation, percutaneous US-guided core biopsy, and 14 gauge tru-cut core biopsy needles. In Group II, the costs before the biopsy, such as repeated US examinations, bilateral mammography, and repeated clinical examinations by the surgeon. were calculated and added to the biopsy costs. For Group I, the number of examinations by the surgeon and the number of follow-ups with US or US+bilateral mammography were determined. We were not able to calculate indirect costs arising from time away from work, transportation, and staff. The calculation of health care staff costs was problematic because the individual performance payments and salaries varied between different health care professionals due to their ranks and status.

# Statistical analyses

A software package (MedCalc<sup>®</sup> Version 11.1.1.0, Mariakerke, Belgium) was used for the statistical analysis. All the results are presented

 Table 1. Direct costs per billable item in US follow-up, US-guided core needle biopsy, and surgical biopsy after wire localization

Procedure	Code <sup>a</sup>	Cost (TL)
Breast US	803.440	16.83
Mammography (unilateral)	801.590	18.70
US-guided wire localization	803.280	32.67
Clinical examination	520.030	15.50
Excisional biopsy	614.380	148.4
Histopathological analysis	910.400	41.03
Specimen radiography	801.590	33.00
Hospital stay	510.030	30.00
Local anesthesia	530.290	9.00
Dressing	530.410	6.00
Guide wire	_	50.18
Percutaneous US-guided core biopsy	802.930	38.50
Core biopsy needle (14 Gauge)	-	44.17
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<sup>a</sup>Health insurance reimbursement codes in "Health Budget Implementation Regulations" (BUT) for 2010.

the mean) and the number of individual observations (n). The appropriate statistical analyses were performed to test whether the differences observed between the study groups were statistically significant. A *P* value < 0.05 was accepted as statistically significant. The mean ages and costs were compared between the patients in Groups I and II (the follow-up groups) and those in Group III using the Mann-Whitney U test. The mean costs of the current study group and scenarios A and B were compared using an analysis of variance (ANOVA) model, and the differences between individual means were evaluated using Tukey's HSD. The overall negative predictive value (NPV) and false negative rate (FNR) on a per-lesion basis were calculated for the initial BI-RADS 3 assessment. Due to the clustered dependency of the data from the patients with multiple lesions, the FNR on a per-patient basis was also calculated. The Wilson score method without continuity correction was used to the calculate confidence intervals for the proportions, sensitivity, and specificity (13).

as the mean values (±standard error of

# Results

The age of study group ranged from 31 to 67 years (mean,  $42.4\pm10.0$  years). About half of the study population was between 40–49 years old. Three-fourths of study population was younger than 50 years old. The mean ages for the patients in Groups I+II and Group III were 46.04±8.9 years and 41.63±10.3 years, respectively. There was a statistically significant difference between the mean ages of patients in Groups I+II (the follow-up groups) and those in Group III (P = 0.0001).

Group I was composed of 213 masses. Of these, 168 remained stable, 16 were actual cysts, 12 decreased in size, and 17 disappeared completely (Fig. 2). Over the long-term, we did not see any malignancy in the 209 women excluded from our study because of their low compliance.

Biopsies were performed for 35 masses in 31 women. Thirteen of the women underwent biopsy at their own or their surgeon's discretion and all of these masses were shown to be benign by histopathological examination. Biopsy was recommended by the radiologist for 20 masses in 18 women because of an abnormal



Figure 2. a–d. A 42-year-old woman with a BI-RADS category 3 mass. The mass shows an oval shape, circumscribed margins and parallel orientation (a). The mass was stable six months (b) and two years (c) later. We recommended routine annual screenings at the end of the follow-up protocol. The mass was stable five years later (d).

interval progression displayed on a follow-up sonogram. Of these 20 lesions, 2 were found to be malignant by histopathological examination (Table 2). Both of these malignancies were observed by the radiologist at the 3rd month's follow-up exam (the first step of the follow-up protocol). One was a 15×9-mm mass in a 43-year old woman that increased in size and had indistinct borders, and an US-guided core needle biopsy showed invasive papillary carcinoma (T1c N0 M0). The second lesion was a 12×11-mm mass in a 51-year old woman that showed an increase of more than 25% from its previous size and a change in shape. A core needle biopsy revealed microinvasive ductal carcinoma in situ (T1 mic) (Fig. 3). These two women were diagnosed as having node negative and stage 1 disease and are still alive. The biopsy results from the 31 patients and 35

masses are shown in Table 2. Of the 35 masses that underwent tissue diagnosis, 23 (65.7%) underwent surgical biopsy after wire localization and 12 (34.3%) underwent US-guided core needle biopsy. In our study, unnecessary biopsies were decreased by 82%. Our biopsy recommendation rate was no more than 11%, and the biopsy rate was 18%. Our follow-up protocol prevented unnecessary biopsies in the majority of the study population by revealing stability or regression. Of the 174 women, 152 (87.3%) had single, and 22 (12.6%) had multiple lesions. In 8 (4.5%) of the women, more than three lesions were observed. The overall NPV was 99.2% (246/248; 95% confidence interval [CI], 98.46%-100%). The FNRs on a per-lesion basis and on a per-patient basis were 0.8% (2/248; 95%CI, 0.2%–2.9%) and 1.1% (2/174; 95%CI, 0.3%-4.0%), respectively.

 Table 2. The histopathological results

 for the 35 solid lesions that underwent

 biopsy

Histopathological results	n
Fibroadenoma	12
Fibroadenomatous hyperplasia	8
Nodular sclerosing adenosis	4
Fibrocystic change	7
Atypical ductal hyperplasia	1 <sup>a</sup>
Papilloma	1
Microinvasive ductal carcinoma in situ	1
Invasive papillary carcinoma	1
Total	35

<sup>a</sup>Surgical biopsy after wire localization revealed negative surgical margins.



**Figure 3.** *a*, *b*. A 51-year-old woman with a BI-RADS category 3 mass (a). The mass showed a change in size and features three months later (b). The size increased at rates of 53% in the longitudinal diameter and 117% in the anteroposterior diameter (from 8.3×5.2 mm to 12.7×11.3 mm). Note the indistinct margins in addition to the irregular shape. A core needle biopsy revealed microinvasive ductal carcinoma in situ (T1 mic).

The mean costs to the patients in Group I (n=143), Group II (n=18), and Group III (n=13) were 114.24±30.1 TL, 400.77±135.7 TL, and 426.89±149.8 TL, respectively. In the follow-up groups (n=161, Groups I+II), the mean cost was 147.57±106.7 TL. We found a statistically significant difference between the cost to the follow-up group (Groups I+II) and the cost to the tissue diagnosis group (Group III, the patients who initially preferred surgical or needle biopsy) (P = 0.0001, Table 3). The costs of the US-guided core needle biopsies and surgical biopsies after US-guided wire localization (including a one-day-hospital stay) without the follow-up protocol were 173.33 TL and 416.43 TL, respectively. The direct costs per billable item associated with the procedural terminology codes (Health Budget Implementation Regulations, BUT codes) in Groups I, II, and III are shown in Table 1.

The overall costs and mean cost for the study (Group I+II+III) population were 29 604.01 TL and 168.20±131.0 TL, respectively. For scenario A, the overall cost and the mean cost per case would have been 75 489.09 TL and 426.89±149.8 TL. Thus, the direct cost savings in the actual study compared with scenario A were 45 885.08 TL in total and 263.70 TL per case. Although 13 patients did not comply with our follow-up regimen, the use of our follow-up protocol decreased the cost of diagnosis by 60% compared with the cost of direct tissue diagnosis as

the initial procedure. The ratio of the cost of immediate breast biopsies to the cost of the follow-up protocol was approximately 3:1. For scenario B, the overall cost and the mean cost per case were 26 753.62 TL and 147.57±106.0 TL, respectively. The direct cost savings obtained by comparing scenario B with scenario A were 46,597.85 TL in total and 279.32 TL per case. There was a statistically significant difference between the mean costs of the current study group, those of scenario A and those of scenario B (P = 0.0001; in the post-hoc Tukey test, scenario A was responsible for the difference) (Table 3).

## Sample cases

The total cost to a sample case that complied with the short-term protocol by undergoing examination four times throughout the two years (Group I) was 129.40 TL. The total cost to a sample case from Group II who underwent surgical biopsy after US-guided wire localization on the recommendation of the radiologist at the fourth visit (at the 18 month follow-up) was 479.60 TL. The total cost to a sample case from Group II who underwent US-guided core needle biopsy at her fourth visit on the recommendation of the radiologist owing to an increase in size was 253.02 TL.

### Table 3. The mean costs among study groups and different scenarios

	Mean cost (TL)	Standard deviation	P <sup>a</sup>
Current study subgroups			
Group I+II	147.5	106.7	0.0001
Group III	426.9	149.8	
Study and scenario groups			
Whole study group (Group I+II+III)	168.2	131.0	0.0001
Scenario A	426.9	149.8	
Scenario B	147.5	106.7	

<sup>a</sup>Mann-Whitney U test for comparing Groups I+II to Group III; one way ANOVA model for comparing the entire study group, scenario A, and scenario B.

Groups I+II included the patients who were fully compliant with the recommendations of the radiologist continue with the follow-up protocol or to undergo biopsy during follow-up.

Group III included patients who did not follow the recommendations of the radiologist and underwent biopsy at their own or their surgeon's request.

Scenario A: The entire study population underwent direct tissue diagnosis.

Scenario B: All of the study patients fully complied with the follow-up protocol (as in Groups I+II).

## Discussion

In follow-up studies, BI-RADS category 3 masses have generally been assessed using a combination of mammography and US (2, 6, 11). However, this combination may not always be available in practice. Radiologists may encounter probably benign nonpalpable solid masses that can be seen on US but that are obscured or not seen on mammography, and they need to manage such cases using US findings alone. The literature suggests that following such masses is an alternative to biopsy (2-5). However, breast centers have different approaches, and some prefer follow-up while others prefer biopsy. Evaluating different strategies and other feasible alternatives to determine the optimal trade-off between costs and benefits is critical, especially in developing countries. Although some scientific data are available to consider follow-up as an alternative clinical approach to breast biopsy, there is no information available about the financial aspects of these two approaches. Although any follow-up protocol requires several hospital visits, it is not clear whether the costs are greater than those of biopsy, which is a one-step procedure. The results of our analysis, which is the first in the literature. indicate that following up solid probably benign masses detected only on US for at least two years at short intervals is a less costly strategy, with a cost savings of 45 885.08 TL in total and 263.70 TL per case compared to that of immediate tissue diagnosis. Our follow-up regimen decreased the cost of diagnosis by 60% compared to the cost of direct tissue diagnosis as the initial procedure. Although we excluded 209 women in our study due to noncompliance, the cost of the follow-up protocol was still approximately one third that of direct breast biopsy. If we had included these women in the calculations of the mean costs, there is no doubt that the ratio would have changed dramatically in favor of the follow-up approach.

A radiological cost-effectiveness analysis compares two alternatives in terms of health outcomes and economic cost. When a diagnostic test is said to be "cost-effective", the additional health benefits that it provides are considered to be high relative to the costs when compared to the alternatives. In other words, if one alternative has lower costs and superior efficacy

with additional health benefits, it is the more cost-effective approach (14-16). Our long-term results show that the follow-up protocol, with its high NPV (99.2%), had the same efficacy as breast biopsy in detecting cancer cases. We detected two malignancies in two women in the first step of the followup protocol with a low FNR (0.8%; 95%CI. 0.2%–2.9%). These women were diagnosed as having node negative and stage 1 disease and they are still alive. In other studies evaluating category 3 masses by US, malignancies were mostly found in their early stages, within the first six months. These studies have reported a high NPV and a low FNR, similar to our study (3, 6, 7. 17). For example, Moon et al. (17) diagnosed 9 out of 14 early-stage malignancies at the first US follow-up. These data demonstrate that a followup protocol is as efficient as direct breast biopsy for diagnosing malignant lesions. Additionally, our follow-up protocol prevented unnecessary biopsies by revealing stability or regression in the majority (82%) of the study population. Protocols without unnecessary biopsies cause less morbidity, with shorter-duration hospital stays, less pain, fewer risks due to general anesthesia, and fewer complications due to tissue diagnosis. In addition to its economic superiority, the same efficacy and these additional health benefits indicate that our follow-up regimen is more cost-effective than biopsy.

Cost-effectiveness analyses have certain methodological requirements, such as efficacy measures, a probabilistic sensitivity analysis to account for parameter uncertainty, a study model (such as a decision-analytic model or regression model). reference cases. strategies for meeting different scenarios, and an adequately long time horizon (15, 18). Our study met most of these requirements, except for the use of quality-adjusted life years (QALY), which is a natural efficacy measure and sensitivity analysis. Thus, we do not present our study as a full cost-effectiveness analysis. Quality of life refers to individuals' state of being pleased, according to their own cultural standards, with the status, aims, expectations and perception of their lives. Ouality of life instruments are widely used as outcome measures and compare the efficacy of a wide range of interventions (15). Quality of life instruments

are classified into two groups: generic and disease-specific. Using QALYs produces an incremental cost-effectiveness ratio, in dollars per QALY. This ratio is used to express the difference in cost-effectiveness between new diagnostic tests or treatments and current therapies (14, 15, 19). A generic quality of life instrument is less sensitive to variation. Av et al. (20) assessed quality of life using a Turkish version of The Psychological General Well-Being Index (a generic quality of life questionnaire) in a Turkish population that included 50 healthy individuals. However, disease-specific instruments can be used to examine areas specific to a disease and have strong sensitivity to variation. In our study, the use of QALYs would have been problematic because disease-specific values have not been determined for our study population. In our opinion, adapting the numerical QALY values from another population to calculate the incremental cost ratio would have given rise to inaccurate results. Instead, we presented a cost-consequence analysis that considered the economic costs and benefits of two alternatives.

Due to limited healthcare resources in our country, radiologists must make challenging decisions every day. Our study examined one of the challenging decisions in breast radiology, and the follow-up results indicate that the best strategy is to employ step-by-step US follow-ups in BI-RADS category 3 lesions, unless an interval change during surveillance prompts tissue diagnosis. We started with a short-term follow-up for at least two years and then recommended age-appropriate screenings. The rationale behind this strategy was that the benign-appearing masses may actually have been invasive carcinomas and that malignancies in young patients can grow rapidly (21–24). Considering that about half of our study population was between 40-49 years old and three-fourths of the study population was younger than 50, the short-term follow-up was crucial for our study group. We believe that close monitoring of probably benign lesions may help to detect rapidly growing malignant lesions at the earliest possible stage.

In our study, 12.6% of patients had more than one breast mass and 4.5% of women had more than three lesions. Multiplicity was demonstrated in 1.7% of the screening examinations (25, 26). Graf et al. (3) detected multiplicity in 7.6% of 409 women in their study. Park et al. (11) found multiple BI-RADS 3 masses on US in 23 of 274 women. Multiplicity, especially multiple bilateral category 3 masses, has been shown to decrease the likelihood of malignancy of circumscribed masses detected on mammography. In our opinion, multiplicity is a strong indication for radiological follow-ups because it is not possible to perform biopsy on all the masses.

This study has some strengths and limitations. One strong point is that it was a prospective, cohort study that included a long follow-up period. The time horizon was long enough to fully capture the benefits and risks of the follow-up strategy. Another strength of the study was that we did not use an assumption model to predict the efficacy of follow-up or morbidity reduction. Instead, we used our actual long-term results. The most prominent limitation of the study was our inability to calculate indirect costs. Indirect costs include staff costs, transportation, associated costs (loss of income due to time away from work and lack of productivity because of emotional or physical effects, unnecessary workups, etc.) (15). It is difficult to assign monetary values to such indirect effects. We were not able to add the staff costs to our analysis due to differences in performance and monthly salary scales for specialists, professors, nurses, and technicians working in different areas and due to differences in the lengths of the procedures.

In conclusion, in category 3 breast masses diagnosed at US, our followup regimen decreased the cost of diagnosis by 60% compared to the cost of direct tissue diagnosis as the initial procedure. Our long-term results indicated that follow-up of solid category 3 masses detected only on US for at least two years at short intervals is a cost-effective alternative to direct breast biopsy. Further studies with similar groups that consider the limitations of the current study are needed to test the reliability of our results. Additionally, the generalizability of the results presented here should be tested in similar studies in other countries with different health-care payment systems.

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## Conflict of interest disclosure

The authors declared no conflict of interest.

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