

**Mammographic Follow-up as an
Alternative to Biopsy: Strengths,
Limitations, Pitfalls**

Edward A. Sickles, M.D.

Probably Benign Findings

Localized

Generalized

Probably Benign Findings - Localized

Cluster of tiny round/oval calcifications

Probably Benign Findings - Localized

Cluster of tiny round/oval calcifications

Noncalcified circumscribed solid mass

Probably Benign Findings - Localized

Cluster of tiny round/oval calcifications

Noncalcified circumscribed solid mass

Focal asymmetry

Probably Benign Findings - Localized

Cluster of tiny round/oval calcifications

Noncalcified circumscribed solid mass

Focal asymmetry

Miscellaneous

Probably Benign Findings - Generalized

Discrete clusters of tiny calcifications

Probably Benign Findings - Generalized

Discrete clusters of tiny calcifications

Scattered / clustered tiny calcifications

Probably Benign Findings - Generalized

Discrete clusters of tiny calcifications

Scattered / clustered tiny calcifications

Noncalcified circumscribed solid masses

Localized Findings

Cluster of microcalcifications	1938
Noncalcified solid mass	2174
Focal asymmetry	741
Miscellaneous findings	73
TOTAL	4925

PPVs for Localized Findings

Cluster of microcalcifications	7	(0.4%)
Noncalcified solid mass	24	(1.1%)
Focal asymmetry	5	(0.7%)
Miscellaneous findings	0	(- - - -)
TOTAL	36	(0.7%)

Generalized Findings

Discrete clusters of microCa⁺⁺	115
Scattered / clustered microCa⁺⁺	539
Noncalcified solid masses	1601
TOTAL	2255

PPVs for Generalized Findings

Discrete clusters of microCa	0	(- - - -)
Scattered / clustered microCa	1	(0.2%)
Noncalcified solid masses	2	(0.1%)
TOTAL	3	(0.1%)

Multiple Bilateral Masses Detected on Screening Mammography: Assessment of Need for Recall Imaging

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OBJECTIVE. When multiple bilateral partially circumscribed masses having a similar appearance are detected on screening mammography, some radiologists recommend recall examination to identify imaging features suggestive of malignancy that are not evident on standard screening views. This study assesses the need for such recall imaging.

SUBJECTS AND METHODS. Cases of multiple masses were identified by reviewing the mammographic reports of 84,615 consecutive screening examinations. Each case of multiple masses was prospectively interpreted as benign, with recommendations for follow-up mammography in 1 year and for aspiration of any palpable masses if clinically indicated. Subsequently diagnosed cancers were identified through data linkage with our regional tumor registry and through our institution's computer-based outcomes tracking system.

RESULTS. Among 84,615 consecutive screening examinations, we identified 1440 (1.7%) cases of multiple masses. Among the multiple-masses cohort, two interval cancers were found. Both were early-stage (T1bN0M0; T1cN0M0) and low-grade (histologic grade 1) cancers. The interval cancer rate among the multiple-masses cohort was 0.14%, which is somewhat lower than the age-matched United States incident cancer rate of 0.24%.

CONCLUSION. The frequency of cancer development and the stage at cancer diagnosis among nonrecalled cases of multiple masses are similar to those observed in the general screening mammography population. Therefore, recall imaging for women with multiple masses does not appear to be justified.

AJR 2000; 175:23-29

Rationale for Mammographic Follow-Up

Can identify “probably benign” lesions

Mammographic Surveillance of Probably Benign Lesions

Author / Yr	Cases	Follow-Up	Frequency	PPV
Wolfe '87	1,356	6-12 mo	6.4%	0.6%
Helvie '91	90	20 + mo	5.6%	1.1%
Sickles '91	3,184	36 + mo	11.2%	0.5%
Varas '92	535	~ 26 mo	2.6%	1.7%
Vizcaíno '01	795	24 mo	5.8%	0.3%
Varas '02	511	24 + mo	3.0%	0.4%

Rationale for Mammographic Follow-Up

Can identify “probably benign” lesions

In F/U, find cancers by interval change

Detection of Cancers in Initial UCSF Study

F/U Exam	Mam Change	No Mam Change	No Mam Done
6 mos	2	0	0
6 mos	8	0	2
1 year	4	0	0
1 year	1	0	0
TOTAL	15	0	2

Detection of All 47 Cancers at UCSF

F/U Exam	Mam Change	No Mam Change	No Mam Done
6 mos	6	0	0
6 mos	23	0	2
1 year	12	0	2
1 year	2	0	0
TOTAL	43	0	4

Rationale for Mammographic Follow-Up

Can identify “probably benign” lesions

In F/U, find cancers by interval change

Cancers still have favorable prognosis

Features of the Initial 17 UCSF Cancers

Axillary node metastasis	2	(12%)
Systemic metastasis	0	(- - -)
Stage 0 + I cancer	15	(88%)
Minimal cancer	8	(47%)

Features of All 47 UCSF Cancers

Axillary node metastasis	4	(9%)
Systemic metastasis	0	(- - -)
Stage 0 + I cancer	42	(89%)
Minimal cancer	25	(53%)

Follow-Up of the Initial 17 UCSF Cancers

None show evidence of recurrence

Median follow-up: 238 months (20 yrs)

Range of follow-up: 213-299 months

Follow-up (node +): 258 & 271 months

Rationale for Mammographic Follow-Up

Can identify “probably benign” lesions

In F/U, find cancers by interval change

Cancers still have favorable prognosis

Avert morbidity of benign biopsies

Reduce induced costs of benign biopsy

Had all probably benign lesions in the initial study been biopsied, the yield of malignancy would have decreased by 34%, from 38% to 25%.

Utility of Previous Mammograms

Lesion decrease

Lesion stability

Lesion increase

Utility of Previous Mammograms

Lesion decrease

- **Screening mammo in 1 year**

Lesion stability

Lesion increase

Utility of Previous Mammograms

Lesion decrease

- Screening mammo in 1 year

Lesion stability

- Surveillance mammo in 1 year
- Screening mammo in 1 year

Lesion increase

Utility of Previous Mammograms

Lesion decrease

- Screening mammo in 1 year

Lesion stability

- Surveillance mammo in 1 year
- Screening mammo in 1 year

Lesion increase

- Tissue diagnosis

Utility of Lesion Increase at Mammo

Increase prompted biopsy in 178 cases

29 of these were cancer (16%)

All 29 cancers were nonpalpable

27 of 29 cancers have good prognosis

Utility of Lesion Increase at Mammo (UCSF)

Increase prompted biopsy in 312 cases

43 of these were cancer (14%)

All 43 cancers were nonpalpable

40 of 43 cancers have good prognosis

The mammographic demonstration of interval change appears to be an important, albeit nonspecific sign of occult malignancy.

Unresolved Issues

Need for full imaging work-up

Need for Full Imaging Work-Up

Promptly identify some benign lesions

Need for Full Imaging Work-Up

Promptly identify some benign lesions

Promptly identify some cancers

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Abbreviations:

BI-RADS = Breast Imaging Reporting
and Data System

PBF = probably benign finding

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Breast Cancer Yield for Screening Mammographic Examinations with Recommendation for Short-Interval Follow-up¹

PURPOSE: To compare cancer yield for screening examinations with recommendation for short-interval follow-up after diagnostic imaging work-up versus after screening mammography only.

MATERIALS AND METHODS: From January 1996 to December 1999, Breast Imaging Reporting and Data System assessments and recommendations were collected prospectively for 1171792 screening examinations in 758 015 women aged 40-89 years at seven mammography registries in Breast Cancer Surveillance Consortium. Registries obtained waiver of signed consent or collected signed consent in accordance with institutional review boards at each location. Diagnosis of invasive cancer or ductal carcinoma in situ within 24 months of screening examination and tumor stage and size for invasive cancer were determined through linkage to pathology database or tumor registry. χ^2 test was used to determine significant differences between groups.

RESULTS: Overall, 5.2% of first and 1.7% of subsequent screens included recommendation for short-interval follow-up, which was similar to likelihood of recommendation for diagnostic evaluation (first screens, 4.6%; subsequent, 2.6%). Most recommendations for short-interval follow-up were based on screening mammography alone (86.2% of first screens, 77.5% of subsequent). Yield of cancer for screening examinations with probably benign finding (PBF) and recommendation for short-interval follow-up based on screening mammography alone tended to be lower than in those with PBF and recommendation for short-interval follow-up after additional work-up (first screens: 0.54% vs 0.96%, $P = .10$; subsequent: 1.50% vs 1.73%, $P = .26$). Proportion of stage II and higher disease tended to be higher for examinations with PBF and recommendation for short-interval follow-up based on screening mammography alone compared with those recommended for short-interval follow-up after additional work-up (first screens: 34.7% vs 24.4%, $P = .43$; subsequent: 27.5% vs 19.2%, $P = .13$).

CONCLUSION: Many first screening examinations include recommendation for short-interval follow-up based on screening mammography alone. Cancer yield for these examinations is low and is lower than that with diagnostic work-up prior to short-interval follow-up recommendation. Absence of diagnostic work-up prior to short-interval follow-up recommendation may result in periodic surveillance of a high proportion of benign lesions.

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Need for Full Imaging Work-Up

Promptly identify some benign lesions

Promptly identify some cancers

Establish a “full-work-up” baseline

Need for Full Imaging Work-Up

Promptly identify some benign lesions

Promptly identify some cancers

Establish a “full-work-up” baseline

Explain findings directly to the patient

Unresolved Issues

Need for full imaging work-up

Lesion size and patient age thresholds

Masses as a Function of Patient Age

Patient Age	Cases	Cancers
< 40	227	2 (0.9%)
40-49	451	5 (1.1%)
50-59	319	5 (1.6%)
60-69	246	4 (1.6%)
70 +	160	3 (1.9%)

Masses as a Function of Lesion Size

Lesion Size	Cases	Cancers
≤ 5 mm	133	1 (0.8%)
6-10 mm	804	11 (1.4%)
11-15 mm	279	4 (1.4%)
16-20 mm	152	3 (2.0%)
> 20 mm	35	0 (- - - -)

Utility of Thresholds Using Patient Age

Age	Follow-Up	Biopsy
< 40	2/227 (0.9%)	17/1176 (1.4%)
< 50	7/678 (1.0%)	12/725 (1.7%)
< 60	12/997 (1.2%)	7/406 (1.7%)

Utility of Thresholds Using Lesion Size

mm	Follow-Up	Biopsy
≤ 5	1/133 (0.8%)	18/1270 (1.4%)
≤ 8	8/653 (1.2%)	11/750 (1.5%)
≤ 10	12/937 (1.3%)	7/466 (1.5%)
≤ 15	16/1216 (1.3%)	3/187 (1.6%)

Provisional Conclusion

Nonpalpable, circumscribed, noncalcified, solid (probably benign) masses should be managed with periodic mammographic surveillance regardless of lesion size and patient age.

Unresolved Issues

Need for full imaging work-up

Lesion size and patient age thresholds

Specific details of surveillance protocol

UCSF Surveillance Protocol

6 months: ipsilateral breast

6 months later: both breasts

12 months later: both breasts

12 months later: both breasts

Mammographic Surveillance Protocols

Author	4 mo	6 mo	1 yr	1½ yr	2 yr	3 yr	4 yr
Sickles		⊕	⊕		⊕	⊕	
Varas	⊕	⊕	⊕		⊕	⊕	⊕
Helvie	⊕		⊕		⊕	⊕	
Vizcaíno		⊕	⊕	⊕	⊕		
Kopans		⊕	⊕	⊕	⊕		

**Why not recommend prompt biopsy
for some probably benign lesions
and recommend 1-year follow-up
for the remaining lesions?**

Prompt Tissue Diagnosis for Some Lesions?

Criteria: age, size, sonographic features

No published evidence of efficacy

Best evidence (age / size) shows no efficacy

1-Year Follow-Up for Remaining Lesions?

Anxiety

- Lower for 1-year F/U than 6-month F/U

1-Year Follow-Up for Remaining Lesions?

Anxiety

- Lower for 1-year F/U than 6-month F/U
- Decreases compliance for 1 & 2-year F/U

Why 6-Month Follow-Up Is a Better Strategy

Prompt tissue diagnosis for some lesions

- Many too many benign biopsies because cannot predict which lesions are cancer**

1-year follow-up for remaining lesions

- Longer delay in diagnosis for the few fast-growing cancers**

Unresolved Issues

Need for full imaging work-up

Lesion size and patient age thresholds

Specific details of surveillance protocol

Palpable circumscribed solid mass

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Abbreviation:

BI-RADS = Breast Imaging Reporting
and Data System

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Follow-up of Palpable Circumscribed Noncalcified Solid Breast Masses at Mammography and US: Can Biopsy Be Averted?¹

PURPOSE: To determine whether palpable noncalcified solid breast masses with benign morphology at mammography and ultrasonography (US) can be managed similarly to nonpalpable probably benign lesions (Breast Imaging Reporting and Data System [BI-RADS] category 3)—that is, with periodic imaging surveillance—and to determine whether biopsy can be averted in these lesions.

MATERIALS AND METHODS: No institutional review board approval or patient consent was required. This retrospective analysis, based on final imaging reports, included 152 patients (age range, 28–77 years; mean age, 48.3 years) with 157 palpable noncalcified solid masses that were classified as probably benign at initial mammography and US. Of 152 patients, 108 underwent follow-up with mammography and US (6-month intervals for 2 years, then 12-month intervals). The remaining 44 patients underwent surgical or needle biopsy after initial imaging. Lesions were analyzed at initial and follow-up examinations. Statistical analysis included Student *t* test and corresponding exact 95% confidence intervals.

RESULTS: In 108 patients who underwent follow-up only, 112 lesions were palpable. In 102 (94.4%) of 108 patients, masses remained stable during follow-up. Lesions were followed for at least 2 years (mean, 4.1 years; range, 2–7 years). In six (5.6%) patients, palpable lesions increased in size during follow-up; these lesions were benign at subsequent open biopsy. No breast carcinoma was diagnosed in the 44 patients with 45 palpable lesions who underwent biopsy after initial imaging. Of 157 lesions, no malignant tumors were observed (exact one-sided 95% confidence interval: 0%, 1.95%).

CONCLUSION: The data strongly suggest that palpable noncalcified solid breast masses with benign morphology at mammography and US can be managed similarly to nonpalpable BI-RADS category 3 lesions, with short-term follow-up (6-month intervals for 2 years). More data, based on a larger series, are required to determine whether this conclusion is correct.

Probably Benign Findings

Seen only at ultrasound

Seen only at MRI

Screening Ultrasound Results

Author	# Exams	Bx (%)	Ca (PPV ₃)
Gordon	12,706	279 (2.2)	44 (15.8%)
Buchberger	8,103	362 (4.5)	32 (8.8%)
Kaplan	1,862	102 (5.5)	6 (6.6%)
Kolb	13,547	358 (2.6)	37 (10.3%)
Crystal	1,517	38 (2.5)	7 (18.4%)
Leconte	4,236	N/A	16
Corsetti	7,615	486 (7.5)	36
TOTAL	49,586	1,625 (3.7) *	178

Other Screening Ultrasound Results

Cancer detection rate: 0.36% (178/49586)

Biopsy yield (PPV₃): 11.1% (126/1139)

Probably benign rate: 6.3% (range 3%-10%)

US-only cancers: 94% invasive, 6% DCIS

US-only cancers: more than 70% \leq 10 mm

US-only cancers: 86% node-negative

Rationale for a Trial of Screening Breast Ultrasound: American College of Radiology Imaging Network (ACRIN) 6666

Wendie A. Berg¹

Mammography is the only screening test to date that has been shown to reduce death rates due to breast cancer. In a report commissioned by the United States Preventive Services Task Force, Humphrey et al. [1] recently reviewed eight randomized controlled trials of mammography and two of breast self-examination. The Edinburgh trial was excluded because of lower socioeconomic status, higher all-cause mortality in the control group, and the lack of masking when evaluating cause of death. Overall, across the seven remaining trials, in women 50 years old or older, a 22% reduction (95% confidence interval [CI], 13–30%) in breast cancer mortality rates was found among women screened at 14 years of observation [1]. In women 40–49 years old, the summary risk reduction was 15% (95% CI, 1–27%) [1] at 14 years of observation. The decrease in mortality rates was almost entirely attributable to a decrease in the size distribution of cancers detected on screening mammography [2]. In the analysis of Tabar et al. [3], 73% of breast cancer deaths in women with cancers smaller than 15 mm at diagnosis were attributable to cancers manifested as branching casting calcifications on mammography. Such calcifications are usually due to ductal carcinoma in situ (DCIS),

often of high nuclear grade with comedonecrosis [4].

Despite the proven benefits of mammography, results have been less promising when the tissue is dense. Dense tissue is common, especially in younger women. In the series of Stomper et al. [5], approximately 62% of women in their 30s, 56% of women in their 40s, 37% of women in their 50s, and 27% of women in their 60s had at least 50% parenchymal densities evident on mammography. Kerlikowske et al. [6] reported results of 27,281 screening mammograms and found the sensitivity to cancer was 98.4% in women 50 years old or older with fatty breasts and 83.7% in women with dense breasts ($p = 0.01$). In women less than 50 years old, the sensitivity was 81.8% in fatty breasts and 85.4% in dense breasts ($p =$ not significant), although the number of cancers was small [6]. In women less than 50 years old with a family history of breast cancer, mammographic sensitivity decreased to 68.8% [6]. Thus, in women with dense breasts, and particularly those at increased risk because of a family or personal history of breast cancer or atypia, methods to supplement mammography are sought.

Although breast self-examination intuitively seems worthwhile, randomized controlled trials have not shown a reduction in

mortality rates. The effect may have been too small to measure within the power and conditions of the trials. The Shanghai trial of 133,000 women randomized to receive instruction in breast self-examination or control groups found no difference in mortality rates; women in the breast self-examination group were 84% more likely to undergo an unnecessary breast biopsy with benign results [7].

No randomized controlled trials have been conducted to evaluate the impact of screening sonography on breast cancer mortality rates. However, in several single-center studies, whole-breast bilateral sonography has been shown to depict small nonpalpable invasive breast cancers not seen on mammography, particularly in dense breasts [8–12]. The survival of patients diagnosed with invasive breast cancer is a direct, but imperfect, function of tumor size [13], and although we presume that this early detection is of benefit, this benefit has not been proven. Until such “surrogate” end points are further validated to reliably predict mortality rates, the efficacy of any new screening test can only be shown if it reduces breast cancer deaths in the setting of a randomized controlled trial. Any population-based screening test to be recommended must be held to a high standard of proof of

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Selected Screening Outcomes (ACRIN 6666)

	US	Mammo
Prevalence Ca rate	0.42%	0.76%
Biopsy rate (excl asps)	5.2%	2.6%
Short-Interval F/U Rate	8.6%	2.2%
PPV₃ (excl cyst asps)	8.8%	33.3%

JAMA 2008; 299:2151-2163.

Screening US: Probably Benign Outcomes

	Mean Age	Masses	Cancers	PPV
Stavros	47	426	2	0.5%
Mainiero	45	148	1	0.7%
Graf	48	448	1	0.2%
Raza	42	356	3	0.8%

Radiology 1995; 196:123-134. J Ultrasound Med 2005; 24:161-167.
Radiology 2007; 244:87-93. Radiology 2008; 248:773-781.

Screening US Only: Prob. Benign Outcomes

	Age	Masses	Cancers	PPV
Stavros	40+	N/A	N/A	N/A
Mainiero	40+	N/A	N/A	N/A
Graf	40+	385	1	0.3%
Raza	40+	N/A	N/A	N/A

Radiology 1995; 196:123-134. J Ultrasound Med 2005; 24:161-167.

Radiology 2007; 244:87-93. Radiology 2008; 248:773-781.

Breast MRI: Probably Benign Outcomes

	Number	Frequency	PPV
Kuhl 2000	198	12.4%	2.4%
Liberman 2003	367	24.3%	10.1%
Kriege 2004	1909	6.6%	1.1%
Sadowski 2005	473	16.7%	5.1%
Eby 2009	1735	7.6%	1.0%
TOTAL	7941	9.4%	2.8%

Radiology 2000; 215:267-279. Cancer 2003; 98:377-388. NEJM 2004; 351:427-437.
JMRI 2005; 21:556-564. AJR 2009; 193:861-867.