

“Probably Benign” Grading in Screening Mammograms: Review of Outcomes in a Five-year Study

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ABSTRACT

Objectives: To evaluate patient outcomes after screening mammograms graded as “probably benign”, and specifically to determine the corresponding frequency of false-negative diagnoses.

Methods: All women with mammograms performed in the Well Women Clinics of Tung Wah Group of Hospitals (Kwong Wah Hospital and Tung Wah Eastern Hospital) from 1 January 2003 to 31 December 2007 were included in this retrospective analysis.

Results: The assessment of “probably benign” was assigned to 4.8% (3182/66,362) of the screening mammograms. Among these 3182 mammograms, 27 were finally diagnosed to have cancer within two years. The percentage of cases designated as “probably benign” but that finally turned out to be malignant was 0.85% (27/3182). The pathological reports for two out of these 27 cases could not be traced. Of the available 25 cases, 17 were at stage 0, six at stage I, and two at stage IIA. None of the lesions were palpable at the time of the diagnosis and they did not have evidence of any systemic metastasis.

Conclusion: At our centre, the assessment of “probably benign” on screening mammograms was on the low side compared to screening programmes elsewhere. In our study population, the percentage of those designated “probably benign” but finally turned out to be malignant was also much lower than the internationally recognised acceptable standards. In our screened population with such a diagnosis, the tumour size, lymph node status, and cancer stages were typical of lesions having a favourable prognosis.

Key Words: Biopsy; Breast neoplasms; Mammography; Mass screening

中文摘要

乳房造影檢查中被評為「可能是良性發現」的病例的最終結果： 一個為期五年的研究

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目的：評估在乳房造影檢查中被評為「可能是良性發現」的病例的最終結果，並找出假陰性診斷的發生率。

方法：2003年1月1日至2007年12月31日期間於東華三院轄下的廣華醫院及東華東院的婦女健康普查部進行乳房造影檢查的女性均被納入本回顧研究中。

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結果：乳房造影檢查被評為「可能是良性發現」的佔4.8%（66,362個樣本中的3182個）。3182例中有27例在兩年內確診為癌症。乳房造影檢查結果為「可能是良性發現」而最終屬惡性的佔0.85%（3182個樣本中的27個）。這27例中有2例未能找到病理學報告。其餘的25例中，17例為零期、6例為一期、2例為二A期。這些病例中的腫塊都不能在應診期間觸覺得到，亦未有證據顯示屬於系統性轉移。

結論：與其他地方的篩檢結果比較，在本中心接受乳房造影檢查而評為「可能是良性發現」的結果較低。與國際認為可接受水平比較，在本中心被評為「可能是良性發現」的結果而最終確診為惡性腫瘤的比例偏低。本研究中被評為「可能是良性發現」的病例，其腫瘤大小、淋巴結期數及癌症期都屬於有良好預後的典型病變。

INTRODUCTION

The major goal of screening mammography is the detection of early stage cancers, but in the process, false-positive biopsies cannot be avoided. The primary rationale underlying a “probably benign” assessment is to reduce false-positive recommendations for biopsies but nevertheless to retain a high detection rate for early stage cancers. This goal is accomplished by defining “probably benign” lesions as those carrying a less than 2% likelihood of malignancy, and by the observation that during periodic imaging surveillance these lesions demonstrate: (a) interval increases infrequently, and (b) that those later found to be malignant are almost always early-stage cancers. At the same time, their diagnoses are delayed until interval progression prompted biopsy. The cost and morbidity of false-positive biopsies can thus be reduced, and enhance the cost-effectiveness of screening mammography.¹

There was wide variability in the use of “probably benign” findings in different screening programmes, and ranges from 1.2 to 14%.²⁻⁴ There was also a large discrepancy between screening intervals in European screening programmes (2 years)⁵ and those recommended by the American College of Radiology (1 year).⁶ The difference in recommendations made it necessary to define short-term interval follow-ups in accordance with the screening intervals between follow-ups in specific screening programmes.

Hong Kong does not have a population-wide breast screening programme organised by the government. The Well Women Clinics of Tung Wah Group of Hospitals at Kwong Wah Hospital (KWH) and Tung Wah Eastern Hospital (TWEH) offered on-demand breast cancer screening services to asymptomatic healthy Hong Kong women on a self-referral basis.

The interval at our breast screening centre was two years, and we recommended a short follow-up interval of one year in patients graded as “probably benign” after full diagnostic imaging. The latter included spot compression, magnified views, and if necessary, supplementary ultrasound examination.

We adopted the United Kingdom National Health Service Breast Screening Programme assessment guidelines, in which “probably benign” assessments were graded as R2.⁷

The “probably benign” assessment used in the Breast Imaging Reporting and Data System came under category 3. For these lesions, the recommendation was to repeat imaging at six months and then annually for two to three years to assess lesion stability.⁴

If the findings showed no changes in subsequent follow-ups for two to three years, then the lesion was considered benign, and regular screening in a normal frequency could be resumed. In contrast, any interval progression increased the probability of malignancy for any mammographic lesion. During the follow-up of a “probably benign” lesion, if it became palpable, increased in size, or underwent a suspicious change in morphology, then a biopsy was recommended.

METHODS

All women with mammograms performed at the Well Women Clinics at KWH and TWEH from 1 January 2003 to 31 December 2007 were included in this retrospective study.

Mammography was offered to women aged older than 40 years, as well as to those aged 35 to 40 years if they had a positive family history of a first-degree relative

with breast cancer at a premenopausal age. Both Well Women Clinics had installed conventional film-screen mammogram machines. KWH used a Lorad MIV machine (LORAD, Danbury, CT, US) and TWEH used a GE Senographe DMR (GE Medical Systems, Milwaukee, WI, US). The film processors were Kodak ML 300 Plus Daylight Loaders (Kodak, US).

Bilateral mammography with routine two-view (mediolateral oblique and craniocaudal) mammograms was applied. We adopted a double independent reading system for all screening mammograms performed at our clinics, with the radiographer as the first reader and the radiologist as the second. Once the mammograms were performed by the clinic radiographers, they reviewed the films. If they detected any suspicious finding, additional views (cone compression or magnification) were acquired before the patient left the clinic. Breast radiologists at KWH read all the films for the second time and called for additional views or supplementary ultrasounds as deemed necessary.

The mammograms were graded by the radiologists according to the United Kingdom National Health Service Breast Screening Programme system from R1 to R5 (R1 = normal / definitely benign; R2 = probably benign; R3 = indeterminate; R4 = probably malignant; R5 = malignant).⁷

There were weekly multidisciplinary mammogram meetings, at which breast radiologists, breast surgeons, and clinicians from the Well Women Clinics and mammographers sat together to review all mammograms rated R2 or higher. These meetings provided a platform to exchange information about cases and to share knowledge between different parties. The management of cases was decided by consensus among those at the meeting. The management options included referral for surgical assessment, recall for additional views or ultrasound, early follow-up and biopsy. Lesion biopsies were usually performed percutaneously by means of fine-needle aspiration, core biopsy and vacuum-assisted techniques. Excisional open surgical biopsy was performed in exceptional cases. In addition to the weekly mammogram meetings, clinical-pathological conferences were held once a month, at which breast pathologists joined in to discuss breast biopsy results.⁸

Any patient with symptoms of a breast lump or bloody nipple discharge was excluded from this study. All of the patients with screening-detected breast cancers

in this period were followed up, and corresponding mammograms, clinical notes, mammography and pathological records were reviewed.

Data Collection

According to the database, 66,362 screening mammograms were performed in the participating Well Women Clinics between 1 January 2003 and 31 December 2007. Of these, 3182 examinations were assessed as “probably benign” (R2). The mammograms and medical records of all of the cases diagnosed as having breast cancer at both clinics during the study period were reviewed by two radiologists, who had been at their practices for 5 and 10 years. For the cases initially graded as “probably benign” that turned out to be malignant within 24 months, the mammograms were reviewed to confirm that the laterality and location of the malignant lesions corresponded to that designated as probably benign. For mammographic lesions, the density of the mammogram, type of lesion (calcification, mass, architectural distortion, focal asymmetry) and sonographic features (mass and distortion) were recorded. Management plans, such as early follow-up (1 year), date of lesion biopsy, as well as the date of and suggestions from the joint mammographic meeting were tracked and reviewed. Outcome measurements included the development of ductal carcinoma in situ or invasive carcinoma within 24 months of the index mammogram. The grades of the pathological specimens were reviewed.

This retrospective study was approved by the institutional authority. The requirement for patient consent was waived.

RESULTS

The assessment of “probably benign” was assigned to 4.8% (3182/66,362) of the screened mammograms findings. In all, 27 of these 3182 patients were finally diagnosed as having cancer within two years. Thus, the percentage of cases designated as “probably benign” that turned out to be malignant was 0.85% (27/3182).

We were able to trace the pathological reports of 25 out of these 27 cases. The operations on the other two patients were performed in private hospitals, and the pathology reports were not available to us for analysis.

Among the 3182 cases, 2650 (83%) proceeded to early follow-up mammograms, while the other 532 (17%) were referred to have biopsies, of which 521

(98%) were histologically benign, while 11 (2%) were malignant. The pathological reports of two of these 11 cases were not analysed; their operations had been performed in private hospitals. Six out of the available nine cases were ductal carcinomas in situ (stage 0). Three were invasive ductal carcinomas with an average diameter of 1.17 cm; all three had stage I disease.

Regarding the 2650 “probably benign” cases followed up with early mammograms, 2569 (97%) showed no significant changes on subsequent mammograms, 81 (3%) of them showed interval changes on early follow-up mammograms and underwent biopsies. Among the latter, 65/81 (80%) were proved to be benign, and 16 (20%) turned out to be malignant. None of the lesions were palpable at the time of diagnosis. Among the 16 patients with malignancies, 11 had ductal carcinoma in situ (stage 0), and five had invasive ductal carcinoma with an average diameter of 1.55 cm. Three out of the five had stage I cases, and the remaining two had stage IIA disease, with single axillary node positive metastases. None of them had evidence of systemic metastasis. Their results are summarised in Figure 1.

For the 27 mammographic lesions originally graded as “probably benign” that turned out to be malignant, seven were palpable masses, and 20 (74%) contained calcifications. None of them exhibited architectural distortion or focal asymmetries.

All of the mammographic findings were reviewed, and all were deemed to strictly exhibit the criteria for “probably benign” lesions.

DISCUSSION

In general, there are three main types of mammographic lesions that can be assessed as “probably benign”. The first is a well- or sharply defined mass that is not clinically palpable (Figure 2). The second is a clustered round / punctate or oval calcification without associated density or distortion (Figure 3). The third is a focal asymmetry in the absence of positive findings on compression view or ultrasound (Figures 4 and 5).

A mammographic mass is a space-occupying lesion, seen on at least two different projections and characterised by convex outer margins. Ultrasound

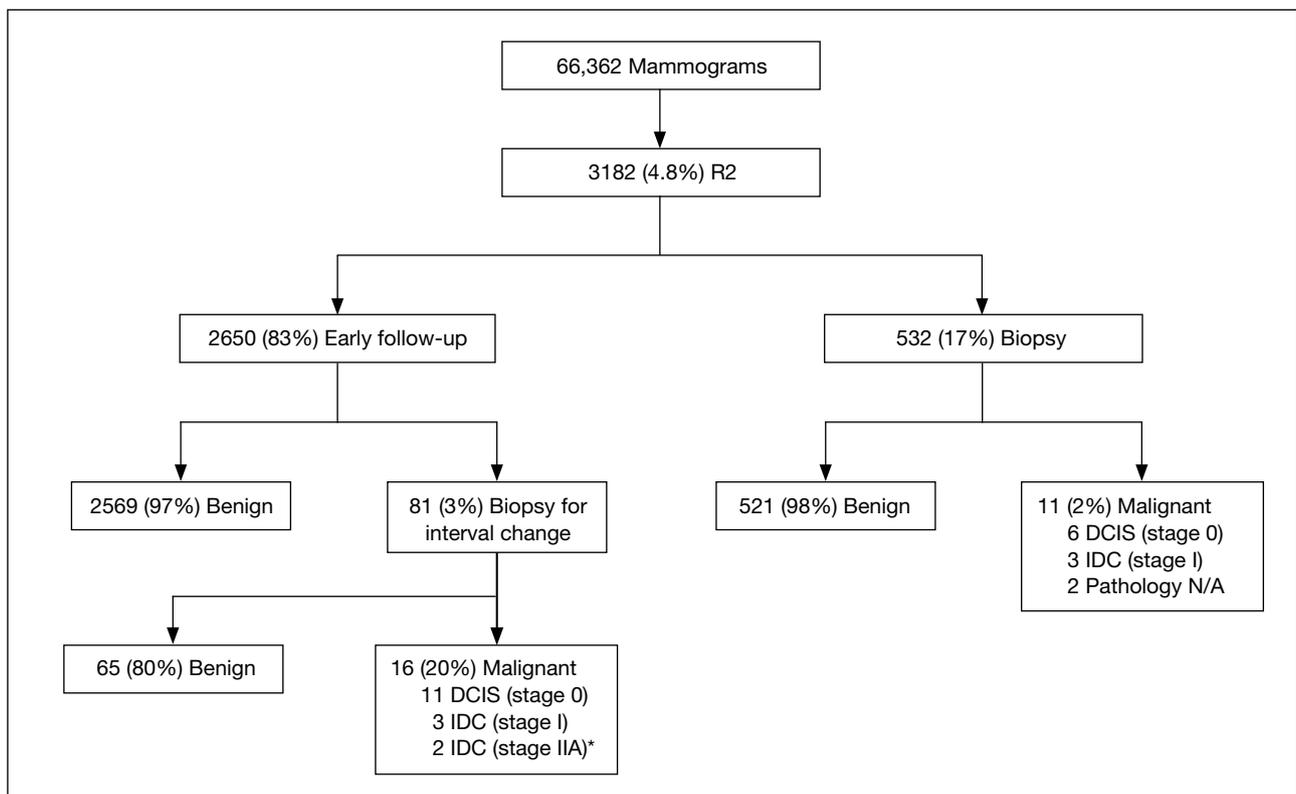


Figure 1. Summary of the results.

Abbreviations: R2 = “probably benign”; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; N/A = not available.

* IDC with single axillary lymph node positive for metastasis.

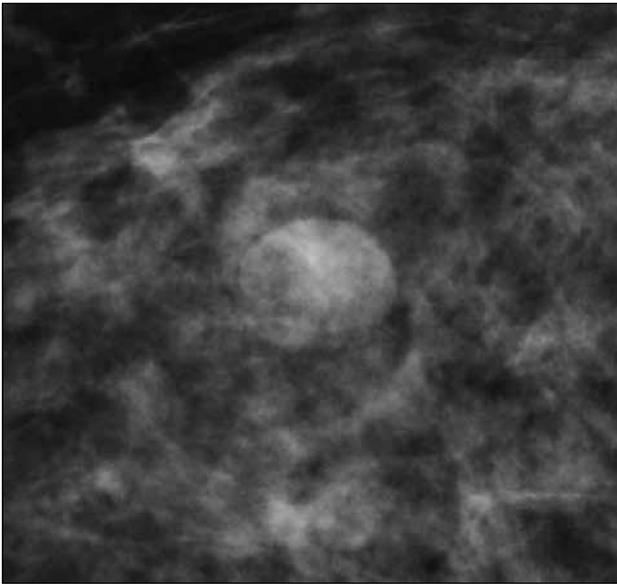


Figure 2. A non-palpable circumscribed mass is noted in a mammogram. It is classified as benign if it turns out to be a simple cyst based on ultrasonography. If it is not a cyst (noted by ultrasound) and there are no other suspicious features, the mass is assessed as “probably benign” and can be managed with periodic mammographic surveillance.

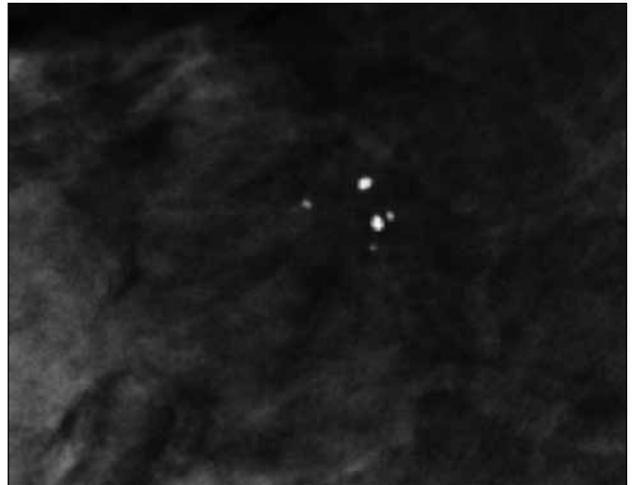


Figure 3. A cluster of round and punctate microcalcifications without associated density nor distortion is assessed as “probably benign”. This can be managed with periodic mammographic surveillance with short-interval follow-up.

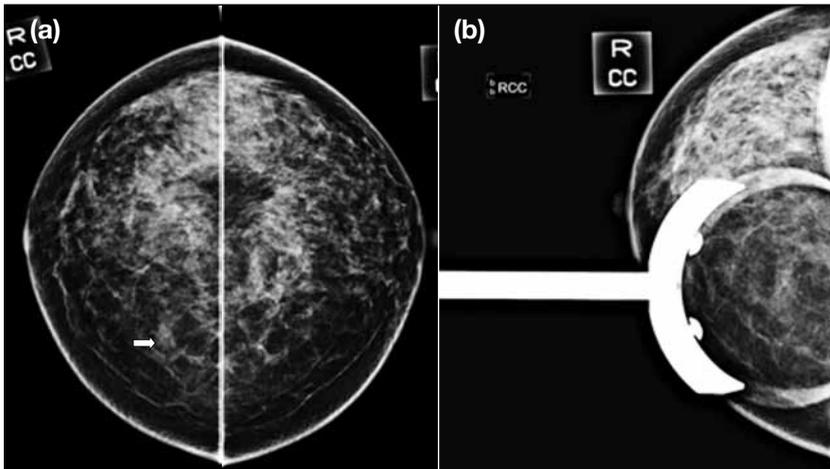


Figure 4. (a) Focal asymmetry (arrow) in the medial aspect of the right breast (right craniocaudal view). (b) Further compression view reveals no underlying mass nor distortion. In the absence of suspicious mammographic or sonographic findings, this can be assessed as “probably benign” and followed up by an early mammogram.

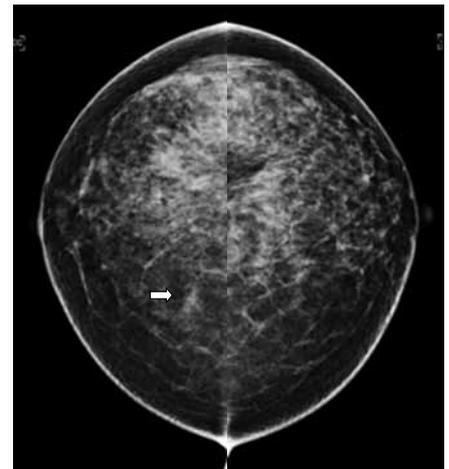


Figure 5. Follow-up mammogram at one year’s time. The focal asymmetry at the right breast is less conspicuous when compared with the old film (arrow).

can be used for the diagnosis of a cyst, skin lesion or intramammary lymph node that should be graded as benign. A “probably benign” mass should be round, oval or lobular, and its margin should be circumscribed. Two-year stability is essential to establish its benign nature. Many times, margins are partially obscured by glandular tissue. In these circumstances, at least 75% of the mass margin should be deemed circumscribed

to qualify as “probably benign”. Spot compression view can help to displace the adjacent tissue to assist in margin assessment. If, however, a mass margin is partially circumscribed and partially indistinct, it should be classified on the basis of its indistinct margins.

A cluster (defined as five or more particles per cubic centimetre) of tiny round or oval calcifications may be

considered probably benign. Round microcalcifications, when small (<1 mm), are frequently formed in the acini of lobules, and are considered benign if they are scattered. The term “punctate” can be used when the round microcalcifications are less than 0.5 mm. A localised magnification view is usually necessary to provide sufficient resolution to portray the round shapes of probably benign calcifications. For calcifications, management recommendations should be based on the most worrisome features that depend on distribution and/or morphology. Although uncommon, tiny round calcifications that are linear or segmental in distribution should not be graded as “probably benign”. An isolated cluster of punctate calcifications could warrant close surveillance or even biopsy if new or associate with an ipsilateral cancer.

A focal asymmetry is visible as an asymmetry of tissue density with a similar shape on two views but completely lacking borders and the conspicuousness of a true mass. It differs from a mass in that its margins are concave-outwards, and it is usually interspersed with fat. It could represent an island of normal breast, but as it lacks specific benign characteristics it might warrant further evaluation. On the spot compression view, a focal asymmetry can become less dense. In the absence of a palpable mass or suspicious findings on mammography and ultrasound, a focal asymmetry may be considered probably benign and managed with short-interval follow-up. If a focal asymmetry is noted to have increased in size on subsequent follow-up, it should be termed as a “developing asymmetry”, and warrants a biopsy.

The assessment of “probably benign” was assigned to 4.8% (3182/66,362) of the screening mammograms at our centre, which was on the low side when compared to the reports of 1.2 to 14% in screening programmes elsewhere.²⁻⁴ In our study population, the percentage of cases designated as having “probably benign” lesions that turned out to be malignant was 0.85% (27/3182), which was also much lower than the 2% rate regarded as acceptable internationally.⁹⁻¹¹

The tumour size, lymph node status, and stage of the cancers found among these “probably benign” lesions in our screening population typically indicated a favourable prognosis.

These findings were the results of the combined efforts of our dedicated breast radiologists, tight quality control processes, regular audits, and multidisciplinary meetings

at our screening centre. Good collaboration between breast team members, including radiologists, surgeons, referring clinicians, pathologists and radiographers, was also essential.

At our breast-screening centre, all mammograms graded R2 or above were reviewed at our weekly multidisciplinary meetings, at which breast radiologists, breast surgeons and clinicians from the Well Women Clinics as well as mammographers gave their expert opinions on the further management of these cases. Final management was decided based on a consensus from different experts, which provided a strong safety net for our mammogram screening service.

Successful application of the “probably benign” assessment relies on the appropriate recommendations for imaging follow-up and patient compliance. If the patient cannot be relied upon to return for imaging follow-up or if imaging follow-up is not feasible due to various constraints, then a prompt biopsy might be the more appropriate management strategy.

From June 2009 onwards, all of the women with mammograms graded as “probably benign” at both Well Women clinics of Tung Wah Group of Hospitals, who needed short-interval follow-ups, were contacted by phone by the referring clinicians. The rationale behind the short-interval follow-up was clearly explained during the conversations, and any questions from the women were answered. In addition, the feasibility of the women returning for the imaging follow-up was also addressed. It was also important for radiologists to allow the referring clinicians to fully understand the advantages of and reasons behind periodic surveillance so that they can explain such information to the women. Through phone consultation, the patient should have neither great anxiety about a possible malignancy nor a total lack of concern about mammographic findings. We hoped this additional move can increase patient compliance with the imaging follow-up and, in return, the effectiveness of our system.

Periodic follow-up of lesions having a low likelihood of being malignant obviated immediate biopsy and decreased the number of women who would require tissue sampling, and the associated morbidity and cost of performing biopsies on every “probably benign” lesion.¹² The positive predictive value of biopsy should also increase due to reduction in the number of interventional procedures that produced benign results.

Periodic mammogram surveillance was also associated with reduced stress when compared with percutaneous or excisional biopsy.¹³ The ideal follow-up protocol for “probably benign” lesions should optimise patient compliance, cost-effectiveness, and early cancer detection. There is as yet no standardised protocol.

The follow-up strategy first described by Sickles¹⁴ was unilateral mammography at six months and bilateral mammography at 12, 24, and 36 months. Some investigators questioned the need for the initial six-month follow-up examination.¹⁵ However, there was indirect evidence that more rapidly growing tumours might benefit from such earlier detection, rather than after 12 months.¹⁶

The screening interval at our centre was two years. For “probably benign” lesions, we recommended a short-interval follow-up of one year. If the lesion remained non-palpable and unchanged on mammography, we would follow-up the case once more after a one-year interval to establish its stability. If there was no interval change after two years, it was graded as benign, and a normal two-year screening interval was resumed.

In June 2009, we changed our recommendation to a six-month unilateral mammogram for the initial follow-up and then annual mammograms to a minimum of two years to establish stability. We planed to conduct an evaluation after implementing this new strategy to compare the results with those of our previous protocol.

CONCLUSION

According to the experience at our screening centre, the use of “probably benign” as an assessment was an acceptable practice with a very low false-negative rate, and was also in line with international standards of management recommendations. There was no universal standard protocol for the follow-up of mammographically detected “probably benign” lesions. Factors that should be considered included: the radiologist’s training and experience, locally accepted screening guidelines, the availability of imaging-guided biopsy, and the balance of the costs for follow-up imaging examinations versus interventional procedures. Communication with referring clinicians and conveying management plans accurately to patients were crucial aspects relevant to compliance with follow-up imaging. Readers should understand how the interplay of these various factors was likely to affect the overall success of mammographic surveillance in their own practices.

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