Review Article

Breast Screening in Singapore: Implications for Pathology

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Abstract

The aim of this review is to discuss the impact of breast screening on pathology. The advent of the national mammographic screening programme in Singapore has led to changes in the manner in which breast specimens are handled in the pathology laboratory, an increased detection of borderline lesions which pose diagnostic challenges, the occurrence of specific issues regarding core biopsies, and the need for awareness of histologic artefacts associated with preoperative needling procedures. There are also economic and workload implications, in addition to the essential requirement for quality assurance and educational programmes to maintain high professional standards. A multidisciplinary approach and commitment to continual professional upgrading are key to surmounting the pathologic challenges brought about by breast screening.

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Key words: Borderline lesions, Quality assurance, Radiologic calcifications, Workload

Introduction

Breast cancer is the commonest malignancy in Singapore females, and has remained the most frequent cancer in local women since the inception of the Singapore Cancer Registry in 1968.[1] It comprises 22.8% of all female cancers, with an age-standardised rate of 54.9 per 100,000 per year. There has been a steady average annual increase in incidence of 3.68%, with the highest rates in those aged 55 to 59 years, having shifted from the previous peak incidence age group of 45 to 49 years.[1] The annual mortality is reported as 14.8 per 100,000 per year (2003).[2]

Mammographic screening has been found to reduce breast cancer mortality by between 20% and 30% in western populations.[3,4] Our own local data from the Singapore Breast Screening Project in the mid-1990s successfully detected early-stage breast cancer, with 64% of cancers being Stage 0 (ductal carcinoma in situ, DCIS) or Stage 1, at a cancer detection rate of 4.8 per 1000 women screened.[5,6] The population-based National Breast Screening Programme (*BreastScreen Singapore*) was therefore launched in January 2002.[7] This programme is overseen by the Health Promotion Board and uses subsidised mammography services at government polyclinics, with designated hospital reading and assessment centres. Over 34,000 women were screened in the first year of the programme, achieving a cancer detection rate of almost 0.4%.[7] As at December 2005, the National Cancer Centre (NCC), a designated assessment centre for BreastScreen Singapore, discovered a total of 245 invasive cancers and 116 cases of DCIS from 67,887 screening mammograms performed since the inception of the programme, giving a cancer detection rate of 5.3 per thousand women screened.

There are implications to pathology in the light of the widespread availability of breast screening in Singapore. These include increasing numbers of radiologically directed breast biopsies, some containing borderline and atypical lesions; the dwindling role of cytology in the face of core biopsies; and the need for more focused pathologic evaluation, translating into increased workload and hence cost. The Department of Pathology at the Singapore General Hospital provides diagnostic pathology support to the assessment centre of NCC and this review in part incorporates the experience gleaned from both the Singapore Breast Screening Project and the ongoing National Breast Screening Programme.

Role of Cytology and the Impact of Core Biopsies

Cytology

Cytology has traditionally been regarded as a simple, cost-effective method of preoperative evaluation of breast lesions. It is frequently used in the assessment of symptomatic breast lesions, allowing therapeutic planning

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and counselling. It reduces operations for benign breast disease and is a very reliable investigative tool, especially when utilised as part of the triple assessment of breast lesions. In the Singapore Breast Screening Project, fine-needle aspiration cytology (FNAC) was performed in 232 women out of a total of 28,231 women screened, with results that generally met targets recommended by the United Kingdom Breast Screening programme.[8] It was concluded that cytology played a useful role in breast screening in Singapore.[9]

Core Biopsy versus Cytology

With the advent of core biopsies, however, the utility of FNAC has diminished, as core biopsies hold advantages of increased absolute and complete sensitivities, and decreased inadequate and suspicious rates. Core biopsies are also less dependent on operator and cytopathological expertise, allowing improved non-operative diagnosis of micro-calcifications. Pathologically problematic lesions such as lobular carcinoma on FNAC are more easily recognised on a core biopsy. Invasion can be assessed, and hormone receptor status readily determined.[10] It is with these considerations that the number of FNAC samples being evaluated at our department, derived from the assessment centre of National Cancer Centre in BreastScreen Singapore, is proportionally and significantly fewer than core biopsy samples.

While this may appear to indicate a dwindling role of cytology in screen-detected lesions, some authorities prefer to regard cytology and core biopsies as having complementary functions, with recourse to core biopsies when cytology is unable to initially provide a satisfactory answer.[10] Core biopsies are also costlier, limited by sampling issues, longer processing time, and higher false negative rates.

Core Biopsy

Core biopsy diagnoses are definitive in the vast majority of cases, with a benign pathologic conclusion that is concordant with the radiological assessment allowing discharge of the woman to routine rescreening, while a malignant outcome results in appropriate therapy. In some instances, other than discordant pathologic-radiologic findings that necessitate further diagnostic evaluation, there are essentially benign conclusions on core biopsies that are, by nature of the lesion found, considered "indeterminate" and hence require open excision for complete removal after core biopsy sampling. Such conditions include the papillary and radial/sclerosing lesions, fibroepithelial neoplasms with accentuated stromal cellularity, and extravasated mucin for which mucocoele-like lesions have to be ruled out (Figs. 1 and 2).[11]

Both papillomas and radial sclerosing lesions are described to have an association with concomitant cancer, and without histological examination of the entire excised lesion, it is difficult to be certain if more sinister foci are present or absent. In their study of 35 percutaneously diagnosed papillomas, Liberman et al[12] found cancer in 14% and high-risk lesions in 17% on subsequent surgery, suggesting that despite a pathologic-radiologic concordance of derivation from a benign papilloma on core biopsy, surgical excision may be indicated. Conversely, 2 other reports have concluded that a benign papilloma on core biopsy remained benign on excision, and only those that demonstrated atypical ductal hyperplasia (ADH) on core biopsy were potentially associated with worse lesions on surgical excision.[13,14] For radiologic stellate lesions that correspond to radial sclerosing lesions histologically, it is generally recommended that complete excision is performed.[15,16] It has been reported, however, that the probability of malignancy being associated with radial scars depends on lesion size and patient age, with a cutoff size of 6 to 7 mm and a threshold age of 40 years, below which cancer was unlikely.[17] The foregoing discussion relates to mass and stellate lesions for which papillary and radial sclerosing lesions are identified respectively on core biopsy. On occasion, there can be incidental micro-papillomas and minute radial scars discovered as part and parcel of a fibrocystic process with calcifications that are the radiological reason for the biopsy. In such instances, further excision may not be indicated.

Similarly, for otherwise histologically benign fibroepithelial neoplasms with some accentuation of stromal cellularity, the possibility of a benign phyllodes tumour cannot be confidently excluded unless the lesion has been excised and well sampled for microscopic evaluation. Expression of p53 and proliferation indices has been suggested as being potentially discriminatory on core biopsies of fibroepithelial neoplasms with stromal cellularity.[18,19]

Mucocoele-like lesions range in spectrum from completely benign appearances to those demonstrating atypical epithelial proliferation, DCIS, and invasive carcinoma. Concern for the finding of extravasated mucin on core biopsies lies in the potential of unsampled atypical and malignant lesions. For these lesions, complete removal either by mammotome or open excision is recommended.[20]

Apart from these "indeterminate" lesions on core biopsies, the finding of in situ ductal carcinoma should not be thought to imply that the entire lesion is non-invasive, as it is not infrequent that the invasive component has not been sampled.

The truly "borderline" lesions of atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH),

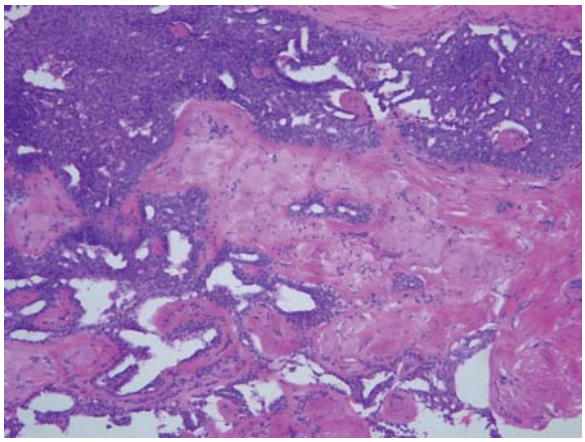

Fig. 1. Part of a radial scar was discovered on a core biopsy carried out for a radiological stellate lesion, with fibroelastotic stroma associated epithelial hyperplasia of usual type. Further excision biopsy showed a radial scar without any evidence of associated cancer.

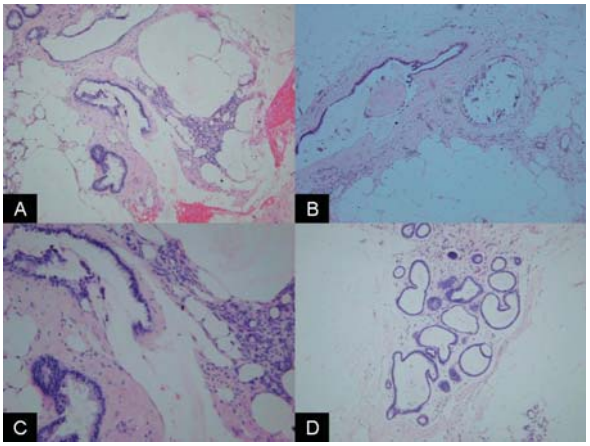

Fig. 2. Core biopsies showed a mucocoele-like lesion with distended duct spaces filled with mucin, some of which had extravasated into the stroma (A, B, C). There was focal atypical epithelial hyperplasia with rigid bridges (D). Subsequent excision biopsy showed low nuclear grade ductal carcinoma in situ associated with a mucocoele-like lesion.

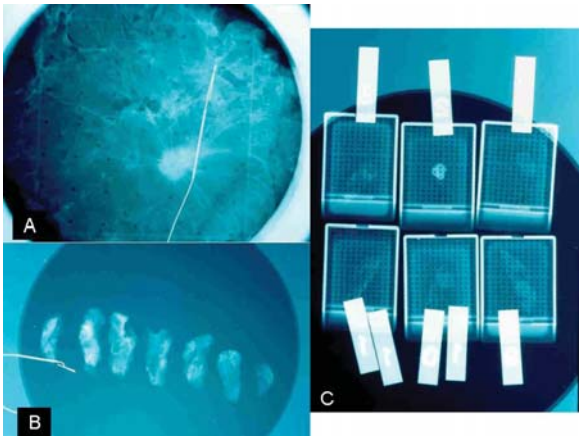

Fig. 3. Specimen radiographs with the guide wire in situ coursing through a spiculated density in an open localisation specimen (A), sliced specimen radiographs (B), and radiographs of paraffin blocks.

Fig. 4. A portable piece of X-ray equipment, the faxitron, which can carry out specimen radiographs within the pathology laboratory.

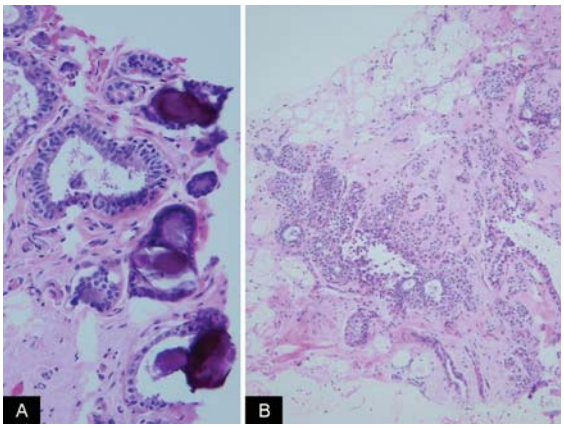

Fig. 5. Core biopsies showing fibrocystic changes with calcifications corresponding to the radiologic calcifications (A). Focal atypical lobular hyperplasia was noted in another core, away from the calcificiations. The woman was discharged to annual follow-up screening.

lobular carcinoma in situ (LCIS), low nuclear grade DCIS, and the emerging entity of columnar cell lesions (CCLs) with atypia are discussed in a later segment (see below).

Table 1 details the lesions on core biopsies for which complete excision is recommended.

Pathological Handling of Radiologically Directed Breast Biopsies

The primary aim in the pathological handling of radiologically directed breast biopsies is identification of the lesion associated with the mammographic abnormality, be it calcifications or a mass. Other objectives are documenting completeness of excision of malignant lesions and providing information on pathologic prognostic parameters.[21]

Specimen radiography is a necessity for confirming that the radiologic abnormality is demonstrated and therefore present in the specimen. It also assists in locating suspicious areas for focused histologic evaluation, and helps ascertain

Table 1. Open Excision is Currently Recommended When Portions of the Following Lesions Are Found in Core Biopsies Performed for Screen Detected Radiological Abnormalities

Core biopsy lesion	Comments
ADH	Some authorities use the terminology of atypical epithelial hyperplasia[21] rather than ADH, as the final diagnosis is determined on the subsequent open excision.
Lobular neoplasia	Controversial, with some regarding its presence (either ALH and LCIS) as requiring further excision, whereas studies have shown that ALH alone on core biopsy has not been found to correlate with DCIS or invasive malignancy on open excision.[22,23] At NCC/SGH, there is careful radiologic-pathologic correlation to ascertain that the radiologic abnormality can be explained unequivocally by histologic benignity. Only incidental, focal, non-pleomorphic, non-necrotic forms of ALH are potentially discharged to annual rescreening.
Papillary lesions	Open excision for complete removal in the presence of a radiologic mass. Incidental micropapillomas are evaluated in conjunction with other histologic findings and may not necessitate open excision.
Radial sclerosing lesions/radial scars	Open excision for complete removal in the presence of a radiologic stellate mass. Incidental microscopic radial scars in which the entire lesion can be defined on the core biopsy and is benign may be omitted from open excision.
Mucinous lesions/extravasated mucin	Currently no recommendation on threshold amount of mucin extravasation in a benign core biopsy below which open biopsy is not indicated.[20]
Fibroepithelial lesion with stromal hypercellularity	Open excision to rule out phyllodes tumour.
Columnar cell lesions with and/or architectural atypia	Many CCLs are benign. Further excision indicated only when there is associated cytologic and/or cytologic architectural atypia.

ADH: atypical ductal hyperplasia; ALH; atypical lobular hyperplasia; CCLs: columnar cell lesions; DCIS; ductal carcinoma in situ; LCIS; lobular carcinoma in situ; NCC: National Cancer Centre; SGH: Singapore General Hospital

that the abnormality has been completely removed (Fig. 3).

Most of these specimens would have had radiologic assessments performed prior to their receipt in the pathology laboratory, and a copy of the specimen radiograph accompanies the specimen to the laboratory. In some instances, especially for open localisation excision biopsies where the specimen is fairly large, sliced specimen radiography can assist in identifying the specific slices in which the radiologic abnormality is found, thereby promoting time-efficient and cost-effective histologic evaluation.

Occasionally, the radiologic abnormality, particularly calcifications, cannot be identified in the histologic sections. In such circumstances, radiography of the paraffin blocks may be of help in determining if the calcifications are still embedded within the particular block in which case further deeper sections to expose the calcifications are required.

It is not infrequent that lesional areas in mastectomies performed for either invasive or in situ carcinomas diagnosed on radiologically directed core biopsies are not readily visible during macroscopic assessment. Identification of the lesional area in question is aided by finding residual haemorrhage or fat necrosis resulting from the preoperative core biopsies; and the availability of clinicoradiologic information as to the exact location of the lesion. Recourse to slicing the mastectomy and subjecting the slices to radiography can also be beneficial in locating the lesional areas.

For practical purposes, small excision biopsies are entirely processed; larger specimens are sampled for the lesion and margins; and if there are no macroscopically detectable lesions, the fibrous parenchyma is passed. Slice specimen radiography will be helpful in the latter. It is noteworthy that all these specimens should not be incised prior to receipt by the laboratory, and that orientating sutures be provided for wide excisions. Frozen sections are contraindicated unless a grossly observable mass is discovered.

For core biopsies performed for radiologic calcifications, separating cores containing calcifications from those without calcifications can be beneficial in directing careful microscopic assessment. Multiple step sections or levels have to be studied.

Though it is possible that further radiologic assessment on specimens received by the laboratory can be brought to the Radiology Department and performed, this can pose logistic problems, and for a pathology laboratory to effectively handle a substantial number of radiologically directed specimens, in-house radiology equipment for radiographing specimens is advantageous. Figure 4 shows such a portable specimen radiography equipment (faxitron).

Calcifications

It is essential that histologic calcifications identified should correspond to the radiologic calcifications under investigation. Previous data from the Singapore Breast

Screening Project found that for 34 cases of screen-detected DCIS, histologic microcalcifications were present in all of them, which were located within DCIS only (38%), within DCIS and benign breast tissue (47%), and outside DCIS, in benign breast tissue (15%).[24] This suggests that benign calcifications are often detected in conjunction with those identified within malignant foci, and if the mere presence of calcifications in a biopsy, in particular a core biopsy, closes the evaluation on the case, it would potentially lead to missed diagnosis of malignancy.

Borderline Breast Lesions

Mammographic screening has led to increased identification of "borderline" breast lesions, which are defined by Rosai[25] as a type of "proliferative process placed somewhere between the usual type of hyperplasia and carcinoma in situ (CIS), both in terms of morphologic features and propensity for the development of invasive carcinoma". Such lesions include atypical ductal and lobular hyperplasia, LCIS, low nuclear grade DCIS. Low-grade DCIS poses difficulty in its distinction from ADH. CCLs with either cytologic and/or architectural atypia represent another form of "borderline" lesion which is being encountered more frequently in mammographic screening due to its associated calcifications.[26]

ADH and Low Nuclear Grade DCIS

ADH resembles low-grade DCIS morphologically.[21] While ADH used to be found in 4% of symptomatic benign breast biopsies,[25] it has seen a markedly increased incidence to about 31% in screen-detected benign microcalcifications. Its presence is associated with an increased risk of invasive breast cancer of 4 to 5 times that of the general population.[27] Diagnosis of ADH is based on cytoarchitectural features and lesional extent, with involvement of less than 2 terminal duct lobular units and with a size measurement of less than 2 to 3 mm. For extensive lesions, a low nuclear grade DCIS would be a more appropriate diagnosis.[21]

ADH and low nuclear grade DCIS are likely lesions in a biologic continuum, and the size distinction is somewhat arbitrary, representing an attempt to avoid excessive treatment for small lesions which are not always obligate precursors to invasive cancer.[28,29]

ADH does not require further surgical excision when incidentally discovered in an excision biopsy specimen. If ADH is found at the surgical margin, however, additional surgery may be advocated in order to determine the true extent of the lesion, since the presence of similar abnormal contiguous foci remaining in the breast may contribute to a more significant lesion warranting a diagnosis of DCIS. If ADH is discovered on core biopsies, open excision is recommended.

Lobular Neoplasia

Lobular neoplasia encompasses both ALH and LCIS. Differing in histologic severity of involvement by lobular neoplastic cells, ALH and LCIS have risks of 4 to 5 times and 8 to 10 times respectively of subsequent development of breast cancer as compared to the general population.[21]

As lobular neoplasia is considered a risk lesion rather than a direct precursor to invasive breast cancer, its finding in excision biopsies does not require additional treatment other than close yearly mammographic follow-up. This concept, however, is being challenged by molecular genetic studies that suggest that some examples of LCIS may be true precursors of invasive cancer.[30] Florid LCIS and LCIS with pleomorphic features and necrosis that prove difficult to distinguish from solid DCIS are treated as for DCIS, with a need for surgical extirpation.

When encountered on core biopsies, radiologic-pathologic correlation is needed to determine if open excision is required. Guiding principles are that if lobular neoplasia is of ALH type, focal and incidentally found, unassociated with the index calcifications (Fig. 5), without florid nor pleomorphic LCIS components, and a histologically benign lesion that can account for the radiologic abnormality that triggered the biopsy is present, then further open excision may not be required (personal communication, Professor IO Ellis). Crisi et al[22] found that ALH on core biopsy was not associated with any lesion worse than LCIS on subsequent open excision, similar to the experience of Renshaw et al.[23] On the other hand, there have been several reports of upgrading to DCIS or invasive cancer on open excision after a core biopsy diagnosis of lobular neoplasia.[31,32]

Columnar Cell Lesions

CCLs are a spectrum of benign to atypical entities having in common variably dilated terminal duct lobular units lined by columnar epithelial cells with/without prominent apical cytoplasmic snouts. As luminal microcalcifications are a frequent accompaniment in these lesions, many such columnar lesions are picked up on radiography.[21,26]

There is as yet no universally adopted classification system for these lesions. The majority of CCLs are completely benign and innocuous. There is a group of CCLs that demonstrate either cytologic or architectural atypia or both. Those with cytologic atypia are regarded as a presumptive neoplastic intraductal alteration also termed as flat epithelial atypia,[33] while those with architectural atypia merge with conventional forms of ADH.[21] CCLs have been discovered in association with lobular neoplasia, DCIS and invasive tubular carcinoma.

The finding of CCLs with cytologic and/or architectural atypia on excision biopsies may require only follow-up.

However, when found on core biopsies, the controversy is whether or not an open excision is required. Our own data suggest that CCL with pure nuclear atypia on core biopsy leads to a lower incidence of upgrading to a worse lesion on subsequent open biopsy, as compared to conventional ADH on core biopsy.[34] Until more information is available on this lesion, a practical approach is for further excision when CCL with significant nuclear and/or architectural atypia is noted on core biopsy.

Artifacts from Needling Procedures

As preoperative diagnostic evaluation is the norm in pathologic assessment of screen detected lesions, the needling procedures of FNA, core biopsy, or localising wire, may lead to artifacts in the open excision specimens. Displaced tumour cells may result in potential overcalls in assessing invasion in a lesion that is otherwise in situ. Regenerative changes in ductal epithelium adjoining the previous needle or core biopsy site with squamoid appearances may also pose difficulty. The finding of adjacent fibroblastic scarring or granulation tissue will help avoid this pitfall.

Multidisciplinary Approach

The importance of a multidisciplinary team approach cannot be overemphasised. Close communication between the principal team members of the radiologist, surgeon and pathologist is critical, with a need for common understanding of terminology used. Decisions are made at regular radiology-pathology correlation meetings whereby any uncertainties are resolved, radiological images reviewed, and histological material evaluated.

Laboratory Implications

Workload

Due to the focused pathologic evaluation, additional time required to carry out radiological studies on submitted specimens, extra sections for identification of relevant histologic calcifications, and processing of more sections, there is overall an increased workload and cost resulting from breast screening pathology.

Specifically, with screening mammography detecting smaller lesions that are amenable to conservation surgery, pathologic margin assessment becomes a key element of these wide excision specimens, and the multiple shave and perpendicular sections needed to accurately assess surgical margins contribute significantly to the overall work. Similarly, with the sentinel lymph node approach becoming accepted practice, intraoperative evaluation of multiple levels of one or more sentinel nodes, as well as immunohistochemistry in the detection of isolated tumour cells, add both time and cost to pathologic interpretation.

Staff and Training

Trained dedicated histotechnological staff who are able to handle such radiologically directed breast specimens in an appropriate manner are ideal. Such staff should preferably not have substantial additional service duties, as the work processes involved in handling these screen-derived specimens are time- and labour-intensive, but necessary for optimum histopathologic evaluation.

Trained dedicated pathology staff to interpret these specimens are also required. Time and care are needed in studying these cases, involving correlation of histology with radiology, comparison of excised tissue with previous core biopsies, resubmitting further sections from specimens that are not completely processed, etc. There is also a need to participate in regular radiologic-pathologic rounds and quality assurance activities.

Trainee pathologists need to be exposed to specific needs of breast screening pathology during their training, and this may involve rotations through the breast service, participation in multidisciplinary conferences, as well as breast tumour boards.

Involvement in a population national breast screening programme also warrants fulfilling a role in data collection. Additional clerical staff, to assist in filling forms and retrieving previous histopathology reports so that final concluded pathologic details can be accurately submitted for centralised collation, are helpful.

Quality Assurance and Education

Involvement in quality assurance and education programmes are essential in maintaining standards in breast screening pathology. This is a requirement under the audit scheme that is conducted regularly for all assessment centres of BreastScreen Singapore. Awareness of evolving concepts in the pathobiology of early neoplastic lesions encountered in breast screening will help reinforce criteria-based diagnoses for some of these challenging lesions. Professional bodies can take the lead in organising academic breast sessions that highlight current and emerging concepts in breast pathology reporting which can help inculcate uniformity in diagnostic criteria. One such existing programme is the Breast Pathology Slide Club that is convened regularly under the auspices of the Chapter of Pathologists, Academy of Medicine, Singapore.

Conclusion

In conclusion, mammographic screening has wide-ranging implications for pathology, from specimen handling, diagnostically challenging lesions, indeterminate core biopsies, radiological correlation, laboratory workload, training and quality assurance issues. Despite these challenges, the advent of breast screening has led to

improved pathology standards due to increased awareness of breast disease, availability of educational programmes and updates, and sharing of professional expertise.

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