When should caution be used with regards to histopathologic findings of imaging-guided breast micro- and macro-biopsies?

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Résumé
Quand se méfier des résultats des micro et macrobiopsies guidées mammaires ?
J Radiol 2006;87:265-72

Le développement des techniques de prélèvements guidés a largement contribué au diagnostic précoc de cancers du sein en aval du dépistage. Néanmoins, dans un faible pourcentage de cas les résultats histologiques ne sont pas satisfaisants du fait de faux négatifs liés à l’inexpérience du prélèvreur ou à un échantillonnage insuffisant particulièrement pour les microcalcifications avec un taux de sous-estimation des hyperplasies canalaires atypiques de 20 % avec des macrobiopsies à 11G et dans ces cas, les prélèvements doivent être répétés. En cas de discordance avec l’imagerie ou de lésion d’hypertrophie épithéliale atypique, la reprise chirurgicale est impérative afin de ne pas manquer un diagnostic maligne. Si la reprise chirurgicale des hyperplasies canalaires atypiques est indiscutable, demeurent les controverses concernant les cicatrices radiaires, les lésions papillaires, l’hypertrophie lobulaire atypique et les cancers lobulaires in situ posant le problème non résolu des surveillances de certaines anomalies bénignes. Une meilleure connaissance des limites des techniques de prélèvements tissulaires percutanés doit permettre d’affiner les indications, améliorer la sélection des patients et ainsi réduire les retards diagnostiques.


Abstract
The development of imaging-guided biopsy techniques has considerably improved the early diagnosis of breast cancers following initial detection by screening. Nevertheless, in a small percentage of cases, histopathologic findings are unsatisfactory owing to false negative errors attributable to operator inexperience or inadequate sample material (this is especially true for microcalcifications with 20% underestimation rates for atypical hyperplasia); repeat biopsy is warranted in such situations. When a discrepancy exists with imaging findings and for cases of atypical epithelial hyperplasia, surgical excision is imperative so as not to overlook or underestimate a malignant lesion. Controversy continues concerning the best approach for radial scars (sclerosing ductal lesions), papillary lesions, atypical lobular hyperplasia and lobular carcinoma in situ: determination of which benign anomalies can merely be followed-up remains a problem. Better awareness of the limitations of percutaneous tissue sampling procedures should lead to refinement of the indications for these techniques and improvement of patient selection and thereby reduce delays in accurate diagnosis.

Key words: Breast pathology. Non malignant breast lesions. Imaging guided core breast biopsy.


Advances in biopsy techniques combined with standardization of biopsy indications have resulted in optimized diagnostic and pre-therapeutic management of patients with breast lesions. Large multi-institutional studies in the US and Germany including thousands of core biopsy and large core vacuum assisted biopsies have established the role of these techniques in the setting of a breast cancer screening program (1, 2). Nonetheless, each of these techniques has pitfalls and limitations. The causes and consequences of these will be reviewed based on data from the literature.

Why caution?

Lesion underestimation

The work by Darling et al. (3) on 139 cases of atypical ductal hyperplasia (ADH) and 289 cases of ductal carcinoma in situ (DCIS) summarizes fairly well the current situation. In this series, the rate of underestimation of ADH was 44% when using a 14G biopsy gun, 39% when using a 14G vacuum assisted biopsy, and 19% when using an 11G vacuum assisted biopsy. For DCIS, the rates of underestimation were 21% (14G, biopsy gun), 10% (11G, vacuum assisted biopsy) (3). Underestimation was due to sampling errors, technique used, biopsy gun versus vacuum assisted, and gauge size (14, 11 and even 8). The number of biopsy samples is very variable. In the literature, reported numbers range between 6 and 27 cores. This may explain some variations in reported results. Burbank et al. (4) report 0%
of underestimation when obtaining 26 cores of tissue with a 14G vacuum assisted system. The amount of tissue with a 14G needle is doubled when using a vacuum assisted system (17 mg with biopsy gun versus 40 mg with a vacuum assisted system); the amount of tissue is about 96 mg with an 11G vacuum assisted system (4, 5).

The overall rate of underestimation also is lower for lesions <10 mm: 10% for vacuum assisted biopsy versus 17.5% for 14G biopsy gun (6). Complete excision of the lesion is possible in 58 to 93% of cases for lesions <5mm even though complete lesion excision at histology occurs only in 6 to 18% of cases (2, 4, 7, 8). Liberman, in a series comparing 466 cases of complete excision to 322 cases of 11G vacuum assisted biopsy, reported an 80% rate of residual cancer (9). In that series, the rate of underestimated DCIS was reduced (6.8% versus 20%) but the rate of ADH while reduced from 31.3% to 18.8% still remained elevated (9). According to Liberman, complete excision of the radiological lesion reduces discordant results from 2% to 0.2% but does not reduce the rate of immediate or delayed repeat biopsy or the rate of unnecessary surgery (9).

The rate of underestimation varies for masses and microcalcifications. In the series from Darling et al. (3), no underestimation was reported for DCIS and ADH presenting as masses when using 11G vacuum assisted biopsy whereas the rate was between 10-19% for lesions presenting as foci of microcalcifications. At 14G, the rate of underestimation for DCIS was 5% for masses and 30% for microcalcifications whereas for ADH the rates were 31% and 83% respectively (3). It would thus appear that complete vacuum assisted excision of small masses less than 5 mm in size is effective with regards to the risk of underestimation. With regards to microcalcifications, the rate of underestimation is lower in the series from Soo et al. (10) with reduction from 33% to 7% when using US guided biopsy. However, there is a selection bias since microcalcifications detectable at US more frequently are malignant and associated with invasive ductal carcinomas or high grade DCIS.

Underestimation related to microcalcifications underscores the heterogeneity of these lesions at histology and demonstrates the value of multiple and contiguous biopsies provided by larger gauge needles and vacuum assisted techniques since 95 to 100% of calcifications are present in the biopsy specimen using this technique whereas only 86 to 94% are found in the biopsy specimen when using smaller gauge vacuum assisted techniques or a biopsy gun (11). According to Liberman et al. (12), the rate of underestimation is less than 2% when 95% of calcifications are included in the biopsy specimen using an 11G system to obtain 14 cores. The imaging features or type of microcalcifications is important since the rate of underestimation may be as high as 21% for amorphous microcalcifications (12).

The underestimation of some types of microcalcifications is also related to technical considerations since it may be difficult to accurately target low contrast, monomorphic microcalcifications arranged in loose clusters. At times, excessive local anesthesia may cause dispersion of microcalcifications. Targeting difficulties may also arise with ill defined masses in dense breasts, with lesion motion, with external throw with vacuum assisted technique, with very small or very hard lesions. The lesion may be missed when using a biopsy gun under US guidance (fig. 1). Underestimation is not related to the number of biopsy sites.

Finally, some lesions may be difficult to differentiate at histology, such as intraductal and lobular neoplasias, which may lead to underestimation.

False negatives (table 1)

The introduction of new biopsy techniques has also decreased the rate of false negative results reported in the literature to range between 3.3 and 4.8% with a 14G biopsy gun and less than 2% using an 11G vacuum assisted biopsy system. Unlike underestimations, false negative results are more frequent with solid masses than with microcalcifications (13-16).

False negative results are related more to imaging-histologic discordance than to inadequate biopsy. In the series by Liberman et al. (16), 56/1785 biopsies under US guidance or on dedicated biopsy tables using 11G or 14G needles did not correlate with histology and 11 of these (24.4%) were cancers at repeat biopsy. In a German multicenter study, a single false negative result at macro biopsy was reported from a total of 2874 patients (0.05%) (2).

The rate of false negative results at surgery is 2.5% (17). As shown by Liberman et al. (16), false negative results are related to targeting difficulties and not related to insufficient biopsy material: presence of multiple clusters of microcalcifications on a same window, lesion visible on a single projection, architectural distortion that is not an indication for image guided biopsy. Image guidance should be promoted for the latter, and post biopsy US (fig. 1) or mammography should confirm that the lesion has been traversed by the biopsy needle. In patients with opacity, radiograph of the biopsy sample is not always helpful (fig. 2). It is important to identify discordant results when a calcified lesion is biopsied and no calcification is present on the sample radiograph and/or at histology and when a BI-RADS 5 lesion is biopsied and histology shows benign features.
in the absence of complete or extended resection (fig. 3). When no calcification is noted at histology, paraffin-block radiography should be obtained, along with additional sections and polarized light evaluation; the radiologist may help by identifying samples without and with calcification. In all cases, it is important to consider the pre- and post-biopsy imaging features, findings at sample radiograph and concordance between imaging and pathological findings in order to fully characterize discordant results.

**Rate of second biopsy**

In about half of cases, repeat percutaneous biopsy is performed immediately, but it may also be delayed up to 24 months (18). Underestimations and false negatives lead to second biopsy. The rate varies between radiologist and pathologist. For the former, the rate depends on the number of biopsy cores, needle size (9% of repeat biopsy at 11G vs 15% at 14G) (14) and imaging features of the lesion. The rate of second biopsy is higher for micro-
calcifications compared to masses because of the higher rate of underestimation. The difference between the rate of second biopsy between 11G and 14G for solid masses is not significant (6% vs 10.7%) whereas it is for microcalcifications (11.6% vs 27.3%). Second biopsies are performed for ADH in 15 to 56% of cases based on different series (14). However, the rate of cancers detected increases on second biopsies (mean of 18.5% at 11G vs 13.7% at 14G) and half of cancers diagnosed on second biopsies using an 11G system were recommended by pathologists (vs 12.5% at 14G) underscoring the importance of the pathologist learning curve in addition to larger biopsy samples (14).

Follow-up of benign lesions

Another reason to be cautious of image guided biopsies is the problem related to follow-up of benign lesions for which no consensus exists. In theory, follow-up at one year is suggested for concordant, benign and specific results. In routine practice, it is rarely indicated and compliance is poor. For patients with benign but non-specific results, follow-up at 6 months is required. Jackman et al. (18) in a series of 299 patients where 259 benign lesions required follow-up over 2-3 years, noted absence of follow-up at 12 and 18 months in 11% and absence of follow-up after 18 months in 4%. In the German study, follow-up at 6 months for all benign diseases was 70% (2). In the study by Cherel et al. (19), 315/459 benign lesions were effectively followed-up and half of them were followed-up at another institution creating a problem for data collection. Goodman et al. (20) compared compliance after breast biopsy using a 14G biopsy gun in 160 patients and reported that indications for surgery for benign lesions are observed in only 74% of cases (52/70) and imaging follow-up in 49/90 cases (but only 30/49 at the recommended time interval) or 53% of cases. Compliance with follow-up was improved when clinical signs were visible. Follow-up of benign lesions is associated with a financial burden and consumes a non-negligible amount of medical time which leads to a decrease in the indications for follow-up of benign lesions with definitive diagnosis and concordant radiologic-pathologic results.

What should one be cautious about?

This parameter was studied by Liberman et al. (21) and Pfarl et al. (22). For Liberman, comparing the learning curve with a 14G biopsy gun and an 11G vacuum assisted system, the rates of success were fairly similar: 83.3 and 85.5% for the first 5 cases, 90 and 92% for the first 20 cases and higher than 96% for both techniques after 20 cases. The rate of false negative is 12.9% with a 14G biopsy gun for the first 15 cases and 2.6% after according to Liberman (21). For vacuum assisted biopsies, the rates were between 7.4 and 10% for the first 15 cases and 0.6% after (21, 22).

The rate of discordance was higher during the first two years (5% vs 2.7%), with targeting issues in 80% of these cases during the first 9 months; the learning curve is longer with lower starting point for microcalcifications when compared to masses (21% of biopsies contain no calcifications during the first 4 months) (21). These results demonstrate that radiologists wishing to learn these procedures must be properly supervised and trained using phantoms. For image guided biopsies, feasibility tests can be used. American and German medical associations require that radiologists be accredited in order to perform these procedures. To our knowledge, no learning curve has been reported for pathologists. The radiologist and pathologist must develop a close working relationship.

When should one be cautious and what should one do about it?

Atypical ductal hyperplasia

The frequency of ADH has increased with the increased use of image guided biopsy, especially vacuum assisted biopsies. Currently, it ranges between 2 and 10% (23, 24). ADH is a significant risk factor since the global relative risk for ADH is 9.8 vs 2.6 for nonproliferative ductal hyperplasia, and is further increased after menopause and in patients with positive family history (25, 26). Definition is qualitative and/or quantitative: extension of lesion to two ducts or size greater than 2 mm. Currently, this entity is included with ductal deoplasms along with non-proliferative hyperplasia and DCIS, but is being reclassified. This entity would be diagnosed on surgical biopsies and not on image guided biopsies. Because of their smaller size (mean size of 10 mm vs 13 mm), complete excision of ADH lesions is more frequent that complete excision of DCIS. However, the rate of underestimation is higher since ADH frequently is located at the periphery of DCIS (3, 24).

Some authors, with the purpose of identifying subgroups of patients, have attempted to establish an imaging-histologic score to predict malignancy (27-29). The following parameters were selected:

- Appearance: micropapillary type, necrosis, nuclear pleomorphism,
- Extension: when the number of clusters (ducts or TDLU) was higher than 4, in situ or invasive malignancy was present in 86.7% of cases, when lower than 2, no malignancy was present on excisional biopsies, and when equal to 3, the probability of malignancy was 50%,
- Complete nature of the excision: for Ely (29), surgery is unnecessary if there are less than 2 or 3 clusters and if most microcalcifications have been removed,
- Imaging appearance: 20% rate of malignancy with evolving amorphous or diffuse microcalcifications, and over 60% when microcalcifications are visible at US (10, 30).

Current recommendations is to perform excisional biopsy on all cases of ADH (23, 24, 31, 32) even if all microcalcifications were removed and an absence of positive family history might argue against it (33). The relative risk with positive family history ranges between 7 and 22 whereas it is between 3.2 and 4.3 in the absence of a positive family history. Still, Cherel et al. (19) followed-up 30/117 cases of ADH, and Travade et al. (34) followed-up 31/62 cases of ADH. Available data from follow-up is not long enough at this time since several years may be needed for ADH to evolve into ductal carcinoma. For most authors, excisional biopsy in patients with ADH at image guided biopsy can only be considered as part of clinical trials.

Apocrine metaplasia

Apocrine metaplasia corresponds to about 3 to 10% of benign biopsy results and typically occurs in women 30 to 50 years of age. It is characterized by cystic dilatation of the TDLU and papillar proliferation, which
when higher than 50% corresponds to focal metaplasia. On imaging, a microlobulated mass without or with calcifications is described; the appearance on US is variable with microcystic foci or solid masses, US sometimes is negative (35). The risk related to apocrine metaplasia is that of associated atypical lesions. The risk would be increased by a 1.2 to 2 factor in patients older than 45 years (36). Spontaneous regression is possible in half of cases with hormonal treatment.

Management of patients with apocrine metaplasia on biopsy is dictated by the associated lesions. Isolated simple apocrine metaplasia is managed conservatively without dedicated follow-up (23, 24).

Radial scar

These lesions are seldom found since image guided biopsy is usually not required except when a focal lesion is identified on US. As such, radial scar corresponds to about 0.1 to 0.6% of image guided biopsies. The risk associated with this lesion relates to the size, number and proliferative nature of the tissue without or with atypia. Jacobs et al. (37) have correlated the risk with atypia, number of lesions (higher than 1) and size (larger than 4 mm). When radial scar is associated with proliferative disease without atypia, the relative risk is 2.5. The relative risk for lesions larger than 4 mm is 3.5 and the relative risk is 4.3 when more than one lesion is present. When radial scar is associated with atypia, the relative risk is 3.5. It increases to 8.8 for lesions larger than 4 mm and to 8.4 when more than one lesion is present. The risk is bilateral for in situ and invasive carcinoma (37).

The rate of associated carcinoma varies in relation to age (>40 years), size (larger than 6 mm) (30% vs 2.6%) and modality of detection: according to Sloane et al. neoplasms is associated with radial scar in 43% of cases when an abnormality is detected at imaging vs 1.2% when no abnormality is present on imaging (incidental lesion) (38).

In the literature, invasive ductal carcinoma and DCIS is reported to be present in 19% of cases of excisional biopsy for radial scar without atypia on vacuum assisted micro- or macrobiopsy (13, 18, 39, 40). Some published reports are discordant due to selection bias and neoplasms are more frequent (40%) in association with speculated lesions than in association with other imaging findings such as microcalcifications, architectural distorsion, or other masses with incidental radial scar (18). False negative results are related to the fact that cancers are found along the periphery of the biopsied lesions.

Currently, excisional biopsy is recommended for all cases of radial scar because the value of follow-up is not known. However, given the increasing number of incidental radial scars diagnosed on biopsies, it would be important to gain further knowledge about the true risk of associated carcinoma. Brenner et al. suggested follow-up when at least 12 cores were obtained and results at imaging and pathology were concordant with absence of ADH (41).

Lobular neoplasms

They represent about 0.5 to 3.9% of surgical biopsies and less than 2% of percutaneous biopsies. The diagnosis of lobular pathology varies with the type of biopsy: the diagnosis of LCIS triples when changing from a 14G biopsy gun to an 11G vacuum assisted technique (42).

The rate of invasive carcinoma is between 5.9 and 11 in premenopausal woman or woman less than 40 years old at the time of diagnosis and when familiar risk factors are present (43). This risk is independent of the size of the LCIS. With regards to atypical lobular hyperplasia, a recent review by Page et al. (44) demonstrates a 3 fold increase in risk for the ipsilateral breast, further increased in the presence of ductal extension and bilateral when ADH is present. Page et al. also stated that this was independent of age and menopausal status; the risk would decrease after modified glandular mastectomies. For Page et al. (44), atypical lobular hyperplasia is more a local precursor than a marker of generalized increased risk for breast carcinoma. From a review of 9 publications on a total of 126 operated patients, the rate of invasive cancer varied between 7.9% for atypical lobular hyperplasia to 22.8% for LCIS (23, 30, 40, 42, 45).

On 70 operated cases of lobular neoplasms from a total of 82 diagnosed on image guided 14G or 11G biopsies, 9 cases of DCIS and 3 carcinomas (2 invasive ductal carcinoma and 1 invasive lobular carcinoma) were detected (30, 40, 42, 45, 46). A feature of lobular carcinomas is their lack of association with imaging abnormalities, accounting for 15 to 71% of LCIS diagnosed on excisional biopsies (23). This appearance also occurs with percutaneous biopsies where isolated LCIS frequently are incidental on biopsies performed for microcalcifications: 22/25 in a series by Berg et al. (30), 11/14 in a series by Liberman et al. (42) (fig. 4). For Foster et al., underestimations are not related to imaging findings (46).

Another feature is the difficulty to achieve histological diagnosis in the presence of ductal extension of lobular neoplasms that may be difficult to differentiate from lobular extension of a DCIS.

Recommendations for lobular neoplasms are not homogeneous. Some criteria may be used such as ductal invasion (risk ≥6.8), number of invaded lobules (higher than 10) and presence of residual calcifications (indicating that the target may have been missed) (30, 44, 49). For some authors, surgery may not be necessary for BI-RADS 3 lesions corresponding to isolated LCIS, is LCIS is incidental in an otherwise benign lesion, or is there is clear concordance between imaging and histological findings. On the other hand, surgery is mandatory if there is overlap with ADH (staining with E-cadherin possible), if additional risks factors are present (radial scar or ADH), if necrosis related or amorphous microcalcifications are present, or is there is discordance between imaging and histological findings: mass, spiculated opacity, residual calcifications (47). For some, and it is the current recommendation, all lobular neoplasms must undergo surgery, while for others surgery is not required. Based on current data, it is not possible to establish clear guidelines since all series are small (48). Notions of family risk factors and follow-up intervals must also be integrated.

Papillomas and papillomatosis

They represent 10% of benign lesions, 1% to 2% of cancers and 0.2 to 4% of percutaneous biopsies (23, 24, 50). They correspond to epithelial proliferation along a fibrovascular core, with spectrum including isolated papilloma, often symptomatic, multiple distal papillomas with associated intraductal neoplastic lesions, papillomatosis corresponding to multiple papillomas with associated ductal hyperplasia, papillary carcinoma corresponding to intracystic DCIS and invasive papillary ductal carcinoma. Diagnosis for the pathologist is challenging. Prognosis is related to the associated lesions, the relative risk
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Fig. 3: Discordant imaging and histological findings: microcalcifications ACR5.

a Mammogram Standard view,

b focal view, magnification,

c comparative focal film 5 years earlier.

d Macrobiopsy: fibroadenomatous changes with calcification,

e Adipose tissue with area of atypical epithelial cells, without calcification (arrow). 

f Surgical specimen intermediate to high grade intraductal carcinoma with calcified necrosis.

Fig. 3 : Discordances radio-histologiques : microcalcifications ACR5.

a Mammographie standard,

b localisé agrandi,

c cliché comparatif localisé 5 années auparavant.

d Macrobiopsie : territoire fibro-adénomateux focalement calcifié,

e fragments adipeux avec prolifération cytologiquement atypique sans calcification (↑)

f Pièce opératoire carcinome endo-canalaire de grade intermédiaire à haut grade avec nécrose calcifiée.

Fig. 4: Magnified focal mammogram: polymorphous microcalcifications ACR4,

a Macrobiopsy: complex proliferative mastosis: non-atypical cylindrical lobular metaplasia with focal secretory microcalcifications (arrow),

c Surgical specimen: lobular neoplasia developing into atypical lobular hyperplasia with secretory microcalcifications (arrow).

Fig. 4 : Mammographie localisée en agrandissement : microcalcifications polymorphes ACR4,

a Macrobiopsie : mastose complexe proliférante : métaplasie cylindrique des lobules non atypique avec microcalcifications sécrétoires focales (↑),

c Pièce opératoire : néoplasie lobulaire allant jusqu’à l’hyperplasie lobulaire atypique avec microcalcifications sécrétoires (↑).
in increased 7.5 folds in the ipsilateral breast in the presence of ADH and in this case, it is more a precursor than a marker of increased risk. False negative results are variable between series based on the material used and related to selection bias since only 50% of biopsied patients undergo surgery. The rate of false negative results is between 0 and 25% (13, 51, 52). The rate of underestimation ranges between 25% using an 11G vacuum assisted system and 40 % using a 14G biopsy gun (50, 52). When imaging findings are concordant and when biopsy is performed using an 11G vacuum assisted system, the accuracy of a benign diagnosis is estimated at 93% (50, 51). Imaging is poorly specific, with imaging abnormalities present in less than 50% of cases and variable with either microcalcifications, single or multiple masses, and asymmetrical densities. Current recommendations are that all papillomas, even benign ones, should undergo surgical excision (23). For multiple authors (40, 50, 52), if results from image guided biopsy are benign, if imaging findings are concordant, and if the lesion on imaging has been completely removed by the biopsy, surgery may not be required and follow-up may be sufficient. On the other hand, if a single core was obtained, it may be more difficult to decide between follow-up and surgery. Surgical biopsy is needed when there is discordance between imaging and histological findings, when an associated lesion is present (ADH), in the presence of papillomatosis, when histological features are atypical or suspicious or non-benign and when the pathologist is uncertain about the diagnosis.

**Fibroepithelial lesions**

They represent 0.05% of biopsies (23). Phyllodes tumors pose no practical diagnostic difficulties. Pathologists must be cautious with very cellular lesions since the risk of underestimation and false negative for DCIS and presence of ADH at the periphery of the lesions (23, 24, 28, 53, 54). However, Carter et al. (54), in a series of 1834 fibroadenomas operated between 1950 and 1968 showed no evidence of increased peripheral atypia or carcinoma in the follow-up of patients with ductal or lobular atypia within a fibroadenoma.

**Mucocles and associated lesions**

There is a continuum between mucinous cysts, atypical mucinous epithelial hyperplasia, mucinous DCIS and colloid carcinomas. Biopsies may not represent the entire lesion. Diagnosis frequently is difficult. Amorphous calcifications are frequently identified on mammograms. Surgical excision is performed when mucinous areas are present and ruptured cysts cannot be differentiated from potentially more aggressive lesions (23, 24).

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