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# Divergences in Diagnosing Nodular Breast Lesions of Noncarcinomatous Nature

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**Nodular breast lesions of noncarcinomatous origin are often of fibroepithelial origin. They may cause classification problems when they are hypocellular or hypercellular; the latter setting may also raise the differential diagnosis of phyllodes tumors. Thirty equivocal nodular breast lesions were collected and one hematoxylin and eosin slide from each was assessed by six pathologists with special interest in breast pathology. The overall reproducibility of classifying these lesions into categories of fibroadenoma, phyllodes tumor or anything else was moderate (kappa value: 0.48). The lack of a uniform nomenclature was not felt disturbing for hypocellular lesions, but the discordant diagnosis of tumors resembling or representing phyllodes tumors was acknowledged to require intervention, such as more obvious implication of guidelines and quality assurance programs aiming at assessing diagnoses and prognostic parameters.** (Pathology Oncology Research Vol 12, No 4, 216–221)

*Key words:* fibroepithelial breast tumors, nodular lesions, phyllodes tumor, phylloid tumor, fibroadenoma

## *Introduction*

Fibroepithelial lesions represent the most common tumors of the breast. Most of them are fibroadenomas (FAs) which are rarely considered to pose diagnostic problems, whereas others represent phyllodes tumors (PTs) which give concerns not only as tumors that should be differentiated from FAs, but also as tumors that should be classified into different prognostic groups on the basis of their morphologic appearance.

FAs are often identified on screening and are generally confirmed by fine needle aspiration (FNA) or core needle biopsy (CNB). However, some may be so sclerotic that they do not yield a sufficiently cellular aspirate, and this may result in a C1 diagnostic category[7, 15] after FNA; these lesions are most commonly diagnosed as B2[7,15] on CNB. On the other end of the spectrum they may be so cellular, that they may raise the possibility of a PT, resulting in a C2-C3 FNA diagnosis depending on the atypia of stromal cells, or a B3 CNB category.

When excised, most tumors diagnosed preoperatively as FA are easily diagnosed as such, but there are a few related lesions such as sclerosing lobular hyperplasia,[19] tubular adenoma,[18] hamartoma[18] or pseudoangiomatous stromal hyperplasia[23] which come into the differential diagnosis, and there are also a few paucicellular lesions that give some concerns about how to call them. These lesions do not have further therapeutic implications in general, but may bias statistics concerning benign excised lesions. Cellular FAs cause diagnostic concerns not only preoperatively but also after excision, although pathologists have more morphologic features available to differentiate them from PTs.

PTs, generally appearing in older women and with greater average size may also range from C3 to C5 or B3 to B5, depending on their stromal cellularity and the presence or absence of malignant features. Their classification might also be challenging in the excision specimen.

In this study, we assessed the reproducibility of the histological classification of nodular breast lesions mainly of

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fibroepithelial nature that were considered to be non-straightforward as concerns their histological diagnosis, even if there was no doubt of their benign or malignant nature.

### *Materials and Methods*

Thirty slides from 30 nodular lesions believed to be fibroepithelial or of fibroepithelial origin or at least related to these were selected from the Pathology archives of the Bács-Kiskun County Teaching Hospital. All represented some features that could question their classification as FA or raised the possibility of a PT. All cases were represented by a single hematoxylin and eosin (HE) stained slide of a formalin-fixed and paraffin-embedded tissue block.

Six pathologists from larger Hungarian oncology centers, all with experience and special interest in breast pathology, all involved in the Hungarian breast screening program were asked to call the lesions according to their own daily routine. Assessment of the slides was performed between September and December 2005. Reproducibility of diagnosing the cases was analyzed using kappa statistics.[10] Problematic issues were looked for on the basis of discrepant diagnoses, and suggestions were sought for on the basis of a common discussion.

### *Results*

Of the 30 cases 12 were selected because of a hypercellular stromal component (category I), 8 because of a hypocellular stroma (category II) either due to myxoid degeneration (IIA) or to sclerosis (IIB), 8 cases because of a prominent intracanalicular pattern (category III), 5 because of a prominent epithelial component (category IV) and a single case due to nuclear pleomorphism, bizarre cells (category V). *Figure 1* illustrates these patterns through some of the study cases. Some of the cases had overlapping features (*Table 1*).

There were 29 diagnoses of PT dispersed among 11 cases, of which only 2 were diagnosed unanimously as PT; but even these were variously categorized according to grade or dignity (*Figure 2*). Five further cases received the diagnosis of FA with phylloid features or fibroadenoma phylloides by one observer each (*Table 1*).

The kappa values for diagnosing a lesion as FA, PT or anything else were 0.39, 0.54 and 0.53 respectively, with a standard error of 0.05, whereas the overall kappa for categorizing the lesions was 0.48 with a standard error of 0.04. These values suggest a moderate reproducibility.[12]

### *Discussion*

This study evaluated reproducibility of classifying non-carcinomatous nodular breast lesions on the basis of a single slide. This is certainly not reflecting the circumstances of diagnosing such lesions, or the real diagnosis itself, which had been originally made on the basis of several slides. The assumption was that these slides represented the worst or most diagnostic area of the lesions.

Of the 30 cases, some represented obviously benign lesions that pathologist could not easily call by a uniform name, but it was felt that this lack of a homogeneous nomenclature could not influence further the management of the patients having these lesions. Although these tumors had a rather large variety of names, the authors felt that they could be lumped together either as FAs and related lesions or as sclerotic/hyalinized benign nodules of similar or different origin. The divergence here was not believed to be disturbing. It is of note that some of the lesions, e.g. sclerosing lobular hyperplasia and tubular adenoma are often discussed together with FAs, as they are very similar in many aspects.[18,19]

Some of the lesions falling into the above mentioned category (and especially their names) deserve some extra attention. For example pseudoangiomatous stromal hyperplasia has been reported as a lesion that may also manifest itself as a nodular mass, and also as a change that may accompany fibroepithelial lesions, gynecomastia and hamartomas.[18,22,23] Hamartomas are rare breast lesions and have been quite often mentioned in *Table 1*; this may be due to publications equating nodular or localized PASH with hamartoma.[6,9]

The rest of the lesions represented hypercellular lesions that raised the differential diagnosis of PTs and the classification of these tumors into prognostic categories. There was no uniform classification used; some pathologists preferred the division into low (intermediate) and high grade PTs, whereas others used the more conservative benign, borderline and malignant classification. Although physicians involved in the treatment of these patients were not questioned, and might understand the given classifications in one or the other institution as they are used, having at least some of the patients opting for a possible treatment or second opinion elsewhere, it would be expected to use a more uniform nomenclature to avoid any confusion arising from calling the same entity differently. Although only a few cases diagnosed as PT were included, even these few cases suggest that the reproducibility of diagnosing these lesions as such is less than optimal; seeking a second opinion in such cases might enhance the reliability of the diagnosis. Some FAs may share features (especially leaf-like projections shown in *Figure 2*) with PTs and can therefore be called as fibroadenoma phyllodes according to some authors,[20] but this may also be the source of confusion, as transition from FAs to PTs has also been suggested.[11]

Although FAs may also recur after incomplete excision, PTs are much more likely to do so, and a wider free resection margin has been advocated for them.[13] Indeed, local excision alone, as performed for FAs, may result in recurrences in more than 10% of the cases.[4] This implies that diagnosing a lesion as PT may have therapeutic consequences even if it is called benign or low grade.

Classification of PTs into prognostic categories depends on several features assessed in conjunction. These include cellularity of the lesion (which may be rather heterogeneous in a given tumor), nuclear pleomorphism, pushing versus infiltrative margins, stromal overgrowth and mitotic activity. Although PTs were classically described as cystic and large (cystosarcoma phylloides) tumors in the elderly, and these clinical features are still of aid, these tumors may also be deceptively small, solid and may also occur in younger patients.[17] The two extremes of the grade or dignity based classifications, when the diagnosis of PT has already been agreed upon are probably easier to recognize, but there are obviously cases that represent real diagnostic challenge. The prognostic classification may be rather subjective, depend-

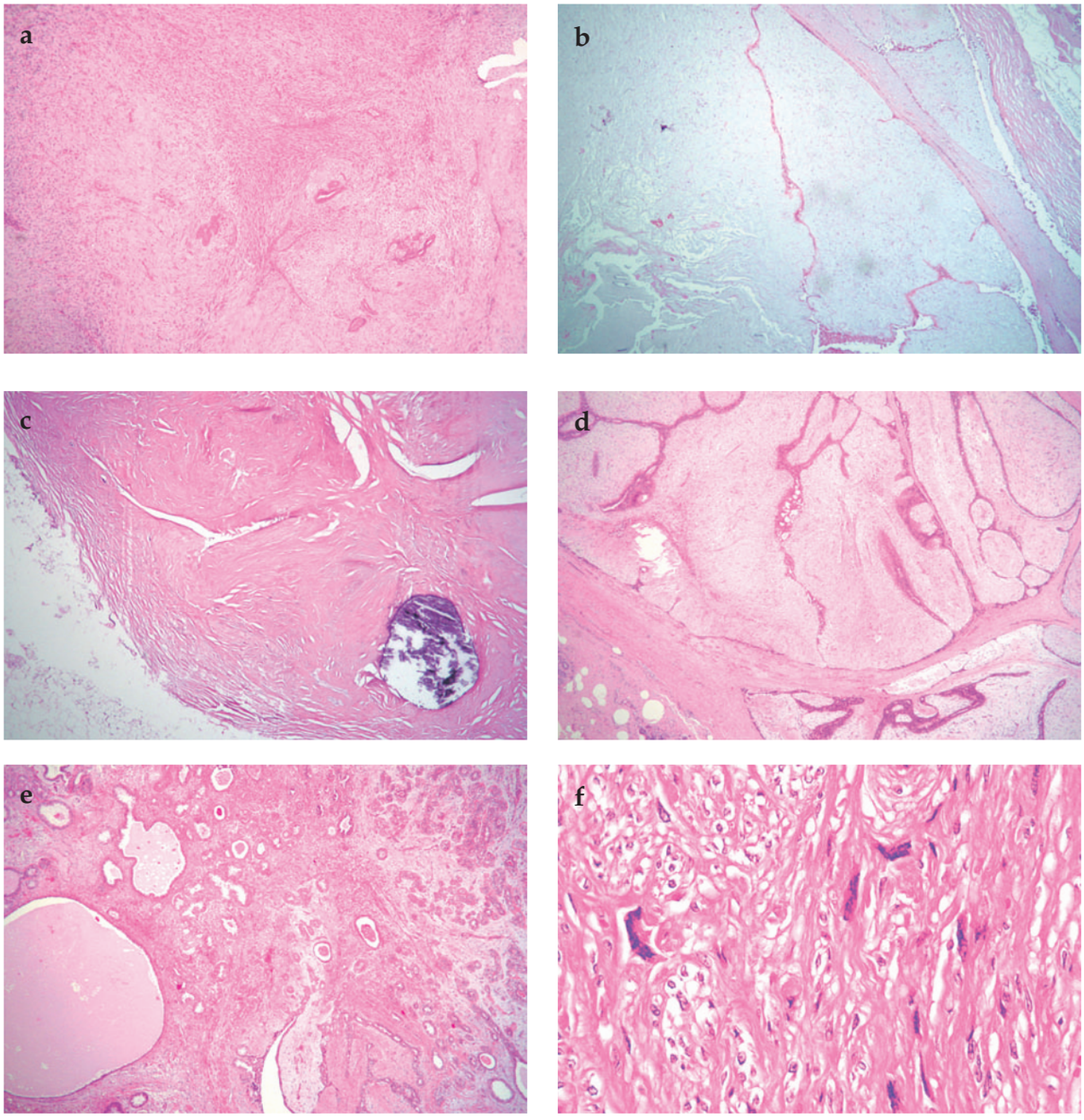


***Figure 1.*** *Illustrative patterns of the nodular lesions from the study.* ***(a)*** *Hypercellular lesion (category I), case 1 (HE, x40);* ***(b)*** *hypocellular lesion, myxoid type (category IIA), case 21 (HE, x40);* ***(c)*** *hypocellular lesion, hyalinized type (category IIB), case 9 (HE, x40);* ***(d)*** *prominent intracanalicular pattern (category III), case 3 (HE, x40);* ***(e)*** *prominent epithelial component (category IV), case 23 (HE, x40);* ***(f)*** *cellular atypia (category V), case 24 (HE, x400). Note that cases 21 and 24 show overlapping features of categories IIA plus III and III plus V, respectively.*

*Table 1.* **Distribution of the diagnoses per cases and per observer**

| | *Basis of selection* | *Observer A* | *Observer B* | *Observer C* | *Observer D* | *Observer E* | *Observer F* |
|---|---|---|---|---|---|---|---|
| 1 | I | **PT (bord.)** | **PT (HG)** | **PT (mal.)** | **PT (LG)** | **PT (mal.)** | **PT (bord.)** |
| 2 | I | **PT (bord.)** | **PT (IG)** | **PT (mal.)** | **PT (LG)** | **PT (mal.)** | **PT (bord.)** |
| 3 | III | FA | **PT (LG)** | FA | FA | **PT (ben.)** | FA |
| 4 | IV | FA | FA-sis | SLH | SLH | tubular adenoma | tubular adenoma |
| 5 | III | FA | FA phyll. | FA | FA | FA | FA |
| 6 | IIB | scler. nodule/ FA vs. ham. | ham. | scler. nodule ex PASH | SLH+PASH | circ. fibr., ham.? | FA scler. |
| 7 | I | FA | FA | juv. FA | juv. FA | FA | FA cellular |
| 8 | IV | complex FA | ductal adenoma | ductal adenoma | complex pap. hyperpl. | ductal adenoma | ductal adenoma |
| 9 | IIB | scler. nodule/hyalin. FA | hyalin. FA | scler. FA | hyalin. nodule | fibr. pseudotumor, FA | FA scler |
| 10 | IIB | scler. nodule/FA vs. ham. | ham./ fibr. nodule | scler. nodule (FA?) | SLH end stage | circ. fibr. | FA |
| 11 | I(rel) | FA-oid hyperpl. | FA | FA | FA | FA | FA apocrine metapl. |
| 12 | III | FA | **PT (LG)** | myxoid FA | FA | FA | FA |
| 13 | I | FA | FA | FA | FA | FA | FA |
| 14 | I | FA | FA phyll. | cellular FA | FA | **PT (ben.)** | FA |
| 15 | IV | FA | tubular adenoma | tubular adenoma | adenosis tumor | tubular adenoma | tubular adenoma |
| 16 | III | FA/ **PT (ben.)** | FA | **PT (ben.)** | FA phyll. | FA-sis | **PT (ben.)** |
| 17 | I | FA | **PT (LG)** | complex FA + ADH | FA+ADH | FA+DCIS | FA |
| 18 | IV | complex FA | complex FA | complex FA | complex FA | adenosis | FA+adenosis |
| 19 | I(rel) | FA | papilloma | nodular PASH | PASH | **PT (ben.)** | FA cellular+PASH |
| 20 | I(rel) | FE proliferation | FA | nodular PASH | PASH | UDH+SH | FA myoid |
| 21 | IIA/III | FA myxoid | FA myxoid | FA myxoid | FA myxoid | FA myxoid | **PT (ben.)** |
| 22 | IIA/I | FA myoid stroma | FE tumor | FA myxoid + PASH | FA | UDH+SH | FA+CCC |
| 23 | IV | complex FA | CSL | ductal adenoma | complex FA | adenosis | complex FA |
| 24 | III/V | **PT (mal.)** | FA phyll. | **PT (bord.)** | **LG phylloid** | **PT (bord.)** | **PT (mal.)** |
| 25 | III/IIA | FA phyll. | FA | **PT (ben.)** | FA | FA myxoid | **PT (ben.)** |
| 26 | I | FA | FA | juv. FA | FA | FA | FA |
| 27 | I | FA | FA | juv. FA | juv. FA | apocrine adenoma | juv. FA |
| 28 | IIB | scler. nodule/fibr. ham. | ham. | FA+PASH | SLH+PASH | ham. | SLH |
| 29 | IIB | scler. nodule | fibr. MP | ben. FE lesion | SLH end stage | circ. adenosis | sclerosis |
| 30 | IIA/III | FA | FA | FA myxoid | FA | FA ADH | FA |

Cases raising the differential diagnosis of phyllodes tumor and having this diagnosis from at least one observer are highlighted.

Abbreviations: ADH: atypical ductal hyperplasia, ben.: benign, bord.: borderline, CCC: columnar cell change, circ.: circumscribed, CSL: complex sclerosing lesion, DCIS: ductal carcinoma in situ, FA: fibroadenoma, FA-oid: fibroadenomatoid, FA-sis: fibroadenosis, FE: fibroepithelial, fibr.: fibrosis or fibrotic, ham.: hamartoma, HG: high-grade, hyalin.: hyalinized, hyperpl.: hyperplasia, IG: intermediate-grade, juv.: juvenile, LG: low-grade, mal.: malignant, metapl.: metaplasia, MP: mastopathy, pap.: papillary, PASH: pseudoangiomatous stromal hyperplasia, phyll.: phyllodes or phylloid, PT: phylloid tumor / phyllodes tumor, scler.: sclerotic or sclerosing, SLH: sclerosing lobular hyperplasia, SH: stromal hyperplasia, UDH: usual type (ductal) hyperplasia

ing on which feature receives more emphasis. Mitotic activity is often overemphasized in pathological practice, although there are no strict numbers that can allow the distinction between benign, borderline and malignant cases.

This is also reflected by the heterogeneity of suggested mitotic index cut-off values for the malignant / high grade category in different references; these include: 3 or more,[1,20] 5 or more[16] and more than 10.[2,21] It must also be noted that despite the fact that mitotic counting is rather standardized for grading breast carcinomas,[5,8] all these recommendations related to PT classification lack an area definition for the high power field. Atypia is also sometimes considered with more weight, although bizarre, atypical cells are not necessarily features of malignancy;[3] their presence could be made responsible for the malignant diagnosis in case 24 (*Figure 1f*). Obviously, all histological features should be taken into account, and a second opinion or at least double reporting could improve the reliability of the prognostic classification of PTs.

Breast cancer screening requires a systemic nomenclature that may enable statistical analysis. Despite the fact that benign lesions are rarely evaluated in this context (except if they represent common differential diagnostic problems), they should also be recorded according to a common language, which seems to lack. *Table 2* summarizes the results of a query between the members of the European Working Group for Breast Screening Pathology; this table shows that rules and guidelines for reporting breast lesions are not generally available, and the European Guidelines for Breast Screening and Diagnosis may perhaps fill in this gap. However, guidelines by themselves are certainly not sufficient. The Hungarian Screening Program has its guiding documents for reporting screen detected lesions,[14] and this alone did not permit the lesions in this study to be reproducibly classified. Screening programs also require some sort of quality assurance schemes which are not a feature of all screening programs (*Table 2*), and also lack from the Hungarian screening. Slide circulations, virtual slide testing, common teaching sessions might all decrease the heterogeneity in reporting, although they do not allow the differential classification of PTs.

This study highlights the lack of a common nomenclature for nodular breast lesions of noncarcinomatous nature. Although these lesions are of lesser concern, a better reproducibility could have been expected, especially in cases where PT enters into the differential diagnosis. Familiarizing

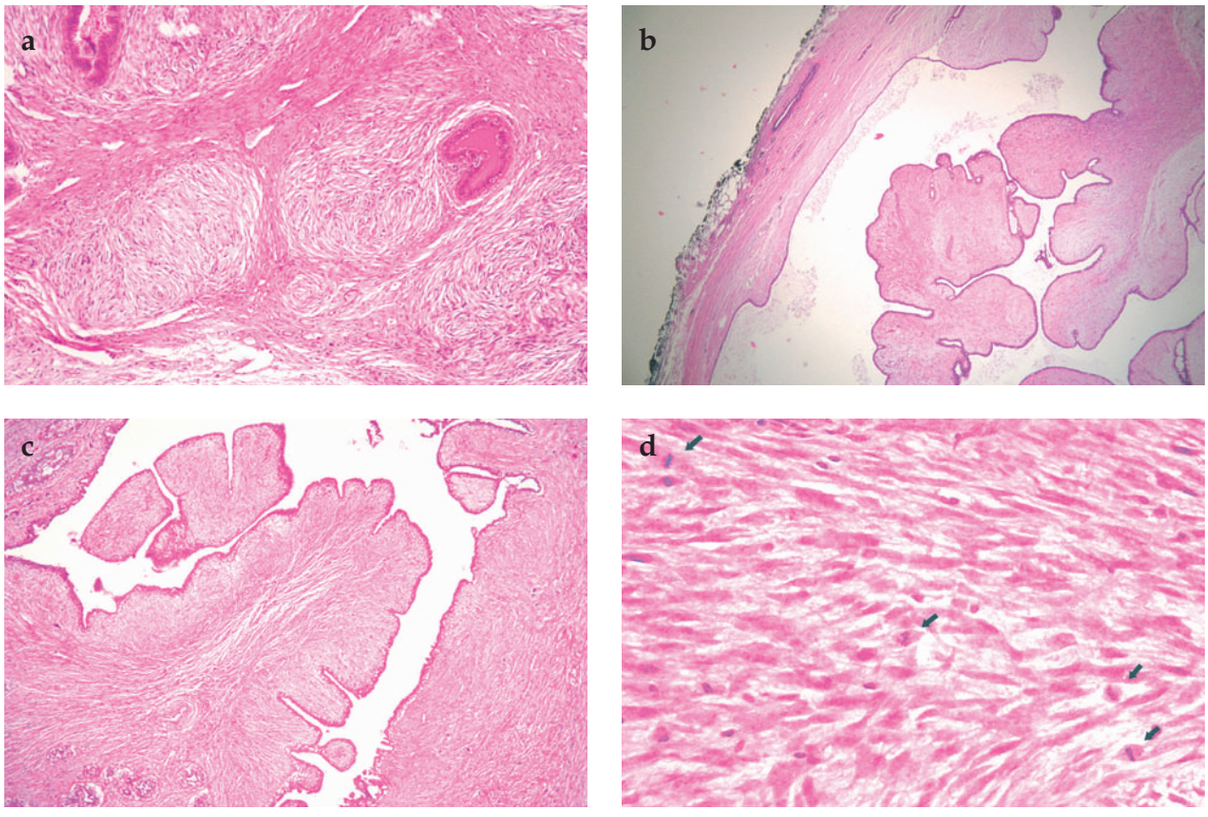


***Figure 2.*** *Illustrative examples from lesions with phyllodes tumor in the differential diagnosis.* ***(a)*** *Case 2 (HE, x100) shows minor stromal overgrowth and hypercellularity;* ***(b)*** *case 24 (HE, x40) demonstrates leaf-like projections;* ***(c)*** *case 25 (HE, x40) shows a minor cystic area with leaf like stromal projections, and also well circumscribed borders;* ***(d)*** *case 1 (HE, x400) illustrates an area with increased mitotic activity with four mitotic figures (arrows) in this single high-power field.*

***Table 2.*** **Survey on the availability of breast pathology guidelines and quality assurance schemes in some European countries**

| *Country* | *Availability of breast pathology guidelines* | *Phyllodes tumors included?* | *Phyllodes tumor categories* | *Quality assurance for diagnoses* |
|---|---|---|---|---|
| Belgium[1] | no | – | – | no |
| France[2] | yes | yes | no | yes |
| Hungary [14] | yes | yes | ben., bord., mal. | no |
| Italy[3] | yes | yes | ben., bord., mal. | yes (for pathology in general, regional) |
| Netherlands[4] | no (general advise to use WHO terminology) | – | LG, HG (personal preference)[4] | no |
| Spain[5] | yes | yes | LG, HG | no |
| United Kingdom [7] | yes (national) | yes | LG, HG | yes |

Source of information: 1. Prof. Maria Drijkoningen, Pathologische Ontleedkunde, University Hospital, Leuven, Belgium; 2. Prof. Jean-Pierre Bellocq, Service d'Anatomie Pathologique, Hopital de Hautepierre, Strasbourg, France; 3. Prof. Anna Sapino, Department of Biological Science and Human Oncology, University of Turin, Turin, Italy; 4. Hans Peterse, Department of Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; 5. Jose Martinez Penuela, Department of Pathology, Hospital de Navarra, Pamplona, Spain
Abbreviations: ben.: benign, bord.: borderline, HG: high-grade, LG: low-grade, mal.: malignant

pathologists with available guideline publications and the introduction of a quality assurance scheme aiming at the diagnosis of breast lesions might improve the homogeneity of diagnoses of mammary lesions. Both the diagnosis and the prognostic classification of PTs seem suboptimal, and this suggests that double reporting them may be advised.

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