Diagnostic accuracy of fine-needle aspiration cytology in histological grade 1 breast carcinomas: are we good enough?

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Financial disclosures and conflicts of interest: none

Abstract

BACKGROUND: Fine-needle aspiration cytology (FNAC) of both palpable and non-palpable breast carcinomas has a high accuracy and sensitivity in dedicated centres. It is generally though that low-grade carcinomas have a distinctly lower sensitivity due to a discrete cellular atypia that might be difficult to appreciate. Grade 1 carcinomas make up about 45 % of screening detected breast carcinomas and about 20 % of symptomatic breast cancers. The aim of this study was to evaluate the diagnostic sensitivity of G1 carcinomas and identify the critical features in the cytological diagnostic work-up of these tumours.

MATERIAL AND METHODS: There were FNAC smears from 494 histologically confirmed grade 1 carcinomas diagnosed during 1996-2004. The cytological diagnoses were compared with the histology.

RESULTS: A definitive malignant diagnosis was given in 382 cases (77.3 %). 16.2 % were diagnosed as equivocal or suspicious, 4.8 % had been given a benign or probable benign diagnosis (false negatives). 13 cases (2.6 %) were unsatisfactory. The complete sensitivity was 92.7%. Invasive ductal carcinomas comprised 81.3 % of all cases. A definite malignant preoperative diagnosis was given in 80.8 % of these. Invasive lobular and tubular carcinomas comprised 7.1 % and 5.5 % of cases, respectively. They received a definitive, malignant preoperative diagnosis in 51.4 % and 55.6 %, respectively.

CONCLUSION: Preoperative FNAC diagnosis of grade 1 breast carcinoma has a high accuracy and sensitivity, especially in ductal carcinomas. Invasive lobular and tubular carcinomas receive a definite preoperative diagnosis in about 50 % of the cases. The main reason for not reaching a definitive malignant diagnosis was

sampling error due to small tumours ≤ 1 cm in diameter, irrespective of tumour subtype.

Key words: breast carcinoma, grading, fine needle aspiration, grade 1 carcinoma, pleomorphism, nuclear size, dissociation pattern.

Introduction

Fine needle aspiration cytology (FNAC) is an integral part of the preoperative multidisciplinary triple approach in the work-up of both symptomatic and screening detected breast lesions in many institutions. Breast FNAC of palpable and non - palpable lesions is reliable and cost effective. The literature reports sensitivity and specificity ranging from around 60 % to 100 %. (1-23) When integrated into the assessment process, it reduces the benign biopsy rate (24). When integrated in the triple test, the chance of detecting a malignant lesion is well over 99 %.

The breast cancer screening programme in Norway has caused a considerable increase in the incidence of low-grade carcinomas. The first screening rounds showed that up to 45 % of detected carcinomas were histological grade 1 (25) in contrast to about 20 % in symptomatic tumours. It has been generally assumed that the accuracy in diagnosing low-grade breast carcinomas on FNAC is substantially lower than in grade 2 and 3 carcinomas, resulting in a high degree of false negative diagnoses in grade 1 breast carcinomas and hence in a large proportion of screening detected breast carcinomas. Some studies have shown that a significant number of false negatives may be caused by interpretation failure of certain histological subtypes, such as lobular (ILC), tubular (TUB), adenosquamous and papillary carcinomas (26;27). The aim of this study was to investigate our results of FNAC on histological grade 1 symptomatic and screening detected breast carcinomas.

Material and methods

Records from 839 cases of histological grade 1 breast carcinomas diagnosed during 1996 – 2004 were retrieved from the files of the department of Pathology, Ullevaal University Hospital (UUS). About 1/3 had been preoperatively investigated outside UUS and FNAC was not available. Smears submitted from one external radiologist were omitted, and only cases where the cytopathologists in our department had done the aspiration were primarily included. Cases which on review revealed a dominant DCIS on histology and where it was obvious that cell material from the DCIS component was predominant in the smears were excluded. Lastly, the relevant, diagnostic smears could not be found in two cases. This left us with FNAC from 494 histological confirmed grade 1 carcinomas. Both Papanicolaou (ethanol spray fixation) and Giemsa (air dried and methanol fixed) stained smears were evaluated. The general diagnostic cytological categories and criteria used in the department are given in table 1.

TNM and grading was taken from the pathology records. The grading had been done according to Elston and Ellis' modification of Bloom and Richardson (28;29). The histological grading was not reviewed. The preoperative cytological diagnoses as well as eventual suggestion of subtypes of carcinoma were recorded. The smears were also evaluated for amount of cell material (scant, moderate or abundant) as well as microcalcifications and myoepithelial cells.

In addition the type of error was evaluated (interpretation vs. sampling error). A diagnosis of less than "carcinoma" in good quality smears with moderately and/or abundant cellularity was evaluated as interpretation error. Suboptimal smears with any kind of technical fault (crush artefacts, improper fixation) and/or scant cellularity were regarded as sampling error. This included smears with no or a limited number

of benign appearing epithelial cells where it was obvious that the tumour had been missed on aspiration.

One observer (MK) evaluated 380 cases independently as part of a medical student's project. 242 of these were also evaluated by joint microscopy by the two observers. Observer two (TS) evaluated the rest independently and overruled observer one in cases of discrepancies. The rest of the cases were evaluated by TS alone. As this was a student's project, no inter observer evaluation was done.

Results

80.3 % of the carcinomas were pT1, 18.2 % were pT2 and 1.5 % pT3 and pT4, respectively. 50.1 % of cases were N0, 16.6 % were N+ and 33.3 % were NX.

An overview of the other results is shown in tables 2 and 3. There were 4.8% false negatives (benign and probably benign cases) (FN) whereas 2.6% were unsatisfactory for diagnosis (table 2). 68.8 % of the unsatisfactory cases were from tumours < 1 cm in diameter (pT1a and pT1b). Three pT2 cases with unsatisfactory FNAC were all ILC.

The complete sensitivity was 92.5 % (434 cases), whereas the absolute sensitivity was 77.3 % (382 cases).

Invasive ductal carcinomas (IDC) comprised 83.4 % of cases (figure 1). ILC and TUB (figures 2, 3A and 3B) made up 5.5 % and 4.5 %, respectively. In 397 (80.3 %) cases a cytological subtype was suggested. 89.6 % of the cases described as ductal on cytology were concurrent with the histological sub typing, whereas only 40 % of ILC and TUB were correctly suggested as subtype on FNAC.

Sampling error (SE) was the main cause of not reaching a definite diagnosis of malignancy on FNAC (66.1 % of cases). In ILC and TUB SE made up > 82 % of cases. Scant cell material was found in 19.7 % of cases and made up 86.7 % of cases with a benign FNAC diagnosis, 75 % of the probably benign cases and 70 % of the equivocal cases. These and 42.9 % of the suspicious cases made up the SE cases. 10.1 % were given a definite diagnosis of malignancy in spite of the scant cellularity.

Abundant cell material was noted in 50.7% of the cases. None of these had been given a benign diagnosis, but 12.5 % had been diagnosed as probably benign, 10 % as equivocal and 18.4 % as suspicious and representing interpretation error (IE) cases. Scattered myoepithelial cell nuclei were found at the periphery of epithelial (carcinoma) cell groups (but not in the background) in 20.2 % of IDC and 39.1 % of TUB. Microcalcifications were found in 45 % of all cases.

Discussion

Sensitivity, percentage of inadequate smears and FN in FNAC of grade 1 breast carcinomas are all well within the QC recommendations in the Norwegian breast screening programme (21). The sensitivity is marginally lower than in previous results from non-palpable breast lesions (22). This is in agreement with the fact that 80 % of the carcinomas in this study were $\leq$ 10 mm and the vast majority would have been non-palpable (this feature had not been recorded). In a previous report of the first four years of mammography screening in Oslo (21) we found an absolute and complete sensitivity of 81 % and 91 %, respectively. The sensitivity of FNAC ranges in the literature from 65 to 98 % (7). It reflects both aspirator and interpretation skills.

FNAC is highly operator dependent (7;30;31). Aspirator skill is also reflected in the inadequacy rate, which was 2.6 % in this study.

Subtyping of carcinomas on cytological material revealed significant differences between IDC, ILC and TUB (table 3). Almost 90 % of IDC were correctly sub-classified as such on cytology, whereas only 40 % of ILC and TUB were correctly sub-classified. Both ILC and TUB have characteristic cytological features reported in the literature (32-43), but none of them are restricted to one subtype only. IDC has a wide range of histological appearances which may be reflected in FNAC. They include features that may also be found in other subtypes. Also, IDC may harbour components of other subtypes such as tubular, mucinous, papillary and lobular which may be found in the smears. The most important is to recognise a papillary subtype, as these may present as a tumour both clinically and radiologically and still be an in situ lesion on histology. The problem of diagnosing in situ versus invasive lesions has been addressed previously (21;44). In case of a cytological papillary carcinoma, we do not attempt to predict eventual invasive growth. The lesion will be resected with free margins, but the sentinel node will not be removed. Apart from that, subtyping does not affect the primary management of the women and is not essential.

Sampling error (SE) was the main cause of not giving a preoperative definite malignant diagnosis irrespective of tumour type (table 3) and the main cause of SE was small tumour size (80 % $\leq$ 1 cm). In IDC the causes were rather mixed and both sampling and interpretation might be a problem.

Sampling is a well known problem in ILC and is due to the abundant sclerotic stroma that is found in most cases. The carcinoma cells usually present with a low - grade, but recognizable atypia, but the cells are characteristically few in numbers. The

characteristic finding in FNAC from ILC would be scant to moderate amount of cells (table 3) diagnosed as suspicious (28.6 %) or as malignant (51.4 %) and where the reservation in the diagnosis is due to a low number of carcinoma cells on the smears (82.4 %, see table 2).

TUB present little atypia in contrast to most IDC, and may be misdiagnosed as fibroadenoma or fibrocystic changes (33;34). Cellular features such as angular tubular structures, single epithelial cells, absence of or paucity of bare oval nuclei are frequently described as distinguishing features (32;33). TUB represented a diagnostic problem as they frequently eluded detection on cytology. 8 (30 %) cases were diagnosed as benign, probably benign or equivocal. 55.6 % (= absolute sensitivity) was given a definitive preoperative diagnosis in our study, whereas the complete sensitivity (malignant + suspicious + equivocal) was 85 %. Mitnick et al. (42) showed an absolute sensitivity of 42 %, which is somewhat lower than our findings. Cangiarella et al. (33) showed a complete sensitivity of 86 %. Despite the discrete cellular and nuclear atypia of TUB, the main cause of not reaching a definitive malignant diagnosis in our material was sampling (table 2).

Although there is a higher false negative rate of TUB and ILC than of ductal carcinoma, the combined incidence comprised only 10 % of the total number of cases. Overall, ILC will make up a larger group, though, as many of them are diagnosed as grade 2 (G2).

There has been an increase in the use of core biopsy (CNB) in the recent years (45;46). CNB has a higher sensitivity for ILC and TUB (42), but considering the incidence, it would be cost efficient and time saving to use FNAC as a first line investigation. Combination of CNB and FNAC has shown a higher sensitivity than FNAC alone (12). However, if the sensitivity of FNAC is high, the additional value of a

CNB will have a marginal effect on the sensitivity. In addition, sampling of small and focal lesions is known to cause diagnostic difficulties even in CNB (47).

Myoepithelial cells were found in a subpopulation of IDC and TUB (20 % and 39 %, respectively), but always in limited numbers. It is important to know this and not diagnose these lesions as benign or probably benign on account of a few myoepithelial cells.

Microcalcifications were a common finding in IDC and TUB (45 % and 65 %, resepectively), but were non-contributory in the diagnostic work-up.

In conclusion, FNAC had a high sensitivity in diagnosing low - grade invasive carcinomas. The main difficulties encountered were related to SE, irrespective of tumour subtype. Small tumour size was the main cause of SE. In contrast to what might have been anticipated, IDC had the largest proportion of interpretation problems.

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Table1. Diagnostic categories and criteria

Cytological diagnostic categories	Cytological diagnostic criteria
unsatisfactory	No/(too few epithelial cell groups present
Benign NOS	Sheets/groups of benign apocrine and/or ductal epithelial cells; a variable number of naked (myoepithelial) nuclei in the background and recognisable myoepithelial nuclei on a number of benign epithelial sheets and groups
Equivocal	Epithelial cells with nuclear changes of uncertain significance
Suspicious for carcinoma	Epithelial cells with some, but not sufficient diagnostic features of carcinoma; often scant cell material
Carcinoma	Variable, buy most often a high cell yield; single population of atypical epithelial cells in irregular and angular clusters; reduced cohesiveness, variable, nuclear enlargement and irregularity; single cells with intact cytoplasm; absence of naked (myoepithelial) nuclei in the background

Table2.Cytologic diagnoses

	frequency	percent
unsatisfactory	13	2.6
benign	16	3.2
Hyperplasia/ Probably benign	8	1.6
Equivocal	23	4.7
Suspicious for carcinoma	52	10.5
Invasive carcinoma	382	77.3
total	494	

Table3. Results of cytologic subtype, cytologic diagnosis, type of error, amount of cell material and microcalcification compared to histologic subtype.

	Histologic subtype						
	ductal	lobular	tubular	mucinous	papillary	other	subtotal
Cytologic subtype (when suggested = 397 cases))							
▪ carcinoma NOS	**106 (86.2%)**	11	4	2	0	0	123
▪ ductal	**206 (89.6%)**	5	10	1	1	7	230
▪ lobular	6	**6 (46.2%)**	1	0	0	0	13
▪ tubular	2	0	**2 (40%)**	0	0	1	5
▪ mucinous	4	0	1	**11 (68.8%)**	0	0	16
▪ papillary	5	0	0	0	2	1	8
▪ other	2	0	0	0	0	0	2
subtotal	331 (83.4%)	22 (5.5%)	18 (4.5%)	14	3	9	397
Cytologic diagnosis (= 494 cases)							
▪ unsatisfactory	9	3	1	0	0	0	13
▪ benign	12	1	3	0	0	0	16
▪ probably benign	6	2	0	0	0	0	8
▪ equivocal	15	1	4	2	0	1	23
▪ suspicious for carcinoma	**35 (8.7%)**	**10 (28.6%)**	**4 (14.8%)**	1	0	2	52
▪ invasive carcinoma	**325 (80.8%)**	**18 (51.4%)**	**15 (55.6%**	**14 (82.4)**	3	7	382
Type of error (in cases not having a definitive malignant preoperative diagnosis = 112 cases)							
▪ interpretation error (IE)	31 (40.3%)	3 (17.6%)	2 (16.7%)	1	0	1	38 (339%)
▪ sampling error (SE)	43 (57.9%)	**14 (82.4%)**	10 **(83.3%)**	2	0	2	**74 (66.1%)**
Amount of cell material (evaluated in 470 cases)							
▪ scant	67	**13**	**9**	2	0	2	93

	(17.4%)	**(41.9%)**	**(36%)**	(11.8%)			
▪ moderate	111 (28.9%)	13 (41.9%)	7 (28%)	5 (29.4%)	0	2	138
▪ abundant	206 (53.6%)	5 (16.1%)	29 (36%)	10 (58.8%)	3	10	239
Microcalcification (evaluated in 451 cases)							
present	173	5	15	4	1	6	204
not present	198	24	8	12	2	3	247
subtotal	371	29	23	16	3	9	451