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Screen-detected breast lesions with malignant needle core biopsy diagnoses and no malignancy identified in subsequent surgical excision specimens (potential false-positive diagnosis)

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ABSTRACT

Although breast needle core biopsy (NCB) is now a standard diagnostic procedure in the triple assessment of screen-detected breast lesions, data on the false-positive diagnoses of malignancy (malignant NCB 'B5' with normal/benign surgery) are lacking. In this study, we have studied a large series of NCBs (101,440) to assess the causes and pitfalls resulting in false-positive NCB diagnoses and to evaluate their impact on patients' management in the screening service. Our results showed that of 40,395 malignant NCBs reported during the period of this study, 174 NCBs are considered as false-positives (0.43%; (95% confidence interval [CI] = 0.37–0.49%)). However, on review, 165 cases (95%) were found to be the result of true removal of the whole lesion in the core with subsequent negative excision biopsy samples (true-positive NCBs). This may reflect sampling of small screen detected lesions and the use of larger core biopsies at assessment. The remaining 9 cases were considered as true false-positive cores, giving a false-positive rate of 0.02% (95% CI = 0.01–0.04%). Analysis of these 9 cases showed that 8 cases, originally diagnosed as DCIS, were classified as borderline lesions or lesions of uncertain malignant potential after surgical excision. The classification and management of such borderline lesions remains controversial and diagnostic surgical excision is usually the optimum management. One case was the result of pathological misinterpretation of fat necrosis as invasive carcinoma. This was the only case that resulted in a significant over-management of the patient. In conclusion, our results showed that the true false-positive rate of NCB is extremely rare. Significant over-management of screen-detected breast lesions as a result of false-positive NCB may be considered almost nil.

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1. Introduction

The role of pre-operative diagnosis in the assessment of screen-detected breast lesions is to attempt to provide a definitive diagnosis. A diagnosis of malignancy allows a rapid referral for treatment, ideally in 1 operative procedure. Definitive non-operative diagnosis of benign conditions is also useful, leading to discharge from the clinic and return to routine recall. This pre-operative diagnosis in breast cancer screening is achieved using triple assessment involving multidisciplinary cooperation between radiologists, surgeons and pathologists. Pre-operative pathological diagnosis is made using fine needle aspiration cytology (FNA) or needle core biopsy (NCB). NCB is now considered as the method of choice for the triple assessment,[1] and the published data suggest that the use of NCB has increased the pre-operative diagnosis rate in screen-detected breast cancers.[2,3] NCB, as compared to FNAC, can provide definite benign diagnoses, reliably distinguish between *in situ* and invasive cancers, and allows the evaluation of histological, prognostic and predictive factors in breast cancer that are required before decisions on subsequent therapy.[4] In addition, it has been reported that the introduction of NCBs has reduced the number of surgical procedures for invasive breast cancer such as diagnostic wire-guided open biopsies.[5,6]

In cancer screening programmes, it is recognised that false-positive results should be reduced to a minimum, since a malignant diagnosis often supports important management decisions and may result in an inappropriate treatment. Therefore, the performance of FNA in breast screening has been previously assessed, and pitfalls and conditions resulting in a false-positive cytology diagnosis have been thoroughly evaluated and guidelines have been published.[7–10] Recently, guidelines on reporting, recording and auditing malignant NCB (B5) with normal/benign surgery have been recently published by the National Health Service Breast Screening Programme (NHSBSP) in the United Kingdom (UK).[11] However, data on the frequency, causes and pitfalls resulting in false-positive NCB are lacking.

In this study, we have examined a large series of NCB of screen-detected breast lesions from all screening units in the UK. We aimed to provide robust data on the frequency, actual causes, conditions and pitfalls resulting in false-positive NCB diagnoses in the screening practice and to assess their actual impact, if any, on breast screening programmes.

2. Materials and methods

This is a retrospective study of all women who attended following invitation for breast screening at 1 of 96 screening services in the UK between 1st April 2004 and 31st March 2007. During this period, 101,440 women (1.8%) underwent assessment with fine needle aspiration (FNA) and/or needle core biopsy (NCB) procedure. Criteria for performing FNA or NCB were nearly always mammographic findings which were not definitely benign following further imaging (extra views and ultrasound). A small proportion (<1%) was performed as a consequence of the patient reporting a physical finding or a radiographer detecting a physical abnormality during mammography. All patients diagnosed on FNA and/or NCB were discussed at a multidisciplinary meeting (MDM) with a breast radiologist, histopathologist and surgeon present and a decision for further action was made. For the purpose of this study, only NCB cases were considered.

NCB results were categorised according to UK guidelines.[9] Categories included B1 = normal, B2 = benign, B3 = lesions of uncertain malignant potential, B4 = suspicious of malignancy, B5 = malignant (B5a = *in situ* malignancy, B5b = invasive malignancy, B5c = malignant (*in situ*/invasive) status cannot be assessed). Outcomes were determined as malignant (*in situ* and invasive) or benign lesions. False-positive NCB is defined as a case that was given a B5 result and which turns out at open surgery to be a benign lesion (including atypical hyperplasia). False-positive rate was defined as the number of false-positive results expressed as a percentage of the total number of carcinomas sampled.[9] Analysis of the results was performed in accordance with the standards specified in the National Health Service Breast Screening Programme (NHSBSP) Publication and European Guidelines.[9,12]

In this study, false-positive NCBs were identified from the NHSBSP national computer system which records data from all screening units throughout the UK. Data related to these false-positive NCBs were collected from the different screening units. These included screening rounds, radiological appearances, radiological opinion, ultrasound opinion, clinical opinion, mammographic and clinical lesions size, type of non-operative and operative procedures, number of NCB attempts, number of open surgical procedures performed to reach a final diagnosis, amount of tissues removed, final histological diagnoses and comments on the further actions that have been taken place (consideration for the transposition of specimens and process for investigating if there was a mislabelling of specimens, sending cases for external review and MDM classification).

3. Results

During the period of this study, 45,840 breast cancer cases were diagnosed following pre-operative assessment (0.8% of screened; 45.8% of women assessed with cytology/NCB). Of these cancer cases, 94.4% were diagnosed after NCB assessment (37,652 malignant core and 2,743 malignant core and malignant cytology combined) (Table 1). In other words, of all NCBs performed during this period, 40,395 (40%) cores were reported as malignant (B5a = 9400, B5b = 30,453, B5c = 542). Of these malignant cores, a total of 204 cases were recorded as false-positive NCBs (B5 core biopsy followed by benign/normal surgical histology) giving a false-positive rate of 0.5%. However, on initial review of their reports, 29 cases were not considered as false-positive NCB and excluded from the subsequent analyses as a result of 1 of the following:

(1) Cancers missed at initial operation (s) and found at subsequent operation (4 cases).
(2) Cases treated by neoadjuvant chemotherapy after a NCB diagnoses (9 cases).
(3) Incorrect data for inclusion as false-positive NCB (cases were diagnosed as malignant on cytology followed by a B3 diagnosis on NCB (1 case), or not followed by NCB (5 cases).

Table 1 – Number of women screened, referred for assessment by cytology and/or core biopsy and total number of cancers diagnosed following assessment during the period of the study.

	Year			Total (2004–2007)
	2004–2005	2005–2006	2006–2007	
Total screened	1,749,167	1,925,275	1,937,471	5,611,913
Total referred[a]	31,616	34,857	34,967	101,440
Total cancers[b]	14,040	15,944	15,856	45,840
% of NCB cancers[c]	93%	94%	96%	94%

a Total number of screened women who were and referred for cytology/core biopsy assessment.
b Total number of cancers diagnosed after cytology and/or core biopsy assessment.
c Percentage of breast cancer cases diagnosed after core biopsy assessment (excluding cytology).

(4) Incomplete data for inclusion as false-positive NCBs (cases awaiting further information on surgery or MDM classification) (8 cases).
(5) Wrong coding of NCB category: (A) In 2 cases, it was stated in the NCB report that the diagnosis is LCIS but coded by mistake as (B5a); and (B) In 1 case, the NCB report was followed by a supplementary amendment to the report and the B5a diagnosis was changed to B4 (suspicious), after external review, before any subsequent surgery.

Therefore, the total number of false-positive NCBs included in this study was 174 cases giving a false-positive rate of 0.4% (95% confidence interval [CI] = 0.37–0.49%).

4. Analysis of false-positive NCBs

Table 2 shows the details of all false-positive NCB. Lesions removed by NCB that were diagnosed as false-positive were more likely to be diagnosed in the incident screening rounds, to be of small size, less frequently presented as mass lesion and were frequently diagnosed by vacuum-assisted wide core biopsy. The majority of these lesions (58%) were categorised as uncertain on ultrasound and/or mammography and were clinically undetectable (83% clinically diagnosed as normal). All these cases were subjected to external and/or local review. External review was performed in 20 cases and was not considered in 139 cases. Mix up of specimen was investigated in 11 cases. DNA testing was performed in 2 cases. On review, the reasons for the inclusion of these 174 NCBs in the false-positive NCB category were as follows:

(1) Complete removal of the tumour in the core (true removal of the malignant lesion by the NCB) and therefore, absence of residual tumour in the excision specimen, which were coded as benign (165 cases; 95%).
(2) True false-positive NCB (lesions on the NCB did not justify the inclusion in the B5 category); this was identified in 9 cases; 8 were reported as B5a and 1 as B5b. All these 9 cases were subjected to external review and the NCBs were re-diagnosed as follows:
    [1] Eight cases were down-graded from B5a (DCIS) to either B3 or B4 as follow: (a) atypical ductal hyperplasia (5 cases); (b) columnar cell change with atypia (1 case); (c) atypia due to focal lactational/secretory changes rather than DCIS (1 case) and (d) pleomorphic LCIS after E-cadherin immunohistochemistry. Interestingly, none of these 8 cases were definitely diagnosed as 'malignant' by the pre-NCB radiological/ultrasound/clinical diagnoses; uncertain in 5 cases, suspicious in 2 cases and benign in 1 case.
    [2] One case was misinterpreted on histology and was diagnosed as fat necrosis (B2) rather than invasive carcinoma (B5b). This case was radiologically uncertain and was benign clinically and on ultrasound examination.

Interestingly, of these 9 true false-positive cases, 7 were associated with microcalcification whilst 2 were associated with stromal distortion; 8 cases were diagnosed as uncertain/suspicious on radiology and ultrasound and 6 cases were removed under digital stereotaxis guidance.

5. Discussion

It is recognised that false-positive pre-operative breast disease diagnosis creates issues involving patient support and management, performance of NCB and data recording. Guidelines for dealing with these issues have recently been published.[11] However, study of the true false-positive rate and the conditions and pitfalls resulting in false-positive NCB are still lacking. Therefore, in this study, we have included a consecutive series of NCB cases over a period of 3 years of all subjects who attended any of the screening units in the UK following invitation from the NHSBSP. All these units follow the same protocols for reporting of NCB in a standardised fashion, providing uniform data on NCB performance in the screening setting and follow the UK published guidelines for dealing with false-positive results.[11] To our knowledge, this study is the first to report on the false-positive NCB of screen-detected breast lesions. Our results showed that of the 40,395 malignant NCBs (B5) included in this study, 174 cases (0.4%) were recorded as false-positive NCBs.

On review of these 174 false-positive NCBs, 165 cases were found to be the result of complete removal of the lesion in the core tissue. The review decisions of these cases were based on the confirmation of the B5 diagnoses in the NCB, the presence of core biopsy site in the excision specimen and matching of the pathological features on both NCB and excision specimen in accordance with the UK guidelines.[11] These results may reflect sampling of small screen detected lesions and the use of larger core biopsies, particularly vacuum assisted at

Table 2 – Characteristics of all false-positive needle core biopsies (NCB) (174 cases) and cases that were completely removed on NCB (165).

	Total false-positive NCBs (%)	Cases that were completely removed on NCB (%)	
		B5a (124 cases)	B5b (41 cases)
Screening round			
Incident screening	121 (70%)	84 (68%)	34 (83%)
Mammographic abnormalities			
Calcification	122 (70%)	101 (86)	13 (33%)
Mass	28 (16%)	13 (11%)	15 (39%)
Stromal distortion	6 (3%)	2 (2%)	3 (8%)
Asymmetric density	11 (6%)	2 (2%)	8 (20%)
Mammographic size			
Median (range)	6 mm (3–30 mm)	6 mm (range 3–30)	6 mm (range 3–18)
Removal by NCB			
Vacuum-assisted NCB	70 (40%)	57 (46%)	9 (22%)
NCB guidance			
Digital stereotaxis	110 (64%)	78 (63%)	26 (63%)
Analogue stereotaxis	15 (9%)	12 (10%)	2 (5%)
Ultrasound	30 (17%)	17 (14%)	12 (30%)
X-ray	18 (10%)	16 (13%)	1 (2%)
B5 NCB attempt[a]			
1st	153 (88%)	109 (88%)	36 (88%)
2nd	17 (10%)	13 (10%)	3 (7%)
3rd	4 (2%)	2 (2%)	2 (5%)
No. of surgical operations			
1	166 (95%)	121 (98%)	36 (88%)
2	7 (4%)	3 (2%)	4 (10%)
3	1 (1%)	0 (0%)	1 (2%)
Lymph nodes sampled	58 (33%)	19 (15%)	38 (93%)
Weight of surgically removed tissue (excluding mastectomies)	44 (6–275 gm)	38 (7–194 gm)	89 (80–275 gm)

a Number of attempts of NCB that resulted in B5 diagnoses; preceding cytology was not considered.

assessment. This was supported by our results which showed small size of the lesions (median 6 mm; as compared to a median of 14–15 mm in screen-detected invasive breast cancer),[13–15] less frequent presentation as mass lesion and the frequent use of vacuum-assisted wide core biopsies with increasing likelihood of sampling of the whole lesion in the core tissues. Complete removal of the tumour in needle cores has also been reported in prostatic adenocarcinoma (the so-called 'vanishing cancer phenomenon', as a result of early detection of low-stage cancers. Previous studies have shown that the percentage of cases with minimal or no residual cancer in the radical prostatectomy specimens following positive cores ranges from 0.5% to 3%).[16–18] Although for the purpose of data entry and recording, these cases are reported as false-positive, from the pathological perspective, these cases are true-positive NCBs and should be excluded from the analysis of false-positive NCB category. From the surgical management perspective, these cases were properly treated; however, further action may not be needed.

In this study, 9 cases were considered as true false-positive cores giving a true false-positive rate of 0.02% (95% CI = 0.01–0.04%) as compared to that of FNA, which range between 0.5% and 1.5%).[19–22] However, on review of these 9 cases, we found that 8 cases were reported as false-positive as a result of down-grading of DCIS in the NCB to borderline lesions or lesions of uncertain malignant potential including atypia and lobular carcinoma *in situ* (LCIS), which according to the current guidelines should be included in the B3 or B4 category.[10,19] However, it should be mentioned that the distinction between atypical ductal hyperplasia (ADH) and low-grade DCIS, between columnar cell change with atypia or some forms of LCIS and DCIS can be difficult, subjective and of low reproducibility in core biopsies. For example, the distinction between low-grade DCIS and ADH is based on the number of ducts involved and the size of the lesion size.[23] Recent molecular and morphological analysis showed that these lesions may represent a spectrum of the same disease and some authors congregate them under the term 'low-nuclear grade breast neoplasia family'.[24] In addition, the histological classification, risk of malignancy and management of these lesions are still controversial, and diagnostic surgical excision is usually the optimum management strategy to assess the extent of these lesions and to exclude any associated malignancy. Importantly, all these 8 patients underwent wide local excision of their breast tissue without mastectomy or lymph node sampling and therefore, up-grading of their NCB lesions did not result in gross over-treatment. In this study, only 1 false-positive NCB case was identified due to a major

pathological misinterpretation; fat necrosis interpreted as invasive cancer, resulting in a significant over-management of the patient.

Interestingly, the number of missed localisation biopsies/cancers found at subsequent operation in this study appears to be low and that most such cases, who quickly have the second operation, will not be usually recorded as a false-positive NCB on the computer system. We also identified that the rate of false-positive varied through the country (data not shown) and this probably indicates different standards of data collection nationally. It is also important to record that false-positive cases included in this study were identified from the national computer system with a possibility that these data may underestimate the total extent of 'false-positives' due to the method of data entry on the computer system (at a unit level). However, as it is apparent that the vast majority of false-positive NCBs identified in this study were the result of true removal by core biopsy sampling, even with more cases to add to this study, the message that true false-positive results rarely occur in the screening scenario is likely to hold true.

In conclusion, our results showed that true false-positive NCBs are very rare. Significant over-management of screen-detected breast lesions as the result of false-positive NCB may be considered almost nil. Our results provide further evidence for the public and health care professionals about the improved performance of breast screening. We would like to emphasise the need for further studies of the borderline lesions/lesions of uncertain malignant potential that are increasingly recognised as a result of improved mammographic detection and may result in false-positive NCB results. Guidelines to improve histological classification of these lesions in NCBs samples and their management are warranted.

Conflict of interest statement

None declared.

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