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Is the appearance of microcalcifications on mammography useful in predicting histological grade of malignancy in ductal cancer *in situ*?

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Abstract. It has been proposed that the grade of malignancy of ductal carcinoma *in situ* (DCIS) of the breast can be estimated by the morphology of microcalcifications found on mammography. We correlated microcalcifications and histopathology in a retrospective blinded review. We reviewed all patients who underwent excisional breast biopsy over a 5½-year period. Mammograms and pathology slides of all patients (n=49) with DCIS of the breast were included in a blinded retrospective analysis. Mammographic microcalcifications were divided into four categories, ''linear branching'', ''coarse granular'', ''fine granular'' or ''no microcalcification''. Independently, pathology specimens were assigned to poorly, intermediately and well differentiated categories according to the consensus classification of DCIS introduced by the European Organisation for the Research and Treatment of Cancer. Two patients had no microcalcifications. 25 (53%) of the remaining 47 patients had ''linear branching'' microcalcifications, 10 (21%) had ''coarse granular'' and 12 (25.5%) had ''fine granular'' microcalcifications. 19 patients (40%) had poorly differentiated, 23 (49%) intermediately differentiated and 5 (11%) well differentiated subtypes of DCIS. 14 (56%) of the 25 patients with ''linear branching'' microcalcifications had poorly differentiated DCIS, 10 (40%) had intermediately differentiated and 1 (4%) had well differentiated DCIS. 3 (30%) of 10 patients with ''coarse granular'' microcalcifications had poorly differentiated DCIS, 5 (50%) had intermediately differentiated and 2 (20%) had well differentiated DCIS. 2 (17%) of 12 patients with ''fine granular'' microcalcifications had poorly differentiated DCIS, 8 (67%) had intermediately differentiated and 2 (17%) had well differentiated DCIS. These findings were not statistically significant. In conclusion, ''linear branching'' microcalcifications tended to be associated with higher pathological grading. However, correlation was poor and there was considerable overlap between categories. Histological type of DCIS cannot be predicted prospectively on mammographic appearances.

Ductal carcinoma *in situ* (DCIS) of the breast is rarely diagnosed clinically [1]. DCIS accounts for one-sixth to one-third of screening-detected breast cancers [2–4]. Special interest has recently been given to the histological subtype of DCIS, as evidence has emerged for a correlation between subtypes and recurrence rates. Furthermore, the probability of development into invasive cancer is related to the subtype of DCIS [5].

Traditionally, DCIS is categorized according to histological architectural characteristics and the presence or absence of comedo necrosis [6]. Architectural classification tends to be subject to interobserver variability [7]. Two major groups of DCIS are broadly distinguished by means of a simple but useful classification: comedo and non-comedo types [8]. Comedo-type DCIS tends to be more aggressive, has a higher recurrence rate and more often converts into invasive cancer than non-comedo forms [4, 5, 9, 10]. Pathologists are now aware of the importance of cytonuclear differentiation [11–13]. White et al [14] found that the predominant nuclear grade was the best predictor of local recurrence. In 1989, Lagios et al [5] combined necrosis, nuclear grade and histological architectural pattern to define four subtypes of DCIS. In 1994, Holland et al [15] proposed a new classification for mammary DCIS, based primarily on cytonuclear grade and which uses histological architectural differentiation as a secondary characteristic. This system defines three main subtypes of DCIS: poorly differentiated, intermediately differentiated and well differentiated. Their model constituted

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the foundation of the consensus classification of the Third DCIS Working Party of the European Organisation for the Research and Treatment of Cancer (EORTC), which currently is a widely accepted histological classification system for non-invasive ductal carcinoma of the breast [16] (Table 1).

Holland and Hendriks [17] have also suggested a correlation between mammographic type of microcalcification and histological subtype of DCIS of the breast. The ability to predict grade of malignancy of DCIS by mammographic appearances could have implications for patient prognosis and choice of therapeutic options.

The purpose of this blinded study was to assess whether mammographic type of microcalcification could be correlated with comedo-necrosis, nuclear grade and EORTC histological subtype, and therefore whether standard mammography is able to predict the subtype of DCIS.

Methods and material

We reviewed the pathology reports of all patients who underwent excisional breast biopsy in our university hospital between January 1993 and August 1998, looking for all cases of DCIS of the breast. All patients on whom both pathology slides and mammography films could be obtained were included in a blinded evaluation. Mammography was performed on a Siemens Mammomat 2 in two standard projections, craniocaudal and lateromedial. The mammograms were re-evaluated in consensus by radiologists with special interest and training in breast radiology. Magnification views were not included in the film reading as these were only available in a minority of cases.

The predominant mammographic types of microcalcification were divided into four categories, "none", "linear branching", "coarse granular" and "fine granular", as defined by Holland and Hendriks [17], in a blinded retrospective evaluation. Pathology specimens were reviewed by an experienced breast pathologist who was unaware of the clinical findings and the mammographic appearances, and who classified the specimens according to their predominant histological subtype. The following histological characteristics were used: (A) architecture (solid, cribriform, papillary, micropapillary, clinging type); (B) presence of comedo necrosis; (C) nuclear malignancy grade (low, intermediate, high) (Table 2); and (D) EORTC grade (well differentiated, intermediately differentiated, poorly differentiated) [16].

For evaluation, nuclear malignancy grade and EORTC grading were correlated with type of mammographic microcalcification.

All data were entered into a PC database (Lotus Approach, Version 3.0, Lotus Development Cooperation, Ratingen, Germany) and further processed on a spreadsheet application (Lotus 123, Version 5.0, Lotus Development Cooperation, Ratingen, Germany). Statistical evaluation was performed using the PC-MEDAS statistical software package, version 1998 (Grund-EDV Systeme, 97206 Margetshöchheim, Germany), using the χ^2 test and Fisher and Yates's exact test for testing the association between microcalcification type and histopathological subtype.

Results

Either mammograms or pathology slides were unavailable in 19 patients. Two patients with well differentiated DCIS had no microcalcifications. 25 (53%) of the remaining 47 patients constituting our study group had predominantly linear microcalcifications, 10 (21%) had coarse granular and 12 (25.5%) had fine granular microcalcifications. Mean patient age was 53.4 years (26.5–77.3 years). Mean tumour size of the pathology specimens was 12.8 mm (range 4–40 mm).

18 (38%) of the 47 patients with microcalcifications had high nuclear grade histopathology, 17 (36%) had intermediate and 12 (25%) had low nuclear grade histopathology.

Numeric correlation of mammographic microcalcification type and nuclear malignancy grade is given in Table 3; it did not reach statistical significance ($p>0.06$). Microcalcification type

Table 1. Definition of EORTC grading of DCIS

EORTC grading of DCIS	
Poorly differentiated DCIS	High NMG, comedo necrosis with amorphous microcalcifications
Intermediately differentiated DCIS	Intermediate NMG, comedo necrosis or single cell necrosis
Well differentiated DCIS	Low NMG, frequently small cell type, micropapillary patterns, necroses rare, fine granular microcalcifications

EORTC, European Organisation for the Research and Treatment of Cancer; DCIS, ductal carcinoma *in situ*; NMG, nuclear malignancy grade.

Table 2. Definition of nuclear malignancy grading (NMG) of ductal carcinoma *in situ* (DCIS)

NMG of DCIS	
High NMG	High nuclear polymorphism; size of nuclei 15–20 μm, coarse chromatin, prominent nucleoli, many mitoses
Intermediate NMG	Moderate nuclear polymorphism; size of nuclei 10–15 μm, chromatin uncharacteristic, prominent nucleoli, some mitoses
Low NMG	Monomorphism of nuclei; size of nuclei<10 μm, dense chromatin, mitoses rare

and EORCT grading were not significantly correlated ($p>0.12$) (Table 4).

Discussion

Since the initial description of microcalcifications in breast cancer by Leborgne in 1951 [18], it has become clear that microcalcifications do not represent the non-invasive precursor of cancer but rather its invasive form [19, 20]. There have been several descriptions of the patho-anatomical correlation between DCIS and microcalcifications [17, 19, 21, 22]. The histological substrate of linear and coarse granular microcalcifications is comedo necrosis [17, 19, 21, 23]. These microcalcifications are amorphous and tend to occur along the central axis of the ductal tree that is filled or covered by the solid architectural type of DCIS, which corresponds best to poorly differentiated DCIS according to EORTC grading (Figure 1b). Depending on their degree of coalescence, amorphous microcalcifications form rod-like structures that may be branching or may have a more coarse granular appearance [4, 17, 20]. There is overlap between these two types and both may be found in the same breast (Figure 1a). A second type of microcalcification consists of laminated concentric layers of calcium and resembles psammoma bodies [17, 19, 24] (Figure 2). These are not the result of cell necrosis but are the product of calcium-loaded apocrine secretions from tumour cells. The size of these bodies is much smaller than that of the amorphous necrotic type. This type is most frequently found in non-comedo DCIS [17, 23], especially in the cribriform subset where these bodies tend to fill the mesh holes of the sieve (cribriform=sieve-like) (Figure 2b).

Knowledge of the histological subtype may have therapeutic importance in managing patients with DCIS. Mastectomy, which was the standard procedure for DCIS until recently [25, 26], may represent overtreatment [27]. Lower grade DCIS less frequently turns into invasive cancer and tends to recur less frequently [28, 29], while patients with comedo types (poorly differentiated DCIS) almost invariably develop invasive cancer when untreated and have higher recurrence rates after breast-conserving resection [30].

It has been suggested that mammography could help in distinguishing the different histological subtypes of DCIS [15, 31]. Holland et al [15] considered that the mammographic appearance showed quite good correlation with their classification of DCIS. This might have implications for management. Microcalcifications associated with more aggressive lesions, ''malignant microcalcifications'' [32], serve as a clear indication for excisional biopsy, whereas more benign-appearing fine granular microcalcifications that tend to be associated with well differentiated DCIS and to have a lower incidence of invasion could be managed less aggressively.

Fine needle puncture and large core needle biopsy [33], especially vacuum-assisted core biopsy devices [34], achieve very reliable results in the presence of microcalcifications. In the presence of microcalcifications that are more likely to be associated with lower grades of

Table 3. Correlation of microcalcification type and nuclear malignancy grading (NMG)

NMG	Mammographic microcalcification type			
	Linear	Coarse granular	Fine granular	Total
Low	3 (12%)	4 (20%)	5 (42%)	12 (26%)
Intermediate	8 (32%)	4 (20%)	5 (42%)	17 (36%)
High	14 (56%)	2 (10%)	2 (17%)	18 (38%)
Total ($\chi^2=8.48$, $p=0.063$[a])	25 (53%)	10 (21%)	12 (26%)	47 (100%)

[a]Maximum likelihood test not significant.

Table 4. Correlation of microcalcification type and EORTC grading

EORTC grading	Mammographic microcalcification type			
	Linear	Coarse granular	Fine granular	Total
Well differentiated	1 (4%)	2 (20%)	2 (17%)	5 (11%)
Intermediately differentiated	10 (40%)	5 (50%)	8 (67%)	23 (49%)
Poorly differentiated	14 (46%)	3 (30%)	2 (17%)	19 (40%)
Total (χ^2=6.90, p=0.12)	25 (53%)	10 (21%)	12 (26%)	47 (100%)

EORTC, European Organisation for the Research and Treatment of Cancer.

malignancy, it could be valid to use core biopsy as the sole method for obtaining specimens for histological assessment.

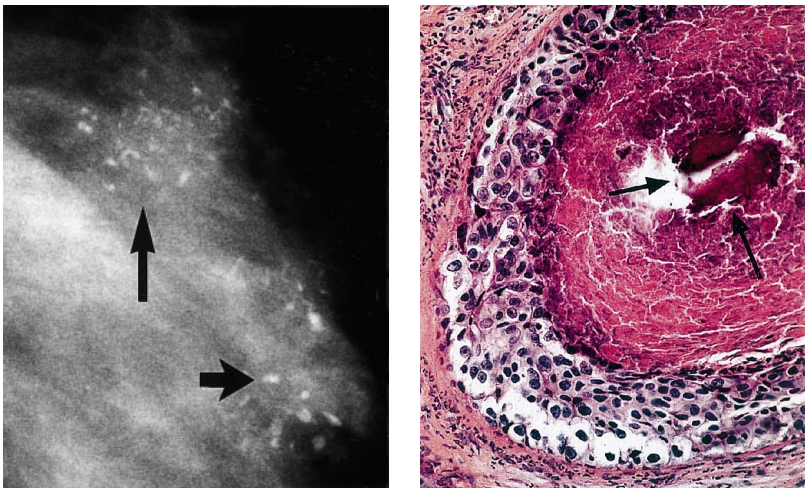
Mammographically, poorly differentiated DCIS was most frequently associated with microcalcifications of the linear type, in 74% of cancers in the present study, but was also seen with coarse (16%) and fine granular types (11%). On the other hand, intermediately differentiated DCIS was found in 10 (40%) of 25 cases of linear microcalcifications. There was a negative correlation between linear microcalcification type and well differentiated DCIS; the linear microcalcification pattern being found in only one case with low grade DCIS.

Intermediately differentiated DCIS (8 of 12; 67%) had the highest proportion of fine granular microcalcifications. However, linear microcalcifications (10/23; 43%) were more frequent than fine granular (8/23; 35%) or coarse granular (5/23; 22%) in intermediately differentiated DCIS.

Holland et al [15] stated that well differentiated DCIS with a non-solid growth pattern is usually associated with multiple clusters of fine granular microcalcifications. In the five cases of well differentiated DCIS in our study, fine granular microcalcification was found in only two. One of five cases of well differentiated DCIS had linear microcalcifications, which were, however, rather faint so that they did not represent a straightforward case of the "malignant microcalcification" type.

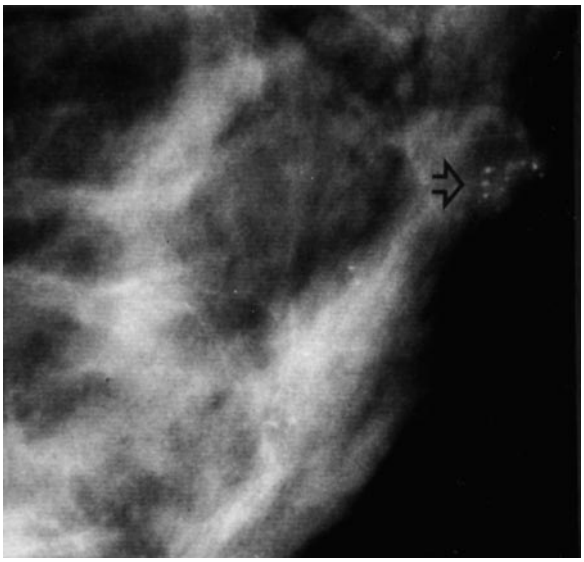
Our findings clearly demonstrate that there is poor correlation between histological types of DCIS and predominant mammographic appearance, with significant overlap. This is consistent with the findings of others [4, 35]. Yeh et al [35] were not able to predict the subtype of DCIS reliably, which may also have been influenced by their material mostly containing well differentiated DCIS [35].

Another difficulty is that DCIS is not homogeneous. There can be multiple radiological types of microcalcification in the same patient and even in the same breast (Figure 1). Moreover, multiple different histological subtypes can also occur in the same breast. Finally, there may be considerable interobserver variability in histopathology assessment, even among experienced pathologists. Holland and Hendriks [17] found considerable overlap of different types of DCIS in patients with

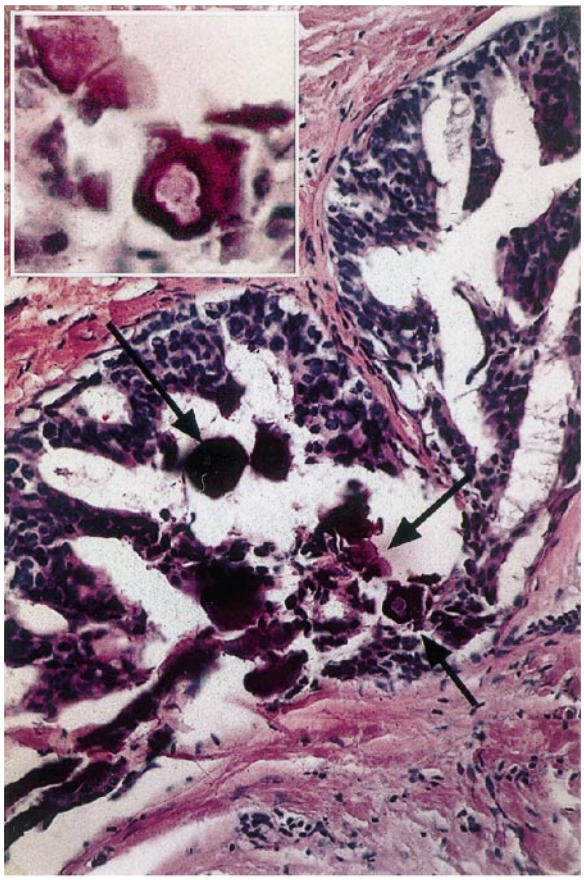


(a) (b)

Figure 1. 74-year-old woman with ductal carcinoma *in situ* (DCIS). (a) Detail of lateromedial mammogram shows predominantly linear branching microcalcifications (long arrow). Coarse microcalcifications are also present (short arrow). Both types of microcalcification are likely to be found in poorly differentiated DCIS. However, a similar appearance is found in intermediately differentiated DCIS and even in isolated cases of well differentiated DCIS. (b) Pathology specimen demonstrates solid type of poorly differentiated intraductal carcinoma, with central comedo necrosis and amorphous microcalcifications (arrows). Low cytonuclear differentiation grade. Hematoxylin eosin staining; magnification 250×.



(a)



(b)

Figure 2. 45-year-old woman with fine granular or punctate microcalcifications in well differentiated ductal carcinoma *in situ* (DCIS). (a) Detail of lateromedial mammogram of the right breast. Cluster of fine granular or punctate microcalcifications (arrow) in dense glandular tissue. (b) Pathology specimen demonstrating well differentiated intraductal carcinoma according to the European Organisation for the Research and Treatment of Cancer (EORTC) classification. High cytonuclear differentiation grade, architecture predominantly cribriform, with small microcalcifications of the laminated type (arrows and inset). Hematoxylin eosin staining; magnification 250×.

"granular" microcalcifications, whereas linear microcalcifications were exclusively found in poorly differentiated DCIS.

Stomper and Connolly [4] in 1992 correlated type of microcalcification with comedo *vs* non-comedo DCIS and found considerable overlap. Theoretically, correlation between the new EORTC grading and type of microcalcification may be expected to be even lower because the EORTC grading also includes factors other than central necrosis, which are less likely to be related to morphological signs in mammography. One the other hand, differentiated DCIS of solid architectural pattern may rarely show marked necrosis [15] resembling linear or coarse granular microcalcifications on mammograms, which could then lead to misdiagnosis of a poorly differentiated DCIS.

Even sophisticated computer calcification analysis could not convincingly overcome the inherent difficulties produced by overlap between different types of mammographic microcalcifications [36].

What is the clinical significance of the finding of linear, coarse or fine granular microcalcifications? The value of the determination of microcalcification morphology lies in the ability to predict the likelihood of malignancy, in other words in the differential positive predictive value [37, 38]. Granular microcalcifications may be found in all subtypes of DCIS, but also in fibrocystic change [17]. Fine granular or punctate microcalcifications have a relatively low positive predictive value for cancer. Liberman et al found only 1 malignancy (9%) in 11 cases of punctate microcalcifications and their material represented a highly selected group of patients in which many similar yet probably benign lesions had not undergone excisional biopsy [38]. The value of finding linear as well as pleomorphic microcalcifications lies in the fact that these entities are highly specific, if not pathognomonic, for DCIS [38]. Breast biopsy is therefore warranted in all patients in which such "malignant microcalcifications" are found [32].

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References

1. Rosner D, Bedwani RN, Vana J, Baker HW, Murphy GP. Non-invasive breast carcinoma: results of a national survey by the American College of Surgeons. Ann Surg 1980;192:139–47.
2. Lagios MD. Duct carcinoma in situ. Pathology and treatment. Surg Clin North Am 1990;70:853–71.
3. Meyer J, Eberlein TC, Stomper PC. Biopsy of occult breast lesions: analysis of 1261 abnormalities. JAMA 1990;263:2341–3.
4. Stomper PC, Connolly JL. Ductal carcinoma in situ of the breast: correlation between mammographic calcification and tumour subtype. AJR 1992;159: 483–5.
5. Lagios MD, Margolin FR, Westdahl PR, Mayre RR. Mammographically detected duct carcinoma in situ. Frequency of local recurrence following tylectomy and prognostic effect on local recurrence. Cancer 1989;63:618–24.
6. Azzopardi JG. Epitheliosis and in situ carcinoma. In: Bennington JL, editor. Problems in breast pathology. Philadelphia, PA: Saunders, 1979: 128–46.
7. van Dongen JA, Holland R, Peterse JL, Fentiman IS, Lagios MD, Millis RR, et al. Ductal carcinoma in-situ of the breast; second EORTC consensus meeting. Eur J Cancer 1992;28:626–9.
8. Rogers RW. Carcinoma in situ (CIS). In: Page DL, Anderson TJ, editors. Diagnostic histopathology of the breast. Edinburgh, London, Melbourne, New York: Churchill Livingstone, 1987; 157–92.
9. Lampejo OT, Barnes DM, Smith P, Millis RR. Evaluation of infiltrating ductal carcinomas with a DCIS component: correlation of the histologic type of the in situ component with grade of the infiltrating component. Semin Diagn Pathol 1994; 11:215–22.
10. Poller DN, Silverstein MJ, Galea M, Locker AP, Elston CW, Blamey RW, et al. Ideas in pathology. Ductal carcinoma in situ of the breast: a proposal for a new simplified histological classification association between cellular proliferation and c-erbB-2 protein expression. Mod Pathol 1994;7: 257–62.
11. Bellamy CO, McDonald C, Salter DM, Chetty U, Anderson TJ. Non-invasive ductal carcinoma of the breast: the relevance of histologic categorization. Hum Pathol 1993;24:16–23.
12. Ottesen GL, Graversen HP, Blichert TM, Zedeler K, Andersen JA. Ductal carcinoma in situ of the female breast. Short-term results of a prospective nationwide study. The Danish Breast Cancer Cooperative Group. Am J Surg Pathol 1992;16: 1183–96.
13. Silverstein MJ, Poller DN, Waisman JR, et al. Prognostic classification of breast ductal carcinoma-in-situ. Lancet 1995;345:1154–7.
14. White J, Levine A, Gustafson G, et al. Outcome and prognostic factors for local recurrence in mammographically detected ductal carcinoma in situ of the breast treated with conservative surgery and radiation therapy. Int J Radiat Oncol Biol Phys 1995;31:791–7.
15. Holland R, Peterse JL, Millis RR, et al. Ductal carcinoma in situ: a proposal for a new classification. Semin Diagn Pathol 1994;11:167–80.
16. Recht A, van Dongen JA, Fentiman IS, Holland R, Peterse JL. Third meeting of the DCIS Working Party of the EORTC (Fondazione Cini, Isola S Giorgio, Venezia, 28 February 1994)—Conference report. Eur J Cancer 1994;30A: 1895–900.
17. Holland R, Hendriks JH. Microcalcifications associated with ductal carcinoma in situ: mammographic–pathologic correlation. Semin Diagn Pathol 1994;11:181–92.
18. Leborgne R. Diagnosis of tumors of the breast by simple roentgenography: calcifications in carcinoma. AJR 1951;65:1–11.
19. Lanyi M. Diagnostik und differentialdiagnostik der mammaverkalkungen. Berlin, Heidelberg, New York, Tokyo: Springer, 1986.
20. Stomper PC, Connolly JL, Meyer JE, Harris JR. Clinically occult ductal carcinoma in situ detected with mammography: analysis of 100 cases with radiologic–pathologic correlation. Radiology 1989; 172:235–41.
21. Millis RR, Davis R, Stacey AJ. The detection and significance of calcifications in the breast: a radiological and pathological study. Br J Radiol 1976;49:12–26.
22. Holland R, Hendriks JH, Vebeek AL, Mravunac M, Schuurmans SJ. Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. Lancet 1990;335: 519–22.
23. Evans A, Pinder S, Wilson R, Sibbering M, Poller D, Elston C, et al. Ductal carcinoma in situ of the breast: correlation between mammographic and pathologic findings. AJR 1994;162:1307–11.
24. Foschini MP, Fornelli A, Peterse JL, Mignani S, Eusebi V. Microcalcifications in ductal carcinoma in situ of the breast: histochemical and immunohistochemical study. Hum Pathol 1996;27:178–83.
25. Kinne DW, Petrek JA, Osborne MP, Fracchia AA, DePalo AA, Rosen PP. Breast carcinoma in situ. Arch Surg 1989;124:33–6.
26. Silverstein MJ, Waisman JR, Gierson ED, Colburn W, Gamagami P, Lewinsky BS. Radiation therapy for intraductal carcinoma. Is it an equal alternative? Arch Surg 1991;126:424–8.
27. Harris JR, Lippman ME, Veronesi U, Willett W. Breast cancer (2). N Engl J Med 1992;327:390–8.
28. Rosen PP, Braun-DW J, Kinne DE. The clinical significance of pre-invasive breast carcinoma. Cancer 1980;46:919–25.
29. Page DL, Dupont WD, Rogers LW, Landenberger M. Intraductal carcinoma of the breast: follow-up after biopsy only. Cancer 1982;49:751–8.
30. Lagios MD, Silverstein MJ. Ductal carcinoma in situ. The success of breast conservation therapy: a shared experience of two single institutional non-randomized prospective studies. Surg Oncol Clin N Am 1997;6:385–92.
31. Ciatto S, Bianchi S, Vezzosi V. Mammographic appearance of calcifications as a predictor of intraductal carcinoma histologic subtype. Eur Radiol 1994;4:23–6.
32. Böcker W, Decker T, Ruhnke M, Schneider W. Duktale hyperplasie und duktales carcinoma in situ. Definition—Klassifikation—Differentialdiagnose. Pathologe 1997;18:3–18.

33. Acheson MB, Patton RG, Howisey RL, Lane RF, Morgan A. Histologic correlation of image-guided core biopsy with excisional biopsy of nonplapable breast lesions. Arch Surg 1997;132:815–8.
34. Gajdos C, Levy M, Herman Z, Herman G, Bleiweiss IJ, Tartter PI. Complete removal of nonpalpable breast malignancies with a stereotactic percutaneous vacuum-assisted biopsy instrument. J Am Coll Surg 1999;189:237–40.
35. Yeh ED, Slanetz PJ, Oyama T, Giardino AA, Koerner FC. Mammographic appearance of ductal carcinoma in-situ (DCIS) does not reliably predict histologic subtype. Radiology 1998;209(P):271.
36. Parker J, Dance DR, Davies DH, Yeoman LJ, Michell MJ, Humphreys S. Classification of ductal carcinoma in situ by image analysis of calcifications from digital mammograms. Br J Radiol 1995;68:150–9.
37. Lanyi M. Formanalyse von 5641 Mikroverkalkungen bei 100 Milchgangskarzinomen: die Polymorphie. Rofo Fortschr Ged Röntgenstr Nuklearmed 1983; 139:240–8.
38. Liberman L, Abramson AF, Squires FB, Glassman JR, Morris EA, Dershaw DD. The breast imaging reporting and data system: positive predictive value of mammographic features and final assessment categories. AJR 1998;171:35–40.