Hypothesis: Nonpalpable malignant-appearing microcalcifications discovered by mammography geographically target the location of the most important abnormality within the breast. Core needle or open biopsy of these microcalcifications will sample or remove underlying proliferative or invasive disease.

Design: A prospective database of 403 consecutive patients undergoing breast biopsy for nonpalpable abnormalities from July 1, 1994, to December 31, 1996, was reviewed to identify biopsies done for indeterminate microcalcifications. Specimens showing atypical hyperplasia, carcinoma in situ, or invasive carcinoma were identified and reviewed by 1 pathologist. The position of microcalcifications larger than 100 µm were recorded in reference to the histological findings.

Setting: A 450-bed referral community teaching hospital in rural Wisconsin.

Patients: Indeterminate microcalcifications were identified on mammograms in 167 (41.4%) of 403 patients. Sixty-one (36.5%) of 167 biopsy specimens contained atypical hyperplasia, carcinoma in situ, or invasive carcinoma, and the slides of these 61 initial breast biopsy specimens were reviewed.

Main Outcome Measures: Relationship of breast histopathological findings to microcalcifications.

Results: In these 61 specimens, 82 areas of atypical hyperplasia, carcinoma in situ, or invasive carcinoma were noted. The microcalcifications correlated with these areas in 43 (52%) of 82 areas on slide review and were present in the most important abnormality in 33 (54%) of 61 biopsy specimens.

Conclusions: Indeterminate microcalcifications identified by mammography may not target the exact location of underlying breast disease. Careful evaluation of the entire biopsy specimen and close follow-up of patients with benign pathologic findings are recommended.


Since 1949, when Leborgne first demonstrated that calcifications seen on breast roentgenograms were associated with cancer, microcalcifications (MCs) have become established as one of the earliest mammographically detectable changes associated with ductal carcinoma in situ (DCIS) and invasive breast cancer (IC). Microcalcifications are the primary indication for approximately 50% of the breast biopsies performed for nonpalpable mammographic abnormalities. The Figure illustrates malignant-appearing MCs detected by mammography.

The current strategy for evaluating and managing MCs makes the important assumption that the MCs are present within or are closely related to the most important underlying pathologic change in the breast. Diagnostic biopsies performed because of MCs undergo specimen mammography to confirm removal of the abnormality, and MCs identified by the pathologist provide further reassurance that the abnormality has been excised. Despite the importance of MCs, relatively little is known about the precise anatomical relationship between the histopathologic findings and the MCs. This relationship has increased in importance as diagnostic techniques have been developed that allow very small amounts of breast tissue to be removed along with the MCs. This study was performed to evaluate the relationship between the calcifications and histopathologic findings in image-guided breast biopsy (IGBB) and needle-localized open biopsy (NLOB) performed on women who had nonpalpable malignant-appearing MCs without parenchymal distortion as their only abnormality on mammography.
PATIENTS AND METHODS

A prospective database of patients undergoing both IGBB and NLOB was established in the Departments of Surgery and Radiology of Gundersen Lutheran Medical Center, La Crosse, Wis, in 1994 with the initiation of our stereotactic breast biopsy program. This database was used to identify all patients who underwent IGBB or NLOB for nonpalpable mammographic abnormalities at our institution from July 1, 1994, through December 31, 1996. Registry data included demographic information, date of biopsy, type of procedure, indication for diagnostic biopsy, number of cores obtained at IGBB, histological findings, American College of Radiology Reporting and Data System (BIRADS) classification,7,8 family history, complications, and subsequent follow-up at 2 years.

Stereotactic biopsies were performed with a prone biopsy table (Lorad Stereotaxic; Lorad Corp, Danbury, Conn) and a 14-gauge core needle (long-throw) automated biopsy device with multiple passes (C. R. Bard Inc, Covington, Ga). Digital mammography was used to localize each lesion, and specimen radiographs were obtained to confirm removal of MCs. Ultrasound-guided biopsies were performed with the use of a 7.5-MHz probe with real-time imaging and the same core needle biopsy device. All open biopsies were performed in an outpatient surgical setting. Needle localization was performed in the radiology suite before biopsy. Biopsies were performed with the patient under intravenous sedation with local anesthesia. Specimen radiographs were obtained to confirm removal of the MCs.

A single pathologist (S.M.W.) reexamined the initial biopsy specimens of 61 patients having undergone a biopsy for nonpalpable malignant-appearing MCs without parenchymal distortion on mammography and whose initial pathologic reading disclosed atypical hyperplasia (AH), carcinoma in situ (CIS), or IC. The exact geographic position of MCs larger than 100 µm was recorded in reference to the histological findings. Microcalcifications smaller than 100 µm may be visible on microscopic review but usually are not visible on mammography.9 Therefore, MCs smaller than 100 µm were not included in the correlation of findings.

Microcalcifications were classified as being associated with the pathologic change if they were (1) identified within ducts involved by atypical hyperplasia or DCIS, or within the malignant glands of IC, or (2) identified within benign ducts of a terminal duct lobular unit otherwise involved by AH or DCIS, or (3) identified within the stroma of a terminal duct lobular unit involved by AH or DCIS, or within the stroma of an IC, and no other cause of their presence was apparent (eg, medial calcification of a blood vessel).

RESULTS

Four hundred three patients were prospectively entered into our registry during the 30-month period from July 1, 1994, through December 31, 1996. One hundred sixty-seven biopsies were performed for indeterminant MCs (BIRADS score, 3-5) without an associated parenchymal abnormality. Sixty-one (36.5%) of 167 patients had AH, CIS, or IC identified at the initial biopsy.

Twenty-five of the 61 initial biopsies were performed by NLOB; the other 36 were performed by image-guided techniques. Sixteen of the 36 patients who had initial IGBB had a secondary NLOB performed as a lumpectomy for further clarification of their diagnosis or treatment of the CIS. These 16 patients included 3 with AH, 10 with CIS, and 3 patients who had a discrepancy between pathologic results of IGBB and mammographic correlation. Six of the initial 36 patients who had IGBB had no further follow-up treatment at our institution. Fourteen of the 36 patients who underwent initial IGBB proceeded directly to mastectomy for treatment.

Eighty-two areas of AH, CIS, or IC were found. Forty-three (52%) of the 82 areas were associated with the MCs seen on slide review. The calcifications were associated with the most important pathologic finding in 33 (54%) of the 61 patient breast biopsy specimens. Eleven (18%) of 61 patients had MCs that were found to be associated with benign histological changes within the breast specimen but had major adjacent pathologic changes that ranged from 3 mm to 2 cm away from the MCs. Seven of these patients had initial IGBB and 4 had initial NLOB. There was no significant difference in the initial biopsy technique between these 2 small groups of patients. The 11 patients with important pathologic findings near but not within the MCs included 4 patients with CIS or IC.
and 7 with atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular CIS.

Further evaluation of the association of MCs with individual types of pathologic findings showed DCIS in 36 (75%) of 48 patients, atypical ductal hyperplasia in 4 (44%) of 9, invasive ductal carcinoma in 3 (27%) of 11, and atypical lobular hyperplasia, lobular CIS, and invasive lobular carcinoma in 0 of 14. Stratification of DCIS by grade and correlation with MCs showed the following: low grade, 13 (81%) of 16 patients; intermediate grade, 11 (85%) of 13; high grade, 13 (76%) of 17, and undetermined grade, 0 of 2. Differences in correlation by grade of DCIS were not statistically significant.

The finding of indeterminate or malignant-appearing MCs on mammography presents a diagnostic and therapeutic challenge. Currently, mammographically detected MCs serve as the primary guide for the radiologist, surgeon, and pathologist during the diagnostic evaluation. When a breast biopsy performed for MCs demonstrates AH or CIS, then the question of whether the MCs targeted the most important abnormality becomes relevant if delayed diagnosis of breast cancer and false-negative IGBB are to be prevented.

Careful diagnostic mammography allows for complete evaluation and characterization of MCs. Previous studies have attempted to correlate radiological and histological features of calcifications with respect to appearance, distribution, and size to improve the accuracy and reliability of core biopsy assessment.10-12 Dahlstrom et al9 noted that calcifications assessed radiologically as being part of a particular type often had a range of histological appearances, showing no statistical correlation between the radiologically assessed pattern of calcification and the histological distribution in tissue sites.9 Dahlstrom et al9 also studied the size of histological calcifications to see which could be visualized mammographically. Twenty-nine lesions with calcification size 100 µm or larger could be correlated with MCs seen on specimen radiographs, while 11 lesions with MCs smaller than 100 µm were not visible radiologically.9 The calcifications associated with DCIS have been noted to have a wide spectrum of mammographic appearances that are related to pathological features including the location of the tumor within the ductal system, the histological subtype, the amount and distribution of calcium formation, and the presence or absence of reactive changes.9

When specifically concerned about the finding of malignant-appearing MCs as the sole abnormality on mammography on which to base a biopsy, one can argue that NLOB may be the most appropriate first step.11 If an IGBB is performed for malignant-appearing MCs as the initial test and a proliferative type of disease such as CIS or AH is found, then an open biopsy is required to further clarify the diagnosis or treat the CIS. A sampling technique such as IGBB provides only a small tissue core in which a small carcinoma (<2 mm) may be designated as atypia.14,15 A core biopsy may also sample atypia and miss an adjacent IC, as these types of disease may coexist in a breast lesion. Given these concerns and after careful discussion between radiologist, surgeon, and the patient, we are more frequently choosing NLOB for patients who have nonpalpable malignant-appearing MCs on diagnostic mammography.

In this study, we found that 18% of patients with a BIRADS score of 3 to 5 had MCs associated with benign tissue, but AH, CIS, or IC were found 3 mm to 2 cm away from the MCs. In these patients, the MCs were not found directly within the ducts or the area containing the atypia or malignant neoplasm. The MCs correlated with the most significant disease in 54% of 61 patients with AH, CIS, or IC and in 75% of 48 patients with DCIS. Conversely, 25% of 48 patients with DCIS had DCIS located some distance away from the MCs. Microcalcifications were the clue to recommend biopsy in these patients, but the MCs did not always target the location of DCIS. These observations are reminiscent of those previously reported by Holland et al,13 who found that mammographic estimates based on the extent of MCs frequently underestimated the histological size of tumors. Selim and Tahan11 noted similar results in their study of 32 patients with MCs. Malignant tissue was not always accurately localized by MCs, and they advised caution when interpreting the finding of calcifications in benign components of small tissue samples.

From our data we can conclude that important pathologic changes may not be intimately associated with histologically identified MCs larger than 100 µm in diameter. This supports the currently recommended practice of careful examination of all breast tissue removed at diagnostic biopsy. However, a relevant question is whether these results are in conflict with the increasingly large clinical experience documenting the utility and very low false-negative rate of IGBB; in one recent series, a careful team approach to the evaluation and management of mammographic abnormalities (incorporating IGBB and NLOB) in more than 1000 patients reported finding only 1 patient with benign disease identified by her IGBB who subsequently developed breast cancer in the index area of the breast studied by biopsy.15 Do our results imply an 18% false-negative rate for breast biopsy of MCs? A closer look at the differences between this study and larger series allows resolution of these apparent discrepancies. First, we studied only patients with nonpalpable MCs without parenchymal distortion. Second, we selected patients with AH, CIS, or IC to evaluate the relationship of the MCs to the known abnormality. Finally, the true rate of malignant neoplasms missed by IGBB may be higher than expected if the outcome of patients unavailable for follow-up in clinical series was known. Fuhrman et al13 documented only 1 false-negative IGBB in 1106 IGBBs with benign findings, but 169 patients never returned for follow-up.

Our finding that 18% of selected biopsy specimens demonstrated disease that was not closely associated with the MCs is in general agreement with previous reports focusing on this patient population, indicating that up to 50% of lesions diagnosed as AH by IGBB are found to contain IC at NLOB. Nineteen percent of CIS diagnosed by IGBB is subsequently found to contain IC, and, if CIS or AH is found, an incomplete classification may be made by the pathologist in up to 33% of IGBBs.16-18
Microcalcifications will continue to be an important indication for breast biopsy. Our findings suggest that MCs do fail to define the distribution of AH, CIS, or IC in up to 18% of patients with malignant-appearing MCs. These findings are in agreement with previous observations and support the current practice of (1) NLOB when IGBB discloses AH and (2) complete examination of all tissue removed in diagnostic breast biopsies.

Malignant-appearing MCs found on mammography will not always directly target the most important underlying breast abnormality in patients with AH or CIS. Breast biopsies that specifically target MCs may leave considerable residual disease in the breast. Although IGBB remains an important tool for evaluating mammographic abnormalities, physicians need to be aware of clinical situations where IGBB alone may be inadequate to fully define the underlying pathologic features or allow for definitive treatment planning. These data reinforce the need for careful evaluation of the entire biopsy specimen and close follow-up of patients with benign pathologic findings.

This study was supported by the R. James Trane Surgical Research and Data Center of the Gundersen Medical Foundation, La Crosse, Wis.

Presented at the 106th Scientific Session of the Western Surgical Association, Indianapolis, Ind, November 17, 1998.

Technical assistance was provided by Johanna Berg in manuscript preparation.

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REFERENCES


DISCUSSION

Mark M. Connolly, MD, Chicago, Ill: I congratulate the authors for exploring a significant limitation of percutaneous core biopsies using a 14-gauge automated biopsy device as could be predicted from Roland Holland’s classic histopathology data. Image-guided breast biopsies are increasingly competitive alternatives to the standard 2-step open biopsy for nonpalpable lesions. Advantages to percutaneous biopsies include lower cost, less scarring with subsequent mammographic changes, and a significant decrease in surgical procedures, in both the largest subset of women, those with benign lesions, as well as those with malignant disease, allowing us to return to a single definitive surgical procedure with greater likelihood of negative margins and facilitating sentinel lymph node biopsy. Limitations include both missed lesions and underestimating ADH and DCIS. The published underestimate rate in DCIS upgraded to invasive cancer is in the range of 15% to 20% and ADH upgraded to DCIS or invasive cancer in the range of 45% to 55% of cases using 14-gauge technique. These rates basically measure the completeness of the core biopsy. It should be noted that with the evolution of larger 11-gauge cores and an increase in the minimum number of cores required, to 10 and greater, and especially newer technologies, such as directional vacuum-assisted biopsies (Mammotome) with larger contiguous specimen volumes, we have shown very marked diminuition in underestimate rates from 0% to 10% in our data and published reports. From your results it appears that, while only 54% had the most significant pathology associated with microcalcifications, only 11 of 61 or 18% was the target microcalcification associated with benign changes, with significant pathology ranging anywhere from 3 mm all the way to 2 cm away from the indexed lesion. Of these, only 4 or 6.5% were DCIS or invasive ductal carcinoma, potential true misses with serious prognostic consequences. Would the authors comment on the possibility that some or all may be truly incidental lesions, not a miss or underestimation, as the target was the microcalcifications? This was most certainly true for the lobular CIS and ALH. The most recent published data on miss rates from a multi-institutional series of greater than 6000 lesions, using your same 14-gauge technique, was 6.8% for microcalcifications, a finding consistent with your numbers.

Further, what is the minimum number of cores you require per biopsy for microcalcifications? Have you considered changing to larger, 11-gauge cores or Mammotome? If not, why? It is known that “probably benign” lesions carry a 2% chance of being malignant. How many of the 106 benign biopsies in your series that had image-guided biopsies went on to have open surgical biopsies? Did you surgeons have confidence that these
were truly negative? What is your postbiopsy imaging protocol? Have any initial benign biopsies been rebiopsied at a later date and found to have DCIS or invasive cancer?

Gerard V. Aranha, MD, Maywood, Ill: How many of your patients who had calcifications had an associated mass? It is in these patients where the correlation is highest with malignancy. Did all of your patients have only microcalcifications, or did a certain percentage have an associated mass?

Dr Landercasper: Dr Connolly, we believe it is possible that 11 (18%) of our 61 patients who had microcalcifications associated with benign lesions but had significant pathology from 3 mm to 2 cm away could have been incidental findings. However, 4 of these 61 patients had DCIS or invasive ductal carcinoma, which is in agreement with other reports in the literature describing the relationship of malignant lesions adjacent to but not within the area of microcalcifications. The average number of cores taken at image-guided breast biopsy is about 10, unless there was a small cluster of microcalcifications that were all removed with less than 10 cores. Our practice is changing and utilizing a greater number of biopsies done with the Mammotome technique. We did not review in this study all of the benign image-guided breast biopsies that were entered into our prospective registry of over 400 patients. We do have follow-up of most of these patients. I am aware of 2 such patients in 2- to 4-year follow-up who have subsequently been found to either have an in situ carcinoma or an invasive carcinoma. We would consider these false-negative image-guided breast biopsies or true misses of the image-guided technique. Our protocol for patient management after an image-guided breast biopsy that shows benign pathology is to carefully check with the pathologist to make sure that they have sectioned the entire specimen. If they have sectioned the entire block and the microcalcifications were identified, but no malignancy was seen, then we recommend rereviewing the mammogram with the radiologist. If the mammogram is highly suspicious (BIRADS 4 or 5) of malignant-appearing microcalcifications, we then have an informed consent discussion with the patient. That informed consent discussion includes either the option of very close follow-up with mammography and physical examination at 3- to 6-month intervals for the subsequent 2 years, or the option of performing an open biopsy with preoperative needle localization. If the image-guided breast biopsy revealed benign pathology but rereview of the mammogram suggests indeterminate microcalcifications that likely are of a benign nature, a BIRADS score of 3, then we often feel comfortable with follow-up of that patient. Our usual follow-up schedule is office examinations at 3- to 6-month intervals for 2 years and 6-month mammography on that side for the next 2 years.

Dr Aranha, no patient in the series reported today had an associated mass with her microcalcifications. An entry criterion for the study was indeterminate microcalcifications as the only abnormality on the mammogram.

ARCHIVES OF INTERNAL MEDICINE
Importance of pH Control in the Management of GERD
Richard H. Hunt, MD

The degree of esophageal mucosal injury that occurs in patients with gastroesophageal reflux disease depends on duration of exposure and pH of the refluxate. Evidence suggests that an intraesophageal pH of less than 4.0 directly correlates with the degree of mucosal injury. The advent of acid secretory inhibitors such as the histamine2-receptor antagonists (H2RAs) and, more recently, the proton pump inhibitors (PPIs) has revolutionized the treatment of patients with reflux disease. However, the evidence linking the degree of mucosal damage to pH of the refluxate has prompted investigators to reevaluate the effectiveness of these agents. The PPIs are significantly more effective than the H2RAs in achieving and sustaining an intragastric pH above 4.0. The results of clinical trials performed with the PPIs indicate a faster rate of healing of erosive esophagitis and of symptom relief than treatment with H2RAs. (1999;159:649-657)

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