Controversies on the Management of High-Risk Lesions at Core Biopsy from a Radiology/Pathology Perspective

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**KEYWORDS**
- Breast high-risk lesion
- Lobular neoplasia
- Papilloma
- Radial scar
- Flat epithelial atypia (FEA)
- Breast core biopsy

**PROLOGUE**

Readers may feel less than satisfied when they discover that there is no consensus as to the appropriate recommendations for follow-up of risk lesions following percutaneous core biopsy. The significance of this article is in the details of the methodologies and results, and much less in the numbers. The overall goal is to emphasize the flaws in current studies.

Many of the studies do not control for inclusion, as well as exclusion, of surgical follow-up, which is being used as the gold standard. Even if surgical follow-up is performed, many studies lack imaging/core biopsy/surgical biopsy/pathology concordance/discordance analyses. Meta-analyses of giant tables cannot make up for flawed methodologies with small numbers. The authors suggest that readers read between the numbers to capture the essence of where the current literature lies. The numbers are tabulated in Tables 1 to 4 in the Appendix. In 2010 there is not adequate data from which to make definitive decisions regarding treatment planning. We still can not agree on how to treat patients after a core biopsy diagnosis of any one of these high-risk lesions. Little progress has been made since the last time this topic was discussed in the 2004 *Radiologic Clinics of North America* by Berg.\textsuperscript{1} Adding more retrospective reviews will take us no closer to discovering the truth, and yet such studies are ongoing.

The solution is a prospective, multi-institutional trial that is all-inclusive for patients to go to surgery without selection biases, that tracks all patients, has meticulous radiology/pathology/clinical correlation, and significant numbers. In many ways, it is rather shocking, almost depressing, to realize how little is known concerning this important topic in spite of decades of investigation, and how this trickles down to almost random health care for thousands of women. Clearly, there is no standard of care.\textsuperscript{2}

**INTRODUCTION**

In the 2004 edition of the *Radiologic Clinics of North America*, Berg\textsuperscript{1} reviewed the literature on the proposed management of several high-risk lesions diagnosed at core biopsy. The overall opinion at that time was to surgically excise all high-risk lesions diagnosed at core biopsy based...
on retrospective data that documented varying frequencies of malignancy on follow-up. In the past 6 years, however, numerous studies have shown that for many of these high-risk lesions, subsequent surgical excision has revealed no cancers or at most a minimal percentage of cancer upgrades.

Two primary reasons for surgical follow-up after any nonmalignant core biopsy are possible: (1) underestimation of malignancy, and (2) radiology/pathology discordance in which the lesion was missed or the expected malignancy results were not obtained. With regard to the high-risk lesions, the debatable question is the former. The concept of underestimation of concurrent malignancy for atypical ductal hyperplasia (ADH) at core biopsy is well established, even when the index radiographic lesion has been completely removed percutaneously. How this concept translates into the management of other high-risk lesions, such as lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), papillomas, radial scar, and flat epithelial atypia (FEA) remains debatable.

How to determine the accuracy of core sampling of a lesion is a question affecting radiology/pathology concordance beyond the scope of this article. In particular with benign or high-risk lesion core results, the radiologist should review the imaging of the procedure to: (1) determine whether the pathology results correlate accurately with the appearance of the lesion, and (2) document in the report the concordance/discordance and recommendation for appropriate follow-up.

The resulting conflicting data in the literature have placed health care professionals in the dilemma of not knowing how to best advise women regarding the need for surgical or clinical/imaging follow-up. Based on an informal survey by the authors that involved 10 academic breast radiologists and pathologists from around the country, it is clear that the issue of management of several high-risk lesions is still controversial. The survey focused on 4 main high-risk lesions: lobular neoplasia (ALH and LCIS), benign papillomas, radial scar, and FEA (Table 1). Anecdotally, radiologists said that management depends on a given surgeon’s preference, consequently varying within a given institution. These differences in personal opinions and lack of consensus in the medical community result in many women either being over treated with surgical excision or under treated and thereby missing a breast cancer. The authors review the literature since 2004 for the aforementioned 4 high-risk lesions highlighting both the radiology and pathology literature to illustrate the current trends in management. Now more than ever there is a calling to prospectively study these specific histologic groups to determine more accurately the true risk of underestimation of malignancy and role of immediate surgical excision.

### LOBULAR NEOPLASIA: LCIS AND ALH

#### Prevalence

Based on data from the Surveillance, Epidemiology and End Results (SEER) Cancer registry, the incidence of LCIS has increased 2.6-fold (95% confidence interval [CI] 2.3–2.9) from 1980 to 2001 likely related to the use of mammography. Obtaining lobular neoplasia on core biopsy and facing the dilemma of what to do with these results is more frequent now than ever, as additional modes for core biopsy, such as magnetic resonance guidance, have developed in the last decade.

#### Pathology Definitions and Related Concerns

Lobular neoplasia is a term that encompasses ALH and LCIS. The cells of both ALH and LCIS are similar in appearance; the cells are small, uniform, discohesive, and generally lack nucleoli. It is the degree of the involvement of the lobular units that distinguishes these 2 entities. While there is disagreement in the literature as to specific criteria to distinguish LCIS from ALH, a widely accepted definition by Page and colleagues requires for LCIS that at least 50% of the acinar units in a lobule be filled and distended by lobular neoplastic cells. The definition of distention was further quantified to require the presence of at least 8 lobular neoplastic cells spanning an individual acinar unit. If a lobular unit does not fulfill these criteria, a diagnosis of ALH is made. Most pathologists recommend maintaining the 2 entities as separate given that follow-up studies show a lower rate in the incidence of the subsequent development of invasive carcinoma for ALH compared with LCIS. Unfortunately, much of the core biopsy literature sums these results into lobular neoplasia. The reader should stay vigilant when comparing studies as to whether results are presented as lobular neoplasia or LCIS and ALH.

Recently, variants of LCIS have been described that do not fit this classic LCIS histopathology, including LCIS with central necrosis and pleomorphic LCIS. Because of the small numbers of cases and lack of significant follow-up data, the natural history of these variants is not well established, but early data suggest that LCIS variants such as these may have a more aggressive behavior. Thus, many clinicians are recommending surgical biopsy when one of the variants of LCIS is present on core biopsy.
Incidental or Direct Sign of Radiographic Finding

A common belief is that lobular neoplasia is an incidental pathologic finding without radiographic correlate.\textsuperscript{18–20} If always incidental, then all core results of lobular neoplasia would be discordant and warrant surgical excision. However, studies have shown that lobular neoplasia can be represented radiographically. Calcifications were directly indicative of LCIS in both the classic and pleomorphic forms,\textsuperscript{13,18,21} and other studies have shown masses to correlate on both mammography\textsuperscript{18,22} and sonography.\textsuperscript{22}

One of the most complete evaluations in poster format was displayed at the 23rd Annual San Antonio Breast Cancer Symposium in 2000 by Tarjan and colleagues.\textsuperscript{23} Their goal was to evaluate the incidence of lobular neoplasia as the direct sign of a mammographic or sonographic lesion. Out of 2280 consecutive core biopsies, there were 108 cases (4.7% incidence) of lobular neoplasia classified per mammographic lesion as mass, calcifications, asymmetric densities, or by sonographic finding of shadowing. In particular, the imaging and pathology were reviewed to determine whether the lobular neoplasia was the primary cause for the lesion or an incidental finding. There were 38 cases of primary lobular neoplasia (1.7% incidence) and 70 incidental cases. The primary cases were 32 calcifications and 6 masses.

The blanket statement that all lobular neoplasia is incidental is not accurate, and core pathology result of lobular neoplasia should not by itself direct recommendation for surgical follow-up.

Controversial Results Regarding Surgical Versus Imaging Follow-up

Many retrospective studies have looked at the presence of malignancy after surgical excision and/or imaging follow-up after core biopsy of lobular neoplasia. Most of the earlier studies were single institution with small numbers since prevalence is exceedingly low for lobular neoplasia, as well as for all high-risk lesions. Studies that recommended surgical follow-up reported malignancy rates of 14% (3/21),\textsuperscript{24} 16% (1/6),\textsuperscript{25} 20% (7/35),\textsuperscript{26} 25% (5/20),\textsuperscript{27} 37% (13/35),\textsuperscript{28} and 50% (9/18).\textsuperscript{29} These are reported individually, as opposed to a range, so that the reader can appreciate how small and inconsistent these ratios are from which much of the literature is derived. In addition, these malignancy rates are based on selected groups who underwent follow-up. Because not all of the patients with lobular neoplasia at core underwent immediate surgical excision or imaging follow-up, the results are skewed. As these studies are retrospective reviews, this selection is not controlled for, leading to significant flaws in the methodology and making generalizations to standard populations difficult at best.

A multi-institutional study from France found a malignancy rate of 19% (10/52) out of 52 undergoing surgery.\textsuperscript{30} The largest study to date is by Brem and colleagues\textsuperscript{31} who reviewed the core results from 14 institutions. Out of approximately 32,000 core biopsies, 278 (0.9%) were ALH and/or LCIS as the highest-grade lesion. Invasive carcinoma or ductal carcinoma in situ (DCIS) was found in 23% (38/164).

### Table 1

<table>
<thead>
<tr>
<th>Physician</th>
<th>ALH</th>
<th>LCIS</th>
<th>FEA</th>
<th>Radial Scar</th>
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All of these studies\textsuperscript{24–32} suggested surgical follow-up based on their rates of underestimation of malignancy. However, there are concerns with all of the studies, large and small, beyond lack of statistical significance, as has been commented on by Kopans.\textsuperscript{33,34} Some studies used data only from immediate post–core biopsy surgical pathology, and others used both surgical pathology and imaging follow-up of variable lengths of time. Most importantly, most studies selected patients by some unknown method for immediate surgical excision. Were patients recommended for surgery because the radiologist believed that all lobular neoplasia is incidental and hence discordant with imaging? Were they selected because imaging was suspicious and hence discordant with pathology results? Or were they selected because of clinical reasons that were discordant with benign results? The corollary issue is that studies do not have data on the patients who were NOT excised or followed, and hence it is not known how those patients may have differed from the tracked cohort.

The study by Brem and colleagues\textsuperscript{31} analyzed their facilities’ data for radiology/pathology concordance/discordance, but noted that the definitions of discordance at each institution were not standardized. Some considered that a diagnosis of lobular neoplasia was incidental and therefore this result without any other pathologic diagnosis to explain the radiographic finding was cause for discordance. Other institutions did not specify their definitions of discordance. Nevertheless, out of the 82 concordant cases undergoing immediate surgery, 17\% (N = 15) of cases underestimated malignancy, and out of the 74 discordant cases undergoing immediate surgery, 28\% (N = 21) underestimated malignancy. So the investigators concluded that regardless of radiology/pathology concordance, surgical excision is warranted.

In contrast, more recent studies meticulously analyzed the issue of radiology/pathology concordance, and consequently concluded that immediate surgery was not indicated because of exceedingly low underestimation of malignancy. Menon and colleagues\textsuperscript{35} reviewed in detail 47 cases of classic LCIS in which core biopsies were performed freehand in 8 cases, with ultrasound guidance in 14, and stereotactic in 25. Of the 8 malignant false-negative cases after immediate surgery (N = 25), 5 cases were missed masses and 2 were missed calcifications. The investigators do not break down the method of coring. Nagi and colleagues\textsuperscript{36} analyzed 98 cases of lobular neoplasia and found an incidental minute focus of invasive lobular carcinoma at surgery in one case and DCIS mixed with LCIS in a second case. No other malignancies were found with imaging follow-up ranging from 1 to 8 years. These investigators concluded that immediate surgery was not warranted routinely and recommended careful imaging/pathology correlation.

The largest study with detailed review of the pathology results was a study by Hwang and colleagues.\textsuperscript{37} The goal of this study was to accurately define specific morphology of lobular neoplasia at core biopsy that might be able to predict the presence of invasive carcinoma or DCIS. Over a decade, 333 core results of lobular neoplasia were collected, of which 41\% (N = 136) went on to immediate surgery; 36\% (49/136) of those cases were ADH with lobular neoplasia. Excluding these cases of ADH, malignancy was found at surgical excision in 23\% (9/39) of cases of LCIS and 2\% (1/48) of cases of ALH. These investigators continued their analyses of the malignant cases where others have stopped. Six of the 9 cases of LCIS were radiology/pathology discordant and the remaining 3 cases were nonclassic LCIS (LCIS with necrosis and pleomorphic LCIS). After excluding discordance and nonclassic LCIS cases, the upgrade was only 1\%. Therefore, these investigators recommend imaging follow-up (not immediate surgery) for the classic form of LCIS after careful radiology/pathology review.

\textbf{Development of Malignancy After Lobular Neoplasia Core Biopsy: Site Locations and Risk}

An argument supporting follow-up in lieu of surgery is the observation that the risk for development of carcinoma in patients with prior biopsy of lobular neoplasia is bilateral and not necessarily at the core biopsy site. Chuba and colleagues\textsuperscript{38} analyzed the SEER data to determine the laterality of invasive carcinoma occurring after LCIS in a study involving 4853 women. They excluded those with the diagnosis of invasive cancer within 1 year after lobular neoplasia to rule out synchronous disease. The minimum cumulative risk was 7.1\% at 10 years for all patients regardless of form of prior biopsy. Form of biopsies were specified into 3 surgical categories: aspirate or core needle biopsies which defined “lesser surgery”, partial mastectomy, and complete mastectomies. There were 178 patients in the subset who underwent lesser surgery and there was a 5.5\% incidence of invasive cancer at 10 years. Acknowledged is the inherent decrease in sampling accuracy of fine-needle aspirates versus core biopsies. The significance, nevertheless, is that laterality for the entire cohort after surgical excision of lobular neoplasia was almost equal: 46\% ipsilateral and 54\% contralateral.\textsuperscript{38} Page and Simpson\textsuperscript{39} note that other studies have
found the incidence of contralateral malignancy to be one-half that of the ipsilateral involved breast. A study by Mulheron and colleagues also arguing against immediate surgery found no carcinoma at final surgical excision in 12 out of 25 women with lobular neoplasia at core biopsy. Moreover, the entire cohort was followed for a mean 5.5 years. Five cancers developed (20%, 5/25): 3 who had undergone surgery and 2 who had been followed with imaging (P = .57). However, malignancy did not arise in the same quadrant as the location of the core in the imaging follow-up group. Immediate surgery neither identified concurrent carcinoma nor did it decrease the frequency of development of subsequent carcinoma. Similar results were reported in a larger series of 50 patients with lobular neoplasia in which 0 malignancies were diagnosed in 21 immediate surgical excisions and 4 malignancies developed at a mean of 6 years, 1 of which was in the contralateral breast. The conclusion was that immediate surgical excision was not warranted, and that lobular neoplasia was only a risk marker for the development of bilateral invasive breast cancer.

**BENIGN PAPILLOMAS**

Papillomas are benign intraductal proliferations that often present in the subareolar region as a palpable mass, but can be multiple, peripherally located in the breast, and incidentally found on imaging. These growths are composed of fibrovascular cores lined by myoepithelial cells and an overlying layer of epithelium. Epithelial hyperplasia can arise within an otherwise benign papilloma, as can ADH (atypical papilloma) and DCIS. The criteria used for making a diagnosis of ADH within a papillary lesion are similar to those used in ducts outside a papillary lesion. However, the criteria distinguishing ADH versus DCIS arising in a papilloma are less well defined in the pathology literature.

Consensus in the literature exists for surgical excision following core biopsy results for papilloma with atypia or multiple papillomas. However, the literature is mixed with regard to the management after a core biopsy of a benign papilloma. As is noted in Table 1, 4 of the 5 radiologists and 1 out of 5 pathologists recommended surgical excision for benign papillomas. This shows an interesting disparity between radiologists and pathologists as well as the lack of agreement amongst specialized health care professionals.

**Controversial Results Regarding Surgical Versus Imaging Follow-up**

The faults previously noted in the retrospective reviews of lobular neoplasia also hold true for benign papillomas. Some of the studies recommend surgical follow-up based on underestimation of concurrent malignancy whereas others do not recommend surgery. Studies with significant malignancy upgrades reported the following frequencies: 7% (4/56), 10.5% (9/86), 17% (20/117), and 29% (7/24). Other studies of similar design reported lower rates: 0% (0/25), 0% (0/67), and 0% (0/17). Sydnor and colleagues reported 1 case of malignancy out of 38 surgically removed and 25 tracked cases. However, the 1 malignant case was LCIS, and by current standards, most clinicians do not consider LCIS to be malignant. Investigators studying high-risk lesions, particularly papillomas and radial scars, have highlighted the differences in underestimation of results as they relate to core needle gauge and tru-cut, spring-loaded versus vacuum-assisted needles. Two studies suggested that removing a large amount of tissue at core biopsy improved the accuracy of the core results.

A shortcoming to all these studies is the lack of analyses of radiology/pathology concordance between the core and surgical pathology results. Liberman and colleagues, however, addressed this parameter directly. There were 5 malignancies (4 DCIS, 1 invasive carcinoma) out of 35 concordant benign papillomas for a prevalence of 14% (5/35). Twenty-five cases went on to immediate surgical biopsy and 10 cases underwent a minimum of 2-year imaging surveillance. Out of the 5 cancers, there was growth or a new mass on mammography in 3 in the follow-up cohort (mean 18 months, range 7–22 months). A fourth patient developed bloody nipple discharge at 21 months. On further inspection of the fifth case of a patient who self-selected to undergo surgery 1 month after core biopsy, the DCIS was 1 cm distal to the site of the papilloma in which no residual papilloma was present at surgical excision. In summary, what seems at first glance to be a study of 14% underestimation of disease is actually a study of 0% upgrades in asymptomatic women with stable mammographic findings.

The importance of radiology/pathology concordance, or rather the lack thereof, is underscored in other studies as well. Ko and colleagues reported 1 case of DCIS out of 42 sent to surgery for analysis and found the malignancy to be one-half that of the ipsilateral involved breast.
because of radiology/pathology discordance. Mercado and colleagues recommend surgical biopsy for all papillomas based on their reported upgrade of 21% (9/42) to DCIS and atypia. However, there were only 2 malignant cases, both DCIS, in which 1 was a case of pleomorphic calcifications and the second case was a new mass in a postmenopausal woman. If both of these patients had been excluded from final analysis because surgical excision would have been warranted based on factors other than the papilloma, zero cases upgraded to malignancy.

Other studies remarked that the malignancies were adjacent to the indexed papilloma and consequently incidental. Sahasrabudhe and colleagues reported 1 case of DCIS out of 19 benign papillomas involving 3 ductulolobular units in the same specimen as a 1-cm large papilloma. Their opinion was that 1 incidental lesion outside the papilloma should not mandate excision for all. The study by Bernik and colleagues reported 7 out of 71 (10%) cases associated with malignancy and an additional 7 cases associated with atypia in the surrounding tissues, defined as “within 3 cm of the indexed papillary lesion,” a distance that in some breasts may be in a different quadrant, and thus possibly unrelated.

These studies reflect neither inaccurate targeting nor an inability by the pathologist to diagnose a benign lesion. Should serendipitous occult malignancy dictate surgery for all patients with benign papillomas? However, Bernik and colleagues suggest, like Mercado and colleagues, that surgical excision is indicated to rule out not only concurrent malignancy but also concurrent atypia given the argument that if the patient is found to have ADH, then the patient’s risk for breast cancer increases, and she can be counseled for possible hormonal prevention treatment with tamoxifen or raloxifene. Hormonal treatment has been shown to reduce breast cancer risk by 70% and the duration benefit is 10 to 20 years after the completion of 5 years of tamoxifen. However, there is no evidence of survival benefit and hormonal treatment is not without its own risk. When diagnosed, it is not known how long patients have had ADH and who is going to go on to develop cancer (Judy Garber MD, Boston, MA, personal communication, January 2010). Therefore, the potential of finding atypia may not be justification for surgery after core biopsy of a benign papilloma.

Can Imaging Help Triage Patients into Surgery Versus Follow-up?

Several studies evaluated imaging features with core results as means to determine the need for surgery versus imaging follow-up. Ko and colleagues reviewed in consensus with 2 radiologists the sonographic features of 69 papillomas (43 benign papillomas, 18 atypical papillomas, 7 intraductal papillary carcinomas, 1 invasive papillary carcinoma). They concluded that when there is imaging concordance using the American College of Radiology BI-RADS Ultrasound lexicon (4th edition) applied to a benign core result, that further surgical excision is not needed. In contrast, Lam and colleagues did not find reliable radiographic features to distinguish benign from malignant when evaluating papillary lesions (papilloma, papillomatosis, sclerosing papilloma, atypical papilloma, and papillary carcinoma). Acknowledged are differences in papillary definitions possibly leading to contrasting results.

Two studies showed statistical significance between sizes of benign and malignant papillomas. Chang and colleagues noted the mean size of 1.4 cm (malignant) versus 0.9 cm (benign) (P = .039), and Kil and colleagues showed differences in size (>1.5 cm) as well as location within the breast, with atypical or malignant papillomas located more peripherally (defined as the posterior third of the breast on mammography or distal third of breast tissue circumferentially at sonography) than benign lesions (P = .017).

Larger studies corroborating these observations, as well as additional imaging features, would be helpful in predicting which patients to follow and which to refer to surgery.

RADIAL SCAR/COMPLEX SCLEROSING LESION

Radial scar and complex sclerosing lesion are terms used to describe a characteristic pathologic stellate lesion at low power containing a central elastotic stromal area often with entrapped benign ducts. At the periphery, ducts and glands radiate away from the central area. These ducts can contain usual type hyperplasia, atypical hyperplasia, even in situ carcinoma. By convention, radial scar refers to a lesion measuring 1 cm or less and complex sclerosing lesion refers to the same histology but for lesions greater than 1 cm.

In the 2004 Radiologic Clinics of North America article by Berg, the overall consensus was for surgical excision of radial scars on core biopsy when there was a mammographic finding of architectural distortion so as not to miss a possible tubular carcinoma, which is the main pathologic differential diagnosis. The study by Lopez-Medina and colleagues highlights this point in that out of the 8 false-negative cases, 4 were tubular carcinomas, with the remaining 4 cases diagnosed as DCIS (N = 2) and infiltrating ductal...
carcinoma (N = 2). Nevertheless, the inability of pathologists to distinguish radial scar from tubular carcinoma has been exaggerated in the literature. The classic histologic findings of radial scar can be confused with invasive carcinoma both pathologically and by breast imaging. However, the entrapped glands within the central elastotic area of radial scars are benign and maintain their basal myoepithelial cell layer. Tubular carcinomas lose that cell layer and are thus invasive. Moreover, immunohistochemical stains, even on core biopsy, can be used to corroborate hemotoxylin and eosin interpretations. Therefore, if the center of the lesions and radiating fibers of the lesion have been included in core biopsies, the argument that pathologists cannot distinguish tubular cancer from radial scar is incorrect and should not dictate surgery.

**Controversial Results Regarding Surgical Versus Imaging Follow-up**

There is literature showing both high and low concurrent malignancy rates based on surgical and imaging follow-up after core biopsy of a radial scar. Becker and colleagues reporting on a large, single institutional study of approximately 15,000 core biopsies, found 227 (1.4%) that included a radial scar at pathology. Of the 125 radial scars without atypia at core biopsy, there were 5 malignancies for a false-negative rate of 4% (5/125), the same percentage as reported by Brenner and colleagues’s multi-institutional study (4%, 5/128). In the literature, frequencies starting with studies advocating imaging follow-up are 0% (0/80) and 0% (0/27); those advocating surgical follow-up are 8% (5/62), 9%, (1/11), 9% (1/11), and 22% (6/27).

Some suggest that the gauge and number of cores markedly influence the accuracy of core biopsy results. The study by Becker and colleagues was performed using a 14-g tru-cut needle in 176 lesions (average number of cores per lesion 6.1) and 11-g vacuum-assisted needle in 51 cases (average number of cores per lesion 32.1). In the cohort, 14-g core biopsy, there were 100 radial scars with benign pathology at core biopsy with 5 cancers (5%, 5/100) at subsequent immediate biopsy. In the cohort, 11-g vacuum-assisted probe, there were 25 cases of radial scar with benign pathology after core biopsy, and no malignancies were detected (0%, 0/25). This difference in needle gauge results was not statistically significant. The study by Resetkova and colleagues specifically studied the 9- and 11-g vacuum-assisted probes. There were no malignancies in the entire cohort of 80 patients. The number of retrieved cores with the 11-g needle was 12 (±4) and with the 9-g needle was 9 (±3). Using a 14-g tru-cut needle, Cawson and colleagues also had 0% malignancies on follow-up of 75 prospectively tracked radial scars. The investigators made the observation, as did Brenner and colleagues, that the number of cores taken (≥5 cores) were more likely to have a correct diagnosis than if fewer were obtained, although this was not statistically significant (P = .09).72

**The Importance of Radiology/Pathology Correlation**

One study specifically observed the association of the core needle tracks at final surgical excision in relation to the indexed radial scar and associated malignancy. Douglas-Jones and colleagues reviewed the 11 false-negative cases out of 281 core biopsies (3.9%) yielding radial sclerosing lesions at core biopsy that were malignant at final surgical pathology. In all cases, the needle tracks made by the core sampling were seen at final pathology. The tracks were observed to have missed the malignancy in all eleven cases by an average of 5 mm (range 1–20 mm) and less than 6 mm in 9/11 cases. This is an interesting observation, and may explain why those studies with a large number of cores were more accurate at final pathology.

Discordance between radiology and pathology may be not only because of inaccurate targeting but also because of incongruence between lesion morphology at imaging and that at pathology. The study by Linda and colleagues may be an example of this. It is the first reported case of a false-negative radial scar using an 11-g vacuum-assisted needle. The radiographic finding was a group of benign-appearing punctate calcifications (Anna Linda MD, Udine, Italy, personal communication, January 2010) not associated with architectural distortion at mammography. The question that radiologists should ponder is whether a radial scar at pathology can manifest as only a cluster of calcifications at mammography. Because radiographs reflect what pathologists see at low-power microscopy, and because radial scars by definition must have a radial configuration of stroma, then can a pathology result of radial scar be concordant with only calcifications when no architectural distortion is present at mammography? In this scenario, is the radial scar therefore incidental? These questions are imperative when analyzing the pathology results with the imaging, and when determining the need for possible surgical follow-up. If a radial scar is
deemed to be incidental after this review, is surgery warranted? The management of incidental radial scars is not certain, although the paper by Brenner and colleagues\textsuperscript{70} reported no malignancies in 28 cases.

Pathology Controversy: ADH Versus DCIS

A tangential concern to issues of radiology/pathology concordance is the acknowledged subjectivity in pathology when diagnosing intraductal proliferative lesions. This controversy highlights that subjective criteria are often used to differentiate usual type ductal hyperplasia from ADH from DCIS. Interobserver variability studies in the pathology literature have shown this lack of consensus but have also indicated that rates of agreement can be improved with consistency in diagnostic criteria and with training of pathologists in those strict criteria.\textsuperscript{75,76}

On this note it is interesting that Brodie and colleagues,\textsuperscript{77} because of a personal upgrade malignancy rate of 34% for radial scar at core biopsy, questioned whether the results by Cawson and colleagues,\textsuperscript{72} with an overall 7% (5/75) malignancy rate of radial scar at core biopsy, reflected an interobserver variation in the diagnosis of ADH versus DCIS at pathology. In response, Cawson and colleagues\textsuperscript{76} had half of the radial scars, not specifically selected, reviewed by another breast pathologist. Although there were no ADH cases (N = 27) that changed to DCIS, 30% of the ADH cases were down graded to “ductal epithelial hyperplasia of the usual type.” Although no malignancies were missed, it is important that diagnoses of ADH, particularly if associated with high-risk lesions, be consistent and reproducible.

FLAT EPITHELIA ATYPIA

The term flat epithelial atypia was adopted by the World Health Organization Working Group on the Pathology and Genetics of Tumors of the Breast in 2003\textsuperscript{79} to define a lesion of the terminal ductal lobular unit that was recognized more than 100 years ago and variably described as clinging carcinoma, atypical cystic lobules, columnar alteration with prominent apical snouts and secretions (CAPSS) with atypia, among others. In FEA, the often cystically dilated ducts are lined by one to several layers of monomorphic, but enlarged, round to oval cells with low-grade cytologic atypia. Although the cells are atypical, there are no architectural changes as seen in ADH or DCIS, such as micropapillary or cribriform growth patterns. As part of the spectrum of columnar cell changes, there may be “floculcent secretions in the lumini of the acini” and these may calcify.\textsuperscript{80} Numerous studies have shown an association between FEA and low-grade DCIS, lobular neoplasia, and tubular carcinoma.\textsuperscript{81–88} Several good recent reviews cover the natural history of this lesion and its clinical significance.\textsuperscript{89–91}

Mammographically, FEA usually presents as clustered, punctate, amorphous, or fine pleomorphic calcifications. Because the calcifications are secondary to secretions of calcium oxalate or calcium phosphate by the epithelium, the calcifications are small and amorphous if within the cystically dilated lobules. If the terminal ducts are involved, the calcifications may be fine, pleomorphic, conforming to the tubular structure of the ducts.\textsuperscript{80}

Controversial Results Regarding Surgical Versus Imaging Follow-up

It is difficult to determine if there is an association between FEA and specific carcinomas because the literature presents conflicting results. The study by David and colleagues\textsuperscript{92} in 2006 was one of the first to question the appropriate management of FEA after core biopsy. These investigators subdivided the atypical columnar cell changes, unlike current standards, into those with and without hyperplasia, as had been recommended by Schnitt.\textsuperscript{89} Most pathologists now lump both categories into FEA. David and colleagues\textsuperscript{92} found 7 cases of carcinoma for a rate of 17.5% (7/40), but only in the cases of FEA with hyperplasia, and only in cases in which the lesion measured 10 mm or greater. Surgical management was advocated for both groups of FEA cases. Other studies advocating surgery report malignancy rates of 14% (9/63),\textsuperscript{93} 17% (2/12),\textsuperscript{94} 20% (3/15),\textsuperscript{95} and 21% (3/14).\textsuperscript{96} Not surprisingly, there are also studies with no malignancy upgrades that recommend only imaging follow-up: 0% (0/41),\textsuperscript{97} 0% (0/20),\textsuperscript{98} and 0% (0/20).\textsuperscript{99} In all 3 studies that noted no malignancy upgrades, the investigators used 11-g vacuum-assisted needles. The number of cores ranged from 6 to 8 for Senetta and colleagues\textsuperscript{97} and 12 to 24 (mean 15) for Noel and colleagues.\textsuperscript{99} In the third study, 74% (14/20) of the cases of calcifications were either entirely or almost completely removed by the vacuum-assisted needle.\textsuperscript{98} The study by Martel and colleagues\textsuperscript{93} has data with some of the longest follow-up. There were 63 cases of FEA out of a total of 1751 core biopsies (3.6%) followed for an average of 6.2 years (range 1–11 years). Nine malignancies developed (9/63, 14.3%) of which 7 were ipsilateral (time to detection, mean 3.7 years [range 2–9 years]) and 2 were
contralateral (time to detection, 7 years). Significant, however, is that 2 of the 7 ipsilateral cases had undergone interval biopsies before the invasive carcinoma diagnosis, but after the FEA diagnosis, and these interval results showed FEA with ADH. It is possible that FEA reflects a slow neoplastic process that may or may not grow into a carcinoma, and hence is a high-risk marker.

In addition to the usual shortcomings of retrospective studies of low-prevalent lesions, the literature on FEA is confounded by lack of agreement in pathology on the definitions of atypia within columnar cell change. Davishian and colleagues\(^9\) studied pathologist interobserver variability in the categories of atypia. Fifty-one cases of atypia, specifically ADH, ALH, and FEA, were distributed, without being identified, to 4 specialized breast pathologists for independent review. Following this review, they gathered for a tutorial session to review the general criteria of atypia on a second set of known cases. The study cases were then re-reviewed as a group to come to a consensus diagnosis for each of the 51 cases. The independent reviews were used to determine the interobserver agreement using kappa statistics. The consensus diagnosis was used to determine the diagnosis for upgrade after surgical excision. Overall, this group achieved a substantially high agreement with an overall kappa value of 0.79 (95% CI 0.69–0.89) and 0.85 for FEA. Two other studies corroborated their findings that interobserver agreement in cases of columnar cell change improved with training.\(^100,101\)

In summary, since the 2003 World Health Organization consensus meeting,\(^79\) studies have shown conflicting results in the frequency of concurrent malignancy at the time of core biopsy of FEA. The trend seems to show that if the core sampling involves large vacuum-assisted needles and a large number of cores such that the mammographic lesion is almost completely removed, then the risk of leaving undetected existing malignancy is extremely low to nonexistent. FEA does seem to be a significant risk factor that warrants close imaging surveillance at the least.

**MAGNETIC RESONANCE IMAGING FOR HIGH-RISK LESION EVALUATION**

Magnetic resonance (MR) imaging has been studied as a potential tool to determine preoperatively the presence or absence of concurrent malignancy with high-risk lesions. Linda and colleagues\(^102\) gathered 79 cases of high-risk lesions (18 lobular neoplasia, 26 benign papillomas, 29 radial scar, 6 ADH) that had been evaluated preoperatively by MR imaging. It is their common practice to perform MR imaging within 2 weeks of core biopsy for high-risk lesions. For this study, the lesions were independently reviewed by 2 radiologists, blinded to the final pathology results, who categorized the lesions into suspicious or nonsuspicious for malignancy. The frequency of nonsuspicious per lesion was: 25/29 radial scars, 11/18 lobular neoplasia, and 15/26 papillary lesions for a total of 51/73 nonatypia high-risk lesions. There were no malignancies at surgical follow-up of the cases categorized as nonsuspicious.

Pediconi and colleagues\(^103\) evaluated MR prospectively using a different methodology. Thirty spiculated masses suspected of being radial scars at mammography underwent preoperative MR imaging. The definition distinguishing radial scar from malignancy at mammography was not specifically noted other than the presence of “radiolucent lines between dense spicules” in 23/30 cases. There were 18/30 cases without enhancement at MR imaging, with no malignancy present at surgical excision. The remaining 12 enhancing lesions were malignant (DCIS or invasive carcinoma).

Two studies of high-risk lesions and MR imaging discuss MR-guided core biopsy. A small study by Sadaf and colleagues\(^104\) in abstract form retrospectively looked at 135 MR-guided biopsies: 8 lobular neoplasias, 2 benign papillomas, 3 radial scars, and 2 FEA. In all cases the biopsies were considered to be successful with a 9-g vacuum-assisted core needle and there were no differences in the number of core samples obtained. There were no differences in the morphologies and kinetics, or lesion type (mass versus nonmasslike) in the malignant and benign groups. The underestimation rate for lobular neoplasia was 3/6 (50%) and FEA 1/2 (50%). No cancers were found in benign papilloma (N = 2) or radial scars (N = 3). Orel and colleagues\(^105\) initial experience of MR core biopsy using a 9-g vacuum-assisted probe reported 85 lesions including 7 cases of lobular neoplasia and 3 radial scars; none had malignancy at surgical follow-up. Of the 4 papillomas diagnosed at MR-guided core biopsy, 3 underwent surgery without malignancy.

These small preliminary studies suggest that MR imaging may be helpful in determining the need for surgical or imaging follow-up after core biopsy. Larger studies are needed to determine if these findings can be generalized.

**CONCLUDING REMARKS**

This article raises more questions than answers, and sadly illustrates that there has been little
progress since the last time this topic was discussed in the 2004 Radiologic Clinics of North America. More retrospective studies will never give us the answer as to how to manage these high-risk lesions after core biopsy, regardless of the imaging modality used to guide sampling. Prospective trials that meticulously track the imaging and pathology for accurate radiology/pathology concordance are sorely needed. Patients who are not surgically followed for gold standard determination must also be tracked to determine if outcomes are similar to or different form those undergoing surgery. Pathologists need to come to consensus as to definitions of ALH versus LCIS, ADH versus DCIS arising within papillomas, and columnar cell change versus columnar cell change with atypia (FEA). These definitions need to be reproducible so that pathologists around the world can accurately apply these features.

We appeal to the radiology and pathology communities to collaborate and test prospective, radiology/pathology, hypothesis driven studies that could provide evidence-based data to guide us in the appropriate follow-up when core biopsy yields a high-risk lesion.


**Table 1**

<table>
<thead>
<tr>
<th>Lobular neoplasia</th>
<th>Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Low prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% (0/12)</td>
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<td></td>
</tr>
<tr>
<td>0% (0/21)</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>1% (1/87)</td>
<td>37,a</td>
<td></td>
</tr>
<tr>
<td>2% (2/98)</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>B: High prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4% (1/25)</td>
<td>35,b</td>
<td></td>
</tr>
<tr>
<td>14% (3/21)</td>
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<td></td>
</tr>
<tr>
<td>16% (1/6)</td>
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<td></td>
</tr>
<tr>
<td>19% (10/52)</td>
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<td></td>
</tr>
<tr>
<td>20% (7/35)</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>23% (38/164)</td>
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</tr>
<tr>
<td>25% (5/20)</td>
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<td></td>
</tr>
<tr>
<td>37% (13/35)</td>
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<td></td>
</tr>
<tr>
<td>50% (9/18)</td>
<td>29</td>
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</table>

<table>
<thead>
<tr>
<th>Lobular neoplasia</th>
<th>Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Low prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% (0/25)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>0% (0/67)</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>0% (0/17)</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>0% (0/63)</td>
<td>53,a</td>
<td></td>
</tr>
<tr>
<td>0% (0/40)</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>0% (0/35)</td>
<td>56,b</td>
<td></td>
</tr>
<tr>
<td>0% (0/42)</td>
<td>58,c</td>
<td></td>
</tr>
<tr>
<td>0% (0/19)</td>
<td>62,d</td>
<td></td>
</tr>
<tr>
<td>2% (1/43)</td>
<td>57</td>
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<tr>
<td>B: High prevalence</td>
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<td></td>
</tr>
<tr>
<td>7% (4/56)</td>
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<td></td>
</tr>
<tr>
<td>9% (9/104)</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>10% (7/71)</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>10.5% (9/86)</td>
<td>47</td>
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</tr>
<tr>
<td>17% (20/117)</td>
<td>48</td>
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</tr>
<tr>
<td>19% (15/80)</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>29% (7/24)</td>
<td>49</td>
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</table>

a Adjusted for radiology-pathology discordance and non-classic LCIS.
b Adjusted for radiology-pathology discordance and a missed lesion at core biopsy.

**Table 2**

<table>
<thead>
<tr>
<th>Benign papilloma</th>
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<tr>
<td>0% (0/25)</td>
<td>50</td>
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</tr>
<tr>
<td>0% (0/67)</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>0% (0/17)</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>0% (0/63)</td>
<td>53,a</td>
<td></td>
</tr>
<tr>
<td>0% (0/40)</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>0% (0/35)</td>
<td>56,b</td>
<td></td>
</tr>
<tr>
<td>0% (0/42)</td>
<td>58,c</td>
<td></td>
</tr>
<tr>
<td>0% (0/19)</td>
<td>62,d</td>
<td></td>
</tr>
<tr>
<td>2% (1/43)</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>B: High prevalence</td>
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<td></td>
</tr>
<tr>
<td>7% (4/56)</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>9% (9/104)</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>10% (7/71)</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>10.5% (9/86)</td>
<td>47</td>
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</tr>
<tr>
<td>17% (20/117)</td>
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</tr>
<tr>
<td>19% (15/80)</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>29% (7/24)</td>
<td>49</td>
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</tr>
</tbody>
</table>

a Adjusted for LCIS classified benign at surgical pathology.
b Adjusted for asymptomatic patients with stable mammograms.
c Adjusted for radiology-pathology discordance and stable mammogram.
d Excluded incidental, minute focus DCIS.

**Table 3**

<table>
<thead>
<tr>
<th>Radial scar</th>
<th>Frequency</th>
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</tr>
<tr>
<td>0% (0/80)</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>0% (0/27)</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>0.7% (2/281)</td>
<td>74,a</td>
<td></td>
</tr>
<tr>
<td>B: High prevalence</td>
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<td></td>
</tr>
<tr>
<td>4% (5/125)</td>
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<td></td>
</tr>
<tr>
<td>8% (5/62)</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>9% (1/11)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>22% (6/27)</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

a Excluded 9 cases of missed lesion at core.
REFERENCES


with histopathologic correlation [special issue]. Radiographics 2007;27(Suppl 1):79–89.


