Factors Influencing the Accuracy of a Core Biopsy Diagnosis of Atypical Hyperplasia. A Perspective on a Frequent Problem

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One of the few diagnostic limitations of stereotactic biopsy evident in initial reports of its utility (Jackman et al, 1994, 1999; Liberman et al, 1995) was a 48-58% rate of underdiagnosing DCIS or DCIS with invasion as demonstrated in a subsequent open biopsy. This initial experience has generated a widely recognized mandate for the necessity of an open biopsy for any diagnosis of ADH in a stereotactic biopsy. However, this mandate is an oversimplification. In fact, use of more precise pathologic and mammographic guidelines can markedly reduce the need for reexcision of stereotactic biopsies demonstrating ADH.

The initial stereotactic experience with ADH reflected use of a small-gauge needle and a spring-loaded gun-type mechanism for sampling the tissue. The requirement to withdraw the needle after every firing, and its small gauge (18 gauge) generated a very limited number of cores and uncertain sampling of the microcalcific target. The use of a newer generation of vacuum-assisted devices of larger gauge (7-11 gauge), often producing ten times the volume of tissue and a much more generous and certain sample of the mammographic microcalcification, reduced the initial rate of underdiagnosis from 48 to 50% to 0 - 18%, depending on the reviewer (Burbank, 1997). Percutaneous excision technologies (e.g. *Intact*, *Senorex*) can achieve even greater degrees of certainty.

PATHOLOGIC VARIABLES

Apart from the size of the tissue sample obtained through different technologies, however, there are other variables that can significantly impact the false negative rate for a stereotactic biopsy. Most importantly, these include how the tissue is processed (Lagios, 2000) and how many levels are obtained (figures). An 11-gauge biopsy core provides a much better chance of sampling a microscopic DCIS since it contains 2.5 X the volume of a 14-gauge gun core. However, this advantage can be entirely lost if the core is sectioned to a depth of only two levels rather than the six or eight that are required to profitably examine the tissue, or if it is processed in such a manner than the core cannot be sampled even with a dozen levels. Such variables are frequently underappreciated by the interventional mammographer.

DEFINITION OF DCIS

Inexperience with the interpretation of stereotactic biopsy material can lead to identifying many diagnosable low grade DCIS in particular as ADH, that is biasing the interpretation towards the safer diagnosis and undercalling the lesion. The problem of upgrades of ADH to DCIS/invasion exists only for DCIS defined as low-grade and specifically nuclear grade I lesions without necrosis. Single duct profiles which exhibit nuclear grade II-III morphology with or without necrosis fall outside of this differential, i.e, they are definable as DCIS even with such limited involvement. A significant number of core andmammotome-type diagnoses of ADH are undercalled and on review actually represent DCIS. Although low grade DCIS was originally defined in minimalist terms as totally involving two duct spaces (Page and Anderson, 1987), more recently Tavasolli and Norris (1990) have imposed a quantitative criterion on such foci requiring that the sum of the

diameters of the involved duct spaces equal or exceed 2 mm. As a result, smaller-gauge biopsies may not sample sufficient ducts to fulfill the quantitative criteria.

SEMI-QUANTIFICATION OF ADH

More recently, attempts at mammographic-pathologic correlation for the stereotactic biopsy have allowed a reduction in the need for universal reexcision. In our recent experience an attempt to semi-quantify both the size of the ADH and the degree of sampling stereotactically, have permitted the recognition of patients who can be followed in a manner similar to patients with microscopic ADH incidental to an open excision biopsy of a benign process, e.g., fibroadenoma, etc. In a sample of twelve to fifteen 11-gauge cores, the presence of microscopic ADH involving up to three TDLU and unassociated with the mammographic target microcalcification is generally followed without recourse to open biopsy. On the other hand, ADH associated with target microcalcification, only a part of which has been excised by the stereotactic procedure, will require an open biopsy.

Ely et al (2001) noted that in 51% of 47 14 or 11 gauge core biopsies with ADH that the ADH was limited to 2 or fewer ductolobular units or duct spaces. None of these were upgraded at subsequent open excision. All upgrades occurred amongst the 32% of the core biopsies which demonstrated ADH in 4 or more ductolobular units or duct spaces.

Lim et al (2001) correlate the extent of microcalcifications (mean 16 mm), the degree of sampling and the number of TDLU involved. In 15 cases of ADH documented with 11 and 14 gauge biopsies, there was only 1 upgrade (6.6%) to DCIS, 4 cases exhibited no residual ADH and 10 ADH only on subsequent excision. The one upgraded patient had an estimated 15% sample of a 70 mm extent of microcalcifications. They propose possible followup for patients with 3 or fewer TDLU involved with ADH in whom at least 30% of the microcalcification are sampled.

Gal-Gombos et al (2000) reviewed 43 ADH cases, 33 based on 11 gauge vacuum assisted biopsy, who underwent subsequent open excision. Two pathologist reviewed the diagnostic material and the protocol required documenting the biopsy site in the excision specimen. There were only 2 upgrades (4.6%) one to DCIS, one to invasive carcinoma

Renshaw et al (2001) recently corroborated this thesis in a study of ADH upgrades. Their practice required complete sectioning of the core material with preparation of 8 slides with 2 - 5 levels per slide. The overall upgrade rate of ADH to DCIS was 14% using 14 gauge and 11 gauge ultrasound and stereotactic biopsies. However none of the upgrades were found to have been completely removed based on a blinded review of themammograms. There were no upgrades to invasive carcinoma.

Sneige et al (2003) reviewed 42 patients with vacuum assisted core biopsy diagnoses of ADH who underwent subsequent re-excision. 3/42 were upgraded to DCIS, but no patient whose mammographic target was completely excised or who exhibited 2 or fewer lobules/duct structures with ADH were upgraded.

RELIABILITY OF DIAGNOSIS OF "ATYPIA: AND ATYPICAL DUCT HYPERPLASIA (ADH)

In addition to the problem of some DCIS being under-called as ADH, some diagnoses of "atypia" (ADH and lobular neoplasia) and ADH specifically are themselves over-called. Most of these represent benign proliferative breast disease without atypia.

Verkooijen et al (2003) found 42% of submitted "atypias" on review were benign; Collins et al (2004) and Jackman and Lagios (2005) noted concordance with submitted diagnoses of ADH specifically in 62% and 57% respectively, while 21 and 26% were entirely benign. In corrollary fashion 38-43% of initial diagnoses of ADH were not confirmed on review. These studies emphasize the lack of uniformly accepted diagnostic standards and the inconsistent utilization of recommended standards in diagnostic pathology practice at present.

PROBLEM OF LOBULAR NEOPLASIA (ATYPICAL LOBULAR HYPERPLASIA AND LOBULAR CARCINOMA IN SITU) AND UPGRADES

Does LCIS or ALH in a core biopsy require open excision?

The finding of either ADH or DCIS within a core biopsy is generally regarded as an indication for a subsequent open biopsy because of the frequency of diagnostic upgrades at excision to either DCIS and/or invasion. In studies of ADH the gauge of the biopsy needle, the number of cores, the number of TDLU (ductolobular units) with ADH and the completeness of sampling of the mammographic target microcalcification impact the frequency of upgrades. Lobular neoplasia (LCIS and/or ALH) is much less frequently encountered than either ADH or DCIS in biopsies (approximately 1.5 percent or less) and the management of the patient with such a diagnosis has not been completely resolved.

However a common feature of studies which have failed to document a significant number of upgrades with an initial core diagnosis of lobular neoplasia is more extensive and thorough examination of the core biopsy specimen and careful mammographic pathologic correlation. Renshaw et al (2002) limited the number of cores per cassette to improve processing and then cut through the entire block with 10 levels for 14 and 11 gauge ultrasound and stereotactic core biopsy material. Liberman et al (1999) noted upgrades at open excision with initial core diagnoses of LCIS in certain specific situations: when the lesion could not be definitively classified as LCIS as opposed to cancerization of lobules; when another marker lesion was present e.g. ADH; and when the diagnosis was discordant with the mammographic target. There were no upgrades when LCIS occurred alone and when the diagnosis was concordant with imaging. Similarly Berg et al (2001) recommended open excision for LN associated with microcalcification only when the mammographic microcalcific target remained, and Bauer et al (2003) recommended open excision only when carcinoma or another marker lesion was present. Berg et al. (2001) reported on 25 cases of lobular neoplasia (15 ALH and 10 LCIS) detected in a core biopsy (40 percent vacuum assisted), 16 of which went on to open excision. Only one of the excisions revealed DCIS, six showed ADH with microcalcification, another showed DCIS but in a patient with known ipsilateral disease. In a more recent study Renshaw et al (2006) showed a very low risk of diagnostic upgrades from lobular neoplasia when the lesion was seen alone, i.e. associated ADH, RS etc.

In contrast studies which fail to adequately examine the pathology specimen, or by correlation fail to confirm that the mammography target has been sampled conclude that open biopsy is necessary for cores with lobular neoplasia (Shin and Rosen, 2002; Dmytraszk et al, 2003).

Histopathology

Morphologically, LCIS represents a solid proliferation of small cells within a TDLU and in a "pagetoid" fashion, i.e. beneath the luminal epithelium of extralobular ducts. Classically, LCIS

exhibits nuclear grade I (NG I) morphology (Table I) and a discohesive pattern of growth. These lesions have been shown to be diploid with a low S phase fraction (Figure 1).

Distinguishing between LCIS and solid, duct-type proliferations within a TDLU in a pattern of cancerization of lobules can be difficult particularly when the ductal CIS also exhibits NG I morphology. Ductal type lesions tend to exhibit a greater degree of cohesiveness and often demonstrate some architectural organization (e.g. subtle microacinar or cribriform structures). The recent introduction of E-cadherin immunohistochemistry has permitted the distinction of most such lesions on the basis of the presence or absence of an adhesion protein located on the cell membranes. Ductal type lesions exhibit a pronounced membranous reaction product while lobular lesions are usually negative, except for myoepithelial and residual luminal epithelial elements (Goldstein et al, 2001).

Pleomorphic LCIS and its significance.

Although lobular neoplasia characteristically exhibits small very uniform nuclear morphology, variants which exhibit more significant nuclear pleomorphism have been long recognized. Haagensen described lobular neoplasia type B as exhibiting larger and more pleomorphic nuclei but found no differences in outcome for this variant in the subsequent risk of an invasive carcinoma. Similarly, Bodian et al. (1996) in an update of this database was unable to demonstrate a significant difference in risk related to the nuclear morphology and cytology of the process.

A small fraction of such cases exhibit zonal necrosis c.f comedo necrosis and dystrophic microcalcification and are detected by mammographic surveillance like duct carcinoma in situ. In the recent past many of these lesions were likely to be classified as duct carcinoma in situ with comedo necrosis and so treated (figure 2). Only since the recent introduction of E-Cadherin immunohistochemistry has the identification of such variant lobular neoplasias become feasible. Several studies have now shown that lobular neoplasia characteristically loses an adhesion molecule (E-Cadherin) which ductal lesions exhibit uniformly. New studies have shown some differences in biomarkers between typical examples of lobular neoplasia and pleomorphic variants. Sneige et al. (2002) noted that pleomorphic LCIS exhibited a much higher Ki-67 (47 percent with Ki-67 greater than 20 percent) and P53 (30 percent) than typical lobular neoplasia. They report a short (mean 17 month) follow-up for seven patients with pleomorphic lobular neoplasia, five of whom had undergone needle localized excision and have a breast at risk. Only one of these five recurred, a patient with an initial margin less than 1-mm, as additional pleomorphic lobular neoplasia. Georgian-Smith and Lawton (2000) report that two of five patients with pleomorphic lobular neoplasia undergoing excision exhibited invasive lobular carcinoma but provide no follow-up data on cases with pleomorphic lobular neoplasia alone after excision. Fisher et al. (1996) relegated all comparable cases of pleomorphic lobular neoplasia (ductolobular carcinoma in situ in his terminology) to treatment as duct carcinoma in situ in the B17 protocol.

Since knowledge of the biology of pleomorphic lobular neoplasia particularly of the type detected by microcalcification is presently so limited, treatment will necessarily represent speculative projections based on the significance of more pleomorphic nuclear morphology, higher proliferative index, or P53 but not on outcome studies. Although it would appear reasonable to excise pleomorphic lobular neoplasia in cases where the mammographic target has only been sampled, re-excision for the presence of the histologic finding alone near or at a margin may be overreaching.

REIMBURSEMENT

The current level of reimbursement for pathologic evaluation of core biopsy material, particularly the larger vacuum assisted 8 and 11 gauge procedures, is based on CPT code 88305 which covers skin and breast biopsies. The level of compensation for the pathologist and the hospital (technical fee) provided by 88305 provides a profit for examining a shave excision of a seborrhoeic keratosis from the forehead (Tables), but establishes a loss for both pathologist and hospital if 11 gauge let alone larger core biopsy material were to be examined with the level of care it deserves. As a result many hospital laboratories simply provide 1 or 2 levels for an 11 gauge core, a number guaranteed to miss some of the pertinent microscopic findings if not miss the diagnosis entirely. Obviously subsequent open excisions which provide a diagnosis in these circumstances will be recorded as upgrades. The "cost savings" which results from this strategem (1 level rather than 6) at $6.00/slide is $30.00 or approximately 0.35% of the cost of a stereotactic core biopsy procedure. Do you know how many levels your laboratory provides for 14 and 11 gauge vacuum assisted biopsies?

SUMMARY

Rather than defining a requirement for an open biopsy, the presence of ADH in a stereotactic core biopsy should first engender a need for quantification and correlation. Although much of the literature on the question of ADH upgrades includes histologic review, mammographic-pathologic correlation to evaluate the extent of sampling is less common.

A word about upgrades of ADH or DCIS to invasive breast cancer. Clearly concluding that a stereotactic procedure is inferior because it cannot exclude invasion is inappropriate. Limitations in defining invasion with a diagnosis of DCIS should be compared to the similar results obtained from an initial needle localization procedure in which more than half are inadequately excised and in which invasion is often found in the re-excision.

Currently, the presence of ADH in a stereotactic biopsy should be evaluated to determine whether or not the pathologic lesion was incidental to the mammographic target, or is part of it but only sampled, that is, with some recognition of the need for pathologic mammographic correlation and the important need to more adequately assess the tissue being involved. The available literature on upgrades of ADH to DCIS and DCIS/invasion does not factor in any of the pathologic factors, i.e., either the technology of tissue processing, the number of levels, or the definition of DCIS or ADH employed. In similar fashion upgrades from lobular neoplasia to either invasive cancer or DCIS can be markedly reduced if not eliminated by employing strict correlative strategems to insure that the mammorgraphic target has been sampled - and not missed, to exclude other potentially more significant processes by review of imaging including ultrasound, and to insure that the lesion identified in the core material is in fact lobular neoplasia and not cancerization of lobules (=DCIS) by appropriately employing E-cadherin immunohistochemistry.

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