

3

Introduction

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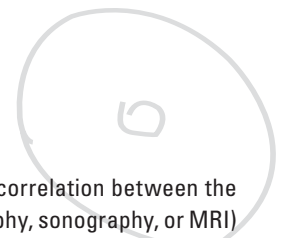
There have been radical changes in the way breast interventions have been conducted in the short span of the last few years; the major advance being the introduction of multiple devices allowing minimally-invasive biopsies to be performed in an office setting, at lower cost than excisional biopsies performed in the operating room. Numerous studies have demonstrated that these minimally invasive procedures have the same diagnostic sensitivity and specificity than open biopsies.

There are two major aspects to consider when choosing minimally-invasive breast biopsies. Those are:

- (a) Guidance: Obviously the modality to be used for image guidance will be dictated by the lesion. Sonographically visible lesions should be biopsied under ultrasound guidance, as this method is more comfortable for the patient and allows real-time monitoring of the biopsy procedure. X-ray stereotaxy will be preferred for lesions optimally imaged with this modality, e.g. those containing microcalcifications. Finally, MRI will be used to guide biopsy in mammography and sonography occult lesions.
- (b) Device: at present there are two major types of collection devices in use: spring-loaded core needle biopsy (CNB) devices, and vacuum-assisted biopsy (VAB) devices. This corpus will not address the use of older techniques, such as fine needle aspiration (FNA), and will present limited information on even newer approaches, such as spiral sampling and RF-based whole-sample removal techniques. Regarding CNB and VAB, there is an ever-growing body of evidence in the literature favoring the latter, especially for stereotactic-guided biopsies, due to their superiority in acquiring larger samples and propensity to reduce histological artifacts, resulting in higher diagnostic accuracy than CNB systems. Unfortunately, their capital and operating cost is superior, complicating the purchasing decision.

Regardless of the chosen biopsy technique, there must be correlation between the pathological results with the detection findings (mammography, sonography, or MRI) that led to the decision to biopsy. Failure to achieve proper correlation is an indication that either the decision to biopsy, and therefore the interpretation of the images, was erroneous; there is a higher likelihood however that the biopsy sample was not properly acquired. Either way, a decision must be made to re-biopsy or follow-up accordingly.

Finally, sentinel node biopsy techniques will be discussed, including mention of indications and implication in patient treatment. The notion of micrometastases is evoked, for which the clinical meaning is not yet well defined. Studies are underway to determine their significance and impact on patient prognosis.



3.1

Lecture 1

An interpretation of core biopsy material: Maximizing the yield and avoiding error

Michael D. Lagios, MD

Introduction

The ability to sample image-detected breast abnormalities by stereotactic or ultrasound-guided core biopsy - which include both core needle (CNB) and vacuum-assisted (VAB) - has revolutionized diagnostic procedures for such lesions. Core biopsy techniques can establish a definitive diagnosis in 90-95% of procedures at both reduced cost and reduced morbidity to the patient. Patient acceptance is generally excellent, particularly when compared to open biopsy which often requires anesthesia. An estimated 65-80% of patients who formerly underwent a diagnostic excision resulting in a benign diagnosis can be spared an open surgical procedure and be relegated to routine follow-up. For those patients with definitive malignant diagnoses, subsequent care can be better planned, both in terms of surgery (bracketed-wire excision, additional preoperative imaging, sentinel node biopsy) and the use of biomarkers which can be obtained from the core material.

To effectively use core biopsy technology, however, requires a much more integrated approach on the part of the radiologist and pathologist. Inattention to these requirements may lead to a misdiagnosis, either because the interventionalist didn't sample the lesion or because the lesion was not exposed histologically even when the biopsy confirmed its sampling.

Variables

The specific technique employed will affect the diagnostic yield. Average weight of a 14-gauge core from a CNB spring-loaded gun type procedure is 17-20 mg. Since the technique requires multiple independent insertions of the needle, it is uncommon to obtain more than six cores, or roughly 100-120 mg of tissue. In contrast, an 11-gauge VAB technique harvests 100 mg of tissue at a time with a single insertion, and 15 sampling for microcalcification lesions are not uncommon. Therefore, an 11-gauge VAB will sample, on average, some 10-15 times the weight of tissue as compared to a 14-gauge CNB procedure.

11-gauge stereotactic cores vary from 2.5 to 3.0 mm in diameter. Since many of the histologic lesions which account for the mammographic target are 0.5 - 1.5 mm in

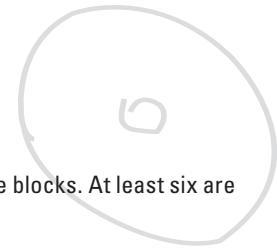
size, step levels are required to adequately screen the tissue blocks. At least six are required to screen a 3-mm core.

A number of artifacts due to the biopsy technique will be seen, particularly with the CNB spring-loaded gun type procedure. These include fragmentation and crushing of the tissue, disruption of duct structures and red cell extravasation, and epithelial implantation along the biopsy tract which can result in diagnostic difficulties in subsequent open excision.

Ideally, the pathologist should review the pertinent preoperative imaging and specimen radiographs for microcalcification to correlate the morphology of the radiographic target with the material in hand. It is unfortunately common practice to delete such review and to rely on a description of the target provided by the radiologist. Hopefully in these circumstances, the pathologist will not be provided with a clinical history of "right breast mass" when the target is an 8-mm focus of pleomorphic microcalcification at 2:30 o'clock, 7 cm from the nipple. Segregation of the core material, to include cores with microcalcifications and those without, often assists in establishing a correlation.

Conclusion

Either CNB or VAB core biopsies properly performed can provide definitive diagnoses for the majority of image-detected abnormalities and at 50% of the cost, and with less morbidity than an open diagnostic procedure. The majority of these diagnoses will be benign and the patient can be subsequently followed by routine surveillance. Pathologic interpretation requires image correlation and can be jeopardized without it.



3.2

Lecture 2

Adequate sampling for difficult cases in stereotactic-guided breast biopsies

Philippe Sébag, MD

Introduction

Stereotactic-guided biopsy requires an experienced physician to be able to accurately sample the lesion; even then some cases may be more difficult to treat successfully. For those particular cases a preliminary consultation is more than useful; in fact it is important to assess the reality of the lesion, and necessary to obtain medio-lateral and cranio-caudal magnification to be sure that the indications are accurate. If so, one would have to check the lesion location in the breast, appreciate breast volume and explain beforehand to the patient that it might be a little more difficult than anticipated. With all those elements at the end of the consultation one should be able to know if the procedure is feasible.

Difficult Cases

More often difficult cases arise in small and thin breasts; however, even in a regular sized breast, lesion location could be a problem. This is true for lesions that are superficial (close to the skin), retro-areolar, deep (close to the pectoralis muscle) and at the union of the lower quadrant of the breast.

Small and thin breasts

For these cases it depends on the stereotactic table you have; if you use a rotating table you should use the lateral arm as it would be easier to operate and there would be no limitation on the depth of the breast, and in this case you will see your needle in a longitudinal view as in ultrasound guidance.

If you do not have a rotating table you will have to manoeuvre the breast so as to obtain the most volume. First, you can inject more local anaesthetic under the skin and/or beside the lesion. Secondly, you can put a plate between the detector and the breast so for your computer you will increase virtually the thickness of the breast; finally, you can strap the breast in a dressing bandage so as to change its form.

Regular-sized breasts: As in the preceding paragraph, the fundamental principle is to manoeuvre the breast.

Superficial: You can increase the distance between the skin and the lesion with an injection of anaesthetic and afterwards, you need to push the needle in order to make the sample chamber disappear. Make a small incision and you will avoid a skin defect. You could also use a lateral arm if you have one and prefer to use this option.

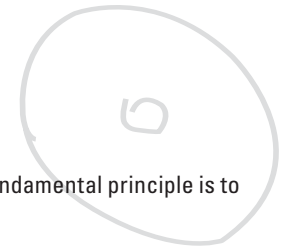
Retro-areolar: When the lesion is close to the areolar, in order to avoid cutting it you should manoeuvre the nipple by rotation so that you don't enter the nipple itself. The lateral arm, if you have one, is easier to use in this case.

Deep: With a frontal approach it is sometimes difficult to target a deep lesion, but you can place the patient's arm in the table's opening so she is positioned to enable you to attain the lesion more easily and accurately. On the rotating table for these cases polar coordinates are useful or you can use the lateral arm, as you prefer.

Union of the lower Quadrant of the Breasts: In these cases the easiest solution is to use the lateral arm; if you don't have one you need to apply a rotation of the breast in order to increase the depth between the side of the lesion and the detector.

Conclusion

With experience, you will see that difficult cases are rare and that the real technical impossibility is either when the target is invisible, or because it is situated on the chest wall.



3.3

Lecture 3


Prognostic features of breast carcinoma from stereotactic biopsy material

Michael D. Lagios, MD

Introduction

Stereotactic core biopsy technology has made a dramatic impact on the ease of obtaining diagnostic material from an occult mammographic focus, and on reducing the costs and the morbidity as compared to conventional needle directed biopsy. Patient acceptance is very high for a procedure which is minimally invasive and requires a fraction of the time of a conventional excisional biopsy. For the minimal two-thirds of mammographic suspicious foci for which biopsy is recommended, and which result in a benign diagnosis, no further surgery is required except in the circumstance in which atypical ductal hyperplasia (ADH) or DCIS is documented with an 18 gauge core (Jackman et al., 1994; Liberman et al., 1997; Nguyen et al., 1996; Reynolds et al., 1996). Larger stereotactic cores, 14 and 11 gauge, obtained with VAB are of sufficient size to permit a definitive diagnosis in nearly all cases (Burbank, 1997). For the third of patients with a cancer diagnosis from the stereotactic biopsy, much more effective treatment planning is available - including more adequate excision volumes with a greater likelihood of negative margins (and in corollary fashion a reduced need for re-excision) and the possibility of sentinel node sampling as opposed to conventional axillary dissection (Kaufman et al., 1998).

Despite the cost-savings, greater patient acceptance and greater accuracy in sampling the mammographic focus, some questions remain. For a growing number of documented T1a and T1b carcinomas, the majority of which are predicted to be node-negative, the prognostic features of the primary carcinoma become very significant. Can the stereotactic core biopsy material provide good information about tumor subtype, grade, receptor protein, oncogenes, ploidy, S-phase fraction, mitotic index? What about those features generally thought to require larger tissue volumes for evaluation: tumor size, angio-invasion, extensive-intraductal carcinoma and margins? How much can be derived from the stereotactic biopsy alone and what features require larger biopsy volumes? In establishing this comparison, however, it is important to compare the two diagnostic procedures, one stereotactic, the other needle directed, and not stereotactic core biopsy versus diagnostic needle-directed biopsy and re-excision.



To make such a comparison we should review the most significant prognostic features available in the biopsy material. Although axillary metastases are known to be the most significant prognostic factor for an individual patient, the majority of mammographically detected invasive carcinomas with a mean size ranging from 11 - 14 mm will be node-negative; this is particularly true for T1a and T1b carcinomas (respectively 1-5 and 6-10 mm in maximum size). Such carcinomas are more likely to be of favorable grade, reflecting another benefit of mammographic detection before clonal progression has occurred (Tabar and Dean, 1994; Helman, 1997). Barth et al. (1997) has recently shown that non-palpable mammographically detected invasive carcinomas are associated with approximately half of the axillary metastatic rate of palpable lesions, e.g. for 10 mm carcinomas the frequency of demonstrable axillary metastases employing conventional technology, is approximately 9 - 10% and for T1a lesions the rate is approximately half of this. For the 50% or more of mammographically detected carcinomas in the T1a, and T1b size range, 90% or more will be node negative, and evaluation of prognosis will be dependent on the features in the biopsy material itself.

TABLE 1

Prognostic features
Apart from nodal status, the most important features are:

A. For Distant Recurrence

Morphology	Corresponding Features
Size	DNA Ploidy Analysis and Proliferation Rates
Tumor subtypes	Oncogene and other biomarkers
Grade	Receptor status

B. For Local Recurrence

Extensive intraductal carcinoma (EIC)
Multifocality/multicentricity
Angioinvasion

All of the prognostic features pertinent to an analysis of a T1 N0 breast carcinoma can be determined from the material available in the core sample. Excellent preservation permits determination of Scarf-Bloom-Richardson grading, mitotic indices, subtype analysis and in many cases in conjunction with the imaging studies EIC status, and occasionally lymphatic invasion. In addition immunohistochemistry permits routine determination of estrogen and progesterone receptors status, and the presence of Her2/neu and p53. Ploidy and S phase fraction can be routinely determined from feulgen-stained sections with image cytometry. First however comes the requirement to assess properly size.

Size

Apart from nodal status, size is the most important prognostic factor for both distant recurrence (metastases) and local recurrence when T3 size is reached. There is a direct relationship between the maximum size of an invasive carcinoma and the risk of axillary metastases and progression (Carter et al., 1989). Carcinomas of smaller maximum size have a smaller frequency of axillary involvement, and the rate of

axillary metastases among nonpalpable, clinically occult carcinomas is half of the rate in those detected by palpation (Barth et al., 1997).

Determination of maximum size with stereotactic needle core technology would inherently appear to be less accurate when compared to the determinations made by a pathologist holding the entirely excised carcinoma in one hand and a rigid metric ruler in the other. This very reasonable supposition, however, ignores the commonplace specifics of practice in which the metric ruler may or may not be applied to the carcinoma, and in which randomly oriented sections of the carcinoma may be recorded, frequently not representative of the maximum diameter.

Tumor size is a basic component of the TMN staging system and size is an essential part of the data base required by JCAH mandated tumor registries. Tumor size, for all its importance and for what intuitively would appear to be a simple determination, is often erroneously recorded. Lack of precision in determining tumor size was reflected in early statements that it had no bearing on prognosis (Fisher et al., 1975). Tumor size as recorded by tumor registrars (TR) is dependent either on clinical estimates which have been shown to be consistently inaccurate, or pathologic measurements which are generally thought to be accurate. However, there are a number of common errors which appear in TR databases which are often inapparent to therapists reading a summary report.

Errors based on gross measurements:

1. Biopsy size for tumor size. It is common that the tumor size recorded reflects pathologic measurements of the biopsy specimen by the pathologist who has failed to record the size of the tumor. TR immortalize this error by reading a text which might state: "Received is a 3.5 x 2.5 x 2.0 cm biopsy with a gritty gray-white scirrhous tumor...". The size of the tumor is not recorded but the registrar uses maximum biopsy size for the T size. In fact the tumor might be T1c (1.5 cm) but no one will know without critical review. Further, gross determination of tumor size often includes the invasive as well as adjacent areas of in situ disease. This measurement can overstate the actual T size of the invasive carcinoma by a significant degree. This can be corrected by size determination from sectioned material using an ocular micrometer.
2. "Eyeball" estimates. It is unfortunately common pathologic practice, even when a ruler is in hand or on the cutting board, to estimate tumor size by "eyeball" measurements. Often pathologists feel confident that they can estimate the

actual size within narrow limits, or by glancing at the tumor and then the ruler, record the size. This procedure is quite common and can be revealed by graphing tumor size and number.

3. Errors related to sectioning of the tumor. Even in circumstances when the pathologist utilizes a metric ruler, laying it against the cleaved naked flesh of the carcinoma, significant errors in determining tumor size can result from the manner in which the breast cancer is sectioned. Because the largest axis of the tumor is parallel to the longest axis of the biopsy, and because pathologists routinely section biopsy material transversely (bread loafing), the largest tumor diameter that can be directly measured will be artificially smaller. Some pathologists noting that the tumor is elongate will try to record the long axis, but often this is done before sectioning (bread loafing) occurs, and invariably measures soft tissue as part of the tumor diameter. Tumor diameter recorded from the histologic section will only document 1 cm and will underestimate the size of the carcinoma.

Sometimes the size of the carcinoma is overestimated. A frequent error results from measuring the tumor size in the biopsy and that present in any re-excision and summing the two. Example: A 12 mm invasive carcinoma is documented in a biopsy but part of the tumor is transected and appears as residual disease in the re-excision.

Both errors of under and overestimating tumor size can be revealed by comparing the pathologic size determination against the direct physical evidence of mammograms and ultrasound studies. In many situations these two modalities reveal consistent sizes which can be tested against the pathology data. Giu et al. (1993) noted that the size of the invasive carcinoma in a large core biopsy equaled the actual tumor size in 45%, while the remainder showed a smaller size in the core than in the tissue. In more than half of this latter group the size differed by less than 4 mm and corresponded to the mammographic size + 1 mm.

Ideally maximum tumor size is determined from measurements of the tumor in slide material since this method can exclude the in situ component and proliferative changes in the adjacent parenchyma, which can be included in gross estimates of tumor size. Although this is certainly far more accurate than a gross estimate, it is highly dependent on the pathologist attempting to sample the maximum diameter of the tumor. Orientation of the specimen, sectioning axis and thickness will all impact on the likelihood of achieving a good estimate. The important thing to remember, however, is that it is only an estimate of tumor size.

Stereotactic CNB are not designed to permit reliable measurement of tumor size, although certainly the size of the carcinoma within the core can be measured by ocular micrometry. In some cases this will actually represent tumor size for T1a and smaller T1b carcinomas, but in all cases correlation with mammographic and/or sonographic studies will be required. Such estimates of tumor size based on correlation of imaging studies with histology can markedly improve the accuracy of the tumor size estimate, whether the biopsy represents a stereotactic core or an open excision.

In summary, size determination of a carcinoma based on stereotactic core biopsy must be correlated with preoperative mammographic and ultrasound measurements of tumor size, in order to provide some estimate of tumor size. However, size determination made by a pathologist should also be correlated with preoperative studies or substantial under or over-estimation of tumor size can result.

Measurement of tumor size in an open biopsy is certainly easier, but in practice it is no more accurate than tumor size estimated from correlated imaging studies and core pathology.

Tumor Subtypes

Certain histopathologic subtypes of invasive carcinoma have distinctive prognostic features, biomarkers and biologies. These include a group of low grade invasive carcinomas with favorable outcomes:

1. Adenoidcystic carcinoma; comprising less than 1% of all invasive breast cancers, has a locally destructive behavior, may recur locally but has not been reliably associated with a single instance of axillary metastasis.
2. Tubular carcinoma; comprising 4-6% of invasive breast cancers, represents the extremely well differentiated end of the duct carcinoma spectrum. Scarf-Bloom-Richardson scoring is 3 (1,1,1), nuclear grade is I and mitotic index is less than 5. Definitions vary from a requirement that all of the carcinoma make uniform single-layered open tubular glands with nuclear grade (NG) I morphology to 75% of the tumor composed of such tubular structures. Axillary metastases do occur even from T1b lesions, however, in my personal experience the frequency of axillary metastases was only 7% for those of mean T1c (12 mm) size (Lagios et al., 1980).
3. Pure mucinous carcinomas. Mucinous carcinomas are characterized by abundant extracellular mucin production so that the carcinomatous cells are literally

surrounded by pools of mucin of their own making. Tumor growth in such cancers is largely expansile, producing a circumscribed soft translucent mass. There is no desmoplastic response. As a result the mammographic appearance may mimic benign circumscribed lesions such as fibroadenoma, intraductal papilloma, etc. The favorable prognosis associated with mucinous carcinomas is only evident when the carcinoma is purely mucinous. Frequently mucinous differentiation is seen as a small part of larger invasive duct carcinomas, and prognosis in these reflect the standard invasive component.

Disease free survival for pure mucinous carcinomas at stage N0 is excellent even to 3 cm (30 mm) size. The favorable prognosis at large size may reflect the fact that commonly less than half of the observable tumor mass is composed of tumor cells i.e. the cellular tumor load is small for the diameter of the mass.

4. Medullary carcinomas. Medullary carcinomas, like mucinous carcinomas, are circumscribed and soft, but not gelatinous to touch. They are characterized by a very high grade nuclear morphology and a sheet-like or syncytial pattern of growth with an expansile tumor border (non-infiltrative). Paradoxically, despite high grade nuclear morphology, high mitotic indices, aneuploid DNA content, high S-phase fractions, and negative receptor status, they have an excellent DFS at N0 status, 80% up to 3 cm (30 mm) diameter at ten years of followup (Ridolfi et al., 1977).

Medullary carcinomas are, however, very rare and in my personal experience the diagnosis is often misapplied to carcinomas which are cytologically similar and appear circumscribed, but lack a uniform syncytial and expansile growth pattern. A pattern of trabecular growth, tubule formation or an infiltrative border should disqualify a lesion as medullary.

In summary the usefulness of the specific low grade histologic subtypes is that they predict for a more favorable prognosis up to fairly substantial size. Stereotactic core technology as presently utilized will not be able to exclude higher grade invasive components in a 4 cm medullary, tubular or mucinous carcinoma. That will require evaluation of material from the lumpectomy. However, this information can be derived from the lumpectomy only if it is extensively sampled, which is not a frequent practice in pathology. On the other hand multiple stereotactic core biopsies, particularly with the 14 or larger gauge vacuum assisted instrument, can subtotally sample T1a and b lesions, and therefore limitations of sampling are pertinent with stereotactic technology only for larger carcinomas.

Grade

The grade of an invasive carcinoma is an independent prognostic feature which is clearly associated with risk of progression and outcome. The most common method of grading is the Scarf-Bloom-Richardson (SBR) system as modified by Elston, which technically should be applied only to ductal (as opposed to lobular) type lesions (Bloom and Richardson, 1957; Elston, 1987). The SBR system is strongly weighted towards nuclear features and evaluates nuclear size, degree of pleomorphism, development of nucleoli and the number of mitotic figures, combined with tubule differentiation, to establish a grade.

Because the SBR system is heavily weighted towards nuclear features, there is a consistent relationship between higher grade nuclear morphology (NG II, III) and aneuploidy/tetraploidy. The grade of a carcinoma is significantly related to disease free and overall survival but only for node-negative subsets (Nealon et al., 1979; Rosen et al., 1993). Berezowski et al. (1998) have shown that the grade of an invasive duct carcinoma in stereotactic cores is concordant with the subsequent excision material in "83% of cases, and one step lower in the remainder".

DNA Ploidy Analysis and Proliferation Rates

Measurements or approximations of the growth rate of a breast carcinoma have been shown to act as independent prognostic variables in multivariate analyses. The most available of these, and in some ways least likely to be adversely influenced by technology, is the mitotic index i.e. the number of mitoses recorded in a consecutive series of ten standardized 400 X high powered fields. Mitotic activity is one of the three equally weighted prognostic features in the SBR system, and plays an even larger role in the modified grading scheme of Dousal et al. (Doussal et al., 1989). There is a significant degree of conformity between mitotic index, and a number of other indirect measurements of proliferative activity including S phase fractionation, Ki-67 and PCNA immunoreactivity and thymidine and bromoxyuridine labeling. Some authors have shown a relationship between mitotic index and mammographic tumor doubling time (Arnerlov et al., 1992).

Mitotic indices are influenced by poor and delayed fixation. They are therefore more difficult to establish from the poorly fixed central portion of a carcinoma, fixed by immersion, than they are from the generally excellent fixed stereotactic biopsy material. The interpretation is somewhat limited by the sample size and 18 gauge stereotactic cores may not produce sufficient cellular sample to establish a mitotic

index, but generally 14 gauge and larger cores, particularly those obtained by vacuum assisted cutting needles do provide sufficient sample.

Well fixed stereotactic core samples of breast carcinoma can be utilized not only for grading and mitotic index, but also for any immunoperoxidase technique including Ki-67, PCNA, ERA/PRA, Her-2/neu, and p53.

Receptor Status

The receptor status of a breast carcinoma has been enshrined as one of the useful prognostic features of a specific lesion. The clinical utility of receptor status is not limited to its prognostic potential but includes its association with the likelihood of hormonal manipulation. The prognostic potential of receptor status however, is largely limited to invasive carcinomas of T2 size with nodal metastases, a size and stage which were the norm when receptor assay was introduced in the mid 70's. For mammographically detected invasive carcinomas of mean 11 mm size and with a 90% probability of node negative status, there is virtually no effect on prognosis. Fisher et al. (1988) had shown that for T1 N0 carcinomas as a whole that receptor status was a much weaker predictor for disease-free survival (DFS) than nuclear grade, and that a positive versus negative estrogen receptor status impacted DFS by only 6-8% depending on pre- or postmenopausal status. A recent clinical practice guideline of ASCO does not recommend use of ER/PR status alone to establish prognostic groupings (Clinical practice guidelines, 1996).

Receptor status is easily determined in stereotactic core material using immunoperoxidase labeled antibodies to specific receptor proteins (ERICA technique) (Alberts et al., 1996). Such techniques have largely supplanted the older cytosol technologies because of reduced cost, shorter turnover time and a simplified technical requirement. Additionally it is less subject to the dilutional and processing artifacts that plagued cytosol technology, and permits direct visualization of the cells exhibiting the protein. Particularly with stereotactic core technique it is not subject to the heat denaturation of the receptor protein occasionally seen in open biopsies in which electrocautery has been used. Jacobs et al. (1997) have shown complete concordance between the core biopsy and subsequent excision in terms of estrogen receptor, p53, Her2/neu and bel-2. Two problems persist: 1. ERICA results are usually not expressed quantitatively as are cytosol results. Although image analysis can provide quantification for ERICA techniques, it has not been shown to be clinically significant - except in the imaginations of clinical oncologists. 2. Occasionally pathologists will read the nuclear reaction product in benign and/

or hyperplastic ductal epithelium as a "positive" reaction in the carcinoma which exhibits no reaction product in the same section. This error can be minimized by recognizing that some benign ductal epithelium will exhibit ERICA-reaction product, and by using an HE stained matching section and an appropriate counterstain in the immunoperoxidase study.

Oncogenes and Other Biomarkers

Immunoperoxidase technology has made available routine testing of an individual patient's invasive breast carcinoma for a host of specific oncogenes, gene products and other biomarkers. It is now practical, and in many cases through commercial laboratories, to test for the presence of Her-2/neu and, p53 overexpression. There is, however, very limited and often conflicting information about the utility of these markers in clinical practice. Cathepsin D had been variously touted as being an independent predictor for DFS, but in some studies it has a negative and in others a favorable impact.

Her-2/neu has been regarded as an adverse biomarker when present, or only when present in conjunction with lymph node metastasis, or to predict resistance to some adjuvant chemotherapy regimens in patients with or without nodal metastases, and resistance to tamoxifen. Her-2/neu is more commonly associated with carcinomas with higher nuclear grade and advanced stage, but membrane specific staining with monoclonal antibodies to Her-2/neu may also be seen in well differentiated (SBR 4,5) duct carcinomas and in duct carcinoma in situ of high nuclear grade. Although not yet proven to be of prognostic significance, the presence of membrane specific staining with Her-2/neu has been used by oncologists in selecting an adriamycin versus a CMF regimen in node positive premenopausal patients. Additionally the advent of successful immunotherapy with monoclonal antibodies to the Her-2/neu receptor protein, now in second stage clinical trials, has made the presence of Her-2/neu receptor protein a requisite for entry in the trial. However the recent ASCO clinical practice guidelines reviewing the literature on Her-2/neu have not shown a significant prognostic effect for Her-2/neu overexpression. There does, however, appear to be a relationship between Her-2/neu overexpression and resistance to Tamoxifen in ER-positive cases.

p53 over-expression represents multiple defective or non-functional copies of a normal tumor suppressor gene. p53 is strongly associated with high nuclear grade, and high proliferation rates in breast carcinoma and has been associated with higher nuclear grade, higher proliferative indices and decreased survival. Although the

recent ASCO clinical practice guidelines find the evidence for the prognostic utility of p53 inconclusive. Subsequent studies have shown significance for Her-2/neu when standardized criteria are used in the testing and grading of the response.

Other Morphologic Prognostic Features: Angioinvasion, Extensive Intraductal Carcinoma, Multifocality

Some morphologic features other than size, subtype, grade and mitotic index, are prognostically useful.

Peritumoral lymphatic invasion predicts a DFS equivalent to a N1 lymph node status (1-3 positive lymph nodes) and should be carefully evaluated since such patients would benefit from adjuvant therapy even in the absence of lymph node metastases. The problem with PLI is that this feature is strongly influenced by fixation and handling. To qualify as lymphatic involvement a potential lymphatic space with a tumor bolus should lack myoepithelial cells and necrosis - features which can be seen in duct carcinoma in situ with artifactual separation from the duct wall due to rough handling, hyperosmolar fixatives, or electrocautery. Likewise, the lymphatic space should exhibit endothelial cells and have a configuration and location making it less likely to represent a terminal ductule of an individual TDLU. Interobserver reproducibility for PLI is low but stereotactic biopsy sampling is at a disadvantage as compared to excision biopsy.

Extensive Intraductal Carcinoma (EIC) reflects significant duct carcinoma in situ, both within and external to an invasive tumor mass, or microinvasive or T1a, b invasive carcinomas associated with DCIS external to the invasive mass. The significance of EIC was first demonstrated by Schnitt et al. (1994) among patients treated by what would certainly in retrospect represent inadequate excision and radiation therapy. The most significant factor for local in breast recurrences within the irradiated field (as opposed to distant metastases) was an EIC-positive status. Later studies would demonstrate that EIC is significant for local recurrence only when the margins of resection are extensively involved with EIC, and that free resection margins (greater than 1 mm) or margins involved in only a focal microscopic fashion would not impact local recurrence free survival. The risk of local recurrence in EIC-positive breast carcinomas is directly related to the likelihood of residual DCIS in the remaining breast (Gage et al., 1996). Schnitt (1995) has shown that the risk of EIC when margins are substantially positive is also related to the age of the patient, and is highest for patients 35 years or younger as opposed to 65 years or older. EIC has no relevance to overall survival or distant recurrence free survival.

Multifocality/Multicentricity. Some invasive carcinomas exhibit multiple separate areas of invasive growth within a quadrant. This is often associated with extensive DCIS within that quadrant and the separate areas of invasion often exhibit distinct histologic patterns i.e. they represent in all likelihood separate de novo invasive events within a broad field of DCIS. Multicentric carcinomas are separate invasive carcinomas defined as: 1) in a separate quadrant from the major or reference cancer; 2) located 5 cm distant from the reference cancer; or 3) located 4 or more cm distant from the reference cancer but without any evidence of intervening DCIS. These different definitions result in part in the great differences in frequency of multicentricity reported in the literature. Multicentricity as defined in 1) and 2) may exhibit intervening DCIS, that is they may reflect separate invasive events within a broad field of DCIS. The third definition (26) would exclude such separate foci even if 4 - 5 cm distant and in another quadrant from being "multicentric".

Regardless of how defined, multifocal patterns of growth are more difficult to effectively treat by segmental resection, since separate areas of invasion may occur up to 3 cm distant with surprising frequency, and may be associated with a larger local recurrence rate. Evaluation of multicentricity/multifocality and extensive intraductal carcinoma requires careful evaluation of preoperative mammograms, specimen radiograms when available, and biopsy material. In my own experience several pathologic clues suggest multifocality. This include lobular or mixed small cell histology, and small low grade and/or tubular carcinomas associated with EIC. Some patients may exhibit clearly separate palpable and mammographically demonstrable carcinomas in separate quadrants, others may exhibit mammographic microcalcification without a clinical mass, but multiple separate microinvasive or T1a foci.

Stereotactic core technology can sample areas of vascular and/or lymphatic invasion, intraductal carcinoma associated with an invasive lesion, and with more difficulty multifocal lesions. Since these features can be quite focal or require sampling outside of the invasive tumor mass for confirmation, stereotactic biopsy alone will rarely do more than hint at such features which are more easily demonstrated in open biopsies. However, even open biopsies, which are either small in volume or sampled in a limited fashion, may not demonstrate extensive intraductal carcinoma as a component, or a multifocal invasive pattern of growth. Correlation with preoperative mammograms, however, may strongly suggest an EIC -positive status which can be confirmed in the core biopsy, or can suggest multifocality which can be addressed in separately directed stereotactic biopsies. From a practical standpoint most such

evaluations will be performed on the basis of the “lumpectomy” or “re-excision”, whether the initial biopsy was a stereotactic core or open procedure.

Conclusion

Stereotactic core technology can significantly reduce the morbidity, anxiety and costs and increase the target accuracy for a biopsy of an occult breast carcinoma compared to conventional needle directed open techniques. However, a persistent bias questions the equivalence of the diagnostic information obtained by stereotactic core biopsy.

For the majority of mammographically detected invasive carcinomas of mean 11 mm size, stereotactic biopsy obtained with the larger 14 and 11 gauge needles, provides adequate material for establishing accurate histologic subtyping, grading, mitotic indices and for immunochemical demonstration of estrogen and progesterone receptor proteins, Ki-67, Her-2/neu and p53 as well as other biomarkers, and ploidy and S-phase fractionation by image cytometry.

Size determination for a carcinoma should be a correlative exercise which compares mammographic and sonographic imaging measurements with measurements from microscopic sections, and such correlation is essential for size determination in stereotactic biopsies. Despite this intrinsic disadvantage, size determination can be more accurate based on correlation as compared to the commonplace imprecision seen in pathology practice. Other significant prognostic features, peri-tumoral lymphatic invasion, extensive intraductal carcinoma (EIC) and multicentricity/multifocality are more easily documented with open biopsy or subsequent lumpectomy specimens.

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3.4

Lecture 4

Ultrasound targeting in difficult cases

Nathalie Duchesne, MD

Rather than a comprehensive textbook on breast biopsies, the following notes are intended to be a succinct summary of tips used daily at our institution to ensure good sampling of ultrasound-guided breast biopsies.

Choosing the best operator

It has been documented that improved accuracy is achieved through increased operator experience. It should be advantageous then for managers of breast centers to ensure that some individuals perform as many procedures as possible; this would optimally benefit everyone, foremost the patients of an interdisciplinary breast center.

Choosing the best guidance

Of course, the primary decision to choose ultrasound over stereotaxy will be the fact that the lesion is visible under that modality. Then, ultrasound guidance is preferred over stereotactic mainly because of these advantages:

Ultrasound vs Stereotaxy

1. More comfortable for the patient;
2. No irradiation;
3. Real-time visualization of needle placement and tissue sampling;
4. No modification of the image post-injection of anesthetic;
5. Lower cost.

Big and fatty breasts can sometimes be challenging, but ultrasound biopsy is worth trying, being much more comfortable for the patient.

The major disadvantage of U/S over stereotactic guidance is that UGBB accuracy is dependent on the operator's sonographical and biopsy expertise.

Choosing needles

Much has been said about advantages of vacuum-assisted over spring-loaded core needle for stereotactic biopsy procedure. For ultrasound-guided cases, the use

of vacuum-assisted needle is certainly justified in the case of small size lesions (<1,5 cm) as demonstrated by Parker et al. [1].



At our institution, the use of vacuum-assisted biopsy was based on homegrown indications that are summarized in Table 1 [2]. A multi-center retrospective study on 13,582 UGBB has demonstrated that using 14G spring-loaded core needle greatly increases the chance of a need for re-biopsy. Given the unacceptable false negative rate of first biopsies and the direct and indirect costs associated with re-biopsies, increased use of vacuum-assisted devices should be considered for UGBB [3].

TABLE 1

Indications for US-Guided VAB

- | |
|--|
| 1. Lesion size smaller than 1.5 cm |
| 2. Lesion close to the pectoralis muscle or an implant |
| 3. Heterogeneous lesion |
| 4. Solid intracystic mass |
| 5. Possible in situ recurrence |
| 6. Parenchymal distortion |
| 7. Asymmetrical density |
| 8. Biopsy technically difficult for core needle because of tissue fibrosis |
| 9. Repeat biopsy because of discordant core result with imaging appearance |
| 10. Request for total excision from the patient |

Choosing the best biopsy path

The shortest path is always the best and unless the lesion is situated in upper middle position (twelve o'clock), the sagittal approach should be favored. Care must be

taken to avoid the cleavage, such as the scar would show, especially if the patient is young and/or wants complete excision of lesion for cosmetic reasons.

Biopsy needle positioning

Core biopsy needle position is right at the tip of the lesion. If the lesion is heterogeneous, specimens of different part of the lesion should be obtained. If it is a BI-RADS 5 lesion, extract specimens not only from the center but also from the branching or intraductal extension. For certain types of vacuum-assisted biopsy apparatus, the needle has to be positioned under the lesion so that the artifact caused by the needle shaft will not obscure the lesion itself and the procedure.

Sub-cutaneous lesions

The needle will preferably be positioned between the skin and the lesion to avoid skin laceration while capturing a specimen.

Dense and/or fibrotic breast or lesion

Given the differences in breast tissue composition among patients, from tough, dense connective tissue to soft, fatty tissue, the force required to push probes into the breast may vary from heavy to light. Under ultrasound guidance, breast biopsy can sometimes be a challenging task, especially when the interventionist encounters resistance from breast tissue. Besides this resistance, the biopsy probe may be deflected away from the target lesion by breast tissue or by the lesion itself, potentially leading to inaccurate placement of the probe.

Various methods have been used to create a path for the biopsy needle. Injection of anesthetics can be used to dissect the tissues. Firing core specimens is another way to create a tunnel for the placement of the biopsy needle in good position. However, these methods can either take extra time or be traumatic for the patient. Nowadays, different types of biopsy probes present with different tips, shaped and cut for better tissue penetration. Nevertheless, when the breast tissue or the lesion itself is very dense, one can use an electro-surgical device to penetrate the breast. Such a device uses radio frequency cutting to reach the target lesion, and to function as an entry port, allowing a biopsy device probe to be inserted. The results from a recent multi-center prospective randomized study [4] demonstrate that the adjunctive use of a radiofrequency introducer has no adverse effect on the vacuum-assisted tissue acquisition function. Also, no RF-induced biopsy artifacts were reported and the ability to obtain a histological diagnosis was comparable to that observed with the vacuum-assisted device alone. It should also be noted that, when properly

anesthetized in the area of the biopsy, no pain related to the use of RF has been encountered. Easier penetration of breast parenchyma particularly for patients with dense breasts was reported [4]. This result is important for small breasts, as many lesions may not be candidate for stereotactic-guided biopsy.

Specimen

Spring-loaded core needles

Number of specimens can vary from 1 to 6. Usually, for BI-RADS 5 lesions, one or two specimens are taken. For BI-RADS 3 and 4, between three and six specimens are usually taken.

Classic vacuum-assisted

Depending on the type of lesion and the reasons for the biopsy, the number of specimens can vary. We take an average of 9 specimens per procedure. We usually try to sample the whole lesion until no more lesion tissue is visible under ultrasound. A metallic clip is then deployed and the patient gets a post biopsy mammogram.

RF vacuum-assisted needle

Positioning the RF vacuum-assisted needle differs from the classic vacuum needle. Since there is 360° capture in RF devices, the operator needs to position the needle in the center of the lesion. Repositioning the needle during the procedure in order to achieve a better sampling is very easy to do, which is one of the advantages of this device [5].

Conclusion

There are numerous key principles that should be considered to ensure good sampling of breast lesions. Depending on the anecdotal experience of each institution, some methods will be preferred over others.

The following recommendations are worth emphasizing to improve the quality of image-guided biopsies:

1. An adequate volume of tissue should be obtained. Ideally, the whole lesion should be sampled. If the lesion is too big, representative specimens of all parts of lesion should be obtained.
2. UGBB should be concentrated to few individuals in order to increase operator experience; it has been proven that this would in turn yield higher accuracy.

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3.5

Lecture 5

Concepts of MR-Guided breast biopsies

Steven E. Harms, MD; Sally S. Harms, MD


Introduction

The capability of performing breast MRI intervention should be an integral part of any breast MR program. In 2003, the American Cancer Society screening guidelines stated “MRI should be performed in centers with extensive experience in diagnostic MRI and the capacity for MR-guided biopsies.” Later that year, the American College of Radiology practice guideline for breast MRI was published. This guideline said “since breast MRI can detect lesions not seen on other imaging methods or by physical examination, the availability of MR-guided biopsy or localization is a valuable adjunct to diagnostic breast MRI.” This year, the new American College of Radiology accreditation program will require biopsy capability for any site desiring accreditation for breast MR imaging. In 2006, one should not consider implementing a breast MR imaging program without the availability of MRI-guided localization and biopsy. It is soon expected that it may be increasingly difficult to offer breast MR imaging without having interventional capability. In this report, we will review the tools necessary for performing breast MRI-guided procedures and provide an example of how this is implemented on a dedicated breast MRI system.

Breast MRI Localization

A variety of tools are now commercially available for performing breast MRI-guided localization procedures. Needles and Kopans wires are available from various companies. Marker kits are also available, that include an introducer, needle, and stylet with a plastic insert. It is accompanied by a needle used to deploy markers after the position of the introducer is confirmed by imaging. The stainless steel markers are visible on MRI, ultrasound, and mammography.

An alternative marker system is hematoma localization. During the imaging procedure, some of the patient’s own blood is withdrawn. About 3 cc’s of this blood is then injected at the desired site. The blood can be visualized on MRI and ultrasound. If the patient is having an excisional procedure, then the blood can be visualized at surgery. This system is easy and inexpensive, but unfortunately, many surgeons are not as comfortable visualizing hematomas with ultrasound as they are the markers.



The most common use of localization in the past was to identify the site for EB. With the use of VAB and other biopsy methods, EB for diagnosis is now less commonly employed. A more common usage of localization in our practice is to better delineate the margins of lesions prior to excision. This procedure is often performed after the histology of the lesion has been proven with a prior biopsy. The most common example of this use is in marking DCIS that often runs in ductal rays rather than forming a discrete ball-like mass.

Breast MRI-Guided Biopsy

MRI-guided biopsy is now becoming a commonplace procedure. A variety of tools are now available for performing the biopsy. Before entering a MRI-guided biopsy, we often attempt a second look ultrasound. Often a lesion can be visualized on a second look ultrasound that corresponds to the MRI lesion even though it was initially not seen on ultrasound. A bit of wisdom, however, is “Don’t guess about the target.” Sonographic false positives are quite common. The lesion should match the location, size, and configuration before substituting a sonographic-guided biopsy for an MRI procedure. However, sonography is less expensive and generally an easier procedure for the patient. Another advantage of sonography is that we often do our second-look ultrasound immediately after the MRI, and when a corresponding lesion is located, a biopsy can be performed in the same clinical session as the MRI. An MRI-guided biopsy would be difficult to perform the same day because the distribution of gadolinium contrast would be in the extracellular phase, and the second dose of contrast may not allow visualization of the lesion over background enhancement. Generally, most sites perform MRI-guided biopsies at least 24 hours after the diagnostic procedure for this reason. We often do sonographic biopsies of MRI-detected lesions on the day of diagnosis.

Single-action MR-compatible core needles are available in 14 and 16 gauge versions. Unfortunately, these needles use titanium alloys and may cut poorly. The sample size is also inferior to what one would typically expect for most mammographic dual action core needles. For this reason, we prefer VAB over CNB. Often, discrete masses seen on MRI can be found on ultrasound. The typical MR biopsy is therefore performed on

the more difficult lesions, which somewhat counterintuitively requires more tissue for histological confirmation. This situation favors VAB over CNB.

A number of vacuum assisted needles are now available for breast MRI. One system is a hand-held device that can be fit into a coat pocket, much less expensive than many of the other systems. This system can be used on multiple modalities besides MRI. A nice feature of the device is the ability to vary the chamber size with a mechanical insert. This can be done virtually on the fly, and changing needles is not necessary. The biggest downside of the system is that it requires multiple passes – each sample must be removed from the needle individually and then the needle replaced for the next sample. Also, there is no closure system on the introducer needle to prevent blood backflow.

The first MRI-compatible system was initially a separate system from the one used in ultrasound and stereo. Now, the same system can be used across all modalities. This is a single-pass introducer system, where multiple cores are stored into a chamber at the distal portion of the needle. Then the chamber is removed and the individual samples are extracted with a basket. There are two needle sizes – the short-chambered needle called the access also has a blunt tip, which helps alleviate the problem of overpenetration. Unfortunately, the needle size must be determined prior to the biopsy, and changing needles requires an entirely different needle set. The biggest advantage to this system is the automatic injection of lidocaine during the procedure. We prefer to use lidocaine with epinephrine so that internal bleeding can be minimized. This is the only system that has a saline lavage that can be employed after the procedure.

Others propose a multi-modality, single-pass device that has a variable chamber size that can be determined electronically on the console. This device has the advantage of being able to switch the sample chamber size on the fly during the procedure without changing needles. Lidocaine can be injected through a port but as opposed to the previous one, this injection is not automatic. The system does not require turning of the needle itself. The sampling pattern around the clock face is programmed on the device console, and no manual turning is necessary. The system is complete with a specially designed marker system. The system also stores the samples in a basket for removal at the end of the procedure.

The first VAB system is now MR-compatible. The biggest advantage of this system is that it can be easily adapted to existing systems in the field. The new system is also multi-modality, and is a single pass system. The company has developed a unique

introducer system with a ceramic knife blade. Some favor this system because of the ability to see the sample chamber on the MR image. For those using in vivo biopsy systems, there exists a more automated introducer approach. This approach differs from the previous two in that samples are not stored in a basket and extracted at the end of the procedure, but extracted a core at a time after each sampling.

A variety of marker systems are now available. Many manufacturers who make MRI-compatible systems use titanium. Titanium is generally not well seen on MRI. Because many of our patients are now undergoing neoadjuvant chemotherapy, a robust marking system is needed since several months may pass from the initial biopsy until the post-chemotherapy imaging. For this reason, we prefer not to use these titanium markers. Large barrel-shaped titanium marker, which actually is well seen on MRI, but one may have difficulty seeing this marker on sonography. For that reason, it has fallen out of favor with many. We prefer a stainless steel marker, which produces a magnetic susceptibility signal void. Such a marker comes with a gel foam pad that is well seen on ultrasound. Unfortunately, this marker does not come in a size that can fit some other manufacturers' biopsy needles. In these situations, we often remove the biopsy needle and use the marker that comes with its own needle.

Carbon-based markers are now on the market. These markers provide a signal void on MRI, but are not as well seen as a stainless steel marker. The major advantage of carbon-based markers is that they will not perturb the magnetic field and will not interfere with MR-spectroscopy procedures. Some sites are now using spectroscopy to follow response to neoadjuvant chemotherapy. Unfortunately, if the patient has a complete response (and many currently do), then the carbon-based marker may not be seen on the post-chemotherapy images.

MRI Stereotaxis

A variety of devices are now being manufactured by third parties for needle guidance for MRI-detected lesions. These devices are often sold in conjunction with a third party breast coil. Most original equipment manufacturers do not manufacture their own stereotactic guidance system.

We use a dedicated breast MRI system where the stereotactic system and the imaging system are both manufactured by the same supplier. The major advantage of this system is that all features are orchestrated to work together for accuracy and ease of use. The dedicated breast MRI has a specially designed table that facilitates access to the breast and axilla for biopsy. Lesions near the chest wall are accessible. Both lateral and medial approaches are possible. The dedicated scanner comes

with a mobile scan console. All the features of the standard scan console can be performed including breast localization and biopsy.

As opposed to any other imaging technique, the major problem with breast MRI-guided procedures is that the lesion demonstrated on breast MRI often disappears about ten minutes post-contrast injection. Therefore, the lesion is often no longer apparent at the time the needle is checked for its accurate positioning. In stereotactic mammography procedures pre- and post-fire images can be obtained to determine the proximity of the target (calcifications or mass) to the needle; however, in breast MRI procedures, the lesion has often disappeared by the time the needle placement images are obtained. This “vanishing target” phenomenon produces some significant constraints on the procedure. First of all, breast immobilization is of paramount importance. If the patient moves, then the needle may be off target and inaccurate targeting may not be suspected until a negative biopsy is returned. The dedicated system uses special immobilization plates that provide approximately twice the area of access compared to most widely used add-on, third party stereotactic systems. These plates consist of grids with one centimeter diameter openings. The grids provide gentle stabilization of the skin and breast tissue. Each breast plate can be tilted to access different breast configurations. One problem with many mobilization devices is incomplete stabilization of the anterior breast and over compression of the posterior breast. This occurs because most plates move in parallel, resulting in over compression of the thickest part of the breast near the chest wall and inadequate compression of the breast near the nipple. By tilting the plates, the compression can be adjusted to conform to the patient’s individual needs.

Another problem with stereotactic procedures is often the inability to access posterior lesions. For many systems, the posterior third of the breast is inaccessible. The plates of the dedicated system come in close proximity to the chest wall. We have been able to do stereotactic procedures on MRI with this system that were not accessible with a widely used stereotactic mammography device.

The system is designed to be as automated as possible when targeting a lesion through the scan console. The operator simply needs to click on the target of the biopsy, then click on a fiducial embedded in the stage, select the appropriate biopsy needle, and the calculations are determined to precisely center the sample chamber on target. The stage is moved into position and a sterile guide is used to direct the needle into the target. This system eliminates the need for calculations of depth and position and tremendously increases the accuracy and the speed of the procedure.

Since the target lesion itself has often disappeared into the background when the needle placement images are generated, the dedicated system places a marker at the site of the original target determination. This marker shows up as a green box. The box will appear on all subsequent images, so that with a glance, the operator can see the introducer needle and determine whether the introducer needle is in the proper position for sampling. Also, at the end of the procedure, this box will show up after the marker has been placed, and one can quickly evaluate the location of the marker relative to the actual target. This system eliminates the need for calculation of needle placement relative to the desired target and greatly speeds the procedure.

Multiple targets are often needed, particularly when DCIS is bracketed. The automated system available with the dedicated scanner allows serial placement of localization needles in the same procedure within the same breast.

Summary

In summary, a variety of commercial devices are now available for MR-guided localization and biopsy. The attributes of these devices vary greatly, but it should be possible to acquire devices that fit the needs of most practices.

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3.6

Lecture 6

Lymph Node Imaging and Intervention

Nancy A. T. Wadden, MD, FRCPC

Axillary Node Imaging

- Axillary lymph node staging most important prognostic indicator of outcome in patients with breast cancer
- Axillary lymph node dissection reference standard
- Sentinel node biopsy removes one or a few nodes to stage the axilla
- Ultrasound evaluation of the axilla with US-guided fine-needle aspiration offers nonsurgical staging of the axilla
- US guided FNAB of most suspicious area
- Minimal morbidity

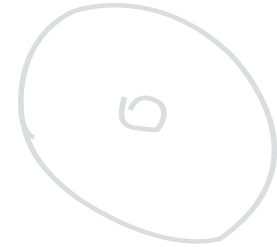
Abnormal lymph nodes – Differential diagnosis

- Primary breast cancer
- Metastatic disease
- Lymphoproliferative disease
- Rheumatoid Arthritis
- TB
- HIV

Lymph Node Imaging

- Criteria apply to axillary, internal mammary and intramammary lymph nodes
- Must assess all criteria
- Mammographic Criteria for suspicious lymph node:
 - Dense
 - Round
 - Absent fatty hilum
 - Size is irrelevant
 - Spiculation suggests extranodal extension of tumor
- Sonographic Criteria for suspicious lymph node:
 - hypochoic cortex
 - eccentric hilum
 - completely replaced hilum

- MR Criteria for abnormal lymph node:
 - T1WI: hyperintense cortex
 - T2WI: hyperintense cortex, hypointense fatty hilum
 - T1 C+: early enhancement and washout – but this can also be seen with normal lymph nodes
- Internal mammary lymph nodes
 - Best assessed with MR
 - Can be imaged and biopsied with ultrasound
- Seen between internal mammary artery and vein
- FNA with ultrasound guidance



3.7

Lecture 7

The Sentinel Lymph Node Biopsy in Breast Cancer

Naim Otaky, MD

Historical background

- 1959 - Ernest Gould et al. coined the term "sentinel node" (SN) in their work on parotid cancer (1).
- 1976 – Cabanas used lymphangiography to visualize the SN in patients with squamous cell cancer of the penis (2).
- 1992 – Morton et al. used blue dye to investigate SNs in melanoma patients (3).
- 1993 – Krag et al. used radiocolloid for mapping SNs in breast cancer patients (4).
- 1994 – Giuliano et al. used blue dye to do the same (5).
- 2008 – Sentinel lymph node biopsy (SLNB) is now the gold standard for the evaluation of nodal status in early stage breast cancer (6).

Patterns of breast cancer metastases and lymphatic drainage of the breast

Breast cancer metastasizes either through lymphatic or vascular channels. Four groups of regional nodes are potential recipients of lymphatic spread:

- axillary nodes
- internal mammary nodes
- para-clavicular nodes
- intramammary nodes

The axilla is by far the most important drainage basin (7). Skin and glandular tissue have a common embryological origin and share common lymphatic drainage: glandular lymphatics drain to the sub-areolar lymphatic plexus which subsequently drains the majority of the breast to the axilla. A deep mammary lymphatic plexus may account for drainage into the internal mammary and para-clavicular nodes (8).

Metastatic spread to these basins is seen in more advanced cancers, and is usually associated with concomitant axillary metastases (9). Intra-mammary nodal involvement is rare and has an unpredictable relationship to axillary metastases (10). The SNs are the first recipients of lymphatic drainage from the breast. If the SNs are free of metastases the remaining nodes will also be free with a high degree of accuracy, specificity and sensitivity.

Why avoid the axillary node dissection (AND)?

70% of patients undergoing AND for staging are found to be free of nodal metastases. The procedure has significant morbidity

Intra-op:

- Axillary vein trauma/ bleeding
- Trauma to the brachial plexus

Short term:

- seroma formation
- infection
- pain
- movement restrictions of the arm and shoulder

Long term:

- lymph-edema
- increased risk of cellulitis of the arm
- axillary and upper arm numbness

Many large series demonstrate a three to six-fold reduction in complication rates with the SLNB technique (11, 12).

Technical considerations in the SLNB

A. What to inject?

Accurate SN identification may be achieved using blue dye, radioisotope-labeled colloid or both.

Blue Dye Only technique:

Involves injecting 5 cc Isosulfan blue dye or 2 cc Patent Blue V dye into the breast. Blue nodes and those with blue lymphatic channels going into them are removed.



Advantages: Low cost, accurate, easy to learn, radiation free, and does not require nuclear medicine facilities (13). Accuracy and false negative rates comparable to the combined approach (14).

Disadvantages: 2% risk of allergic reactions. Most are minor skin eruptions. Anaphylaxis is seen in 0.25-0.5% of patients (15). Corticosteroids and antihistamines are effective in treating minor skin reactions. Pressors may be required in cases of anaphylactic shock. Long term discoloration (tattooing) of the skin at the site of injection (16). Does not allow for the evaluation of the internal mammary chain of nodes.

Radiocolloid only technique:

Involves the injection of small doses of radio-labeled colloidal agents into the breast (in North America, 0.25 – 1 mCi of 99mTechnetium sulfur colloid). Hot nodes having counts higher than 10% of the hottest node as determined by an intra-operative gamma probe are removed.

Advantages: Radiation exposure minimal (equivalent to 4% of dose administered for a bone scan). Identification success rates equivalent to those for blue dye (17). Allows for the assessment of the internal mammary nodes especially when combined with lymphoscintigraphy

Disadvantages: It requires a nuclear medicine facility and a gamma probe. Higher cost.

Combined technique:

Is Ideal, especially for surgeons with limited experience. Could improve identification success rates and lower false negative rates (18)

B. Where to inject?

Multiple injection sites have been proposed: subareolar, periareolar, intradermal, peritumoral and intratumoral. There is high concordance among the injection sites making them all acceptable alternatives (19, 20). Combining injection sites (superficial and deep) might increase the number of sentinel nodes detected (21). If the intention is to sample internal mammary sentinel nodes then a peritumoral or intratumoral injection of radio-colloid might be the preferable route (22, 23).

C. When to inject?

Blue dye injections are done intra-operatively five minutes before the axillary skin incision is made. Radio-colloid injections are usually done 30 minutes to 8 hours prior to surgery, but could be done the afternoon or evening the day before surgery (24). Higher doses may be required if the injection is to be done the day before surgery.

D. Lymphoscintigraphy (or not)?

Lymphoscintigraphy is not necessary for accurate identification of the SN. It may facilitate identification of the sentinel node for surgeons learning the procedure. It may improve detection rate in patients who have increased risk of intra-operative failed localization (eg. obese patients). Absence of a hot spot on lymphoscintigraphy predicts inability to localize the SN with a gamma probe and could be a good indication for the addition of blue dye to the localization procedure (25).

E. Internal mammary sentinel nodes

The significance of internal mammary sentinel nodes is a subject of debate (9, 22, 23). As previously mentioned, the vast majority of breast cancers, regardless of location, drain into the axilla. When internal mammary nodes are involved, concomitant axillary nodal metastases are seen in the majority of cases. Isolated internal mammary sentinel node involvement is rare, and is seen more frequently with tumors in the internal quadrants. Identification of internal mammary SNs requires the use of radio-colloid with lymphoscintigraphy.

Removal of such nodes is associated with increased morbidity (bleeding, pneumothorax, pain). Removing internal mammary sentinel nodes may result in upstaging a few patients and adding chemotherapy and or loco-regional radiotherapy to their adjuvant treatment when such treatment may have been otherwise omitted. The morbidity of the procedure has to be weighed against the modest potential benefit to a few patients when deciding whether or not to sample internal mammary SNs.

F. Intramammary Sentinel Nodes (intraMSNs) (10):

Identified in association with axillary SNs in 0.2% of cases. Positive intraMSNs do not necessarily predict axillary lymph node metastasis. When intraMSNs and axillary SNs are identified, they should all be removed. Management of the axilla should rely on the status of the axillary SNs and not that of the intraMSNs. The presence of intra-mammary lymph nodes should be documented by careful pre-op imaging since that would facilitate their localization should they qualify as sentinel nodes.

G. How many nodes are enough?

Some authors have suggested limiting the number of SNs removed to a maximum of 4 since the only positive sentinel node is rarely identified in the 4th or higher node (26). Others studies suggest that arbitrarily limiting the number of SNs excised could substantially increase the false negative rate (27). Adherence to accepted criteria for the identification of SNs is probably the wisest approach.

H. Factors Influencing SN identification Failure:

Lower SN identification rate has been identified with the following factors (28, 29):

- increased age
- obesity
- medial tumor location
- surgeon inexperience
- non-palpable tumors

Pathological Assessment of the Node (When and How?)

A. Intra-op assessment:

An intraoperative assessment either by frozen section or by touch imprint cytological analysis provides very accurate information regarding the status of the SNs (90% sensitivity, 100% specificity) (30,31). Such analysis allows for immediate axillary clearance when the sentinel node has metastatic disease and reduces the number patients requiring re-operation. However, an inability to offer intra-operative evaluation of the SLN is not a contraindication to performing the procedure since the morbidity of re-operation is far less than the morbidity of an unnecessary AND

B. Post-op assessment:

No accepted pathology standard for the analysis of the SN. Differences exist in:

1. number of levels examined from each node
2. the use of immunohistochemical examination of negative nodes

Increasing the number of levels analyzed and the routine use of immuno leads to discovering more metastases, most of which are either micro-mets or isolated tumor clusters whose clinical significance is unclear (see section VII). This leads to a higher number of NEGATIVE completion AND (32)

Beyond morbidity reduction: Other Advantages of the SLNB

The SLNB technique is more sensitive than the AND Introduction of the SLNB technique has resulted in an increased number of node positive cancers (33).

More accurate staging allows better planning of adjuvant therapy that may lead to improvements in survival (34). Axillary recurrence rates following SLNB are low, ranging from 0%-3.6% (35).

What to do with the Results? Mets, Micro-Mets, and Isolated Tumor Cells

Definitions (36):

Isolated tumor cells (ITC): single tumor cells or small cell clusters not larger than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but that may be verified on hematoxylin & eosin (H&E) stains. ITCs do not usually show evidence of malignant activity, e.g., proliferation or stromal reaction.

Micrometastasis: metastasis larger than 0.2 mm but not larger than 2.0 mm

Metastasis: metastatic deposit larger than 2.0 mm

It is widely accepted that patients with metastases larger than 2 mm in a SN should undergo completion AND Patients with ITC have a very low risk of non-SN metastases and most agree that completion AND can be safely avoided in these patients (37). The management of patients with micromets is controversial and decisions on whether or not to complete the AND should be made on an individualized basis. Van Zee et al., and Chagpar et al. (38, 39) have developed models that can help predict the probability of non-SN metastases. These models could be useful in limiting the number of patients having a negative completion AND.

Contra-Indications to SLNB – Debunking the Myths

The following are contraindications to SLNB:

- Breast cancer patients with biopsy proven lymph node involvement.
- Patients with clinically evident lymph node involvement (eg. bulky/matted axillary or supra-clavicular nodes or patients with abnormal internal mammary nodes on imaging).
- Patients with biopsy proven lymph node involvement or clinically evident lymph node involvement who have undergone neo-adjuvant chemotherapy regardless of response to that therapy (high false negative rate of SLNB) (40).
- Patients undergoing prophylactic mastectomy with no documented abnormality on complete pre-operative evaluation (41)
- Patients with ductal carcinoma in-situ (DCIS), with a few exceptions (see below).

The following are NOT contraindications to SLNB:

- Patients with breast augmentation (42)
- Patients who have undergone previous breast surgery (regardless of location of previous incision) (43)
- Pregnant patients (44)
- Patients with multi-focal or multi-centric breast cancer (45, 46)
- Patients with recurrent breast cancer (47)
- Patients with Paget's disease of the breast (all patients with Paget's disease should have SLNB even if invasion is not documented pre-op given the high incidence of associated invasive cancer (48).
- Patients undergoing surgery for DCIS with a mass lesion >1.5 cm, extension of high grade DCIS >2.5 cm on imaging, or cancerization of lobules seen on biopsy (49, 50)

Conclusion

The SLNB is now the standard of care for the nodal assessment of patients with early breast cancer. Variations and controversies in harvesting and evaluation techniques still exist. Regardless, there is no doubting the tremendous superiority of the SLNB over the standard AND Most patients with early stage breast cancer are candidates for SLNB with very few exceptions.

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3.8

Lecture 8

Defining micrometastasis and interpretation of sentinel lymph node biopsy

Michael D. Lagios, MD

Historically, the majority of axillary metastases were of large size and often apparent by gross examination. Microscopic examination to confirm smaller metastases became routine, but even in the mid 1970s, processing both halves of an axillary lymph node to screen for metastases was uncommon. It is important to realize that all of the available prognostic information regarding nodal status, size of metastasis, number of nodes involved, and extranodal extension is predicated almost entirely on gross metastases, those 2 mm or more in size.

The application of sentinel lymph node technology was a revolutionary innovation in breast cancer oncology which spared the majority of women who require axillary staging the morbidities and risks of a standard level I and II dissection and which provides greater certainty that the nodal status will be accurately classified by sampling the node most likely to be involved, and at lesser cost.

As part of the focus on the sentinel node, pathologic practice changed from a sample of half of a lymph node to multiple thin slices of a single node with appropriate levels and cytokeratin immunohistochemistry capable of identifying metastases so small they might otherwise be overlooked in H and E stained sections. Twenty years ago, the identification of axillary metastases of 2 mm or less, termed micrometastases, generated considerable discussion regarding their significance and outcome studies then and now suggest little adverse impact from such a metastasis. Immunohistochemistry compounded the problem by finding isolated cytokeratin-positive cells and clusters 0.2 mm or less in size. Hansen et al (2007) in a recent 8 year prospective followup of patients with a SLN procedure found no impact of N0 (i+) on DFS. Patients whose SLN contained micrometastases (N1mi) had a DFS of 89.6% - not significantly different from N0.

Maibenco et al (2006) recently provided SEER-based 12 year outcome data for micrometastases (0.2 – 2.0 mm) in T1 invasive carcinomas with a standard axillary dissection (N 43,921). There was a modest impact of micrometastases on survival overall (<5%), but no significant impact for T1a,b (< 10 mm) carcinomas, those of low grade or those in patients over 65 years of age. The AJCC staging manual notes that single micrometastases generate the same survival as N0 status.

The clinical significance of isolated IHC-identified cells and clusters of < 0.2 mm in size or less, is a subject of controversy. However, no prospective study has shown a clinical adverse impact from such Ametastases@ and the American College of Pathologists and the AJCC, and in particular in the revised sixth edition of the Staging Manual, have formally advocated that such involvement not be used to upstage patients or be the basis for adjuvant treatment. Immunohistochemistry for sentinel nodes is currently recommended only as part of an established clinical trial or research protocol. Some argue that immunohistochemistry facilitates the recognition of legitimate micrometastases (0.2-2.0 mm in size). However, given the frequency of immunohistochemistry-positive cells in otherwise negative axillary lymph nodes, the problems of misinterpretation and unnecessary adjuvant treatment outweigh the potential benefits. A number of studies have found that IHC identified single cells and cell clusters may reflect an artifact of surgical procedures rather than malignant cells capable of independent metastasis. Certainly there is no benefit of a SLN procedure for patients with pure DCIS. Several studies have utilized polymerase chain reaction technology to identify cytokeratin in the SLN. Such technology increases the expense of the screening and compounds the interpretive problem: Should adjuvant therapy be recommended on the basis of a PCR-positive sentinel nodes for which no identifiable pathologic metastasis can be demonstrated?

Examination of the Sentinel Node

Examination of the sentinel node spans an enormous spectrum of compulsive behaviors: from intraoperative serial frozen sections and immunohistochemistry for the entire node, requiring an hour or more of operator time, to the best available technology for a community hospital laboratory where the pathologist is the operator. Our own practice is fairly representative in our community. Intraoperative examination is based on sectioning of the sentinel node with imprint and smear technology stained by DifQuik. The nodes are fixed in 10% formalin and following fixation are sectioned into segments of approximately 1.5 mm thickness. An initial H and E stained section and three subsequent levels are prepared of each block. No immunohistochemistry is performed or reported.



The technique of sentinel lymph node examination outlined has its limitations. Micrometastases less than 2 mm in size can be missed, but in many studies, not with any greater frequency than employing formal frozen section which generally destroys a significant part of the nodal tissue before an interpretable section can be obtained. We utilize sentinel lymph node technology using the isosulfan blue or toluidine blue dye technique. The surgeon generally samples one to three additional nonsentinel lymph nodes. The sentinel lymph nodes identified by isosulfan blue tend to be fewer in number than by corresponding radioisotopic techniques which reflect the frequent delay between the administration of the isotope and the surgery. Cases in which the sentinel node is later found to have a micromet and the additional nodes are negative are generally not recommended to undergo level I and II axillary dissection. In our experience, the yield is too small and rarely does the finding of an additional nonsentinel positive node (usually harboring a micrometastasis) alter therapeutic recommendations.

RT-PCR technology has been advocated by proponents as a method to avoid missing SLN metastasis undetected by conventional intraoperative examination i.e. frozen section and/or imprint cytology. However the sensitivity of the technology for macrometastases (>2 mm) is not significantly superior to conventional examination. For the commonest type of SLN metastasis missed intraoperatively i.e. N1mi (0.2 – 2.0 mm) RT-PCR technology has a potential advantage over conventional intraoperative examination, however compared to the stage as determined in permanent sections RT-PCR technology has a lower sensitivity – 78% for metastases > 0.2 mm with an overall positive predictive value of 84% (Viale et al, 2008). Some studies have demonstrated a potential false positive rate as well – 27% of SLN-negative by conventional examination by both HE and IHC were “positive” by RT-PCR (Gimbergues et al, 2007). Commercially available RT-PCR technology entails substantial investments in equipment (~\$45,000), personnel training and costs for individual tests. Additionally the estimated intraoperative time required varies from 30-40 minutes, far longer than required for conventional intraoperative exam.

Given that conventional permanent sections may miss a micrometastasis in 10% of cases (based on “occult” metastases rate in re-examined negative SLN), and given that 10% of micrometastases are associated with another non-SLN metastasis, approximately 1 patient in 100 will be incorrectly staged as node negative and actually exhibit another metastasis, 90% within the T1mi range, at axillary dissection. On the other hand relying on RT-PCR results to determine need for axillary dissection may result in a substantial rate of unnecessary axillary dissections with resultant

morbidities. Finally commercial literature for RT-PCR technology notes that staging will only be determined by histology not RT-PCR results.

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3.9

Self-Evaluation



1. All ADH, LCIS, or ALH lesions found at minimally invasive breast biopsy should be surgically excised:

- a. True
- b. False

2. To adequately screen the tissue blocks sent after minimally invasive breast biopsy procedure, the pathologist should:

- 1: Perform step levels;**
- 2: Perform at the most 3 levels for a 3-mm core;**
- 3: Review pre-op imaging and specimen radiographs if done;**
- 4: Rely on description of lesion provided by the radiologist.**

- a. 1,3
- b. 2,4
- c. 1,2,3
- d. 4
- e. All of the above

3. When there is good radiological-pathological concordance for a lesion with a histological diagnosis of benignity, one should:

- a. Return to routine annual screening
- b. Return to routine bi-annual screening
- c. Recommend a 3 mo follow-up
- d. Recommend a 6,12,24 mo follow-up

4 A superficial lesion should be sent to surgical excision since not amenable in any way to stereotactic biopsy:

- a. True
- b. False

5. For superficial lesions seen on ultrasound, one should position the needle between the skin and the lesion to avoid skin laceration while capturing a specimen:

- a. True
- b. False

6. Regarding Sentinel Lymph Node Biopsy:

- 1: Not all patients with invasive breast cancer should have SLNB;**
- 2: All patients with DCIS should have SLNB;**
- 3: There is no advantage of using both blue dye and isotope during the procedure;**
- 4: There is a risk of allergic reaction to blue dye**

- a. 1,3
- b. 2,4
- c. 1,2,3
- d. 4
- e. All of the above

7. If a Sentinel node is found to have micrometastases and the additional nodes are negative, it is generally recommended to undergo level I and II axillary dissection:

- a. True
- b. False