than 4.2 mm was 80% sensitive and 80% specific for malignancy [18]. If the cutoff was lowered to 2.3 mm, the sensitivity increased to 95%, but specificity dropped to 44% [18]. Vassallo described that diffuse cortical thickening was associated with malignancy in 47% of cases [10]. Duchesne found cortical thickening of >2 mm in 35% of all pathological nodes, and when present, a cortex of >2 mm was associated with malignancy in 30% and benignity in 70% [16]. A lobulated cortex is reported to be found in approximately 20% of malignantly involved nodes and is associated with malignancy in between 53 and 73% of patients [16, 17].

The variable accuracy of such findings, however, makes each morphological features, either alone or in combination, insufficiently reliable to assist in the decision as to whether an individual patient should be advised to proceed straight to ALND or undergo SLN biopsy. Any preoperative staging therefore requires needle biopsy to substantiate subsequent clinical decision making.

Comparison of published axillary lymph node biopsy performance data is presented in Table 5. The majority of publications on axillary node biopsy have used FNAC, and a wide range of sensitivities have been reported (21%–94%). Although FNAC was included in this study, the results were disappointing, especially the very high inadequate rate that does not match most other published series. The most likely reason for this is that FNAC on breast lesions has not been practised routinely in our institution since 1994 when CB replaced FNAC. None of the radiologists therefore has any recent experience in FNAC outside of this study, which was also why needle washings rather than smears were used for specimen preparation. Our experience in CB and the very encouraging results in breast diagnosis compared with FNAC [19, 20] made us wish to evaluate CB accuracy in staging the axilla. We modelled our series on the Nottingham trial of axillary CB [12], which biopsied 48 (29%) of 166 patients using one or two passes with a 14G needle. Their criteria for node biopsy were morphologically abnormal nodes with cortices greater than 2 mm in diameter and a LS:TS greater than 2. Overall sensitivity for detecting lymph node metastasis was 42%. The rationale for our study was to see whether submitting a greater proportion of patients to biopsy would result in improved sensitivity. In our series 87% of patients were biopsied, but the sensitivity for detecting lymph node metastasis only increased to 53% (95% confidence interval 41 to 65). This modest increment in sensitivity when compared with the Nottingham trial was only achieved by the addition of substantial numbers of negative biopsies. This may be partly explained by inadequate sampling of the affected node or possibly by biopsy of a node other than the SLN. A separate pathological review of the SLNs is this series is currently underway to see how many exhibit evidence of recent previous CB, which may reveal how often the actual SLN is being sampled during percutaneous biopsy. It is therefore

disappointing to report that this aggressive biopsy approach does not appear to have resulted in a commensurate improvement in sensitivity.

Who then should be biopsied, and is node morphology important in guiding more intelligent biopsy? In this series, if the lymph node is morphologically normal on US, then malignancy is subsequently found in 36% of cases. However, CB of these nodes diagnosed malignancy in only 3 of 25 (12%). Until data correlating axillary node biopsy to targeting of the SLN are available, there seems little justification in trying to improve sensitivity of axillary lymph node biopsy by increasing the numbers of passes or the needle gauge. More intelligent targeting of the SLN is clearly required, and experimental work using radionuclide isotope [21] or US contrast agents [22] to aid identification of the SLN shows promise. Suga et al. have shown that injecting intra-parenchymal contrast can delineate sentinel nodes on computed tomography [23]. However, if biopsy of morphologically normal nodes is unrewarding at present, what criteria should the radiologist use to identify and biopsy the nodes? From the present series, and other published reports, it would seem reasonable to biopsy those nodes that are: greater than 10 mm in maximum transverse dimension, or have a cortex that is 4 mm or greater in thickness, have a uni- or multi-lobulated cortical margin, or have an absent hilum.

The entry criteria in this study were initially restricted to patients with larger tumours and then only to patients with smaller tumours of higher grade to focus resources on a population with a reasonable expectation of nodal involvement. The background level of nodal involvement in any study population will clearly affect the sensitivity achieved. Table 5 shows that the highest needle biopsy sensitivities are achieved in trials with high likelihood of metastatic disease. For CB, Topal's series had a high (85%) level of nodal metastasis and a 91% sensitivity [24]. For FNAC, Duchesne's series had a 78% level of lymph node metastasis and a 94% sensitivity [16]. It is likely, therefore, that the sensitivity for detecting lymph node metastases would drop if our entry criteria had included patients with invasive tumours of any size.

No major complications have been reported in any of the series reviewed in this paper. As far as we are aware, there has not been a single report of axillary vascular damage from an axillary node biopsy. There have also been no reports of lymph node needle biopsy adversely affecting subsequent SLN biopsy, although published numbers of CB, which might be expected to have a greater affect on lymphatic drainage of axillary nodes than FNAC, are currently extremely small. The SLN of one patient in this series could not be identified at the time of surgery, which was attributed to a post-needle biopsy haematoma. As stated above, this has not been previously reported in the literature, although it should also be taken into consideration that there is a technical failure rate for SLN biopsy, without prior needle biopsy, of between 1 and 4% [25, 26].

Table 5 Comparison of published performance statistics of ultrasound-guided axillary lymph node biopsy

Reference	This study	Topal et al.	Damera et al.	This study	Duchesne et al.	Bonnema et al.	van-Rijk et al.	de Kanter et al.	Duerloo et al.	Krishnamurthy et al.	Sapino et al.	K-Boumeester et al.
Reference no.	-	24	12	-	16	14	11	15	18	28	131	27
Date	2008	2005	2003	2008	2005	1997	2005	1999	2003	2002	2003	2003
Biopsy method	CB	CB	CB	FNAC	FNAC	FNAC	FNAC	FNAC	FNAC	FNAC	FNAC	FNAC
Number of patients	139	39.0	166	89	40	150	726	185	268	103	298	183
Lymph node positivity of study population	53%	85.0%	39%	55%	78%	41%	31%	47%	45%	77%	30%	46%
Nodes identified on ultrasound	134 (96%)	39 (100%)	103 (62%)	85 (96%)	100%	93 (62%)	NS	69 (37%)	93 (35%)	103	NS	183 (100%)
Number of biopsies	121 (87%)	39 (100%)	48 (29%)	89 (100%)	100%	54%	176 (24%)	69 (37%)	66 (25%)	103	95 (32%)	183 (100%)
Needle gauge	16	16.0	14	21/22	18	21	21/22	21	NS	20/21	22	21
Average number passes	2.9	2.0	2	1	NS	NS	NS	NS	NS	2.0	NS	NS
Inadequate rate	4.1%	0.0	NS	53%	NS	NS	NS	NS	11%	0%	11%	27%
% of all metastatic nodes diagnosed on biopsy	53%	91.0%	42%	31%	94%	63%	21%	36%	31%	50%	56%	44%
% of macro-metastatic nodes diagnosed on biopsy	62.3%	NS	NS	38%	NS	NS	NS	NS	41%	NS	NS	NS
% of micro-metastatic nodes diagnosed on biopsy	8.3%	NS	NS	0%	NS	NS	NS	NS	3%	NS	NS	NS

NS = not specified

Two published series have recorded false-positive results when using FNAC. Kuenen-Boumeester et al. had 3 cases in a series of 183 patients, and Van-Rijk et al. reported 1 false-positive FNAC in their study of 726 patients [11, 27]. To date, there has not been a single reported case of a false-positive CB from an axillary lymph node in a patient with invasive breast cancer.

Axillary lymph node US and biopsy have enabled the detection of 53% of patients with metastases in this series and obviates the need to perform initial SLN biopsy in such patients. However, a SLN biopsy is still required in patients with benign lymph node core biopsy. This study shows that lymph node US morphology is important when deciding whether and which node should be biopsied. We would suggest biopsy of those nodes that are: greater than 10 mm in maximum transverse dimension, or have a cortex that is 4 mm or greater in thickness, have a uni- or multi-lobulated cortical margin, or an absent hilum. More sophisticated

techniques are required to enable the SLN to be identified and biopsied under image guidance, which will provide a further improvement in preoperative diagnostic sensitivity for patients with axillary lymph node metastases.

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BARD

BIOPSY SYSTEMS

Memorandum

To: Biopsy Sales & Marketing

From: Brian Haas

Date: February 19, 2010

Subject: American College of Surgeons: Consensus Paper on Image Detected Breast Cancer

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Report Overview:

This report highlights the findings and recommendations of a panel of interdisciplinary physicians participating in the third Consensus Conference in search of best practices in the diagnosis and treatment of image detected breast cancers. Meeting in 2001, 2005, and most recently 2009, the panel's objectives have been to re-address issues on the diagnosis and treatment of image-detected breast cancers taking into account relevant advancements in medicine and technology. The report was authored by Melvin J Silverstein, et al, and was published in the Journal of the American College of Surgeons in October 2009.

Key Findings:

Percutaneous Biopsies:
- Percutaneous Needle Biopsy (PNB) demonstrated accuracy equivalent to open surgical biopsy and is the optimal initial tissue acquisition procedure for image-detected breast abnormalities. It represents "best practice" and new "gold standard" for initial diagnosis - replacing open biopsy in this role.
- Ultrasonography of the axilla should be performed for all suspicious lesions to assess morphologically abnormal nodes. If abnormal node is detected, confirmation of malignancy using ultra-sound guided core biopsy allows surgeon to proceed directly to axillary dissection rather than sentinel node biopsy.
- PNB can establish a definitive benign diagnosis for majority of image detected abnormalities, eliminating need for open surgery.
- Greater use of PNB can save large amounts of money, minimize potential disfigurement to patients and decrease morbidity without any loss in diagnostic accuracy.
- In the U.S. 35-40% of 1.7M biopsies are still open surgery. If 90% of them had core biopsies instead, annual savings would be $1.1 billion based on Medicare reimbursement figures.
- Vacuum-assisted devices may be preferable when very small masses are biopsied because they can be removed in their entirety.
- Sonographic guidance is preferred for biopsy of all lesions visible by ultrasound.

Tissue Markers: A tissue marker should be inserted at the time of biopsy in virtually all patients with consideration of the following:
- Marker placement aids subsequent localization of malignant lesions for excision.
- Marker placement may prevent unnecessary re-biopsy at a different facility in the future for those lesions thought likely to be benign.
- If more than one lesion is biopsied, markers of different configurations should be used to unequivocally distinguish between them.
- Radiologic marker placement at the time of ultrasound-guided axillary node biopsy may facilitate subsequent confirmation of proper node recovery.

Good Selling!

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Image-Detected Breast Cancer: State-of-the-Art Diagnosis and Treatment

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In 2001 and 2005, a conference panel comprised of an interdisciplinary group of physicians specializing in the diagnosis and treatment of breast disease met to discuss their experiences with image-detected breast cancer and draft a report detailing points of consensus.[1,2] A third, similar group (composed of approximately 50% of the members of the first and second groups and 50% new attendees) met in June 2009 to reassess some of the issues debated by the earlier panels, discuss the available evidence and implications of new and ongoing investigations, and develop current recommendations for diagnosis and treatment of image-detected breast cancers. Consensus was reached by the Panel on a number of the challenging issues faced by patients and physicians. All physicians who participated in the conference are listed in the Appendix.

Five basic concepts arrived at during the 2001 conference were reaffirmed in 2005 and were again accepted. These include describing disease using objective measures, such as size, grade, nodal status, biologic markers, etc; the ability of screening mammography to reduce breast cancer mortality, at the price of requiring additional tests and possible overtreatment of some women; the progressive nature of breast cancer and the value of early detection in widening treatment options and improving outcomes; the highly variable growth rate and phenotypic evolution of breast cancers; and the benefits of early recognition and adequate treatment of ductal carcinoma in situ (DCIS). Other relevant issues considered in the previous consensus conferences were readdressed and revised to account for advances and new information in the intervening 4 years. The remainder of this article will present the Panel's conclusions

on these topics. Limited references are given, mainly to point the reader to guidelines and standards created by other groups.

Some modes of diagnosis and treatment discussed by the Panel are widely used in the community; others are considered investigational. The conclusions of the panelists represent the results of their own research, clinical experiences, familiarity with the professional literature, and points of consensus arrived at through conference discussion. They should not be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results or of interventions performed in the context of clinical trials.

IMAGING AND BIOPSY

General statement

The Panel uniformly agreed that the training, experience, and expertise of the radiologist interpreting a breast-imaging examination are of paramount importance. It endorsed continued subspecialization and regular continuing medical education for any radiologist interpreting breast-imaging studies.

There was extensive discussion regarding the portability of digital breast-imaging examinations. The lack of standardized formatting is a universal frustration that can lead to needless repetition of examinations and even biopsies. The Panel encourages the relevant accrediting bodies to work with vendors to standardize this technology. Facilities performing breast-imaging should promptly provide those images and the software to view them to a patient or medical facility requesting them at a nominal fee or at no charge.

Mammography

Mammography currently remains the only imaging modality that is recommended for routine screening for breast cancer in the general population. To be successful in reducing breast cancer mortality, screening mammography must be performed on a regular basis, as shown in numerous randomized controlled trials. The Panel supports the cur-

Abbreviations and Acronyms	
ADH	= atypical ductal hyperplasia
AJCC	= American Joint Committee on cancer
ALH	= atypical lobular hyperplasia
ALND	= axillary lymph node dissection
APBI	= accelerated partial breast irradiation
BI-RADS	= American College of Radiology Breast-Imaging Reporting and Data System
DCIS	= ductal carcinoma in situ
MIBB	= minimally invasive breast biopsy
SLN	= sentinel lymph node
UICC	= International Union Against Cancer.

rent recommendation of the American Cancer Society that women of average risk undergo screening mammography on a yearly basis, beginning at age 40. The upper age limit for undergoing screening mammography should be based on comorbidity.

Results of the Digital Mammography in Screening Trial (DMIST) were published after the second consensus conference.[3] This study demonstrated no difference in the cancer detection rate between analog and digital mammography for the cohort as a whole. However, digital mammography was superior to film-screen mammography in detection of breast cancer in certain subgroups: young women (age 49 years or younger), women of any age with mammographically dense breast tissue, and pre- and perimenopausal women. This has helped justify the rapid deployment of digital mammography, which has lower spatial resolution but higher contrast resolution and a higher signal-to-noise ratio than analog mammography. Digital mammography also results in a slightly lower radiation dose.

Digital mammography provides other advantages that cannot be matched by analog mammography, such as reduced cost of archiving, ease of retrieval, and the ability to transmit studies through electronic networks so that "soft copies" can be read at remote reading sites. Digital mammography currently has a 60% market penetrance and will likely replace analog mammography altogether in the coming decade. However, lack of access to digital mammography should not deter a woman from having screening mammography services because screen-film (analog) mammography is still a valuable life-saving technology.

Conventional digital or analog mammography is limited by superimposition of normal breast parenchyma that can both obscure an underlying malignancy and generate false positive findings. Digital tomosynthesis, a cross-sectional x-ray technique, minimizes the impact of overlapping structures in the breast and should facilitate cancer detection. Clinical trials are currently underway to establish the efficacy of tomosynthesis and define its role in future practice.

Computer-aided detection

Mammographic computer-aided detection has been shown to improve the cancer detection rate in both screening and diagnostic populations for experienced, novice, and part-time mammographers. The Panel believed that computer-aided detection might reasonably replace a "second reader" in the screening setting. But it is critical that computer-aided detection should serve only as a perceptual aid to the radiologist; once a potential finding is visualized, the radiologist must exercise his or her judgment to determine if the finding is actionable.

Diagnostic ultrasonography

Breast ultrasonography is presently considered primarily a diagnostic tool. It is most commonly used to characterize lesions initially detected through mammographic screening or to evaluate patients who present with clinical findings such as a palpable mass. The goal of diagnostic breast ultrasonography should be to make the overall imaging assessment more specific, helping to guide further care (ie, additional imaging followup or immediate biopsy). The American College of Radiology Breast-Imaging Reporting and Data System (BI-RADS) risk assessment categories should be used.[4]

In the setting of a suspicious lesion, the ipsilateral breast should be scanned sufficiently to determine the extent of the index lesion and to assess for any satellite or synchronous lesions. Ultrasonography of the ipsilateral axilla should be performed for all suspicious or biopsy-proven invasive lesions to assess for morphologically abnormal nodes. If an abnormal node is detected, confirmation of malignant involvement by ultrasound-guided core biopsy or fine-needle aspiration biopsy will allow the surgeon to proceed directly to axillary dissection rather than sentinel node biopsy. Radiologic marker placement at the time of ultrasound-guided axillary node biopsy may facilitate subsequent confirmation of proper node recovery.

Screening ultrasonography

Routine screening with breast ultrasonography is not currently recommended. The American College of Radiology Imaging Network (ACRIN) trial 6666 demonstrated that, among a group of high-risk women with dense breast tissue, the addition of screening ultrasonography to routine screening mammography increased the detection of breast cancer from 7.6 to 11.9 per 1,000.[5] Unfortunately, the technology suffered from low specificity, with a high num-

ber of false positive findings resulting in an excess of unnecessary biopsies. A subset of intermediate risk patients with dense breasts who do not meet recommended thresholds for screening MRI might benefit from screening ultrasonography after they are made aware of the specificity limitations.

This trial also showed that performing screening breast ultrasonographic examinations was very time consuming for radiologists, raising concerns about the feasibility of widely implementing this approach. The efficacy of automated whole breast ultrasonography systems is currently being studied. This technology may facilitate the acquisition of the examination sufficiently to overcome this problem.

Diagnostic magnetic resonance imaging

The Panel spent a considerable amount of time discussing the increasing use of and evolving data on the role of breast MRI. Breast MRI has become a commonly used imaging modality in the 4 years since the previous consensus meeting. The Panel agreed that, in skilled hands and with the use of MRI computer-aided detection software, breast MRI is often helpful in patients with a newly diagnosed breast cancer for:

1. Defining the extent of the index lesion;
2. Determining whether additional foci of malignant disease are present elsewhere in the ipsilateral breast;
3. Assessing for axillary and regional metastases;
4. Pretreatment evaluation of patients with newly diagnosed breast cancer who have had breast augmentation;
5. Assessing whether occult contralateral malignant disease is present;
6. Assessing chemotherapeutic response and residual disease extent after chemotherapy; and
7. Evaluating residual disease in patients with close or positive lumpectomy margins.

In many practices, breast MRI appears to significantly reduce the incidence of positive pathologic margins and to aid in preoperative planning of breast-conserving treatment. But in the randomized Comparative Effectiveness of Magnetic Resonance Imaging in Breast Cancer (COMICE) trial, preoperative evaluation with MRI was not associated with a reduction in the reoperation rate.[6] There is as yet no evidence from randomized trials that performing MRI will reduce the risk of local recurrence in patients undergoing breast-conserving therapy or improve survival. In some situations, performing MRI may increase the mastectomy rate. But MRI can also allow some patients who otherwise would have had a mastectomy to undergo breast-conserving surgery.

MRI may be especially helpful in patients with infiltrating lobular carcinoma who have difficult clinical and conventional imaging examinations. MRI may also sometimes give useful information regarding tumor extension to or involvement of the skin, nipple, deep fascia, and chest wall.

Insurance companies often require a positive histologic diagnosis before approving the use of MRI. But this policy could adversely affect patient management because the biopsy procedure itself may produce artifacts that can affect accurate interpretation of the MRI. For patients with a high probability of having malignancy (BI-RADS 4C and 5 lesions on mammography or ultrasound), prebiopsy MRI can allow more accurate demonstration of disease extent and facilitate more effective biopsy procedures and subsequent surgical planning. The Panel urges insurance companies to approve MRI for these patients.

MRI is also indicated in the postoperative setting, where there is suspicion of significant residual disease, in patients with newly diagnosed adenocarcinoma in the axilla with an occult primary, and in patients in whom there is a question of tumor recurrence after initial breast-conserving therapy. MRI may be beneficial in the surveillance of patients who have undergone breast reconstruction.

MRI may be useful in cases where the mammographic, ultrasonographic, and clinical findings are inconclusive and no focal finding is apparent (eg, spontaneous bloody single-duct nipple discharge, silicone injections, subtle architectural distortions, etc).

Screening magnetic resonance imaging

A number of international clinical trials support the use of MRI as a screening modality for patients at high risk of developing breast cancer. The Panel endorsed the American Cancer Society guidelines regarding screening MRI.[7] Appropriate candidates include:

1. Women with a lifetime breast cancer risk of 20% to 25% or higher based on predictive models;
2. Those with BRCA 1 or 2 mutations or those having a first-degree relative with a BRCA 1 or 2 mutation who have not yet been tested themselves;
3. Individuals who have had radiation therapy to the chest between ages 10 and 30; and
4. Women with Li-Fraumeni syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and their first-degree relatives.

The commonly used predictive models may not reliably identify all women at high risk. Also many women who have significant risk may fail to meet the American Cancer Society threshold for screening. In the Panel's view, screening MRI may also be appropriate for other individuals, such as those with a lifetime breast cancer risk estimated to be 15% to 20%; a personal history of invasive breast cancer

or ductal carcinoma in situ; a previous diagnosis of atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ; and mammographically dense breasts, particularly given emerging data suggesting that increased breast density itself may confer significant increased risk for the development of breast cancer. Patients should be informed about the risks of false positive and negative examinations and the fact that survival differences have not been demonstrated with MRI screening.

Inappropriate uses of breast magnetic resonance imaging

MRI should not replace careful diagnostic mammographic views or ultrasonography in the setting of an abnormal clinical examination or screening mammogram. Because MRI can miss some cancers, MRI findings should not prevent performance of a diagnostic biopsy of mammographically, clinically, or sonographically suspicious findings.

Magnetic resonance imaging technique

The Panel strongly endorses the accreditation of breast MRI centers and the development of minimum quality standards. Because of the high sensitivity of breast MRI and its ability to detect lesions not seen with mammography or ultrasonography, breast MRI should not be performed in centers that do not offer MRI-directed biopsy, unless they are affiliated with a center willing to perform this service. MRI of both breasts should be performed in a single session on a high field strength magnet (1.5 tesla or higher) using a dedicated breast coil. Acquisition of images in the axial and sagittal planes or by an isotropic three-dimensional approach that allows reformatting to any plane is recommended. High spatial and temporal resolution images are required and preferably should be acquired simultaneously. Dynamic information suggesting a benign process should not deter biopsy of lesions that are morphologically worrisome. Because of the inability to confirm the presence of the imaging target in the MRI-guided core specimens, meticulous radiologic-pathologic correlation should be used, and the radiologist should have a low threshold for reimaging to confirm that the MRI target has been satisfactorily sampled.

All panelists strongly agreed that irrevocable treatment decisions must not be made based on MRI findings without histologic confirmation. Breast MRI should be interpreted in the context of the patient's mammogram, ultrasound, and clinical examination, as well as previous surgical and pathologic history, risk factors, and menopausal status. In premenopausal women, an attempt should be made to schedule the examination between the 7th and 14th day of the menstrual cycle to minimize parenchymal enhance-

ment and false positives. Interpretation should be performed by radiologists specializing in breast imaging.

The Panel strongly encourages the use of the guidelines of the American College of Radiology for the performance of breast MRI[8] and the use of the lexicon for breast MRI included in the 2003 edition of their Breast Imaging Atlas.[9]

Molecular breast imaging

Molecular imaging tools for breast cancer detection take advantage of functional differences between normal and cancerous tissues. These include breast-specific gamma imaging, which uses technicium-99m sestamibi as an imaging agent, and positron emission mammography, which uses fluourine-18-deoxyglucose. Although there is currently little published literature on the performance of these tools, the available information suggests that they may have equivalent sensitivity and improved specificity when compared with breast MRI. It is recommended that these adjunctive tools be used only after high-quality standard imaging is performed; their results should not prevent performing a biopsy recommended after conventional imaging. Either breast-specific gamma imaging or positron emission mammography may be used as an alternative to breast MRI when MRI is not available or is contraindicated in a particular patient. Both tools may be valuable in preoperative surgical staging. Breast-specific gamma imaging may also be useful as an additional problem-solving tool in some situations. Attempts should be made to reduce their radiation dose, and continued multicenter prospective research trials to establish their place in the imaging armamentarium are encouraged.

Physical examination and risk assessment

Currently, more and more patients are presenting for screening mammography without seeing a primary care physician. The management of such self-referred women presents the radiologist and breast centers with additional challenges. It is well known that some cancers not identified by mammography can be detected by physical examination. So breast centers may consider offering patients clinical breast examination performed by trained breast health care specialists (a nurse practitioner, physician's assistant, or physician). If palpable lesions are found, the patient should be referred for more detailed radiologic workup and biopsy as necessary.

Breast centers may also consider offering risk assessment analysis to their screening population. This can initially be performed by asking pertinent questions concerning personal and family history. Patients identified as potentially at increased risk may then be triaged for more in-depth analysis. Professionals trained in genetic counseling can provide a comprehensive assessment of risk, advise women

on issues regarding genetic testing, and review surveillance and chemoprevention options.

Minimally invasive breast biopsy

The Panel agreed that percutaneous needle biopsy (also known as minimally-invasive breast biopsy, or MIBB) has demonstrated accuracy equivalent to open surgical biopsy and is the optimal initial tissue-acquisition procedure for image-detected breast abnormalities. A major benefit of using image-guided percutaneous breast biopsy as the initial procedure is its ability to establish a definitive benign diagnosis for the majority of image-detected abnormalities, eliminating the need for the patient to undergo an open surgical diagnostic procedure. The use of percutaneous biopsy for diagnosis significantly reduces the overall cost of treatment and potential disfigurement of patients with breast lesions.

For those with malignant diagnoses, needle biopsy permits preoperative staging, acquisition of histologic and biomarker data, consultation with appropriate specialists, and planning for surgical resection and axillary nodal sampling. All of these result in a greater likelihood of an adequate resection on the first attempt and avoidance of subsequent reexcision. In addition, percutaneous biopsy allows for early discussion of eligibility for clinical trials.

In spite of the fact that there are few patients for whom needle biopsy is technically not feasible, an alarming 35% of initial diagnostic breast biopsies in the United States are still done using open surgical techniques. It was the Panel's unanimous opinion that percutaneous needle biopsy represents "best practice" and should be the new "gold standard" for initial diagnosis. It should essentially replace open biopsy in this role. The Panel called on the medical community to change their current practice if they are using open surgical breast biopsy as a standard diagnostic procedure. Surgeons should audit their practice and make adjustments to decrease their rate of open biopsy for initial diagnosis to less than 5% to 10%.

Percutaneous histologic tissue-acquisition techniques include core biopsy (typically 12 to 18 gauge), vacuum-assisted biopsy (typically 7 to 12 gauge), and larger tissue-acquisition systems. A tissue marker (clip) should be inserted at the time of biopsy in virtually all patients for several reasons. Marker placement aids the subsequent localization of malignant lesions for excision, particularly when small. Patients with larger lesions may receive neoadjuvant systemic therapy so they should have a marker placed at the time of biopsy in order to ensure the ability to accurately excise the region of the tumor after completion of treatment. Finally, placement of a marker may prevent unnecessary rebiopsy at a different facility in the future for those lesions thought likely to be benign. If more than one lesion is biopsied in the same breast, markers of different configurations should be used to unequivocally distinguish between them. Postprocedure mammography in two orthogonal views is indicated to document accurate lesion sampling, ensure that sonographic and mammographic targets correlate, and document marker location in relation to the biopsy site.

Stereotactic mammographic guidance with specimen radiography is generally the most appropriate biopsy technique for microcalcifications and for noncalcified lesions not visible on ultrasound; vacuum-assisted biopsy devices should be used with stereotactic biopsies to reduce sampling error and minimize histologic underestimation of disease. Even with the use of a vacuum-assisted biopsy device, approximately 10% to 20% of patients with core biopsies demonstrating atypia are found to contain DCIS or invasive carcinoma at surgical excision.

Sonographic guidance is preferred for biopsy of all lesions visible by ultrasound. Either core needle or vacuum-assisted biopsy devices provide satisfactory sampling, although a vacuum-assisted device may be preferable when very small masses are biopsied because they can be removed in their entirety. Although fine-needle aspiration cytology is useful for lymph node evaluation, it is less desirable than histologic tissue-acquisition techniques for evaluation of primary breast lesions and should not be used for that indication when core biopsy is readily available.

Correlation of histologic and imaging findings is essential in each case. Radiologists and pathologists working together should ensure that pathology findings adequately explain the imaging findings. The radiology or pathology reports should document that assessment. Histologic diagnoses after percutaneous needle biopsy can be divided into malignant, high risk, and benign categories. Benign pathology results that do not explain the imaging findings are considered discordant and require rebiopsy. Percutaneously diagnosed high risk lesions include atypical ductal hyperplasia (ADH), radial scars, and papillary lesions. The Panel generally supports current recommendations for patients with these high-risk lesions to undergo surgical excision because of the possibility of associated DCIS or invasive cancer. But some institutions use algorithms that may yield sufficiently low upgrade rates to avoid excision of selected lesions. Some data suggest that the rate of diagnostic upgrading may be reduced with the use of vacuum-assisted devices and the acquisition of a larger number of samples (more than 12) per lesion.

The need to advise excision for patients with lobular neoplasia (ALH and lobular carcinoma in situ) incidentally diagnosed on percutaneous core needle biopsy generated substantial debate. Data from different studies on the risk

of histologic upgrading are conflicting. The Panel did not reach consensus on this issue. Some believed that it is reasonable but not mandatory to perform excision after a core needle finding of lobular neoplasia. The majority believed that excision was required and that all centers should track and monitor their "upgrade" rate. But as stated earlier, some institutions use algorithms that may yield sufficiently low upgrade rates to avoid excision of these lesions, particularly when incidental to radiologic findings.

The Panel strongly endorsed the use of second opinions from experts in breast pathology for diagnoses of "high risk" lesions (ADH, ALH, and lobular carcinoma in situ) before a decision is made between surgical excision and imaging followup. This recommendation results from the significant degree of diagnostic disagreement regarding these specific diagnoses among practicing pathologists. A number of other proliferative lesions, including columnar cell lesions without atypia, should not be included in the "high risk" category.

PATHOLOGY AND PROGNOSTIC ISSUES
General
The Consensus Panel reaffirmed that breast cancer is a remarkably heterogeneous disease, with broad variations in behavior. Interpretation by the pathologist, including the assessment of tumor size, the surgical margins, combined histologic grade, examination of the sentinel node, and evaluation of immunohistochemical and gene-based assays, are critical to decision-making. There are no professional society or regulatory guidelines regarding the qualifications required of pathologists interpreting breast biopsies, comparable to those existing for the qualifications of radiologists reading mammograms, nor are there mandated performance standards for pathologists. The Panel strongly believes that breast specimens should be interpreted by pathologists experienced in this area to ensure optimum patient management, and it recommends establishment of continuing medical education requirements and practice standards for pathologists interpreting breast biopsy material.

Reporting of pathology specimens
Standard grading and size determination are currently the most reliable predictors of outcomes for patients with invasive cancers with uninvolved axillary nodes. The use of the Nottingham Combined Histologic Grade, which combines glandular differentiation, mitotic count, and nuclear grade, is strongly encouraged by the American Joint Committee on Cancer (AJCC), the International Union Against Cancer (UICC), the College of American Pathologists (CAP), and other organizations. Each of these three components should be separately recorded.

When reporting DCIS, the final pathology report requires documentation of nuclear grade, the presence or absence of zonal comedo-type necrosis, the predominant architectural patterns, the measured extent of the lesion, and the measured histologic margin width. This requirement presupposes an oriented specimen that has been correlated with imaging and completely and sequentially processed. The panel affirms the recommendations of the 1997 DCIS Consensus Conference[10] regarding recording of specific features of DCIS and the recent College of American Pathologists guidelines for tissue processing for DCIS specimens.[11]

Evaluation of specimens from minimally invasive breast biopsy
The amount of tissue processed after MIBB should ensure that a cancer will not be missed and that a benign lesion can be confirmed. Specimens should be fully embedded and thoroughly sectioned, with levels appropriate to sample the core biopsy and to establish an accurate diagnosis.

The term *multifocal process* is appropriate only in the context of open excision and should not be used in describing percutaneous biopsy specimens obtained from a single lesion. Similarly, no comment should be made regarding margin status for an MIBB. Knowing the size of the lesion on the core is valuable if no additional cancer is found at excision. Explanatory comments about the extent and characteristics of atypical findings are useful.

The pathologist's ability to establish and report an accurate diagnosis of an image-detected abnormality is compromised when the imaging findings are not available. Correlation of pathology and imaging studies by the pathologist is mandatory. Review of all imaging is necessary for this determination and includes specimen x-rays and the radiologist's reports and BI-RADS assessment. The radiologist or the pathologist (or both) should document whether the findings are concordant or discordant. Each institution should have a policy and routine procedure in place for performing this task. The Panel strongly endorses having a radiology/pathology correlation conference, where the histologic results of all minimally invasive breast biopsies are reviewed and correlated with the radiologic images. Regardless of the establishment of a multidisciplinary conference, communication between the pathologist and radiologist is mandatory in the event that there is a discrepancy between the imaging and pathologic results. Performing further biopsy should be recommended for patients with discordant results, either by repeat percutaneous biopsy or needle-localized excision.

After MIBB, florid ductal hyperplasia may be mistakenly diagnosed as ADH or ADH misdiagnosed as DCIS. The Panel encourages the use of expert second opinions for

patients with a diagnosis of ADH and other high-risk lesions for which open biopsy is being considered. Outside slide material should always be reviewed before definitive surgical treatment and should be available for comparison to the excision slides.

Excision specimen handling

Surgical excision should avoid excessive electrocautery because this interferes with making an accurate pathologic and immunohistochemical assessment. After excision, surgeons should present the pathologist with an oriented specimen. Margins should be inked by the surgeon or pathologist to preserve the three-dimensional orientation of the specimen. When the resection is for DCIS and, ideally, for all cancers, the specimen should be processed sequentially in its entirety.[11] Very large specimens should be sampled in a rigorous and documented fashion, allowing targeted return to the specimen for additional material, if needed.

Mass lesions that are grossly palpated should be measured in three dimensions and subsequently sectioned to demonstrate the maximum size of the mass (tumor). This maximum diameter should also be evaluable on at least one histologic section.

Specimen radiography or specimen ultrasonography should be routinely performed for all excisions of image-detected abnormalities to help document the success of the procedure in finding the target. Specimen radiography should use two 90-degree orthogonal views. Compression of the specimen is not needed to obtain adequate images and should be avoided. Such compression can fracture the specimen and create false (artifactual) margins after inking.

Specimen radiography, including the sequentially sectioned specimen, will help document the adequacy of excision margins, whether the lesion presented as microcalcifications or as mass. It may also help if the procedure is guided by ultrasound or MRI. Specimen radiographs should always be presented to the pathologist for radiographic and pathologic correlation.

Tumor size and margin assessment

The concept of tumor size originated in an earlier era, when cancers were generally diagnosed as large palpable lesions and uniformly treated with mastectomy. Assessment of tumor size was usually based on gross examination. Today, the term *size* has come to refer to two very different entities. One of these may be termed *prognostic size*, that is, related to the risk of developing distant metastases. Prognostic size is the maximum extent of the largest invasive component and is used as the T category for staging purposes in the current AJCC and UICC classifications. This must be de-

termined by the pathologist by direct measurement from the microscopic slides.

The second meaning may be termed *surgical size* or *extent*, which includes the full extent of the malignant process. This includes both the invasive lesions and DCIS components. Extent is generally larger than the prognostic size and is critical in determining the ability to perform cosmetically acceptable breast-conserving excision with adequate margins. Information from all imaging studies is needed to assess extent.

As an example, a patient with a lesion that is made up of a 1-cm infiltrating ductal carcinoma within a 5-cm DCIS would be considered to have a prognostic size of 1 cm (T1b) and an extent of 5 cm. Although the patient's overall prognosis should be excellent, it may be difficult to excise her lesion with margins adequate for breast-conserving therapy. There may be large variations in the accuracy of recorded tumor extent because of variability in pathologists' practices. Many pathologists often still record only gross size without input from preoperative imaging.

The Panel felt strongly that both prognostic size and extent should be clearly described by the pathologist and should be based on radiologic-pathologic correlation and sequential reconstruction. Mapping the extent of the entire lesion is essential in making treatment decisions. Invasive and noninvasive components should be measured and reported separately. Prognostic size and extent should be described to the nearest millimeter. For image-detected cancers, understanding the preoperative extent determined by imaging can avoid surgical errors.

The relationship of both invasive tumor and DCIS to each margin should be described separately. The closest margin for an invasive component or DCIS focus will determine the overall margin status used for making further decisions regarding local therapy. Evaluation should be made with the knowledge of all imaging findings and an attempt should be made to identify and report all pathologic findings.

Tumor markers

Estrogen receptor, progesterone receptor, and HER2 receptor status have documented clinical usefulness as tumor markers and should be obtained on all patients with invasive breast cancer. The estrogen receptor and progesterone receptor may be important in the management of patients with DCIS who are considering hormone therapy. Receptor results should include intensity of staining (using a scale of 0 to 3+) or the percentage of positive tumor cells, or both.

Fluorescent in situ hybridization assay in experienced hands may be more accurate and reproducible in assessing HER2 status than immunohistochemical assays; but both

can be subjective. The Panel unanimously agreed that fluorescent in situ hybridization should be obtained for all patients with immunohistochemical 2+ scores. The majority of the Panel also believed it should be obtained for 1+ scores. The utility of HER2 determination for the management of patients with DCIS has not been established.

Mitotic count is highly predictive of outcomes. Similar information is given by other measures of proliferation, such as Ki-67.

Recent studies have shown that multigene expression analysis of either fresh-frozen tissue or paraffin-embedded tissue may be useful for classifying breast cancers, predicting response to chemotherapy, and assessing prognosis, particularly for node-negative and hormone receptor-positive cancers. Whether or not these multigene reverse transcriptase-polymerase chain reaction or microarray assays will better predict prognosis than standard histologic grade, computer-assisted risk-assessment algorithms, quantitative immunohistochemical, or fluorescent in situ hybridization measurement of estrogen receptor, HER-2, and proliferation indices is the subject of ongoing investigation in prospective trials.

The Panel encourages the permanent storage of tissue blocks and frozen tissue samples as a safeguard for the individual patient and as a unique resource for future investigations. Ideally slides, tissue blocks, and pathology records should be retained for 20 years.

TREATMENT ISSUES

Sentinel lymph node biopsy

A substantial body of evidence shows that sentinel lymph node (SLN) biopsy performed for initial pathologic axillary staging is accurate and causes significantly less morbidity than axillary dissection. The first results of one of the randomized trials comparing SLN biopsy to conventional level I to II axillary dissection found no difference in survival between the two arms.[12] Sentinel lymph node biopsy should now be considered "best practice" and is recommended for pathologic axillary staging for most patients with invasive breast cancer.

There are several acceptable methods for performing lymphatic mapping using radioactive tracer, blue dye, or both, with injections placed either in the subareolar region, the peritumoral breast, or intradermally. Surgeons (in collaboration with nuclear medicine physicians) should select the technique that works best in their own center. Lymphoscintigraphy is not needed to allow adequate recovery of axillary sentinel nodes. It does allow preoperative detection of drainage to the internal mammary nodes and ectopic or accessory nodal sites, but there is no consensus on the value of removing such foci for patients with primary breast can-

cer. Lymphoscintigraphy may be of value in patients requiring nodal staging who have locally recurrent cancer or a second ipsilateral primary who have previously undergone SLN biopsy or have had an incomplete or unknown axillary node dissection.

Sentinel lymph node biopsy has the advantage of identifying, for the pathologist, those nodes most likely to harbor metastases. This allows a more focused and intensive analysis, using multiple serial sections, step sections, and special stains.

Pathology laboratories should have an established protocol for SLN evaluation. Intraoperative evaluation, although not able to detect all SLN metastases, permits performance of completion axillary dissection at the same operative session for the majority of patients with positive SLNs, provided that the physician and patient have agreed beforehand that this will be done. The plan of action in the event that an SLN cannot be identified should also be discussed with the patient preoperatively. (The failure of experienced teams to identify the SLN is frequently a result of metastatic axillary adenopathy.) In general, axillary dissection should be performed for patients with invasive cancer who have had unsuccessful mapping if they have a significant probability of having positive lymph nodes, for example, T1c or greater lesions, high grade, lymphovascular invasion on core biopsy, etc.

Standard current intraoperative techniques for examination of SLNs include frozen section and imprint cytology (touch preparation). Both have limited sensitivity compared with permanent sections and require assessment by an experienced pathologist. In 2007, the United States Food and Drug Administration approved a method for intraoperative molecular analysis of sentinel nodes (based on real-time reverse transcriptase polymerase chain reaction). This technology has the potential to make SLN evaluation less subjective and reduce the need for second operations on the axilla. In addition, the molecular assay has a particularly high negative predictive value for absence of N1 or N1mic status. Although such assays may be useful as an adjunct to current histologic techniques, the ultimate value in patient management will be determined in on-going studies aimed at correlating quantitative levels of nodal involvement with the risk of involvement of nonsentinel axillary nodes and with important clinical outcomes, such as local recurrence (with or without completion axillary dissection), distant recurrence, and breast cancer-specific survival.

Handling of the sentinel node must be left to the discretion of the surgeon and pathologist. They must use techniques that they feel are most successful in their institution and that are appropriate for each individual patient. It is appropriate to discuss with the patient preoperatively

which intraoperative techniques will be used and their potential impact on intraoperative decision-making.

The routine use of cytokeratin immunohistochemistry for detection of SLN micrometastases is now common throughout the United States, although it is not recommended by the Panel or the College of American Pathologists. The Panel awaits the results of two large prospective trials that will determine the prognostic significance of nodal micrometastases and isolated tumor cells.

Evidence indicates that surgeon experience improves the results of SLN biopsy. Adequate training and case volumes are required for surgeons offering SLN biopsy.

Patients should be made aware of the small risk of a false negative result with SLN biopsy. In the Panel's view, this small risk is outweighed by SLN biopsy's established staging accuracy and reduced morbidity.

The Panel considered at length the issue of which individuals with a positive SLN biopsy, outside a clinical trial, can safely avoid undergoing completion axillary lymph node dissection (ALND), particularly those with minimal SLN involvement (defined as deposits measuring less than 0.2 mm [pN0(i+)] in the AJCC staging system) or micrometastases measuring 0.2-2 mm (pN1mic). Completion ALND is the historical standard for management of patients found to have positive axillary nodes on permanent sections. But many surgeons have increasingly abandoned routine return to the operating room for completion ALND in patients with minimal involvement or micrometastases, believing that exposing the great majority of these patients to its potential increased morbidity is not justified by the uncertain potential benefits for a few patients. Unfortunately, there are limited data on the effectiveness of alternative treatment options for patients with positive SLNs in preventing axillary recurrence; these include giving axillary radiotherapy or no further specific axillary treatment except for that provided by irradiation of the breast. Such approaches do not provide additional information on the extent of axillary involvement (ie, the total number of positive nodes) that is important in estimating prognosis and may be helpful for some patients in deciding on specifics of systemic therapy and radiation therapy.

The significance of minimal involvement (pN0i+) is uncertain, although an increasing body of data suggests such patients have limited or no additional risks of axillary failure or developing distant metastases compared with patients with uninvolved nodes. The Panel agreed that, at present, such findings should not by themselves be used to justify giving additional regional or systemic therapy, so return to the operating room for ALND is not indicated.

Most studies show an increased risk of distant failure for patients with axillary micrometastases (pN1mic), com-

pared with those with uninvolved nodes. The value of completion ALND for such patients is controversial, with different Panel members having diverging opinions on whether or not completion dissection should be done. Some studies suggest that patients with a single SLN containing a micrometastasis have a risk of involvement of non-SLNs of less than 10%, but other series find much higher rates of non-SLN involvement. Many surgeons use nomograms designed to predict the likelihood of non-SLN metastasis to help decide whether or not to perform completion ALND, setting a threshold for when this surgery will be done. Unfortunately, these nomograms often require information not always available in the operating room and are not particularly reliable for micrometastasis. Available evidence is insufficient to identify specific subgroups of patients having a very low risk of non-SLN residual nodal metastases (eg, less than 5% to 10%). Moreover, studies examining the success of alterative treatment approaches in preventing axillary recurrence in these patients have generally contained few patients or had short followup, or both, with the exception of the Dutch Micrometastases and Isolated Tumor Cells: Relevant and Robust or Rubbish (MIRROR) study.[13] The Panel concluded that current evidence is insufficient to determine whether completion ALND is preferable to the two other approaches for patients with micrometastases. Further information on this subject will hopefully be available soon from the American College of Surgeons Oncology Group Z0011 trial, completed in 2004, that addressed this issue by randomly allocating patients with positive SLNs to either ALND or no specific axillary treatment beyond that provided by irradiation of the breast. (This trial was closed early because of inadequate accrual but still enrolled 891 patients.) Two European trials comparing these alternatives are still in progress. Unfortunately, results from these trials are not likely to be available for some time to come.

In summary, the Panel believed that (outside a clinical trial) decisions after a positive SLN biopsy must be made in the context of the overall treatment plan, but at present, completion ALND should be offered to most patients with a positive sentinel node diagnosed in the operating room. For patients whose positive node is discovered on permanent histopathology, ALND should be performed for those with macrometastases (deposits greater than 2 mm), should be optional for those with micrometastases (with consideration of axillary irradiation instead in patients having breast-conserving therapy), and should not be performed for those with metastases smaller than 0.2 mm. Patients with positive SLNs who choose not to undergo ALND should be informed of their potential increased risk of axillary nodal recurrence.

Ductal carcinoma in situ

The majority of cases of DCIS are currently detected as mammographic microcalcifications. The initial diagnosis of DCIS will generally be based on an MIBB. The pathologic findings from an MIBB must be integrated with all imaging information before a therapeutic decision is made. Ultimately, the final treatment decision requires careful examination of all excised tissue and must include removal of all radiographically and clinically abnormal tissue.

The Panel agreed that invasive cancers likely develop from in situ carcinomas and that most DCIS lesions have the potential to develop into invasive cancer, although, in some cases this may take many years. Longterm followup of DCIS treated with surgery alone suggests that grade, size, margin width, necrosis, and age play the most important roles in determining risk of subsequent invasive disease.

A metaanalysis of all four randomized trials that compared excision alone to excision plus radiation therapy (more than 3,600 patients) showed that radiation therapy reduced the relative local failure rate by more than 50% for all patients but did not improve breast cancer-specific or overall survival.[14] The prospective trials were not powered to define subsets whose absolute benefit from radiation therapy is so small that the risks of radiation therapy outweigh the benefits. Inability to define such a subset was the result of inadequate pathologic methodology by current standards. The panel strongly endorses the new College of American Pathologists guidelines that have the potential to avoid this problem in the future.

A number of retrospective single institution and prospective cooperative group studies suggest that for some patients the absolute benefit of radiation therapy in reducing local failure rates may be so small that omitting radiation therapy is an acceptable alternative. Such favorable subgroups include individuals older than 60 years with smaller, widely excised lesions (especially margins equal to or greater than 10 mm) of low- and intermediate-grade histology. Based on these data, in 2008, the National Comprehensive Cancer Network (NCCN) accepted excision alone as an alternative treatment for patients with "low risk" DCIS, although this entity was not explicitly defined.[15]

The role of hormonal therapy for patients with DCIS is unsettled, and there are currently no guidelines available to assess benefit based on risk of recurrence. The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-24 showed a small but significant reduction of local invasive recurrence as well as new contralateral breast cancer in patients with DCIS treated with tamoxifen for 5 years after excision and radiation therapy. Tamoxifen did not have a significant impact on ipsilateral in situ recurrences.

There is evidence that the benefit of tamoxifen in this trial was confined to patients with estrogen receptor-positive DCIS, which comprises about 80% of cases. In contrast, tamoxifen did not reduce the risk of local failure in patients with DCIS treated with lumpectomy with or without radiation therapy in the United Kingdom, Australia, and New Zealand trial. Aromatase inhibitors are currently being evaluated as an alternative to tamoxifen for adjuvant therapy of DCIS in postmenopausal women.

Although tamoxifen reduced the risk of developing new contralateral breast cancers in patients with DCIS, neither the United Kingdom, Australia, New Zealand trial nor the National Surgical Adjuvant Breast and Bowel Project B-24 trial showed any survival benefit. Tamoxifen is associated with side effects that are life altering (eg, hot flashes and vaginal dryness) and potentially life threatening (eg, increased incidences of endometrial cancers and venous or cerebral thromboembolic disease), particularly in older individuals. A risk-benefit analysis should be performed for each individual patient to assess the appropriateness of using tamoxifen. For low risk lesions that are widely excised, the benefit is likely to be very small and could be outweighed by the risks, especially in older women who have a higher incidence of serious toxicity from tamoxifen.

Because DCIS, by definition, does not metastasize to regional lymph nodes, SLN biopsy generally has no role in the staging of DCIS. But since the diagnosis of DCIS is most commonly made using percutaneous biopsy techniques, the possibility of finding an invasive cancer at the time of definitive surgery must be considered. In light of this, the Panel supports performing SLN biopsy in patients with DCIS who will undergo mastectomy, because the morbidity of the procedure is low and because SLN biopsy cannot be performed later if occult invasive cancer is identified in the mastectomy specimen. In addition, for patients contemplating breast-conserving surgery, performing SLN biopsy at the time of breast excision may be considered for any patient with lesions in whom there is a high probability of finding invasion on the final pathology examination. Such DCIS lesions include those that are palpable, those with equivocal microinvasion on core biopsy, those that are high grade, and those larger than 4 cm in radiographic extent. An alternative approach for such patients is to excise the lesion initially, with SLN biopsy to be performed at a later date, for the small percentage of patients who are found to have occult invasive cancer.

Oncoplastic surgery

Oncoplastic surgery combines sound oncologic surgical principles with plastic surgical techniques. A formal course on oncoplastic surgery has been given at the American Society of Breast Surgeons Annual Meeting for 5 years and

has routinely been fully subscribed, indicating the intense interest in the subject among surgeons. Coordination of the surgical oncologist and plastic surgeon is encouraged and may help to avoid poor cosmetic results after wide excision. In addition, oncoplastic surgery may increase the number of women who can be treated with breast-conserving surgery by allowing surgeons to perform larger breast excisions with negative margins and acceptable cosmetic results. Combined with proper use of neoadjuvant chemotherapy and breast imaging, oncoplastic surgery can further increase the breast conservation rates. The Panel strongly supported the incorporation of oncoplastic techniques into surgical breast cancer practice. In cases where mastectomy is indicated, the Panel recommends that immediate breast reconstruction be routinely available for appropriate patients.

RADIATION ONCOLOGY
Treatment of invasive cancers with lumpectomy without radiation therapy

There is strong evidence that giving radiation therapy after excision improves breast cancer-specific survival rates, compared with observation, for patients with a high risk of local failure. The 2005 Early Breast Cancer Trialists' Group meta-analysis showed radiotherapy reduced the 10-year local recurrence rate from 29% to 10% for patients with uninvolved axillary nodes, resulting in a 5% reduction in the 15-year breast cancer-specific mortality rate (from 31% to 26%).[16]

More recent studies, including randomized trials performed in North America and Europe, show that local recurrence rates after excision plus antihormonal therapy may be quite small (10% or less) for certain highly selected subgroups of patients with invasive cancer not receiving radiotherapy. Although we do not yet know the optimal parameters of selection for such an approach, favorable subgroups may include individuals older than 65 to 70 years of age, those with smaller lesions, hormonally sensitive cancers of low- and intermediate-grade histology, and those with wide tumor-free margins. It may be acceptable to omit radiation therapy in some such patients. However, antihormonal therapy by itself cannot remedy the effects of inappropriate patient selection, inadequate surgery, or the avoidance of radiotherapy.

Accelerated partial-breast irradiation

Accelerated partial breast irradiation (APBI) is an approach that may allow more patients to undergo breast-conserving therapy more quickly, at lower cost, and with less risk of longterm complications. Techniques include brachytherapy (with interstitial implantation, balloon catheters with single or multiple lumens, or open single-entry devices with multiple

lumens), external-beam radiation therapy, and single-dose intraoperative radiation therapy. More than 20 studies using interstitial implantation or balloon brachytherapy have shown excellent 5-year local control with low complication rates, including two prospective American studies with 7- and 10-year followup. As yet, however, only one modern randomized prospective clinical trial has been published comparing APBI with whole-breast radiation therapy.[17] With a median followup of 66 months in 258 patients, there was no significant difference in local recurrence rates between the arms with improved cosmesis in the APBI arm.

There are few studies of APBI for patients with DCIS, although such patients are included in trials addressing this approach, such as the joint trial being conducted by the National Surgical Adjuvant Breast Project and Radiation Therapy Oncology Group (RTOG). But because the pattern of failure for DCIS is similar to that of invasive breast cancer, it would seem likely that APBI would be as effective for DCIS as it is for invasive cancer.

At present, the optimal pretreatment evaluation, selection criteria, and technical parameters, including how to choose between the different methods for APBI, are not known. Several professional societies, including the American Society of Breast Surgeons, the American Brachytherapy Society, and the American Society for Radiation Oncology (ASTRO) have promulgated guidelines for the use of APBI outside formal protocols, though they do not agree on all the specifics.[18-20]

Breast-imaging technology, particularly MRI, has proved to be a valuable aid in selecting patients for APBI by detecting patients who may have multicentric breast cancer. Patients aged 50 or older with estrogen receptor-positive, node-negative, invasive cancers or DCIS measuring 3 cm or smaller with uninvolved microscopic margins were originally eligible for the National Surgical Adjuvant Breast Project B-39/RTOG 0413 trial, but they are no longer allowed to enter because of their low rate of local relapse. The Panel thought it reasonable to treat such "low risk" patients outside a clinical trial. The Panel agreed that "high risk" patients currently eligible for this trial should be treated within the context of a clinical trial. These high risk criteria include patients younger than 50 years old, with either invasive cancers or DCIS, positive axillary nodes, and patients aged 50 or older with hormone receptor-negative invasive cancer. Patients who should not be treated with APBI include those with invasive tumors or DCIS larger than 3 cm pathologically, those with four or more metastatic nodes or any number of positive nodes with extracapsular extension, positive final microscopic margins, and those who have been treated by neoadjuvant che-

motherapy. Certain subgroups of patients, such as large-breasted women or those with earlier breast augmentation, may have lower toxicity from APBI than traditional whole-breast irradiation. It is also possible to treat patients undergoing oncoplastic surgery (which usually closes the partial mastectomy cavity) with interstitial brachytherapy, external-beam methods, or intraoperative radiation therapy. For oncoplastic patients, giving APBI with postoperative intracavitary devices is not possible unless an adequate cavity has been left behind. Regardless of whether they are entered in a formalized trial or not, patients should be fully informed of the rationale, benefits, and risks of APBI as compared with whole-breast irradiation.

Accelerated whole-breast irradiation
Several prospective randomized trials have compared accelerated whole-breast irradiation (using fraction sizes of 2.5 to 3 Gy or more to total doses of 39 to 42.5 Gy) with longer regimens using smaller daily doses (total dose of 50 Gy in 2-Gy fractions). These trials have shown that these regimens have equivalent rates of local control and cosmesis at 5 and 10 years. It seems reasonable to use accelerated regimens for many patients similar to those entered into these trials. However, there are few data on the accelerated approach for particular subgroups of patients, such as those receiving chemotherapy, those needing a tumor bed boost (and how the boost should be given), patients requiring nodal irradiation, or patients with large breasts. There are also radiobiologic concerns that patients treated with larger fraction size may be at a disproportionate risk for developing late complications. A consensus panel was recently convened by the American Society for Radiation Oncology to address the optimal use of accelerated regimens.

MEDICAL ONCOLOGY
General
Patients should undergo careful history and physical examination after diagnosis of image-detected invasive breast cancer. A chest x-ray, complete blood count, and liver function tests should be obtained to assess for occult metastases and comorbidities that may affect systemic management. Computed tomography, radionuclide bone scan, or positron emission tomography should, in general, not be performed for asymptomatic lower risk patients (eg, T1N0) because the benefit of staging is outweighed by the risk of false positive results, cost, and limited positive predictive values.

Systemic adjuvant therapy for image-detected invasive breast cancer
Decisions regarding the use of systemic adjuvant therapy for patients with image-detected invasive cancer should be based on weighing the projected risk reduction of both recurrence and mortality afforded by specific therapies against the short- and longterm toxicities of therapy (eg, cardiomyopathy, leukemia). Patients are best counseled about these treatment options when an assessment of the absolute risk reduction is provided along with absolute risks of short- and longterm side effects based on their age and medical condition.

A number of resources available to physicians and patients through the Internet may be valuable in determining projected absolute benefits of therapy for defined risk categories. The program Adjuvant! Online gives estimates of recurrence (local and distant combined) and mortality risk and the associated benefits of adjuvant therapy, based on a statistical model using patient and tumor characteristics (www.adjuvantonline.com). The National Comprehensive Cancer Network guidelines for systemic therapy can be accessed at www.nccn.org.[15] All resources are limited by available data; for example, Adjuvant! does not include HER2/neu or progesterone receptor status as the majority of the trials used to calculate relative risk reduction did not include HER2 testing or central hormone receptor status assessment. In addition, relative risk reduction is not adjusted for tumor biology other than grade and estrogen receptor status, which may overestimate or possibly underestimate the potential benefit of chemotherapy.

Gene profiling
Gene profiling techniques for assessing risks of distant recurrence have become available since the last consensus conference. Two of the more commonly used assays have been validated using several sets of archival material. A reverse transcriptase polymerase chain reaction (RT-PCR)-based 21-gene test, which includes 16 cancer-related and 5 reference genes, was derived from a subset of available tumor blocks and validated with data from randomized trials. It is performed on formalin-fixed paraffin-embedded tissue and can be used to provide prognostic and predictive information for patients with node-negative, estrogen receptor-positive breast cancer and, more recently, for patients with low risk node-positive disease. As with any assay, there should be a clear plan about potential treatment decisions that will be based on the results of the test before it is ordered.

A 70-gene microarray-based test is also available in the United States but requires fresh tissue that must be saved in special transport media. This assay can potentially address prognosis for both patients with estrogen receptor-positive and estrogen receptor-negative disease. At present, data from the 70-gene test provides prognostic information but has not been validated for predicting response to treatment. These assays frequently provide a different estimate of risk

than Adjuvant! because they are based on individual tumor biology and can segregate tumors based on risk of distant recurrence (rather than overall recurrence), which correlates more closely with survival. Both genomic tools are relatively independent of size and appear to be independent of standard clinicopathologic criteria.

There remain uncertainties regarding the use of these tests in deciding whether to use adjuvant chemotherapy or not for an individual patient, beyond their additional expense. The studies validating the predictive power of the 21-gene test were performed on a subset of patients with long followup from two large randomized trials; the trial comparing chemotherapy plus tamoxifen to tamoxifen alone used an older type of combination chemotherapy (CMF). There are few data on its use in very young women and the benefit of chemotherapy in the intermediate risk group is indeterminate. The 70-gene assay has been evaluated in various databases, but not in a clinical trial setting. Although it appears that patients with good prognosis tumors do well regardless of the use of chemotherapy, this predictive function requires prospective validation. Two large randomized trials, Trial Assigning Individualized Options for Treatment (TAILORx) (using the 21-gene test) and Microarray in Node Negative Disease May Avoid Chemotherapy (MINDACT) (using the 70-gene assay) hope to answer several of these questions for both patients with node-negative and, eventually, node-positive disease.[21,22]

Hormonal therapy

Hormonal therapy should be considered for all patients with estrogen receptor- or progesterone receptor-positive invasive cancers, or both. Tamoxifen is effective in patients of any age, and aromatase inhibitors have demonstrated improved outcomes compared with tamoxifen when given up-front after diagnosis, or after a course of tamoxifen, but can only be used in postmenopausal women. Regardless of the agents used, hormonal therapy should be given for at least 5 years. The American Society of Clinical Oncologists, the National Comprehensive Cancer Network, and the St Gallen guidelines support the use of aromatase inhibitors in postmenopausal patients based on superior disease-free outcomes when used instead of or sequenced with tamoxifen.[15,23,24] For premenopausal women, the role of oophorectomy or ovarian suppression with GnRH agonists in addition to hormone therapy remains uncertain and is being studied in large trials.

Tamoxifen is metabolized to its most active metabolite, endoxifen, by the enzymes CYP2D6 and CYP2C19. Based on retrospective data, polymorphisms in CYP2D6 resulting in poor or absent metabolism of tamoxifen appear to affect both the severity of side effects and potentially the degree of benefit from this agent. At this time, no clear standards exist to guide the use of CYP2D6 polymorphism testing in routine decision-making regarding hormone therapy, particularly in premenopausal women. But patients on tamoxifen should be advised not to take drugs (including some common antidepressants) that are known to inhibit CYP2D6.[25]

Chemotherapy is recommended for patients with hormone receptor-negative tumors, typically greater than 1 cm, and higher risk hormone receptor-positive disease. For women with node-negative estrogen receptor-positive, or low risk node-positive tumors, gene profiling can aid in decision-making, with higher risk patients receiving chemotherapy followed by hormonal therapy and low risk patients receiving hormonal therapy alone. When chemotherapy is used for lower risk, estrogen receptor-positive disease, nonanthracycline regimens such docetaxel and cyclophosphamide can be considered because they have fewer longterm toxicities. For higher risk cases, anthracycline and taxane-based therapies are recommended. Whether or not anthracyclines can be omitted in certain patients based on assessment of tumor HER2 gene amplification or topoisomerase II gene mutation or deletion remains unknown and is under investigation in prospective trials. Ongoing studies with biomarker data will help determine optimal regimens for specific tumor biologic subsets in the future.

The benefits of chemotherapy in addition to hormonal therapy for women older than age 70 with hormone-responsive cancer are unclear. It is easier to determine the relative benefits of chemotherapy for hormone-receptor-negative or HER2-positive disease, where chemotherapy is generally highly effective and the risk of recurrence is highest in the first 5 years after diagnosis. In contrast, 50% of the risk of recurrence for patients with slower-growing estrogen receptor-positive disease occurs after 5 years, making the benefits of chemotherapy in older women harder to assess or to justify. Other competing causes of mortality should be considered when making treatment decisions, particularly for this latter group.

HER2 positive breast cancer

The addition of trastuzumab to chemotherapy (along with hormonal therapy and radiation therapy as indicated) is now recommended for patients with HER2-positive tumors with positive axillary nodes and for patients with HER2-positive, node-negative disease with higher risk features (eg, tumor larger than 1 cm or hormone receptor-negative). The absolute projected benefits of trastuzumab must be weighed against the small risk of cardiac toxicity, known to be higher in patients with preexisting cardiac disease (including hypertension) and older age. The use of trastuzumab is controversial for patients with node-negative HER2-positive tumors that are less than 1 cm in

size. These patients may still have a considerable risk of recurrence and could benefit from a limited course of chemotherapy with trastuzumab. It is not known if the benefit of trastuzumab will be seen in combination with hormonal therapy in the absence of chemotherapy or with single-agent chemotherapy.

ECONOMIC ISSUES

Therapeutic and diagnostic innovations have resulted in marked improvement in disease-free survival for the average woman with breast cancer. However, advances in technology and the introduction of new tests and techniques have placed increasing pressure on the financial system. Twenty years ago, a newly diagnosed patient with breast cancer received blood work, urinalysis, mammography and a chest x-ray before surgery. Postoperatively, estrogen and progesterone receptor assays were performed on the tumor. Today, that same patient will have preoperative mammography, ultrasonography, and probably an MRI in addition to any appropriate metastatic workup that might include positron emission tomography-CT. Many will have a radionuclide injection, guide-wires placed, the insertion of a balloon for radiation therapy, etc. She will also have measurement for HER2 status and perhaps genetic testing, gene profile testing, or both.

At the same time that costs are rising because of new technology, inadequate reimbursement of critical but less glamorous portions of the diagnostic and treatment pathways threatens to prevent further advances in patient outcomes. Reimbursement for mammography, a life-saving technology, is presently so inadequate that many radiology groups in the United States suffer a financial loss from performing it. Inadequate reimbursement along with very high medico-legal liability has created a disincentive to providing the service, resulting in a critical shortage of quality mammography facilities and in some areas a marked delay in access.

Histopathologic evaluation of sentinel lymph nodes, specimens from minimally invasive breast biopsies, or excision specimens of screen-detected lesions require careful mammographic and pathologic correlation, histologic evaluation of multiple levels of the specimen, and on occasion, immunohistochemical evaluation. Yet, such time consuming, intensive work is compensated at the same rate as many far less complicated procedures, often below the actual costs of the service. Inadequate reimbursement has created a severe economic disincentive that constitutes a major barrier to outstanding state-of-the-art medical care.

An example of an area in which large amounts of money can be saved while decreasing morbidity without any loss of diagnostic accuracy is in greater use of percutaneous breast biopsy. Approximately 35% to 40% of 1.7 million annual breast biopsies in the United States are still performed as open surgical procedures. If 90% of these 625,000 women had core biopsies rather than open biopsies, the annual savings would be $1.1 billion, based on Medicare total reimbursement rates of $1,165 for core biopsy and $3,169 for open biopsy in Southern California in 2009. Because most insurance companies pay somewhat more than Medicare, actual savings could be even higher.

Greater savings might come in other areas as well. It is possible that many of the 110,500 women estimated to be diagnosed annually with ADH, ALH, lobular carcinoma in situ, papillomas, radial scars, and columnar alteration with atypia could be managed without open excision.

Perhaps as many as one-third of the 62,000 patients diagnosed annually with DCIS could be treated with excision without radiotherapy. Such shifts would result in major financial savings for the health care system, and would reduce morbidity and out-of-pockets costs for patients caused by time out of work. Similarly, gene profiling has been shown to downstage risk of invasive disease more often than upstaging risk, resulting in a net reduction of chemotherapy usage.

As we pointed out earlier, many aspects of these issues are controversial. Nonetheless, it is clear that our current reimbursement structure creates serious obstacles to patient care. Such inadequacies must be rectified to ensure that the gains achieved in breast cancer treatment and survival during the last quarter century can be expanded. Finally, many newer innovations may generate significant cost savings that can fund their application.

In conclusion, the past two decades have seen major improvements in our ability to cure patients with breast cancer. These advances have been achieved largely through the use of screening mammography to detect lesions at earlier points in their evolution. Image-guided percutaneous biopsy, improvements in surgical technique, the widespread use of breast-conserving therapy, the substitution of sentinel lymph node biopsy for axillary dissection and innovations in radiation therapy have immeasurably improved the quality of life for patients with image-detected breast cancer. The Panel unanimously considers image-guided breast biopsy and SLN biopsy "best practices" and urges their incorporation into all breast care. Systemic therapy has played an increasingly important role in the care of such patients and is becoming more tailored based on individualized risk-to-benefit considerations and a better understanding of tumor biology. Further advances will depend on optimally using and reimbursing existing methods and systematically investigating new diagnostic and treat-

ment modalities. Increased physician and patient participation in clinical trials and prospective studies will greatly accelerate the latter process.

Appendix

How this document was written:

An agenda of issues to be discussed and questions to be answered was developed during the 6 months before the Conference. The group met at a hotel in Newport Beach, CA. All Consensus Panel members were present for the entire conference from Wednesday evening, June 10, until Saturday, June 13 at noon, with the exception of one who had to leave early. Panel members gave brief focused presentations on the agreed upon issues, followed by group discussion. The Panel was divided into five subgroups by specialty. During the course of the conference, each subgroup kept notes on issues within their field of expertise and was responsible for piecing together a section of the Consensus Statement that reflected their subgroup's position on various issues. In addition, three scribes took detailed notes of every issue discussed, consolidated them, and made them available to the Panel.

A writing committee (Ira Bleiweiss, Steve Harms, Roger Jackman, Suzanne Klimberg, Robert Kuske, Michael Lagios, Gary Levine, Abram Recht, and Melvin Silverstein) met after the conclusion of the conference to piece together a very rough draft of the Consensus Statement. A senior editorial group (Michael Lagios, Abram Recht, and Melvin Silverstein) was formed to advise, oversee, and edit the entire document during development.

Over ensuing weeks, subspecialty sections were developed and reviewed in detail by each member of the appropriate subgroup. Comments, corrections, additions, and suggestions were sent to the editorial center at Hoag Memorial Hospital Presbyterian in Newport Beach, CA. Revisions were made, and the section was recirculated. Each panel member had multiple chances along the editorial process to make changes within their subsection. When the subsection was completed, it was reviewed by the entire subcommittee, reedited, and revised as many times as necessary to get agreement on its final form. Once all subsections were accepted by their subcommittees, the entire document was assembled and reviewed by all participants. Changes were circulated among the entire group. After many revisions, the Consensus Document was accepted by all. The *Journal of the American College of Surgeons* made no changes other than minor editing.

Acknowledgment:

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