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

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In 2001, an international 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 to draft a special report detailing points of consensus.[1] A second, similar group (comprised of approximately 50% of the members of the first group and 50% new attendees), met in January 2005 to reassess some of the issues debated by the original panel, discuss the 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. All physicians who participated in the conference are listed in the Appendix.

Relevant issues considered in the first Consensus Conference are taken up again here, with revisions made as needed to account for advances that have occurred during the intervening 4 years. Some modes of diagnosis and treatment discussed by the Panel are widely used in the community; others are 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.

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Accepted basic concepts

Five basic concepts arrived at during the 2001 conference were accepted again and are reprinted here with slight modifications.

Early disease is a misleading term. Terms such as *early* or *late* are subjective and should be avoided. Instead, objective measures such as tumor size, histologic type and grade, nodal status, and biologic markers should be used to ensure uniformity in description and between clinical studies.

There is scientific evidence from randomized controlled trials that screening with mammography lowers mortality from breast cancer. Screening reduces the size at which tumors are detected and decreases deaths from breast cancer.

Breast cancer is a progressive disease at all its stages, and timely treatment and earlier detection can alter the natural course of the disease. Screening and detection of disease in preclinical or premetastatic stages affects treatment decisions and outcomes.

The rate of tumor growth is a function of both tumor and host characteristics. Genotypic and phenotypic drift (worsening) of the malignancy grade or dedifferentiation occurs, albeit at different rates, in different cancers and age groups.

Recognition and adequate treatment of ductal carcinoma in situ (DCIS) prevents future invasive events and is a cost-effective strategy. Given unlimited time, many untreated DCIS lesions will progress to invasive disease, but at a rate that will vary by tumor type and from patient to patient.

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Abbreviations and Acronyms

APBI = accelerated partial breast irradiation
DCIS = ductal carcinoma in situ
FISH = fluorescent in situ hybridization
NSABP = National Surgical Adjuvant Breast Project
SLN = sentinel lymph node

Imaging and biopsy

Screening and ancillary imaging

Mammography is currently the only imaging modality that should be used routinely to screen patients for breast cancer. Screening with ultrasonography is being investigated as an adjunct to mammographic screening; routine screening with ultrasonography, however, is currently not recommended.

There are increasing data supporting the use of MRI screening for younger patients at high risk of breast cancer because of the presence of a BRCA1 or BRCA2 mutation or strong family or personal history of breast cancer. The increased cost of MRI is acceptable in a population with a high prevalence of the disease. The high negative predictive value of breast MRI can effectively exclude infiltrating cancers larger than 5 mm. This is of great importance for high-risk patients, but the impact on survival using MRI is not known.

Lesions detected by screening mammography generally require additional evaluation with other imaging methods. Targeted diagnostic ultrasonography is useful in characterizing masses. It might also be helpful in detecting otherwise unsuspected invasive disease in lesions presenting as microcalcifications. In addition, for lesions presenting as masses, tumor size evaluation with breast ultrasonography is more accurate than mammography.

For cancers containing invasive and noninvasive components, a combination of imaging methods (mammography with magnification views, ultrasonography, MRI, or all) may yield the best estimates of overall tumor size (the size and geographic distribution of all invasive and noninvasive components).

Ultrasonography of the involved breast quadrant and axilla is recommended for patients who have Breast Imaging Reporting and Database System (BI-RADS) 4 or 5 abnormalities. If additional suspicious breast lesions or more extensive malignant breast disease is detected by ultrasonography, the extent of disease can be mapped with ultrasound-guided biopsies.

If an abnormal axillary 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. The value of sonography in assessing the extent of malignant breast disease and involvement of axillary lymph nodes is maximal when sonography and sonographically guided biopsies are positive for malignancy. If sonography shows only normal-appearing axillary lymph nodes, or if core biopsy or fine-needle aspiration of abnormal-appearing lymph nodes is negative, the surgeon should not be deterred from a sentinel lymph node procedure that would have otherwise been performed.

Breast MRI

The Panel spent a considerable amount of time discussing the increasing use and evolving data on the role of breast MRI. They agreed that, in skilled hands, breast MRI may be helpful 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 whether contralateral malignant disease is present;
4. assessing response and the extent of residual disease after neoadjuvant chemotherapy;
5. evaluating the breasts in patients with newly diagnosed adenocarcinoma in the axilla with an unknown primary;
6. pretreatment evaluation of patients with newly diagnosed breast cancer who have had breast augmentation with silicone- or saline-filled implants;
7. postoperative settings in which there is suspicion of residual disease; and
8. patients in whom mammography, ultrasonography, and clinical findings are inconclusive and no focal finding is apparent (eg, spontaneous single duct nipple discharge, diffuse microcalcifications, extensive cysts or fibroadenomas, silicone injections, subtle architectural distortions, and so forth).

MRI of both breasts can be performed in a single session, obtaining both high-resolution and dynamic information (ie, the time-course of contrast uptake and washout). Dynamic information should not deter biopsy of morphologically suspicious lesions.

Focal or segmental abnormalities seen only on MRI are typically either benign proliferative changes or ductal carcinoma in situ. These are conditions in which pathologic evaluations are facilitated by acquisition of larger tissue samples, so it is strongly recommended that these biopsies be performed with 11-gauge or larger vacuum-assisted technology.

Tools for performing MRI-directed biopsies are commercially available, and this capability should be available in most communities. Breast MRI should not be performed as a standard procedure in a setting where minimally invasive histologic investigation of the abnormality is not possible.

All panelists strongly agreed that irrevocable treatment decisions (for example, mastectomy rather than breast conservation) must not be made based solely on MRI findings without correlation of other imaging modalities and image-directed histologic confirmation using either second-look ultrasonography or MRI for guidance. Breast MRI should be interpreted in the context of the patient's mammogram, ultrasonography, and clinical examination, and should be performed by radiologists specializing in breast imaging.

Some members of the Panel believed that MRI could be used to establish the need for biopsy for patients with focal, low suspicion ultrasonographic or mammographic findings, but most thought that the use of MRI for aiding benign-malignant differentiation is unproved. Benign findings on breast MRI should not dissuade biopsy of a lesion classified as BI-RADS 4 or 5 based on traditional criteria.

The Panel strongly encourages the use of the guidelines for the performance of breast MRI released by the American College of Radiology in 2004 and the lexicon for breast MRI included in the 2004 edition of the *Mammography Quality Standards Act (MQSA) Guidelines.*

Minimally invasive breast biopsy

Four years have passed since publication of the first consensus conference on image-detected breast cancer. At that time, the attendees indicated that percutaneous tissue acquisition techniques should be available for appropriately selected patients. The Panel thought that it was now time to substantially strengthen that statement, and uniformly agreed that minimally invasive breast biopsy is the optimal initial tissue-acquisition method and the procedure of choice for image-detected breast abnormalities. It should be readily available to all patients with image-detected lesions. They uniformly agreed that there are relatively few patients for whom excisional biopsy should be the initial procedure for diagnosis; there are few patients on whom minimally invasive breast biopsy is so difficult to perform, for technical reasons, that open biopsy is needed. The Panel agreed that a major goal of modern breast medicine is to minimize the number of patients with benign lesions who undergo open surgical breast biopsies for diagnosis.

Percutaneous histologic tissue-acquisition techniques include large-core biopsy (typically 12 to 14 gauge), vacuum-assisted biopsy (typically 7 to 11 gauge), and larger tissue-acquisition methods. A definitive diagnosis of cancer made using a minimally invasive breast biopsy permits optimal preoperative workup and planning. This may include a preoperative MRI and provision for the use of intraoperative ultrasonography. When a diagnosis of cancer has been made preoperatively, incisions can be planned and definitive surgery can generally be performed as a single procedure. With a preoperative diagnosis of cancer, clear margins are more likely to be obtained, sparing patients the additional morbidity of a second procedure and resulting in substantial cost savings.

Since the earlier conference, data have matured about needle acquisition techniques and avoidance of sampling error. In general, stereotactic guidance using vacuum-assisted devices with larger (11 gauge or greater) needles is the preferred approach for lesions presenting as microcalcifications without a mass. This method permits contiguous and more complete tissue acquisition than smaller-gauge needles.

Ultrasonography is the preferred biopsy guidance method for lesions visible on ultrasound. For smaller lesions (1 cm or less), percutaneous excision using a vacuum-assisted device is desirable because sampling error is substantially reduced in these patients and characterization of important pathologic parameters is more reliable. For larger (greater than 1 cm) BI-RADS 4 or 5 masses, l4-gauge core needle biopsy is sufficient, although even in such instances, pathologic parameters may be more reliably characterized when larger gauge needles are used. If percutaneous biopsy results in removal of the entire lesion or a substantial portion of it, a clip or other marking device should be inserted at the time of biopsy.

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. Regardless of the instrument used, correlation of histologic and imaging findings is essential.

Open biopsy procedures are not required in patients with histologically benign findings on percutaneous biopsy if imaging and pathologic findings are concordant. This includes small or incidental radial scars without

atypia, which can be definitively diagnosed as benign if multiple large cores are used.

Since the previous conference, additional data have become available about the need for surgical excision after percutaneous biopsy demonstrating a "high-risk" lesion. Patients with high-risk lesions, including atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ found on percutaneous biopsy may have DCIS or invasive cancer at the same site and should generally undergo surgical excision. The incidence of missing such important findings is markedly reduced with the use of vacuum-assisted biopsy and larger-gauge needles.

For some individuals with high-risk histologic findings, in whom careful correlation of imaging and histologic findings is concordant or breast MRI is normal, followup without surgical excision may be reasonable. Such patients remain at risk and should be monitored appropriately. The Panel strongly endorses the use of second opinions from experts in breast pathology about the precise pathologic diagnosis before deciding on such a course.

Pathology and prognostic issues

The second Consensus Panel reaffirmed that breast cancer is a remarkably heterogeneous disease with broad variations in behavior. The pathologist's interpretation, including assessment of microscopic tumor size, surgical margins, combined histologic grade, examination of the sentinel nodes, and the evaluation of immunohistochemical results, is critical to decision-making. There are no professional societies or regulatory guidelines about qualifications required of pathologists interpreting breast biopsies comparable with those that exist for radiologists reading mammograms. The Panel strongly believes that breast specimens should be interpreted by pathologists experienced in breast pathology interpretation to ensure optimum patient management.

Reporting

Currently, tumor size and standard grading are the most reliable pathologic predictors of outcomes for patients with invasive cancers without axillary nodal involvement. Both require careful evaluation.

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 recorded separately.

When reporting DCIS, the final pathology report requires documentation of nuclear grade, presence or absence of zonal comedo-type necrosis, predominant architectural patterns, measured extent of the lesion, and 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 DCIS Consensus Conference[2] about optimal tissue processing and reporting of specific features of a resection specimen for DCIS.

Evaluation of specimens after minimally invasive breast biopsy

After a minimally invasive breast biopsy, the amount of tissue processed for histologic diagnosis should ensure that a cancer will not be missed and that a benign lesion can be confirmed. Specimens from minimally invasive biopsy procedures should be fully embedded and thoroughly sectioned with appropriate levels to establish an accurate diagnosis.

The term *multifocal process* is not appropriate in the context of minimally invasive breast biopsy specimens and should not be used because some physicians might mistake this terminology to mean that the patient has widespread disease not amenable to breast conservation. No comment should be made on the margins of a minimally invasive breast biopsy, although explanatory comments about the extent of changes are useful.

Correlation of pathology and imaging studies is mandatory. The radiologist, the pathologist, or both must document this correlation. Each institution should have a policy and routine procedure in place for performing this task. The Panel strongly endorses a radiology and pathology correlation conference at which the histologic results of all minimally invasive breast biopsies are reviewed and correlated with the radiologic images. In case of discrepancy between the imaging and pathologic results, communication between the pathologist and radiologist is mandatory.

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 to the pathologist. In cases of percutaneous biopsy

of microcalcifications and mammographically localized open biopsies, the pathologist should review the specimen radiograph.

Overdiagnosis of atypical ductal hyperplasia as DCIS after minimally invasive breast biopsy is of concern, largely because some atypical ductal hyperplasias have similar histology to that of low-grade DCIS. The Panel encourages the use of expert second opinions when the distinction between atypical ductal hyperplasia and DCIS is equivocal and, for most patients, additional tissue for histologic evaluation should be obtained.

Specimen handling for surgical excisions

After open surgical excision, surgeons should present the pathologist with a specimen labeled to preserve three-dimensional orientation. Margins should then be inked. When the resection is for DCIS, and, ideally, for all cancer resections, the specimen should be processed sequentially in its entirety or, with very large specimens, sampled in a rigorous and documented fashion, allowing targeted return to the specimen for additional sampling, if necessary.

Specimen radiography or specimen ultrasonography (in the case of lesions that can only be seen with ultrasonography) should be routinely performed for all excisions of image-detected abnormalities to help document the success of the procedure in finding the target. Note that many lesions detected only by ultrasonography are visible on a specimen radiograph even when not prospectively visible on mammography. Documentation with specimen ultrasonography is required only in those rare instances in which the radiograph is unrevealing.

When specimen radiography is performed, two views (including an orthogonal one) are preferred. Substantial 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 that of the sequentially sectioned specimen, will help document the adequacy of excision margins, whether the lesion presented as microcalcifications or a mass. It may also help when the procedure is guided by ultrasonography or MRI. In all cases in which specimen radiography is available, it should be reviewed by the pathologist for radiographic-pathologic correlation.

Tumor size and margin assessment

The concept of how to define tumor size originated in an earlier era, when cancers were generally diagnosed as large, palpable tumors 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*, which is related to survival and the risk of developing distant metastases. The prognostic size is the maximum extent of the largest invasive component, which is used for staging purposes in the current American Joint Committee on Cancer and International Union Against Cancer classifications. This must be estimated by the pathologist by direct gross measurements, if possible, and confirmed by microscopic measurement from slides when appropriate.

The second meaning may be termed *overall size*, which includes the full extent of the malignant process. This includes all invasive lesions and DCIS components. Overall size is generally larger than the prognostic size, is related to the probability of local recurrence, and is critical in determining the ability to perform cosmetically acceptable breast conserving surgery with adequate margins. Information from mammograms, ultrasonography, and MRI should be correlated with pathology to establish the best estimate of both prognostic and overall sizes.

A patient with a lesion made up of a 10-mm infiltrating ductal carcinoma within a 50-mm ductal carcinoma in situ would be considered to have a prognostic size of 10 mm (T1b) and an overall size of 50 mm. Although the patient's overall prognosis should be excellent, it may be difficult to excise her lesion with adequate margins to treat her with breast-conserving therapy.

The Panel strongly agreed that both prognostic and overall sizes should be clearly described by the pathologist. Mapping the extent of the entire lesion is essential in making treatment decisions. Invasive and noninvasive components should be measured and reported separately. Size should be described to the nearest millimeter. The relationship of both invasive tumor and DCIS to each margin should be described separately. The closest margin for either the invasive component or DCIS will determine the overall margin status used for making additional decisions about local therapy.

Tumor markers

Estrogen receptor status, progesterone receptor status, and HER-2 status have documented clinical usefulness as tu-

mor markers and should be obtained on all patients with invasive breast cancer. Estrogen receptor and progesterone receptors are useful in determining choice of therapy, particularly hormonal therapy. Data also suggest that hormone receptor-negative tumors have a slightly higher benefit from chemotherapy. Estrogen and progesterone receptor status should be obtained in patients with DCIS if hormone therapy is being considered.

HER-2 status may help with prognosis, choice of cytotoxic therapy, choice of hormonal versus cytotoxic therapy, and eligibility for clinical trials. The exact weight of HER-2 status in decision-making needs more study, with some trials showing a lower benefit from tamoxifen therapy and a higher benefit of anthracycline therapy in HER2-positive patients.

HER-2 status refers to whether or not the gene is amplified or the protein is overexpressed in a tumor. Amplification is most often measured by the fluorescent in situ hybridization (FISH) assay and overexpression by immunohistochemistry, and their results are closely correlated in the majority (85%) of tumors. Most of the discordances involve low-level (2+) protein overexpression, in which about a third of the cases are amplified, also at a generally low-level (two- to threefold). Although there are proponents of both assays, many experts see them as complementary and recommend immunohistochemistry for all primary testing followed by FISH in equivocal (2+) cases. Using this strategy, tumors with little or no expression (0 and 1+) are directly reported as negative, those with high (3+) expression are reported as positive, and equivocal (2+) tumors are retested by FISH and reported as positive if amplified and negative if not. Other experts recommend the use of FISH alone but, if performed properly, both strategies produce similar results.

Mitotic count is highly predictive of outcomes. Similar information is given by other measures, such as S-phase fraction or Ki-67, but mitotic count is readily available and more reliable. 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.

Treatment issues

Image-guided breast conserving surgery

The effectiveness of lumpectomy plus radiation therapy (breast conserving therapy) as an alternative to mastectomy is well established. Successful breast conserving therapy requires that the surgeon obtain clear histologic margins around the primary tumor. Unfortunately, reports from experienced centers demonstrate a "positive margin" rate of up to 30%. When the diagnosis of cancer is unknown before the breast operation, positive margin rates are even higher. So the Panel strongly believes that minimally invasive breast biopsy should be performed before definitive treatment in every possible case.

Several strategies help reduce the number of women who require return to the operating room for reexcision or mastectomy. These include the use of intraoperative ultrasonography to guide the initial resection and the placement of bracketing localization wires to define the limits of the resection. New technologies may also lead to more accurate resection of the neoplasm. These include preoperative lesion mapping with MRI and ultrasonography, and more sophisticated localization devices placed immediately before operation.

Sentinel lymph node biopsy

The Panel strongly endorsed sentinel lymph node (SLN) biopsy as the preferred method of pathologic axillary nodal staging for clinically node-negative, image-detected breast cancers. Although there are no longterm outcomes results yet from randomized trials (such as the National Surgical Adjuvant Breast and Bowel Project [NSABP] B-32, the ACOSOG Z-0010, and the Milan Trial), comparing SLN biopsy to conventional level I–II axillary dissection as the initial pathologic axillary staging procedure and there are no data comparing these two procedures as treatment for patients with negative nodes, there is a substantial body of evidence to indicate that SLN biopsy can be performed accurately, that this reflects the true status of the axillary nodes, and is associated with considerably less morbidity than axillary dissection.

Sentinel lymph node biopsy has the advantage of identifying, for the pathologist, nodes most likely to harbor metastases. This allows a more focused and intensive analysis, using multiple serial sections and, under some circumstances, immunohistochemistry.

Pathology laboratories should have an established protocol for SLN evaluation. Intraoperative evaluation of sentinel nodes, although not completely able to detect minimal volume metastases, allows performance of completion axillary dissection at the same operative session for the majority of patients, provided that the physician and patient have agreed ahead of time that this will be done in the event of a

positive intraoperative assessment. The plan of action when a SLN cannot be identified should also be discussed with the patient preoperatively.

The sentinel node should be examined intraoperatively using imprint cytology (touch preparation) or frozen section if a concurrent axillary dissection is planned and predicated on this finding. In the hands of experienced pathologists, touch preparations are preferred because they are as likely to sample small metastases as are frozen sections, but the touch preparations consume less nodal tissue.

The surgeons on the Panel strongly agreed about performing intraoperative evaluation of the sentinel node to reduce the need for a second operative procedure and, in particular, when return to the axilla at a later date might prove extremely difficult, for example, after an immediate latissimus dorsi flap reconstruction or immediate reconstruction with a free flap using blood vessels in the axilla. Overall, the Panel thought that handling of the sentinel node must be left to the discretion of the surgeon and pathologist, and that they must use the techniques they are comfortable with and that are appropriate for each individual patient.

Patients should be made aware of the possibility of a false-negative result with SLN biopsy. In the Panel's view, this risk is outweighed by SLN biopsy's established staging accuracy and reduced morbidity. Evidence indicates that surgeon experience improves the results of SLN biopsy. Adequate training and patient volume are required for surgeons offering SLN biopsy.

The plan of action when SLN metastasis is identified during the procedure should be discussed with the patient preoperatively. Completion axillary dissection should be performed routinely for most patients whose metastases are identified intraoperatively, except for those on clinical trials studying this issue. The routine use of cytokeratin immunohistochemistry for detection of minimal-volume SLN metastases (micrometastases or isolated tumor cells) should be discouraged until the results of prospective trials are available to determine their prognostic significance.

The significance of minimally involved (0.2 mm or smaller) axillary nodes is unresolved as to whether additional axillary treatment, systemic treatment, or both are indicated. The Panel agreed that currently, such findings should not by themselves be used to upstage the patient or to justify giving local, regional, or systemic therapy. The potential value of completion lymphadenectomy, under this circumstance, with respect to improved staging, local-regional control, and selection of subsequent therapy is unknown, but must be weighed against the increased morbidity. The majority of the Panel members concurred that completion dissection is not currently routinely indicated for patients with such minimal SLN involvement, although there was some disagreement on this point.

Whether axillary dissection can or should be avoided for patients with SLN metastases larger than 0.2 mm discovered on permanent hematoxylin and eosin stained microscopic sections is controversial. Current evidence is insufficient to identify specific subgroups of patients having a very low risk of residual nodal metastases (eg, less than 5% to 10%), but estimates can be made using the Memorial Sloan-Kettering Web site, www.nomograms.org. Available data about the risk of additional nodal metastases when the SLN is found to harbor metastases should be discussed with each patient. Options for these patients include performing completion axillary dissection, giving axillary radiotherapy, or giving no additional specific axillary treatment.

These approaches (completion axillary dissection, giving axillary radiotherapy, or no additional specific axillary treatment) have different implications as to the accepted goals of axillary therapy (to determine prognosis, to achieve regional nodal control, and to make decisions about systemic therapy) and as to the potential goal of improving survival. Evidence is currently insufficient to determine whether completion axillary dissection is preferable to the two other approaches, but it is the historic "gold standard" against which the other modalities should be measured. Unfortunately, data to determine which of these approaches is best will not be available in the near future because the American College of Surgeons Oncology Group Z0011 trial closed early because of inadequate accrual (Z0011 randomized sentinel node positive patients to completion dissection versus observation). It is currently unclear if sufficient numbers of patients were accrued on trial Z0011 to detect differences between groups. Fortunately, European trials comparing these alternatives are in progress.

Considering the current lack of objective data, the Panel believed that decisions about what to do after a positive SLN biopsy must be made in the context of the overall treatment plan. Currently, completion axillary dissection should be offered to most patients with metastases greater than 0.2 mm. Patients who choose to

omit completion axillary lymph node dissection after the finding of a positive sentinel node should be informed of the potential increased risk of axillary nodal recurrence and its consequences and other options for treatment, such as radiation therapy.

Treatment of ductal carcinoma in situ

Diagnosis and treatment of DCIS will generally be based on the results of a minimally invasive breast biopsy, which must be integrated with all imaging information before a final therapeutic decision is made.

The Panel agreed that invasive cancers likely develop from in situ carcinomas and that all DCIS lesions have the potential to develop into invasive cancer, although in some patients, this may take many years, exceeding in some cases the life expectancy of the patient.

Randomized trials have shown that radiation therapy after lesion excision for DCIS substantially reduces local failure for patients with tumor-free margins, but radiation therapy does not produce a survival benefit. Single-institution studies suggest that for some patients, the absolute benefits of radiation therapy in reducing local failure rates may be so small that omitting radiation therapy is acceptable to the patient. Such favorable subgroups likely include older individuals with smaller, widely excised DCIS lesions of low- and intermediate-grade histology. Recently completed and ongoing trials in North America and Europe are attempting to evaluate whether such results can be replicated in a multiinstitutional setting. Currently, however, there are no data from randomized trials to confidently determine which combinations of patient age, margin status, tumor size, and histologic features will result in an "acceptable" risk of local failure (ie, 10% or less at 10 years) for patients with DCIS treated without radiation therapy.

Hormonal therapy did not reduce the risk of local failure in patients with DCIS treated with lumpectomy without radiation therapy in the single randomized trial to date examining this topic (United Kingdom, Australia, and New Zealand Trial). This trial and the B-24 trial (NSABP) had conflicting results about the impact of tamoxifen on local failure rates in patients treated with lumpectomy and radiotherapy. The reduction in local failure rate for patients treated with tamoxifen in the B-24 trial was limited to patients with estrogen receptor positive DCIS.

Although tamoxifen reduces the risk of developing new contralateral breast cancers in patients with DCIS, neither the United Kingdom, Australia, or New Zealand trial nor the NSABP B-24 trial showed any survival benefit from tamoxifen. Likewise, the role of tamoxifen for contralateral breast cancer risk reduction in patients who undergo ipsilateral mastectomy for DCIS remains controversial. Tamoxifen may cause side effects that are life-altering (eg, menopausal symptoms, hot flashes, vaginal discharge) and life threatening (eg, increased incidence of endometrial cancer, thrombosis, and pulmonary embolus), particularly in older individuals. A risk-benefit analysis should be performed on an individual patient basis to assess the appropriateness of tamoxifen therapy.

There is evidence that the benefit of tamoxifen is confined to patients with hormone receptor-positive DCIS. For low-risk lesions that are widely excised, the benefit may be very small and could be outweighed by the risks, especially in older women who have a higher frequency of tamoxifen-related morbidities. Aromatase inhibitors are currently being evaluated as an alternative to tamoxifen for adjuvant therapy of DCIS in postmenopausal women.

Because DCIS, by definition, does not metastasize to regional lymph nodes, SLN biopsy generally has no role in the staging of DCIS. But because the diagnosis of DCIS is most commonly made using minimally invasive breast biopsy techniques, the possibility of finding an invasive cancer in some patients at the time of definitive surgery must be considered. In light of this, the Panel supported 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, SLN biopsy may be considered for any patient with DCIS when there is a reasonable probability of finding invasion on final pathologic examination. Such lesions include those that are palpable, lesions with equivocal microinvasion on core biopsy, 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.

Treatment of invasive cancers with lumpectomy without radiation therapy

Currently available evidence, including recently published results from randomized trials in North America and Europe, suggests that for some patients with invasive cancer treated with hormonal therapy, the absolute

benefits of radiation therapy in reducing local recurrence after excision might be quite small. So it may be acceptable to omit radiation therapy in some of these patients. Although we do not yet know the optimal parameters of selection for such an approach, favorable subgroups may include older individuals, those with smaller, hormonally sensitive cancers of low- and intermediate-grade histology, and those with wide tumor-free margins. Hormonal therapy cannot, however, remedy the effects of inappropriate patient selection or inadequate surgery.

Recent trials in patients with T1 cancer with negative axillary nodes that show a lower risk of local failure after excision plus tamoxifen do not show that the addition of radiation therapy improved breast cancer specific or overall survival (eg, the Ontario-British Columbia trial, Cancer and Leukemia Group B trial 9394). But these trials have insufficient followup to determine whether or how much radiation therapy might improve longterm outcomes.

Longterm radiotherapy data are available from the 2000 Oxford metaanalysis, but they do not reflect the image-detected patient population that we are discussing here. They were accrued at a time when most patients presented with palpable and generally node-positive breast cancers. For patients with a high risk of local failure after excision alone (eg, 30% or more), especially those with positive nodes, the metaanalysis revealed that adding radiation therapy improves breast cancer specific survival.

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. Several nonrandomized studies using interstitial implantation had excellent 5-year results in preventing ipsilateral breast tumor recurrences, but they contained only small numbers of highly selected patients with invasive cancer. The American Society of Breast Surgeons has completed accrual of more than 1,500 patients to a registration study of APBI (using a balloon catheter delivery system) in selected patients at low risk for local recurrence. Early findings demonstrate that the approach is safe and well tolerated, but longterm recurrences and cosmetic results are not yet available. There are no published data on the results of APBI for patients with DCIS, although such patients are being evaluated in current trials.

There are no data yet from contemporary randomized trials comparing APBI with whole-breast radiation therapy. Such trials are currently underway (for example, the recently opened NSABP B-39/RTOG 0413 trial in North America). At this time, patients and physicians are best served when APBI is performed as part of a clinical trial.

Oncoplastic surgery

Oncoplastic surgery combines sound oncologic surgical principles with plastic surgical techniques. Breast surgical fellowships should be encouraged to include training in oncoplastic techniques. 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. In cases where mastectomy is indicated, the Panel recommended that immediate breast reconstruction be available.

Minimally invasive breast surgery

The Panel was intrigued by the possibility of performing minimally invasive breast cancer therapy using either percutaneous internal resection to completely remove the tumor or interstitial ablative therapy that destroys the carcinoma without the need for resection. Tools for complete percutaneous removal are being developed. Techniques of interstitial ablative therapy currently under investigation include laser interstitial therapy, radiofrequency, high-frequency focused ultrasonography, cryoablation, and microwaves. One or more of these investigational approaches may, in time, become effective alternatives to conventional open excision. An important challenge for this approach is how best to determine whether residual disease remains in the breast after ablation. Imaging techniques, such as MRI, may help achieve this goal. For now, such approaches remain investigational and use of these modalities is discouraged outside the context of clinical trials.

Systemic adjuvant therapy for image-detected invasive breast cancer

Patients should undergo careful history and physical examination after diagnosis of image-detected invasive breast cancer. It is reasonable to obtain a chest x-ray, complete blood count, and liver function tests to assess patients for comorbidities that may affect their manage-

ment. CT or radionuclide bone scans should not be performed for asymptomatic clinically node-negative patients because benefits are outweighed by the risk of false-positive results and a low yield of true-positive results.

Decisions about the use of systemic adjuvant therapy for patients with image-detected invasive cancer should be based on the projected risks of recurrence and death and the risk reduction afforded by specific therapies, balanced against the short- and longterm toxicities of therapy (eg, cardiomyopathy). Patients are best counseled about these treatment options when absolute risk reduction is discussed and compared with risk reductions presented in relative terms.

A number of sources available to physicians and patients through the Internet may be very valuable in helping make such assessment. Estimates of recurrence and mortality risk and the associated benefits of adjuvant therapy based on patient and tumor characteristics are available at the Web site, www.adjuvantonline.com. Guidelines for systemic therapy can be accessed at, www.nccn.org.

Hormonal therapy should be considered for all patients whose risk is sufficient to warrant intervention and who have estrogen receptor- or progesterone receptor- positive cancers: tamoxifen for patients of any age and aromatase inhibitors, either after or instead of tamoxifen, for postmenopausal patients. Regardless of the agents used, hormonal therapy should be given for at least 5 years.

Chemotherapy is recommended for patients with hormone receptor-negative tumors, and higher-risk hormone receptor-positive patients whose risk is sufficient to warrant intervention. Regimens should include both an anthracycline and taxane for patients with higher-risk lesions and a good performance status. Studies currently are open that are designed to determine an optimal regimen. The benefit of chemotherapy in addition to hormonal therapy for women over 60 years of age with hormone-responsive cancer, or for those over 70 years of age with any cancer, is unclear. Other competing causes of mortality should be considered when making treatment decisions, particularly for this latter group. Systemic therapy may not be of benefit for patients with very low-risk lesions (such as tumors of low histologic grade smaller than 1 cm). For such patients, a reasonable option may be to omit systemic therapy.

The integration of biologic therapy targeting HER2 (trastuzumab) into the adjuvant setting is the subject of active ongoing clinical investigation. In April 2005, two phase III trials of adjuvant trastuzumab were stopped early after a preliminary joint interim analysis demonstrated an improvement in the primary end point of disease-free survival and in the secondary end point of overall survival for the group receiving trastuzumab. The trials, conducted by the NSABP and the Intergroup, compared trastuzumab plus chemotherapy with chemotherapy alone as adjuvant therapy for women with nonmetastatic, stage II and III, HER2 positive breast cancer. More detailed data on the nature of the benefits and side effects are awaited.

Recent studies have shown that multigene expression analysis of either fresh-frozen tissue or paraffin-embedded tissue is potentially useful for classifying breast cancers, predicting response to chemotherapy, and assessing prognosis. But there are many technical issues and uncertainties about this approach. For example, microarray gene expression analysis traditionally requires mRNA extracted from fresh-frozen tumor tissue, the process is not yet standardized, there are numerous competing platforms, and it is expensive. It is not yet clear how much additional information is given by such assays, compared with more widely available or less expensive measures, such as proliferative indices or mitotic rate. Nevertheless, the Panel is optimistic about this approach and strongly supports more research and validation of these techniques.

Economic issues

Technologic innovations, improved skills of the professionals, and better understanding of the natural history of the disease have resulted in marked improvement in disease-free survival for the average woman with breast cancer. Continued improvement in outcomes, however, is threatened by inadequate reimbursement for critical portions of diagnosis and treatment.

Reimbursement rates for screening mammography, which is clearly responsible for improvements in breast cancer survival, are so inadequate that for many radiology groups in the US, the procedure results in a financial loss. The Panel expressed concern that the availability of high quality diagnostic imaging may be challenging to support with current rates of reimbursement.

Image-guided percutaneous breast biopsies are less invasive, less traumatic, less disfiguring, and less costly than open surgical biopsies. Reimbursement should be adequate to make these options widely available.

Evaluation of specimens from minimally invasive breast biopsies, excision specimens of screen-detected lesions, and sentinel nodes requires careful mammographic and pathologic correlation, histologic evaluation of multiple sections, and on occasion, immunohistochemical evaluation, yet, such time-consuming, intensive work is compensated at the same rate as many far less complicated procedures. Such inadequacies must be rectified to ensure that the gains achieved in breast cancer survival during the last quarter century can be expanded.

In conclusion, the last half of the 20th century saw the development of several revolutionary innovations in breast cancer care. Foremost among these was the development of mammography as both a screening tool and a diagnostic tool. Mammography markedly reduced the size and stage at which breast cancers were detected and accelerated efforts at breast conservation.

In the 4-year interval since our first Consensus Conference, both ultrasonography and MRI have become more widely available and accepted. MRI has been shown to have great potential for determining the extent and focality of malignant disease within the breast and as a screening modality in high-risk populations.

Two additional recent innovations, percutaneous minimally invasive breast biopsy for diagnosis, and the substitution of SLN biopsy for a standard level 1 and 2 axillary dissection, were discussed as promising innovations at our first Consensus Conference. During the interval, minimally invasive breast biopsy has been recognized as the optimal diagnostic procedure for image-detected breast cancer; and SNL has become the preferred approach for axillary evaluation of an image-detected breast cancer. Both have resulted in marked reductions in the cost of treatment and have spared many women from an unnecessary open surgical biopsy and the potential morbidity of an axillary dissection.

A continuing reevaluation of treatment modalities emerged from the current Consensus Conference, which recognized the utility of pathologic subset analysis. These data may be used to select patients who are at an extremely low risk of recurrence. Many of these women can be spared adjuvant radiation therapy, chemotherapy, or hormonal therapy.

Innovations in treatment, including the use of oncoplastic techniques to preserve cosmesis, although still achieving an adequate resection and accelerated partial breast irradiation, have become more available and can enhance results for an individual patient.

The use of molecular signatures to define the risk of distant recurrence or the likely response to a chemotherapeutic regimen for an individual patient has recently emerged. New developments in this area are eagerly awaited but will require rigorous comparison with conventional, and, currently, far less expensive prognostic indicators. The summary effect of all of these innovations has been to provide more focused and more effective care with a reduced risk of morbidity and mortality for breast cancer patients.

Advances in outcomes will depend on optimally using existing methods and systematically investigating new diagnostic and treatment modalities. Increased physician and patient participation in clinical trials and prospective studies is strongly recommended by the Panel and will greatly accelerate the advancement of breast cancer diagnosis and treatment.

Appendix

How this document was written

At the conclusion of the conference, a small group (the Writing Committee) met for three hours and drafted an overview document. A professional science writer listened to the entire conference and took copious notes. She took the overview and pasted within appropriate sections hundreds of comments, that were made during the consensus conference. Three of us (MJS, MDL, and AR) then edited the entire document and divided it into three main sections (imaging, pathology, and treatment). The participants were divided into three subcommittees: imagers, pathologists, and clinicians, consisting of medical, surgical, and radiation oncologists. The sections were then e-mailed to one reviewer at a time. Pathologists reviewed the pathology section, imagers reviewed the imaging section, and clinicians reviewed the treatment section. Each review was then returned to the editorial center at the University of Southern California, and the suggestions were incorporated into the document if appropriate. Once each section had been reviewed by every member of the appropriate subcommittee, the completed section was then reviewed by the entire subcommittee and reedited. This took multiple drafts and revisions. Once all sections were accepted by their subcommittees, the entire document was assembled and reviewed by all participants. Changes were circulated among the entire group and after many revisions, the document was accepted. The entire editing process took just under 4 months. The *Journal of the*

American College of Surgeons made no changes, other than minor editing.

The conference was attended by senior representatives from the *Journal of the American College of Surgeons* and from the Department of Continuing Education, Keck School of Medicine, University of Southern California.

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REFERENCE

1. Image-detected breast cancer: state of the art diagnosis and treatment. International Breast Cancer Consensus Conference. J Am Coll Surg 2001;193:297–302.
2. Consensus Conference Committee. Consensus Conference on the Classification of Ductal Carcinoma In Situ, April 25–28, 1997. Cancer 1997; 80:1798–1802.