Proceedings of September 2003 National Meeting

Improving Information About Treatment Options for Women with Stage Zero Breast Cancer

National Center for Policy Research for Women & Families

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The National Center for Policy Research for Women & Families held a national meeting, *Treatment Options for Ductal Carcinoma in Situ and Lobular Carcinoma in Situ,* on Monday September 22, 2003, under a contract from the Office on Women's Health in the United States Department of Health and Human Services, and with additional support from the National Cancer Institute and NIH's Office for Research on Women's Health.

The meeting took place at the National Institutes of Health in Bethesda, Maryland from 8:30 a.m. to 4:30 p.m. The meeting, which was by invitation only, brought together a dozen of the country's most knowledgeable and well-respected experts on DCIS and LCIS, including surgical oncologists, medical oncologists, radiation oncologists, radiologists, and pathologists.

The goal was to find the common ground and to determine areas of agreement among experts regarding treatment recommendations that could be made available to patients, health care professionals, and cancer support groups.

Stage Zero Breast Cancer

The number of women in the U.S. diagnosed with DCIS or LCIS has increased dramatically in recent years. Research indicates that there are significant regional disparities in the treatment of early-stage invasive (Stage 1 and 2) breast cancer, as well as treatment disparities related to the type of medical facility, the age of the physician, and patient age. Although there is little research specifically on treatment disparities for DCIS or LCIS, it appears that some of these treatment disparities may apply to either or both.

For the last few years, many experts have agreed that breast-sparing surgery is an appropriate therapeutic option for many patients with DCIS, and that LCIS does not require surgery beyond the initial diagnostic biopsy. Nevertheless, many patients across the country are undergoing mastectomies for low grade DCIS and bilateral mastectomies for LCIS. These examples indicate that the research results that are already available are

not always having as much impact as expected on the treatment of DCIS and LCIS patients nationwide.

Participants in this conference discussed research and clinical information about the effectiveness of various treatment options for DCIS and LCIS. Since there are disagreements on several diagnostic and treatment issues, we focused on looking for areas of agreement and recommendations that can be made to patients and providers. Our goal was to ensure that DCIS and LCIS patients, regardless of their income, age, race, ethnicity, where they live, and where they receive medical care, have access to accurate, understandable information about their treatment options.

The conference included 17 participants and 9 observers.

Participants

Jeffrey S. Abrams, MD, Associate Chief, Clinical Investigations
National Cancer Institute
Laura Esserman, MD, MBA, Professor, Surgery/Radiology
University of California San Francisco
Suzanne Haynes, PhD, Senior Science Advisor
U.S. Department of Health & Human Services
Wanda Jones, DrPH, Director of Office on Women's Health
U.S. Department of Health & Human Services
Michael D. Lagios, MD, Medical Director
Breast Cancer Consultation Service
Terry P. Mamounas, MD, Associate Professor of Surgery
Northeastern Ohio Universities College of Medicine
Medical Director of the Aultman Cancer Center
Beryl McCormick, MD, Clinical Director of the Department of Radiation Oncology
Memorial Sloan- Kettering
David Page, MD, Professor of Pathology & Epidemiology
Vanderbilt University Medical Center
Abram Recht, MD, Deputy Chief of the Department of Radiation Oncology
Beth Israel Deaconess Medical Center
Eva Rubin, MD, Clinical Director, Breast Imaging, Montgomery Radiology Associates
Montgomery, AL
Stuart Schnitt, MD, Co-Director of Anatomic Pathology
Beth Israel Deaconess Medical Center
Melvin J. Silverstein, MD (by telephone)
Director of the Harold E. & Henrietta C. Lee Breast Center
USC/Norris Cancer Center
Fattaneh Tavassoli, MD, Director of the Breast and Gynecologic Pathology
Yale University School of Medicine
Timothy Whelan, MD, Associate Professor of Medicine, McMaster University**,**
Director of the Supportive Cancer Care Research

William Wood, MD, Chairman of the Department of Surgery
Emory University School of Medicine
Diana Zuckerman, PhD, President and Executive Director
National Center for Policy Research for Women & Families
JoAnne Zujewski, MD, Medical Director of Clinical Research Operations
National Cancer Institute

Observers

Sharon Horwitz, MD, Chairperson of the D.C. Chapter of "Women in Medicine"
American College of Physicians
Janet Joy, PhD, Senior Program Officer & Staff Director of the Breast Cancer Project
National Institutes of Medicine of the National Academies
Anna Levy, MS, Deputy Director
National Cancer Institute, Office on Women's Health
Lorna Patrick, Public Health Advisor
National Cancer Institute, Office of Education and Special Initiatives
Elizabeth Patterson, MD, Representing the National Medical Association
University of Pennsylvania, Former Faculty of the Breast Imaging Section
Mark R. Somerfield, PhD, Director of Clinical Affairs
American Society of Clinical Oncology
Jennifer L. Brooks, PhD, Senior Policy Research Associate
National Center for Policy Research for Women & Families
Jill Follows, RN, JD, Senior Health Policy Fellow
National Center for Policy Research for Women & Families
Elizabeth Santoro, RN, MPH, Health Policy Fellow
National Center for Policy Research for Women & Families

The topics that were discussed include imaging, pathology, surgery, radiation therapy, and other adjuvant treatment. The goal is to provide information that would be useful to patients, physicians, and other healthcare professionals.

This summary has been reviewed by all participants. Observers also had the opportunity to review this summary but the document does not include their views and is not intended to reflect the views of their organizations.

Lobular Carcinoma In Situ (LCIS)

What is LCIS?

There is considerable controversy about the definition and nomenclature of LCIS. Since LCIS is not harmful , calling it "carcinoma" or "cancer" is unnecessarily frightening to patients. There was agreement that what is commonly called LCIS is a proliferation of neoplastic cells with a characteristic pattern that does not extend beyond the lobules of the breast. It does not metastasize, but is indicative of a patient's future risk of developing invasive breast cancer in either breast, estimated to be about .5% -1% per year

over the next 10 years. Therefore, LCIS slowly but steadily increases the risk of developing invasive breast cancer over 10 to 20 years, compared to the average risk of women who do not have LCIS. That increased risk will be larger or smaller according to other factors, such as family history. The risk of invasive cancer is slightly lower in the contralateral breast compared to the breast in which the LCIS was diagnosed. Nevertheless, most women with LCIS will not develop invasive breast cancer.

LCIS should be considered a condition to be managed rather than a disease that needs to be treated. It is a marker of increased breast cancer risk, and that risk can be reduced by treatment and other strategies. The panel agreed there is no need for surgery after biopsy in the breast where LCIS has been diagnosed and no need for biopsy or other surgery in the contralateral breast.

The focus of the meeting was on treatment, rather than terminology. However, participants agreed that LCIS is not cancer and the term was frightening to patients. The 2003 World Health Organization classification of breast cancer lists “lobular neoplasia” as the preferred designation rather than LCIS. There have been efforts to change the term “LCIS.” For example, for many years a closely related condition has been referred to as atypical lobular hyperplasia (ALH) but not every physician uses the term and ALH is frequently misdiagnosed as LCIS. There was a range of opinions among participants on how essential it was to change the "LCIS" terminology in order to reduce over-treatment resulting from fear of being diagnosed with "cancer." Some participants strongly believe that the current terminology creates serious problems, and others shared those concerns but thought that it would be very difficult to persuade doctors to use a different terminology.

Imaging

LCIS is found incidentally in breast biopsies performed for both clinical and mammographic indications. It is most often detected on biopsies that were performed because of microcalcifications identified on a screening mammogram. The microcalcifications are usually associated with the benign rapid production of cells in adjacent breast tissue rather than with the LCIS lesion itself.

Pathology

It was agreed that the pathologic diagnosis of LCIS is based on cellular features and their pattern of growth rather than location. It can be described as a neoplastic proliferation of epithelial cells that are confined to the mammary ductal-lobular system. It is known for multicentricity and bilaterality. Classic LCIS is characterized by the smaller type A and the larger type B cells, which are diploid with low proliferation rates. Variant forms such as those with comedo necrosis and pleomorphic nuclei (referred to as pleomorphic LCIS) are increasingly being recognized. There is emerging evidence that there are some variants of LCIS that may be different. Pleomorphic LCIS appears to have features of higher grade lesions. However, because they are rare, and because outcomes are not well understood, there is uncertainty about these lesions and consultation with an expert should be sought.

On a genetic level, some studies suggest that LCIS is caused by mutations that inactivate e-cadherin. LCIS is almost always hormone receptor positive; however, pleomorphic higher grade lesions may not be. It was also agreed that there are no pathologic features of LCIS that are consistently associated with the subsequent risk of invasive cancer. Consequently, pathologists are not able to determine if a patient has a high or low risk. There was no agreement on where to draw the line between atypical lobular hyperplasia (ALH) and LCIS.

What about Core Needle Biopsy?
There was discussion about what should happen if LCIS is discovered on a core needle biopsy. No agreement could be reached on the necessity of performing additional imaging or repeat needle or excisional biopsy on women with LCIS found by core needle biopsy. However, there was agreement that the decision to perform, or not perform, additional diagnostic evaluation in these patients should be governed by whether the imaging features were concordant with the histologic findings. For example, if a mass or highly suspicious focus of calcifications prompted the original biopsy, a diagnosis of LCIS alone would only rarely explain the imaging findings. An additional evaluation, usually involving another biopsy, would often be necessary to ensure that the suspicious area on the mammogram was adequately excised.

The Role of Surgery
There is no established role for surgical treatment of LCIS beyond the diagnostic biopsy. Surgery is performed after an abnormal mammogram to determine whether a cancer is present. If the diagnosis of LCIS is based on an excisional biopsy, there is no need for further surgery. If diagnosis is made by core needle biopsy, then subsequent management may require additional imaging, depending on the level of concordance between the imaging and the biopsy material. It was also agreed that there is no need for pathologists to report on the margin status in excision specimens, unless an unexpected invasive ductal carcinoma or DCIS were detected.

The expert panel agreed that LCIS itself is not a direct risk to life, and that the condition itself poses no danger. Instead, it is a signal of increased risk of developing a potentially dangerous disease. LCIS alone is not an indication for prophylactic mastectomy of one or both breasts. It is important to explain to each LCIS patient that bilateral mastectomy would not affect her survival, and that the risks usually outweigh the benefits. However, some conference participants oppose bilateral mastectomy in virtually every case, while others believe that the patient should be able to choose to undergo a bilateral mastectomy, after discussing the option with her physician, and taking into account prior experience, family history, and the personal impact of the various alternatives.

Radiation Therapy
Radiation therapy does not have a role in the management of LCIS.

Adjuvant Therapy
There is no established role for chemotherapy in the management of LCIS. Although the risk of invasive breast cancer is only about .5% -1% per year over the next 10 years, this

is at least twice the risk compared to the average woman, and in some cases considerably higher. Tamoxifen can be used to reduce the risk of invasive cancer in women with LCIS.

Management and Treatment
Management decisions should be based on competing health risks and patient preferences. The treatment of LCIS should reflect the fact that the goal is to manage risk rather than to treat cancer. Rarely, there will be unusual or rare lesions of higher grade or large size (referred to as pleomorphic LCIS) that may warrant more aggressive management.

If cancer develops after LCIS, there is a higher chance that it could be of the invasive lobular type and therefore somewhat more difficult to detect on a mammogram. The need to improve strategies for screening was discussed, but no agreement was reached.

MRI does not have an established role in the evaluation of women with LCIS, but may in the future for women with very dense breasts who are at high risk of breast cancer.

Ductal Carcinoma in Situ (DCIS)

What is DCIS?
DCIS is most frequently defined as a non-invasive ductal cancer. Dr. Wood pointed out that in situ "cancers" are not true cancers, since they lack the capacity to invade or metastasize. Several participants agree with Dr. Wood; however, since DCIS can become an invasive cancer, there is no agreement about whether DCIS can best be described as a non-invasive cancer or as a condition that is not cancer but can progress to cancer. Dr. Tavassoli agreed with Dr. Wood and expressed concern that the word "carcinoma" should be changed since it leads to over-treatment. She prefers alternative terminology, Ductal Intraepithelial Neoplasia, but several others in the group disagreed. Although there was disagreement about whether DCIS should be called cancer, all the experts agree that DCIS is a non-invasive condition that is commonly called cancer and that patients should be told that it is different from other breast cancers.

There is agreement that DCIS can usually be treated with breast-sparing surgery rather than mastectomy unless the DCIS is extensive throughout the breast. A decision to perform a mastectomy due to cosmetic concerns is reasonable when DCIS is large or multi-focal, or when the DCIS cannot be surgically removed with a rim of normal tissue around it (clear margins).

The panel members agreed that radiation may not always be necessary after lumpectomy, because the risk of a local recurrence in some patients is already low even without radiation. Such patients are most likely those with small areas of low grade DCIS with wide margins. However, the group was unable to agree on exactly what combinations of tumor size, pathologic grade, margin width, and patient age are needed to safely omit radiation therapy. Additional research is needed to get agreement on these parameters.

Imaging

There has been an increase in detection of DCIS in recent years, due to the more widespread use of screening mammography. In earlier years, DCIS was sometimes detected in a clinical exam, but in recent years it is almost always detected by the appearance of calcifications on a mammogram. The calcifications that are biopsied are usually in the DCIS lesion, but may be unrelated to the DCIS.

It was agreed that there is insufficient evidence to predict outcome based on mammography. Nonetheless, the characterization of DCIS by imaging is important. This usually involves performance of magnification views in at least two projections. The need for surgical removal and pathological assessment are influenced by:

- the presence or absence of calcifications
- the type of calcifications
- the extent of the calcifications

When a biopsy or lumpectomy is being performed because of calcifications, the breast tissue that has been surgically removed should be examined with mammography to make sure the calcifications in question have been removed. Compression of this tissue is necessary to make sure it contains the calcifications targeted for surgical excision, but it was agreed that compression should be minimized and only enough to assure adequate imaging. It was also emphasized that the performance of orthogonal views of the tissue specimen with markers placed to define margins is extremely helpful and should be encouraged.

The role of MRI is under review.

Pathology

Proper specimen evaluation is essential, including specimen radiography for lesions detected because of an abnormal mammogram. Pathologic examination should include classification of the DCIS, evaluation of microscopic margins, and an assessment of the location of the microscopic calcifications, including an estimate of the size or extent of the lesion.

There was a difference of opinion among pathologists about how extensive the analysis of pathologic specimens should be; for example, how many slides should be examined per unit of tissue, and how much time the pathologist should spend examining each slide. During the meeting, considerable time was spent on the importance of careful evaluation of pathology specimens. Several participants expressed concern that efforts to save money by less comprehensive pathology analyses short-change the patient and ultimately cost more because patients are more likely to be over-treated. Those pathologists agreed that a more thorough examination of resections for DCIS would help patients and ultimately save money by improving the information available for appropriate treatment. One pathologist pointed out that the benefits of more slides would be lost if pathologists spent less time with each slide and therefore missed lesions that are difficult to detect.

The Role of Surgery

Everyone agreed that DCIS is not invasive breast cancer, and there was general agreement that the best course of action is a multi-pronged approach to treatment.

All apparent disease should be excised with a sufficient rim (margin) of normal tissue around it. Complete excision is desirable and effective, but may not be accomplished if the size of the lesion is large in comparison with the size of the breast.

The type of surgical procedure is influenced by patient preferences, age, breast size, extent and grade of lesion, margin width, and the results of the mammogram and pathology analysis.

The orientation of the specimen by the surgeon and the classification of the extent of the lesion by the radiologist and the pathologist are especially important when surgical options are being considered.

Specimen handling as outlined in the 1997 Philadelphia Consensus Conference was described as essential by several participants, but the specifics were not discussed at the meeting.

Mastectomy: Mastectomy does not influence the risk of mortality, but there are short-term and long-term health problems associated with mastectomy, and the loss of a breast can be traumatic.

Nevertheless, there are circumstances when mastectomy may be the preferred treatment option:

- a lesion is so large that lumpectomy would distort the shape of the breast, so that the result would be cosmetically unacceptable to the patient
- there is persistent margin involvement even after one or more attempts at excision (there was agreement that it is acceptable to do more than one attempt)
- if the patient prefers a mastectomy after an informed discussion of the equivalent safety of breast-sparing therapy and other advantages and disadvantages of both surgical options have been clearly explained

There was agreement that bilateral mastectomy is not recommended based on a diagnosis of DCIS in one breast.

The expert panel also agreed that radiation should not be recommended after mastectomy.

Breast-Sparing Surgery: There are well-known and widely accepted parameters used to decide on the use of breast-sparing surgery, including patient preferences, cosmetic result, margin width, nuclear grade, tumor size, age, results of post-operative mammography, and other histologic features. The difficulty is assigning values to them and deciding how to use them**.** These choices will not influence mortality, but could prevent recurrence. The endpoints are breast preservation, prevention of invasive

recurrence, minimizing the risks of treatment such as radiation and mastectomy, and lowering the risk of dying of invasive breast cancer.

The NIH Consensus Conference in 1991 agreed that for most patients with invasive early-stage breast cancer, breast-sparing surgery is preferable to mastectomy because it has an equivalent survival rate and preserves the breast. However, it is a common misconception of patients that mastectomy results in a better chance of survival.

For DCIS, most women also have a choice of treatment options. Each patient comes with her own set of values, and the trade-offs are different for each woman. Breast-sparing surgery followed by radiation is as safe as mastectomy and usually preferable. This option should be discussed with patients prior to having any type of breast surgery. However, women should not be pushed into a particular course of treatment unless there are clear reasons why one treatment option is preferable to the other for that individual patient.

What are Clear Margins?

A clear margin means that, in the tissue that is surgically removed, there is a rim of normal tissue surrounding the DCIS. This provides confidence that all of the DCIS has been removed. However, how much tissue or margin is necessary is a controversial issue, and considerable time was spent trying to reach agreement.

For patients who are considering excision without radiation therapy, some participants believe that the 1994 selection criteria for the Eastern Cooperative Oncology Group (ECOG) study provide useful parameters, although the study results are not yet available. Those criteria suggested that margins must be 3 mm or greater and be clear in all three dimensions, depending on the size of the lesion. Low grade lesions were to be no more than 2 ½ cm in size with a minimum of 3 mm margins. High grade lesions were to be no more than 1 cm in size with 3mm guaranteed margins. However, many participants were opposed to assigning numerical values because there are insufficient data to draw conclusions. These values can be influenced by many factors, and there was disagreement about whether providing these numbers as a guide is a better alternative than providing nothing at all.

It was agreed that wide surgical margins tend to reduce recurrence, with or without radiation, but may result in a less cosmetically appealing result. It is therefore necessary to balance the desire for wide margins with concern about cosmetic outcome, since most patients with DCIS will never have invasive breast cancer, even if they have narrow margins.

Since the survival rate for DCIS is extremely high regardless of type of treatment received, radiation therapy may be unnecessary for many DCIS patients; however, there was no agreement about how the specific information about clear margins could be used to determine which patients need radiation therapy and which do not. All participants agreed on the need to have uninvolved margins even for patients receiving radiation

therapy. Uninvolved margins are defined as having no DCIS at the outer edge of the surgically removed tissue.

Radiation Therapy

Radiation therapy after breast-sparing surgery generally reduces the risk of recurrence by at least 50%. Most women with DCIS are candidates for breast-sparing surgery and most participants agreed that breast-sparing surgery should usually be followed by radiation therapy. However, radiation adds to the cost of treatment and some women do not have access to radiation therapy because of the cost, their work or family responsibilities, or where they live. Also, for some women who have a low risk for recurrence, the radiation therapy may not add much absolute benefit in terms of reducing the chance of recurrence. Some meeting participants strongly believe that it would be unwise to use radiation if there was already an extremely low risk of local recurrence, such as for patients with small tumors and wide margins. However, there was no agreement on how to identify women at very low risk by defining small tumors and wide margins. On the other hand, if a woman has other health problems so that there is little concern about a long-term cure, there was agreement that this could justify the consideration of not using radiation.

There was agreement that the side effects, logistics, and the impact that this option will have on one's lifestyle during the treatment phase should be thoroughly explained to the patient. However, there was disagreement about how serious the side effects of radiation are.

Currently, approximately 50% of DCIS patients in the United States do not receive radiation therapy. There is disagreement among the participants about whether these statistics prove that radiation is not necessary or indicate that many women are not receiving appropriate treatment according to current research knowledge. Women in the U.S. are less likely to undergo radiation when the DCIS lesion is small and found to have widely negative margins. The advantages and disadvantages of radiation should be discussed with treating physicians, but the participants did not agree on exactly what advice should be given.

Tamoxifen

Tamoxifen decreases the future risk of recurrence after breast sparing surgery and radiation. Future risk of cancers in either breast is also decreased. It is unknown whether tamoxifen improves long-term survival, since long-term survival is very high for all patients who are treated, whether or not they take tamoxifen. Other hormonal agents such as raloxifene and aromatase inhibitors are also likely to benefit patients, but clinical studies are ongoing and there are no data available currently about their benefit for DCIS.

This option should be discussed with the patient and participation in clinical trials can be offered as well. Ongoing studies compare women taking tamoxifen and undergoing radiation therapy with patients taking an aromatase inhibitor plus radiation therapy. A study in the United Kingdom comparing tamoxifen versus placebo in patients not receiving radiotherapy did not show a reduction in recurrence, but the interpretation of

these results is open to questions due to the design of the study. Therefore, several meeting participants believe more studies are needed before conclusions can be drawn.

Estrogen Receptor (ER)

More data on estrogen receptor status are needed to assess who will benefit from hormone therapy. Based on the single study that has examined this question, ER positive women benefit from tamoxifen, but it is less clear whether women with ER negative DCIS do or do not. More research would be helpful to support these conclusions.

Acceptable Treatments for DCIS

Excision alone, excision with radiation and/or tamoxifen, and mastectomy are all potentially appropriate treatment options for DCIS in certain circumstances. Treatment decisions should be based upon the patients' preferences and the estimated chance of recurrence with these different treatments. This estimate is based on the size of the DCIS, the lesion's margin status, and other pathologic features. There is agreement on the safety of lumpectomy with radiation compared to mastectomy, but there is a lack of agreement on which patients should receive radiation or tamoxifen.

There was agreement about two issues related to lymph nodes. Participants agreed that axillary staging procedures are very rarely needed. There is no evidence that using special staining techniques, such as immunohistochemical (IHC), to identify scattered tumor cells in axillary nodes has sufficient prognostic value to affect treatment and therefore there was agreement that it should not be done, except for research purposes.

Surveillance

It was agreed that patients need to be followed carefully, but there are many plausible strategies and no agreement was reached on the specifics of how often to do follow-up visits. At a minimum, annual mammography should be performed; there is no agreement on which patients need mammography every six months or more frequently.