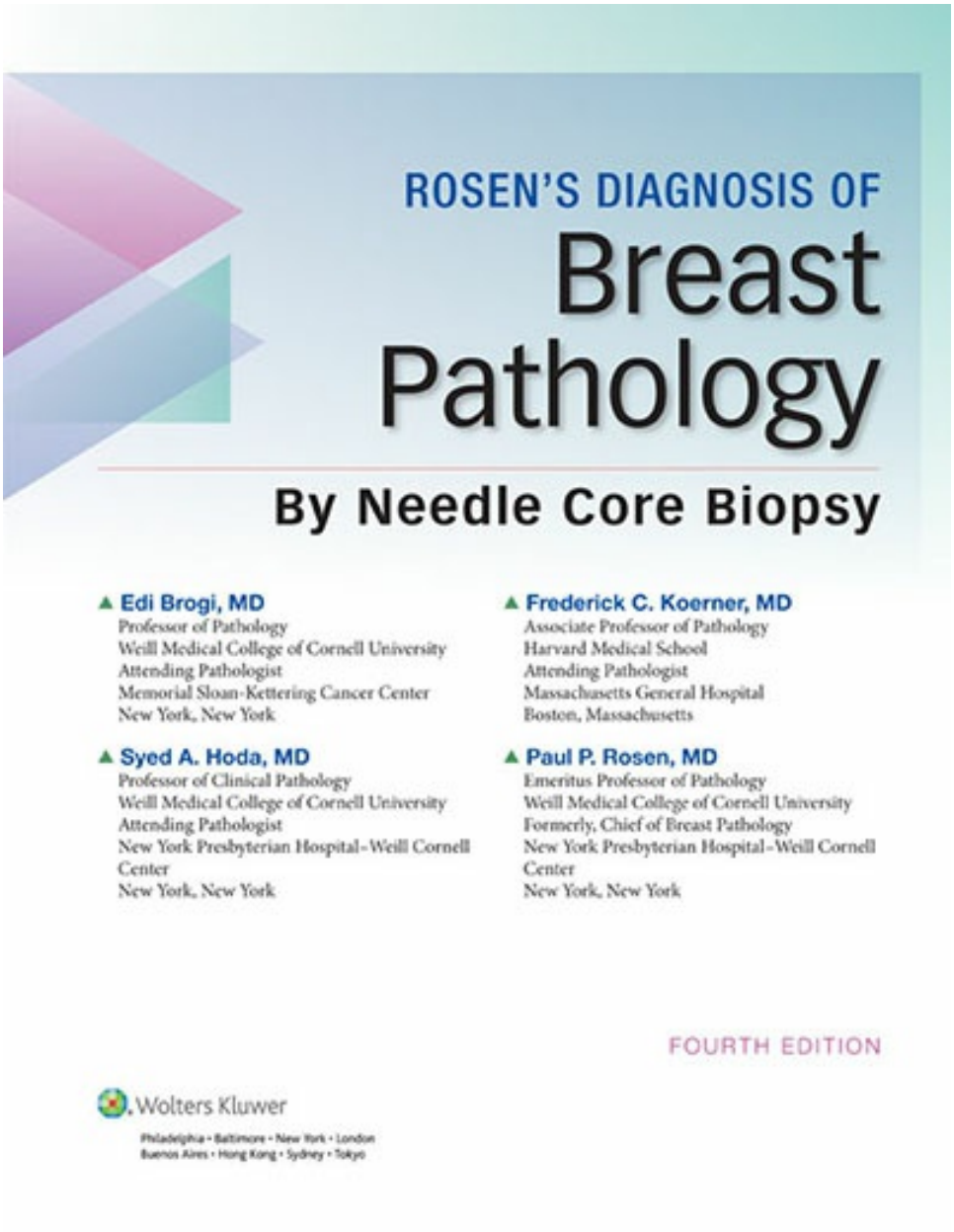
ROSEN'S DIAGNOSIS OF

Breast Pathology

By Needle Core Biopsy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Preface to First Edition (Updated)

Prior to the widespread implementation of breast conservation therapy, the role of the pathologist in breast cancer care was limited to making the diagnosis from tissue obtained by surgical biopsy and documenting the extent of the tumor after a mastectomy was performed. These two events typically centered around a single operative procedure in which the diagnosis made with a frozen section was followed by a mastectomy and axillary lymph node dissection. Presently, considerably more information is required to recommend breast cancer treatment that may employ more than one of the major existing therapeutic modalities: surgery, radiation, and chemotherapy. An important part of the data used for therapeutic decisions is generated by the pathologist using routine histopathologic procedures and immunohistochemistry.

The complex multifactorial description of breast pathology now considered to be standard practice has expanded the diagnostic report from a brief one- or two-line statement, such as "Infiltrating duct carcinoma, grade II; negative lymph nodes," to a catalog of data one or more pages in length, often including many statements indicating the absence as well as the presence of features regarded as relevant to therapeutic decisions and to prognosis. A partial list of this information includes classification of the carcinoma, histologic grade, nuclear grade, tumor size, and statements about vascular invasion, the proportion of the in situ component in invasive lesions, subtype of in situ carcinoma, multifocality, and proximity of carcinoma to margins of excision. Immunohistochemistry is used to characterize the distribution of estrogen and progesterone receptors, as well as other biomarkers and oncogene expression which are part of pathology reports. Proliferative activity may be estimated by the pathologist using immunohistochemistry.

Other advances have added to the complexity of the pathologist's role in breast cancer treatment. Primary among these is the widespread use of needle core biopsy procedures, especially for the diagnosis of nonpalpable mammographically detected lesions. Stereotactic needle core biopsy is an extremely valuable tool in planning breast conservation therapy because it can establish the diagnosis of nonpalpable lesions before operative surgical intervention. Needle core biopsy procedures often yield diagnostic samples,

but in a significant number of cases, the material obtained offers ambiguous findings that do not provide a specific diagnosis on which to base therapy. This is a limitation of the procedure and not a failure on the part of the pathologist or radiologist. When this situation arises, it is necessary for physicians caring for the patient to consider the entire clinical situation. This process of reflection is often referred to as "clinical correlation."

Many mammographically detected nonpalpable lesions present the pathologist with challenging diagnostic problems when excised intact and viewed in context with surrounding tissues. The appearance of such lesions in the incomplete and often disrupted form of needle core biopsy samples can substantially increase the degree of difficulty. The major differential diagnostic problems encountered in these specimens include:

- reactive changes versus recurrent carcinoma after lumpectomy
- benign sclerosing lesions (radial scar) versus infiltrating carcinoma
- papilloma versus papillary carcinoma
- fibroadenoma versus cystosarcoma
- atypical duct hyperplasia versus intraductal carcinoma (DCIS)
- DCIS versus DCIS with (micro)invasion
- spindle cell tumors (metaplastic carcinoma vs. sarcoma)
- vascular lesions (angioma vs. angiosarcoma)

Although self-evident, it is important to understand that the diagnosis made with a needle core biopsy specimen can be based only on the samples available to the pathologist and that these samples are not always representative of all of the pathologic findings in a given case. Consequently, carcinoma may be found in up to 50% of surgical biopsies after a needle core biopsy diagnosis of atypical hyperplasia, and microinvasion may be present in about 20% of surgical excisions after a needle core diagnosis of intraductal carcinoma. Three principles offer guidance in the use of the needle core biopsy procedure for the diagnosis and treatment of breast lesions:

- Anything can turn up.
- What you see is what you have, and it may not be all there is.
- What you have may be all there is.

The emergence of the needle core biopsy procedure as a major diagnostic tool epitomizes the growing complexity of the interaction of radiologists, surgeons, and pathologists in the diagnosis and management of mammary

diseases, especially in the era of breast conservation therapy. Specialization in medicine has created circumstances in which the specialist physician is increasingly dependent on the assistance of colleagues who have acquired complementary expertise. This evolving situation has contributed to the team approach to disease management reflected in this volume. The intentional limited scope of this presentation, which focuses on diagnosis, does not permit the inclusion of contributions from other important members of the team, including surgeons, radiotherapists, and medical oncologists who depend on these diagnoses to implement therapy.

Paul P. Rosen, MD

Introduction to the Third Edition (Updated)
Breast Imaging and the Origin of Needle Core Biopsy

Noninvasive techniques have been employed to study breast lesions since the beginning of the 20th century. The usefulness of this approach in the clinical setting has been dependent on technical advances that permitted the radiologist to detect lesions that were inapparent to the patient and physician, including clinically occult carcinomas. A consequence of this advance has been the need for a close working relationship between the practitioners of several medical specialties. The result is certainly one of the important examples of "team" management that requires the cooperative efforts of medical specialists to provide effective patient care.

The Beginning of Breast Imaging

Two methods of nonsurgical investigation of the breast were studied in the 1920s and early 1930s, namely, transillumination and radiography. As Cutler (1) reported, the idea for transillumination as a means of diagnosis "was first developed among the members of the laboratory staff of Memorial Hospital during the routine examination of breast specimens." Cutler also stated that "at the suggestion of Dr. Ewing, . . . Adair attempted to transilluminate breasts but encountered technical difficulties, chiefly due to the excessive heat developed by the transilluminating lamp." Although Cutler improved upon the light source, it is clear that transillumination offered little as a method of diagnosis except possibly as a way to distinguish between cystic and solid lesions. With widespread acceptance of needle aspiration of cysts, transillumination was abandoned and has now been replaced by ultrasonography.

The earliest radiologic studies of the breast reported in the United States in the 1930s by Fray and Warren, by Seabold, and by Lockwood were contemporaneous with similar investigations in Europe (2–7). When first employed clinically, it was apparent that roentgenography might prove helpful in the diagnosis of so-called early breast carcinoma. The definition of "early" has changed appreciably since this concept was introduced. This change is exemplified in a 1932 report by Fray and Warren (2) that described a 54-year-old woman who, on clinical examination, was thought to have chronic cystic mastitis. Roentgenologic examination revealed "a

small area of dense tissue with irregular margins . . . in the left breast." The lesion proved on biopsy to be a carcinoma "the size of a walnut." It was concluded by the authors that the early status (of the tumor) was reflected not only by its small size but also by the absence of macroscopic involvement of pectoral muscles. Today, the case described by Fray and Warren would be considered operable and potentially curable, but not "early." Within a relatively short period, the term "early" has come to be used for lesions of microscopic dimensions, often detectable only by imaging techniques that include mammography, ultrasonography, and magnetic resonance imaging (MRI).

The initial mammography studies were met with skepticism. In 1931, Seabold (5) described the mammographic findings in a series of cases presented to the Philadelphia Academy of Surgery. The summary of the discussion that followed his report included the following comment:

> Dr. J. Stewart Rodman said that any attempt to make the diagnosis more exact is certainly praiseworthy. Being a surgeon, however, he is not sure but that sometimes x-ray men have somewhat vivid imaginations. . . . The clinical diagnosis of carcinoma of the breast and chronic cystic mastitis is not ordinarily difficult, and therefore until we have x-ray evidence of a more positive value we had best go a little slow in accepting evidence which is contrary to clinical findings.

Gunsett and Sichel (7) stated in 1934 that their x-ray images might be useful in some cases, but that radiologic distinctions between benign and malignant lesions were not precise enough to form a basis for surgical treatment. They concluded that mammography would not replace biopsy as a diagnostic procedure. The warning offered in these comments is applicable today. The clinician faced with a palpable abnormality in the breast should not depend only on mammography to decide whether biopsy is required. On the other hand, advances in clinical mammography and the development of stereotactic biopsy instruments have made it possible to detect and perform biopsies on nonpalpable lesions found by "x-ray men" who "have vivid imaginations" (5).

The Beginning of Pathology–Radiology Correlation

The need to relate radiologic findings to the histopathologic examination of breast tissue has been appreciated since the earliest x-ray images of the breast were obtained. In 1913, Albert Salomon (8), a surgeon at the University of Berlin, described a method for obtaining roentgenograms of serial sections of surgical breast specimens in order to correlate histologic

observations with the specimen x-rays. The histologic appearance of calcification within a mammary carcinoma was described in his paper. Salomon may be credited with the first reported example of breast specimen radiography, and he deserves recognition for investigations that anticipated later developments in mammography and specimen radiography.

Detailed pathologic–radiologic correlations were carried out in the late 1920s by Dominguez (9–11) in Montevideo, Uruguay. Dominguez was especially interested in studying the properties of calcifications in breast lesions. In addition to specimen radiography, he undertook biochemical analyses of the calcium content of breast tissue. Conway (12) described the clinical radiologic appearance of calcification in breast cysts and sarcomatous tumors, but failed to appreciate the potential usefulness of calcification as an x-ray marker for carcinoma. Lockwood (3) stressed the importance of correlating pathologic and radiologic findings, but did not obtain x-rays of specimens, nor was there any mention of mammary calcification as an indicator of carcinoma in his report. Warren (6) described two cases thought roentgenologically to be carcinoma but reported to be benign on pathologic examination that "could not be studied because the specimens were thrown out before films could be made to locate the supposed small area of malignancy seen at the original examination."

The observations of Salomon, and later Dominguez, that calcium deposits in mammary carcinoma could be visualized radiologically remained largely unappreciated for nearly two decades. They were again brought to attention by Leborgne (13,14) in Montevideo, who developed a technique for soft tissue roentgenography that made it possibly to identify small tumors and calcifications in clinical mammograms. He noted that "the roentgenographic study of the operative specimen also permitted the localization of the tiny calcifications for histopathologic study, and thus aided in finding a small cancer that would otherwise have been overlooked." As had Gershon-Cohen and Colcher (15) some years earlier, Leborgne anticipated the role of mammography for detecting preclinical cancer when he stated:

> We firmly believe that the recognition and demonstration of this roentgenographic sign constitutes one of the easily observed aspects in which mammary cancer is presented, especially in its ductal form . . . and (is) therefore susceptible of detection in prophylactic examinations of women who do not yet present clinical tumor symptomology. With a systematic prophylactic roentgenographic examination of all women with antecedents of cancer in their family, we enter a new stage in the fight against mammary cancer.

The Origins of Needle Core Biopsy

The origin of modern needle core biopsy sampling of the breast to obtain a tissue specimen for histologic diagnosis is entwined with the history of needle aspiration biopsy and parallels the development of clinical mammography. Needles have been used to obtain samples for diagnosis from various anatomic sites since the middle of the 19th century (16). Needle aspiration sampling of the lung (17,18) and lymph nodes (19–21) was described by 1914. Many of the early biopsy attempts involved aspirating cells with a needle attached to a syringe. The aspirated blood and cellular material were expressed onto a slide and spread thinly to create a cytologic preparation.

The application of the needle aspiration biopsy technique to the diagnosis of neoplastic conditions attracted attention early in the 20th century. In 1921, Guthrie (22) reported that needle aspiration could be employed to evaluate the causes of lymph node enlargement. A method for aspirating cells from lymph nodes and the preparation of stained slides from this material was described in detail by Forkner (23,24), who also reported his experience using these samples for the diagnosis of cancer, including three women with adenocarcinoma in axillary lymph nodes.

The first concerted effort to employ the needle aspiration technique to the diagnosis of cancer was undertaken at Memorial Hospital in New York. In 1922, Ellis (25), a technician working under Dr. James Ewing, described cancer cells in cell block specimens of pleural fluid. Ellis concluded that "the diagnosis of cancer from direct smears is hazardous, but when one has made thin paraffin sections of suspected material and their evidence is fortified by some confirmatory clinical data, positive diagnosis may often be obtained." Four years later, Hayes Martin, a surgeon at Memorial Hospital; Fred Stewart, then the junior associate of Dr. Ewing; and Ellis began to use the aspiration biopsy technique in patients with head and neck cancer (26). In succeeding publications, they documented the applicability of the aspiration biopsy technique to a variety of tumors and defined the role of this procedure in the clinical management of cancer patients (27,28).

The Memorial Hospital technique proved to be the forerunner of what are now two largely separate methods of diagnosis: fine-needle aspiration (FNA) and needle core biopsy. The specimens obtained by Martin and his clinical colleagues included disaggregated cells for cytologic examination, equivalent to FNA today, and fragments of tissue that they described as the clot, a counterpart of the modern needle core biopsy specimen. Ewing, Stewart, and their colleagues were not prepared to rely entirely on cytologic smears, as evidenced by the importance they attached to the "clot,"

described in the following commentary by Godwin (29):

> After the material is obtained in the syringe, the negative pressure is released to obviate splattering of the aspirate in the syringe. With the rake, the material is placed on several slides and gently smeared by approximating two slides and pulling them apart. The remaining material is placed on a small piece of blotting paper or fibrin foam and put in formalin for later paraffin section. This is designated as the clot.

The clot was "helpful in many instances where the smear is not diagnostic and in making a more definitive diagnosis as to the type of tumor" (29).

The system of aspirating tumors for diagnosis implemented at Memorial Hospital in the 1920s and 1930s evolved as a result of experience gained by the participants in this effort. In a later review, Godwin (30) observed:

> The interpretation of aspirates, as with other pathological material, is certainly not without pitfalls. It requires experience. It is necessary that a sufficient number of cases be available for both clinician and pathologist to maintain their efficiency. The pathologist must know the clinical setting, the normal cells of the region, and the nature of lesions to be anticipated in the area.

Breast Specimen Radiography

Technologic developments in imaging have played a major role in advancing the use of needles to obtain tissue samples from lesions in superficial and visceral locations. The impetus for improving needle biopsy techniques for breast lesions began with the increasing utilization of mammography in the 1960s and 1970s. The mammographic detection of nonpalpable lesions presented a diagnostic challenge to the radiologist, surgeon, and pathologist, and led to the development of methods to localize nonpalpable lesions so that they could be found and excised by surgeons and sampled in the pathology laboratory. Various localizing procedures were introduced, employing needles, wires, dyes, and other markers placed in or near the lesion under mammographic or ultrasound guidance. After localization by the radiologist, the surgeon was guided by the marker. Radiographic examination of the specimen (specimen radiography) has been employed to confirm excision of a nonpalpable abnormality and to help the pathologist pinpoint the lesion for histologic examination (31–33). Specimen radiography has been particularly useful for lesions containing calcifications.

Under optimal conditions where a surgical biopsy was recommended for mammographic abnormalities with calcifications that were considered to be

suspicious for carcinoma, 25% to 30% of the excised lesions proved to be carcinoma (32,33). Thus, for each patient with a biopsy sample that revealed carcinoma, three underwent surgical excision of a benign lesion. The surgical management of nonpalpable breast lesions without calcifications was more difficult because specimen radiography was not very reliable for confirming the adequacy of excision. The availability of the modern needle core biopsy procedure to sample nonpalpable mammographically detected lesions made it possible to avoid surgical biopsy in a substantial number of women. Friese et al. (34) analyzed Surveillance, Epidemiology, and End Results (SEER)-Medicare data for 45,542 patients with intraductal and invasive stage I to II breast carcinoma diagnosed between 1991 and 1999. The frequency of needle core biopsy as the first procedure increased from approximately 20% in 1991 to 30.9% in 1999 ($p < 0.0001$), and there was a concomitant decrease in initial surgical biopsy procedures. Women who had a needle core biopsy procedure initially tended to have fewer surgical procedures overall than those whose first biopsy specimen was obtained surgically.

Modern Needle Core Biopsy Techniques

The introduction of stereotaxic devices in the 1970s resulted in improved needle localization and made it possible to obtain needle biopsy samples from nonpalpable lesions more efficiently (35,36). One of the first papers described a "stereotaxic instrument" that facilitated "percutaneous needle biopsy of the breast for microscopic diagnosis" (37). The authors reported that "the sampling site can be located at a precision of ±1 mm. The instrument can also be used for positioning of metal and dye indicators for guiding surgery and for postoperative identification of excised tumors." Linkage of this computer-guided localization system with the automated biopsy gun introduced in the 1980s (38) led to the development of modern stereotaxic core biopsy instruments (39). Ultrasound-guided core biopsy has proven to be particularly effective for nonpalpable lesions without calcifications. Stereotaxic MRI and ultrasound-guided core biopsy procedures are now widely used for the diagnosis of breast diseases. These technologies provide efficient methods for sampling small areas rapidly, with less morbidity and expense than surgical excision (40–42). Multifocal lesions are also accessible with this approach (43).

The use of needle biopsies for the diagnosis of breast lesions has expanded greatly in the past 25 years. A study based on Medicare patient data from 1990s found that only 24% of patients had undergone a needle biopsy (34). A population-based study from Florida published in 2011

reported that 70% of breast biopsies were needle biopsies (44). Analysis of Medicare data for the period 2003 to 2007 revealed that needle biopsy had been used in 68.7% of the 89,712 patients surveyed (45). In the latter study of Medicare patients, the likelihood of multiple carcinoma-related procedures was significantly ($p < 0.001$) lower among patients diagnosed by a needle biopsy (33.7%) than for those who did not have a diagnostic needle biopsy (69.6%) with an adjusted relative risk in the non-needle biopsy group of 2.08.

The Pathologic Examination of Needle Core Biopsy Specimens

Needle core biopsy procedures provide the pathologist with tissue specimens that are processed to produce histologic sections. While satisfying the preference of surgical pathologists for a tissue sample rather than a cytology specimen, needle core biopsy samples create new diagnostic problems and challenges. To some extent, these difficulties arise from the partial view of a lesion in the core biopsy specimen. This problem can be compounded by the heterogeneous nature of some tumors such as papillary and fibroepithelial lesions as well as carcinomas (46). The context of surrounding tissue afforded by sections of surgical biopsy specimens, important in some instances, is largely lacking in needle core biopsy samples. Nonpalpable lesions are frequently small abnormalities that can be difficult to interpret even in a complete excisional biopsy specimen, and they should not be submitted for frozen section examination except in extraordinary circumstances (47).

False-negative results for needle core biopsy samples are lower when specimens are obtained by using techniques that produce larger samples such as 11-gauge and vacuum-assisted instruments (48,49). Failure to sample a carcinoma that is present is more likely to occur in cases where the target is solely microcalcifications than a mass lesion (50). Consequently, intraductal carcinoma, especially the noncomedo type, is more likely to be missed than is invasive carcinoma. False-negative needle core biopsy samples can usually be appreciated prospectively because of discordance between the imaging studies for which the procedure was performed and the pathology diagnosis (51).

Relatively common diagnostic problems encountered in needle core biopsy specimens include the following: columnar cell lesions and atypical hyperplasia, radial sclerosing lesions and papillary tumors, lobular atypia, and lobular carcinoma in situ (LCIS). Unusual tumors previously encountered only in surgical biopsy specimens such as pseudoangiomatous stromal hyperplasia, mucocele-like lesions, myofibroblastoma, metaplastic

carcinoma, and hemangiomas are now the targets of stereotaxic needle core biopsy procedures (47,52). Today, virtually any lesion that occurs in the breast may appear on the pathologist's microscope in a needle core biopsy sample. The purpose of this book is to provide guidance in the interpretation of diagnosis of needle core specimens and the pathologic changes that occur in the breast as a result of these procedures.

Lesion Localization

The accuracy of needle core biopsy sampling is so precise that imaging evidence of the target may be lost after the procedure, and in some cases the lesion itself may be entirely extirpated (53,54). When all imaging evidence of carcinoma has been removed, up to nearly 80% of patients have residual carcinoma in a subsequent excisional biopsy. Lee et al. (55) reported that the MRI-targeted lesion was completely extirpated in 30% of carcinomas diagnosed by MRI-guided vacuum-assisted needle core biopsy. Nonetheless, 64% of patients whose MRI-detected lesion had been removed had residual carcinoma. Liberman et al. (56) found that the mammographic target was entirely removed in 100 of 214 (47%) carcinomas and that carcinomas remained in 79% of cases after complete removal of the imaging abnormality.

To assist the surgeon and pathologist in finding the site of a prior needle core biopsy where part, or all, of the lesion may have been removed, a clip may be placed in the biopsy cavity at the conclusion of the procedure. Sometimes, multiple clips are used to bracket a lesion or to mark more than one biopsy site. Clips of differing shapes are available, and various types may be employed with mammographic, sonographic, or MRI-guided biopsy procedures (55,57,58). Migration of clips (59), extraction of the clip during a vacuum-assisted biopsy procedure (60), and loss of the clip during surgical excision have been reported.

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DCIS Is DCIS Is DCIS

A Controversial Introduction to the Fourth Edition

As is apparent to most readers, the title to this discussion is a paraphrase of the oft-repeated and celebrated first line of Gertrude Stein's 1913 poem "Sacred Emily," which reads as, "Rose is a rose is a rose is a rose." Some say that Stein drew inspiration for this line from Juliet in Shakespeare's "Romeo and Juliet," who argued that Romeo would be the man she loved regardless of his Montague family ties when she said, "A rose by any other name would smell as sweet." However one puts it and whatever name is applied, a rose is a rose, although some varieties are red and others pink or white, and some roses smell sweeter than others. Apples are apples, although some are sweet and others are tart. Which brings us to ductal carcinoma in situ or DCIS. DCIS is DCIS regardless of the variety.

This discussion offers a rational, fact-based summary of current knowledge about DCIS as it effects treatment. In this space it is not possible, nor probably useful, to attempt a review of all of the voluminous published literature on this subject. The material presented has been selected to emphasize the highlights of the evolution of our understanding of DCIS and how this process led to the current treatment dilemma, and to consider some prospects for the future. Other writers might, in some instances, have selected different material or have chosen to emphasize their own contributions. The absence of any reference here should not be interpreted as an unfavorable opinion of that report.

As will become apparent in what follows, considerable progress made in the treatment of DCIS during the past half century has brought us to a crossroad as expressed by Esserman and Yau (1) in the title of their editorial titled "Rethinking the Standard for Ductal Carcinoma In Situ Treatment". The following essay is devoted to that issue.

The History of the Concept of In Situ Carcinoma

In the mid-19th century, it was widely believed that all neoplasms, including those with epithelial features, were derived from connective tissue cells or primitive mesenchyme (2).The recognition, approximately 160 years ago, that invasive carcinomas were preceded by a phase of growth that originated in epithelium, a stage later referred to as in situ, was a major

advance in understanding neoplastic disease. When Robert Remak (3) proposed, in 1854, that epithelial neoplasms were derived from the epithelial germ layer, his suggestion was referred to as an "extravagant hypothesis". In 1865, Thiersch's (4) research led him to conclude that squamous carcinomas of the skin and oral cavity arose from the epithelium at these sites, thereby anticipating Broder's use of the term *in situ carcinoma* in the oral cavity by 67 years. Coincidentally, the epithelial origin of carcinoma was recognized in France in 1865 by Cornil (5), who used the mammary gland as a model for his research. Cornil's (6) work included illustrations showing the close similarity between cells confined to the epithelium of origin (in situ) in lobules and the characteristic linear growth pattern of the invasive component now referred to as invasive lobular carcinoma. In 1867, Waldeyer (7), a German anatomist, illustrated the origin of mammary carcinoma from hyperplasia to invasion of the lobular and extralobular connective tissue. Writing about "primary acinar carcinoma" of the breast in 1928, Ewing (8) quoted Cornil.

One of the most complete descriptions of the origin of invasive mammary carcinoma from intraepithelial (in situ) carcinoma was published in 1931 by Cheatle and Cutler (9), who stated that:

> There are appearances of malignancy which prove conclusively that the carcinoma process in the breast begins in an epithelial neoplasia in ducts and acini which continues to grow there before and after there has been a transgression of normal boundaries by epithelial cells whose parents are still within the normal but distended structure. In these instances there is no doubt that these epithelial cells inside the normal boundaries are as histologic malignant as those that have transgressed them . . . the new property possessed by the epithelial cells of being able to invade, grow, and metastasize in outside tissues has been acquired and transmitted by their parent cells within normal boundaries.

This quote from Cheatle and Cutler is also notable for its reference to "epithelial neoplasia," which has been in wide use since the 1970s, and the intimation that invasive carcinoma arises when in situ carcinoma cells acquire and are distinguished by the capacity to invade, which is evidenced by their location but not by their appearance. Although the cells of in situ and invasive breast carcinoma may not be distinguishable histologically out of their microanatomic context, it is clear that invasive carcinoma cells have acquired properties that distinguish them from their in situ ancestors and/or that the surrounding host tissue has been altered to permit invasion to occur. Unraveling this puzzle will be a major step toward developing treatment

strategies that are targeted at the characteristics of in situ lobular or duct carcinoma and/or the host environment in an individual patient.

Introducing the term in situ carcinoma in 1932 with reference to squamous carcinoma, Albert C. Broders (10) emphasized the clinical importance of treating the in situ stage of carcinoma when he wrote,

> . . . if carcinoma in situ appears alone, its recognition is necessary, for failure to recognize it may constitute an error of omission fraught with grave danger to the patient; if it goes unrecognized carcinoma is allowed to masquerade as a benign or not more than a precancerous process with the possibility of its becoming too far advanced to be amenable to treatment.

The idea that leaving in situ carcinoma *untreated* posed a "grave danger" to the patient was to dominate the treatment of breast carcinoma, leading to the widespread use of mastectomy for LCIS and DCIS for decades thereafter.

Anecdotal Reports of Untreated DCIS Prior to 1978

Untreated in this and other comparable reports means that no intervention other than the original diagnostic biopsy was performed to excise a palpable abnormality. Margins were not cleared, and no further surgery was performed after the initial excision. In most cases, the patients were not under surveillance in this era predating the regular use of mammography. This would not qualify as adequate breast conserving surgery by today's standards, and under these circumstances, it is not surprising that the first evidence of subsequent carcinoma was almost always a mass representing invasive carcinoma.

Prior to 1978, there were no prospective published studies of untreated DCIS and no retrospective studies of a large cohort of consecutive patients. Anecdotal reports before 1978 (11–14) described a total of 48 selected patients, including some with papillary and comedo DCIS, who had not been treated for a variety of reasons. During an interval of 1 to 12 years, 21 of the 48 patients (43.8%) were found to have subsequent carcinoma. The largest series in this group consisted of 25 women with untreated DCIS in a consecutive cohort of 200 DCIS patients treated at a single institution (12). There were various reasons for the absence of treatment other than the diagnostic biopsy. Carcinoma other than the original DCIS was found during follow-up of 1 to 8 years in 5 of the 25 (20%) women. The subsequent carcinomas were described as being "within or nearby the previous excisional site."

A Systematic Study of Untreated LCIS and DCIS

As the basis for a systematic study of the "natural history" of untreated LCIS, Rosen personally reviewed all available histologic slides from breast biopsies interpreted as not showing carcinoma at Memorial Hospital in New York City between 1940 and 1950 (15). The material reviewed consisted of 12,052 slides from 8,609 cases. This exercise uncovered 124 instances of previously undiagnosed and/or untreated in situ carcinoma (99 LCIS and 25 DCIS), representing 1.4% of the entire cohort. Because in this time period it was customary to sample a very limited portion of a grossly benign-appearing biopsy specimen, the average number of slides available per case was 1.4. Consequently, the 1.4% frequency of undiagnosed in situ carcinoma in these patients is probably a low estimate. Follow-up was sought for all of the 124 patients. The results were reported separately for LCIS (15) and DCIS (16).

The Example of LCIS

For nearly 30 years after its recognition, the standard treatment for LCIS was a mastectomy. Beginning in the 1970s, controversy began to swirl around the treatment of LCIS. The Memorial Hospital report (15) and other similar follow-up studies of patients with LCIS in one breast that was not treated after the initial diagnostic biopsy showed that:

a. the risk of subsequent invasive carcinoma was nearly equal in both breasts;
b. the majority of subsequent carcinomas were of the duct rather than lobular type; and
c. the interval to the appearance of subsequent carcinoma was a decade or more in a substantial number of patients.

These observations led some clinicians and researchers:

a. to consider LCIS exclusively to be a "marker" for increased breast carcinoma risk;
b. to urge that the lesion be referred to by such terms as "lobular neoplasia," or as "lobular intraepithelial neoplasia" (LIN), rather than carcinoma; and
c. to recommend that management after diagnosis consists of expectant follow-up limited to clinical and imaging examinations.

Eschewing further surgery and lacking an effective method for preventing

invasive carcinoma in untreated women with LCIS, this strategy focused on the "early" diagnosis of DCIS or invasive carcinoma to offer the greatest chance to cure in women with LCIS who were not treated by mastectomy.

Controversy has now largely subsided in regard to LCIS as chemoprevention using selective estrogen receptor modulators and aromatase inhibitors has become available for treatment. The pendulum has now swung to a more rational position, with the understanding that LCIS is both a "marker" for duct-type breast carcinoma risk and a nonobligate precursor to invasive lobular carcinoma, although we have not yet discovered attributes of the lesion that characterize these potentials. As a consequence, prior concerns about LCIS have largely been laid to rest, and there is again relatively widespread acceptance of the term lobular carcinoma in situ. An updated discussion of LCIS can be found in Chapter 18.

"It's Like Déjà Vu All Over Again": Is DCIS a Marker or a Precursor?

Attention has now turned to DCIS, with questions being raised about the use of the word carcinoma for all these lesions and the need for any treatment after a diagnostic biopsy. This state of affairs is represented by the conclusion expressed by Esserman and Yau (1) that "much of DCIS should be considered a 'risk factor' for invasive breast cancer and an opportunity for targeted prevention," as well as by newspaper articles about DCIS with subtitles such as "Doubt Is Raised Over Value of Surgery for Breast Lesions at Earliest Stage" (17).

It will become apparent in the discussion that follows that the most pressing issue now in the forefront about DCIS is not what to call it or how it "should be considered," but rather to determine the most beneficial therapeutic program for each patient, "Rethinking the treatment of DCIS" is nothing new. The issues were clearly stated almost four decades ago by Hutter (18) in an essay titled "Is Cured Early Cancer Truly Cancer?"

> The real issue here is not whether the pathologic diagnosis of microscopic cancer is valid . . . the real issue is how to manage patients with these lesions today; acknowledging that we do not yet have the diagnostic capability to separate those patients with lesions which will progress from those which will not.

Follow-up of Untreated DCIS Reported in 1978

The Memorial Hospital Study

The 25 DCIS patients identified retrospectively by Rosen represented 0.3% of the cohort of 8,609 patients with a breast biopsy that was diagnosed as benign (15). Two of the 25 also had LCIS. Clinical records were found for 15 patients. The average age of the patients when the biopsy containing DCIS was performed was 48.2 years (range, 34–59 years). The majority presented with a mass that proved to be due to fibrocystic changes. All of the DCIS was low-grade, typically micropapillary type, with focal solid and cribriform areas. Follow-up was available for 10 patients averaging 21.6 years (range, 7–30 years) among whom 7 (70%) were subsequently found to have carcinoma (5 invasive duct, 1 medullary, and 1 DCIS). All subsequent carcinomas developed in the ipsilateral breast, usually in the same quadrant as the original DCIS. Included among the seven were the two women who originally had DCIS and LCIS, one of whom developed invasive duct carcinoma 6 years later whereas the other had non–low-grade DCIS 11 years later. Overall, the interval to subsequent ipsilateral carcinoma averaged 9.7 years (range, 10 months to 24 years).

Subsequently, four of the seven patients developed metastatic carcinoma, including two who died of breast carcinoma and two who were alive with metastases at last follow-up.

Reports of Untreated DCIS After 1978

Other follow-up studies of untreated DCIS appeared between 1978 and 2000 (19,20). The data from these and prior studies were reviewed by Leonard and Swain (21) in 2004 and by Erbas et al. (22) in 2006. The varieties of DCIS included in these reports were papillary, comedo, and noncomedo types. After follow-up ranging from 1 to 28 years, the frequency of progression to invasive carcinoma varied from 14% to 75%, with 50% or greater progression in half of the studies and an average progression rate of 43%.

The Vanderbilt University Study

The most important study after 1978 is that of Page et al. (19), first reported in 1982, with published updates in 1995 (23), 2005 (24), and 2015 (25). In these reports, the authors document more than 40 years of follow-up in a single series of women with untreated DCIS identified at Vanderbilt University and associated hospitals. This series has many features in common with Rosen's study reported in 1978 (12) and will be reviewed in some detail here.

Page's study began with 28 patients found to have untreated DCIS in a

retrospective review of slides from nearly 12,000 biopsies previously reported to be benign (19). The 28 DCIS cases represented 0.24% of the reviewed biopsies. The average number of slides reviewed from a reviewed biopsy was 2. The types of DCIS were described as ". . . typical cribriform patterns, micropapillary carcinomas and intermediate forms. . ." Two patients also had LCIS. Age at the time of biopsy ranged from 33 to 80 years (average age, 52 years). Among the 25 women with follow-up of more than 3 years at the time of the initial report, 7, or 28%, had developed invasive breast carcinoma within 10 years of the original biopsy. The average interval to invasive carcinoma was 6.1 years. All subsequent invasive carcinomas were in the breast that harbored DCIS, and five were clearly in the same quadrant.

The second publication from this series, which appeared 13 years later (23), reported that invasive carcinoma had been detected in two additional women in the ipsilateral breast 15 and 31 years, respectively, after the biopsy that harbored DCIS. Consequently, at the time of this second report, 9 of the original 28 patients (32%) had developed invasive carcinoma, which resulted in the deaths of 5 women. In addition, 25 years after the original biopsy with DCIS, one woman required a mastectomy for treatment of extensive noncomedo DCIS in the same quadrant as the original DCIS. Thus, the complete tally of patients who required treatment at the time of the report was 10/28, or 35.7%.

A third publication updating the status of the original 28 patients reported that 11, or 39.3%, had developed invasive carcinoma in the breast that initially harbored DCIS, including three after intervals of 23 to 42 years (24). At this time, the median follow-up of women who did not develop invasive carcinoma was 31 years. If one includes the woman who was treated by mastectomy for extensive DCIS, the 12 subsequent carcinomas represent 42.9% of the study cohort. At the time of this report, 5 of the 11 women who developed an invasive recurrence had died of metastatic carcinoma.

A 2015 report (25) combines the follow-up of the original 28 women with 17 ". . . other more recently identified patients" for a total of 45 patients. The source of the latter group is difficult to discern in this publication, and the updated follow-up status of the initial 28 patients is not presented separately. Overall, it is reported that 16 of the 45 patients (35.6%) developed invasive carcinoma in the same breast as the DCIS over a period of 3 to 42 years with an average interval to invasive carcinoma of 13 years.

At the time of last follow-up in this report, 30 of the 45 women were

deceased, including 7 (15.6%) who developed distant metastases and died of breast carcinoma 1 to 7 years after an invasive breast recurrence.

Interim Comment-1

The foregoing unique retrospective studies with long-term follow-up of untreated low and intermediate-grade DCIS demonstrated a substantial risk for progression to invasive carcinoma extending over decades in the absence of clinical and mammographic follow-up. The study by Rosen et al. (15) was significantly hampered by the lack of follow-up for 15 (60%) of the 25 patients with untreated DCIS. Although the 6 women with subsequent invasive carcinoma represented 60% of the 10 patients with follow-up, they were only 24% of the entire study cohort. The actual frequency of subsequent ipsilateral invasive carcinoma most likely lies somewhere in the vicinity of 39.3% reported by Page et al. (23) and 43.8% in collected anecdotal reports prior to 1978 cited earlier.

Some of these patients experienced invasive breast recurrences and eventually died of metastatic breast carcinoma, but the results of these studies do not permit an estimate of the effect of postlumpectomy invasive breast recurrence on survival in the context of current medical practice.

Perhaps influenced by these data and largely anecdotal information about the even greater, accelerated postlumpectomy risk for progression to invasive breast recurrence associated with high-grade DCIS, complete mastectomy remained the standard surgical treatment for DCIS until the advent of breast conserving surgery in the 1980s. Thereafter, data began to accumulate about the results of treatment by lumpectomy alone with close clinical and mammographic surveillance, largely in a prospective, investigational setting. These latter studies differ from those of Rosen, Page, and others described earlier in that the diagnosis of DCIS was known, surgery was usually performed to achieve negative margins to the extent possible, and the patients were carefully followed prospectively with mammography.

Nonrandomized Prospective Studies of DCIS Treated by Breast Conserving Surgery Alone and Mammographic Surveillance

California Study by Lagios et al.

Over a 15-year period, Lagios and his associates assembled 79 patients with DCIS lesions who had no treatment after mammographic and pathologic complete excision of unifocal DCIS no larger than 25 mm (average 6.8 mm). Ninety-two percent of the foci of DCIS had been detected

by mammography, and all were followed clinically with mammography. A report published in 1990 (26) described 10 recurrences (12.7%) after a median follow-up of 68 months. Half of the recurrences were invasive and half were DCIS. The rate of recurrence was higher in patients with comedo DCIS or cribriform DCIS with necrosis (9/36, 25%) than in those with low-grade forms of DCIS lacking necrosis (1/43, 2%). These results highlighted the more rapid recurrence rate of high-grade DCIS, even after apparently complete excision of small lesions, and the benefit of careful clinical surveillance with mammography, which makes it possible to detect some instances of recurrent DCIS before they progress to invasion. Nevertheless, in this series of carefully selected patients, approximately 6% progressed to invasive carcinoma while under surveillance in little more than 5 years.

With follow-up ranging from 1 month to 136 months after a breast recurrence was detected, all of the patients were alive with no evidence of breast carcinoma.

Jefferson University Study by Schwartz et al.

This study of carefully selected patients was conducted by Schwartz et al. (27), who collected 70 patients (72 involved breasts) with 83.3% detected by mammography and 16.7% found incidentally between 1978 and 1990. At the time of the report, follow-up ranged from 18 to 168 months (median 47 months), during which time 11 of the 70 patients (15.3%) had had a recurrence. The mean time to recurrence was 34 months (range, 8–85 months). Eight of the recurrences were in the form of DCIS and three were invasive carcinomas (one with nodal metastases). All recurrences were detected by mammography as new calcifications. The initial DCIS in 10 patients with recurrent DCIS was at least partly of the comedo type, and 8 recurrent DCIS foci at an original biopsy site had comedo features. No patient with incidentally detected DCIS had had a recurrence at the time of the report.

In subsequent years, additional patients with DCIS diagnosed by mammography or found incidentally were enrolled by Schwartz and his colleagues in their study of treatment by lumpectomy alone. A 2004 publication about 151 patients with a median follow-up of 65 months reported 42 (29.8%) recurrences that were detected 11 to 97 months after lumpectomy (28). The median time to recurrence was 28.5 months. Follow-up of patients without recurrence ranged from 15 to 201 months (median 86 months). Among the many prognostic factors analyzed as potential markers of increased risk for recurrence, only lesion size larger than 15 mm and the presence of comedo necrosis were statistically significant.

At the time of the report, all patients who had had a breast recurrence were clinically free of systemic disease, including a woman whose invasive breast recurrence was accompanied by nodal metastases.

Interim Comment-2

The studies by Lagios et al. (26) and Schwartz et al. (27,28) confirm the proclivity of comedo DCIS to rapid invasive recurrence even for foci that measured 1 cm or less in excisions that had negative margins. Although it was possible in both studies to detect the majority of recurrences as DCIS before invasive carcinoma arose, despite careful surveillance with mammography about 5% of patients in both studies had invasive recurrences within about 5 years of the original biopsy (Lagios et al., 5/79 or 6.3%; Schwartz et al., 3/70 or 4.2%).

The studies thus far reviewed do not demonstrate in a systematic way that having a breast recurrence, whether DCIS or invasive, is associated with an increased risk for developing metastatic breast carcinoma or death due to breast carcinoma when compared with women who do not experience a breast recurrence after lumpectomy for DCIS.

Randomized Clinical Trial of DCIS Treated by Conservative Surgery and Surveillance

National Surgical Adjuvant Breast Project (NSABP) Protocol 6

NSABP Protocol 6 was a randomized trial intended to study patients with clinical stage I and stage II invasive breast carcinoma randomized to lumpectomy alone, lumpectomy with breast irradiation, and total mastectomy. All patients had an axillary dissection. During the course of pathology review after randomization had occurred and treatment was begun, it was discovered that 78 of the 2,072 (3.8%) randomized patients only had DCIS, including 2 who also had LCIS (29). Excluding those treated by mastectomy, 29 had been randomized to lumpectomy with radiation and 21 to lumpectomy only. Comedo necrosis was present in 72% of the DCIS specimens; combinations of papillary, cribriform, and solid foci were seen in 58%; and only 6% were classified as having a pure or predominant papillary pattern. The size of DCIS was 2.2 ± 1.3 cm, with only one clinically occult lesion found by mammography.

During follow-up ranging from 32 to 88 months, overall seven patients with DCIS (9%) treated by lumpectomy had breast recurrences all of which developed in or near the quadrant where DCIS had been present previously. Five of these recurrences were found in women treated by lumpectomy

alone (5/21, 23.8%) (DCIS-2; invasive-3), and two in women treated by lumpectomy and radiation (2/29, 6.9%) (DCIS-1; invasive-1). The authors reported that "no clinical or pathologic features were recognized to allow for the prediction of local breast recurrence." These results suggested that radiation was helpful for suppressing occult residual DCIS that was responsible for breast recurrences after lumpectomy for DCIS with negative margins.

At the time of last follow-up, six of the patients with a breast recurrence were alive without evidence of breast carcinoma, and one had metastatic breast carcinoma.

Randomized Clinical Trial of DCIS Treated by Conservative Surgery, with or without Radiotherapy, and Surveillance

NSABP B-17 Trial

Following up on the inadvertent randomization of DCIS patients in NSABP Project 6, the NSABP B-17 trial was specifically designed to compare the outcome of DCIS patients treated by lumpectomy alone ($n = 403$) with those who had lumpectomy with breast irradiation ($n = 410$) (30). A requirement for entry into the trial was that lumpectomy margins be microscopically clear. In this trial, about 80% of the DCIS in both arms was detected by mammography only, about 19% by mammography and clinical exam, and only about 3% by clinical exam alone. Slightly more than 75% of the measured DCIS lesions in both arms were 1.0 cm or less.

There were 141 breast recurrences (79 invasive and 62 DCIS) in the lumpectomy only arm (35%; annual failure rate = 3.36), and 81 failures (44 invasive; 37 DCIS) in the lumpectomy plus radiation arm (19.8%; annual failure rate = 1.65). These data reveal a 52% reduction in breast recurrences associated with breast irradiation after lumpectomy for DCIS with negative margins. The cumulative incidence of recurrence at 15 years was reduced from 19.4% in the lumpectomy only arm to 8.9% when radiation was added to lumpectomy.

In the B-17 trial, the addition of radiotherapy to lumpectomy did not result in a significant reduction in deaths during the period of follow-up when compared with lumpectomy alone (hazard ratio = 1.08, 95% CI: 0.79–1.48). Overall, there were 358 deaths in the B-17 trial cohort at the time of the 2011 report. Only 72 (18.7%) of these deaths were breast carcinoma–related, with a 15-year cumulative incidence that was slightly lower in the lumpectomy alone group (3.1%) than in patients who had a lumpectomy plus radiation (4.7%), a difference that was not statistically significant with a

hazard ratio of 1.44 (95% CI: 0.71–2.92). Also important was the finding that the cumulative probability of death due to breast carcinoma was 10.4% 10 years after an invasive recurrence, and only 2.7% after recurrence as DCIS.

Nonrandomized Clinical Trial of DCIS Treated by Conservative Surgery Alone and Surveillance Supplemented with Tamoxifen

Eastern Cooperative Oncology Trial

This one-arm prospective study involved two groups of patients who received lumpectomy that was supplemented in some cases by tamoxifen (31). One group consisted of 565 women with low- and/or intermediate-grade DCIS measuring 2.5 cm or less, and the other was composed of 105 women with high-grade DCIS measuring 1 cm or less. Clear margins of at least 3 mm and excision of all mammographic calcifications were required for inclusion in the trial. Mean tumor sizes in the two groups were 6 and 5 mm, respectively. Patients were accrued between 1997 and 2002. Following the release of results of the NSABP B-24 Trial showing that recurrences were reduced by the addition of tamoxifen (30), patients were offered this option, which was chosen by 31.3% in the low/intermediate-grade group and 28.6% in the high-grade group.

The median follow-up for all patients was 6.3 years when the data were analyzed for a report that appeared in 2009 (30). At that time, there were 49 breast recurrences in the low/intermediate-grade group (8.6%) with 53% invasive and 47% DCIS only. The high-grade group had 17 breast recurrences (16.2%), among which 35% were invasive and 65% DCIS only. The 7-year breast recurrence rates were 10.5% and 18% in the low/intermediate-grade and high-grade groups, respectively. Even within the relatively short-term follow-up in this report, breast recurrences continued to occur between the 5th and 7th years after lumpectomy, leading the authors to comment that "the increase in IBE (ipsilateral breast events or recurrences) beyond 5 years warrants caution regarding the clinical implications of our results . . . thus, substantially longer observation is warranted to determine whether omission of radiation is appropriate for some patients with DCIS." The report did not indicate whether tamoxifen had an effect on the rate of breast recurrences in either group.

The 5-year survival rates were 95.7% (95% CI: 94–97.4) and 97% (95% CI: 93.6–100) for the low/intermediate- and high-grade groups, respectively. At the time of the report, there had been no deaths caused by breast carcinoma.

There were 23 (3.8%) new contralateral breast carcinomas in the low/intermediate-grade group (65.2% invasive) with a 7-year rate of 4.8% (95% CI: 2.7–6.9). In the high-grade group, the six (5.8%) new contralateral breast carcinomas were all invasive with a 7-year rate of 7.4% (95% CI: 1.4–13.3).

Randomized Clinical Trial of DCIS Treated by Conservative Surgery and Breast Irradiation, with or without Adjuvant Tamoxifen

NSABP B-24 Trial

In this trial, follow-up was available for 1,799 patients who were randomly assigned to tamoxifen or placebo after treatment by conservative surgery supplemented with breast irradiation (30). The median follow-up was 163 months. About 85% of the measured DCIS lesions in both arms were 1 cm or less, and at least 80% were detected by mammography alone. Margins were reported to be involved or unknown in about 25% of cases in both study groups. When compared with outcome after radiation + placebo, radiation + tamoxifen resulted in a 32% reduction in invasive breast recurrences. The 15-year breast recurrence rate was 10% in the radiation + placebo arm and 8.5% after radiation + tamoxifen. Twenty-two of 39 (54%) deaths after an invasive breast recurrence were due to breast carcinoma. The occurrence of invasive breast recurrence was associated with a significantly increased risk of death (hazard rate of death = 1.75, 95% CI: 1.45–2.96, $p < 0.001$), whereas recurrence of DCIS did not significantly affect mortality in this study. The 15-year cumulative death rates were 2.7% and 2.3% after radiation + placebo and radiation + tamoxifen, respectively.

Interim Comment-3

The following conclusions can be drawn from the results of the preceding clinical trials:

a. Breast recurrences in women previously treated by lumpectomy for DCIS almost always occur in the same quadrant as the initial DCIS, frequently in the same location, regardless of margin status of the original lumpectomy;
b. The addition of breast irradiation to lumpectomy results in an overall reduction of about 50% in the incidence of breast recurrences;
c. Approximately 55% of breast recurrences after lumpectomy are invasive, regardless of whether irradiation was added or not added;

d. Breast irradiation alone probably does not reduce the cumulative incidence of breast carcinoma deaths after DCIS is treated by lumpectomy;
e. The addition of tamoxifen to lumpectomy and breast irradiation resulted in a reduction of invasive breast carcinoma recurrences of about 30% when compared with lumpectomy and irradiation alone;
f. The average time to recurrence after lumpectomy is shorter for high-grade than for low/intermediate-grade DCIS. As a consequence, follow-up of at least 10 years is necessary to reliably gauge the effect of a treatment program on the rate of recurrence;
g. When recurrences are detected after lumpectomy, they are more likely to be invasive if the initial DCIS was low/intermediate grade than if it was high grade. This circumstance probably reflects the frequent presence of more abundant, readily detected calcifications in high-grade DCIS leading to earlier detection of recurrences before invasion has developed;
h. Combined data from the B-17 and B-24 trials revealed that the 15-year cumulative incidence of contralateral breast carcinoma ranged from 10.2% to 10.8% for various treatment groups except those who received breast irradiation and tamoxifen, among whom the incidence was 7.3%. Overall, the majority (67.4%) of contralateral carcinomas were invasive; and
i. Invasive breast recurrences can be a source of fatal metastatic carcinoma, even after low/intermediate-grade DCIS, although most invasive breast recurrences are adequately controlled when detected in the course of clinical surveillance.

Epidemiologic Study of Breast Carcinoma Mortality Following Lumpectomy and Breast Irradiation for DCIS

Narod et al. (32) studied breast carcinoma mortality rates in 108,196 women younger than 70 years with a diagnosis of DCIS recorded from 1988 to 2011 in the Surveillance, Epidemiology, and End Results (SEER) database. No pathology review was conducted. In the entire cohort, consisting of patients treated by mastectomy, lumpectomy alone, and lumpectomy with breast irradiation, breast carcinoma-specific mortality was 3.3% (95 CI: 3.0–3.6) at 20 years. The risk of death due to breast carcinoma in all women with DCIS was 1.8 (95 CI: 1.7–1.9) times greater than expected when compared with the United States population, and the risk decreased with increasing age at diagnosis (17.0 for women diagnosed before age 35 years, and 1.4 for women older than 65 years at diagnosis).

Other factors reported to be associated with higher breast carcinoma mortality after DCIS were larger DCIS size, higher grade, and ER-negative DCIS.

After 10 years of follow-up, the risk of ipsilateral invasive recurrence after lumpectomy for DCIS was significantly lower after breast irradiation (2.5%) than in the absence of breast irradiation (4.9%), but this did not translate into a significant reduction in breast carcinoma mortality (0.8% with irradiation vs. 0.9% without irradiation). Among the 956 women with DCIS who reportedly died of breast carcinoma, 210 (22%) had an invasive ipsilateral recurrence, 165 (17.3%) were reported to have had an invasive contralateral carcinoma, 20 (2.1%) had invasive carcinoma of undetermined laterality, and 517 (54.1%) had no documented invasive ipsilateral recurrence or contralateral carcinoma. The latter 517 women represent about 0.05% of the entire study cohort of 108,196 women.

On the basis of their epidemiologic data suggesting that about 0.5% of women who died of breast carcinoma after treatment of DCIS did not have a reported ipsilateral invasive recurrence or invasive contralateral carcinoma, Narod et al. (32) drew the following highly speculative conclusion:

> Cases of DCIS have more in common with small invasive cancers than previously thought. . . . Some cases of DCIS have an inherent potential for distant metastatic spread. It is therefore appropriate to consider these as de facto breast cancers and not as preinvasive markers predictive of subsequent invasive cancer.

Interim Comment-4

The epidemiologic study by Narod et al. (32) included patients treated by mastectomy, lumpectomy followed by breast irradiation, and lumpectomy without breast irradiation. The data confirm the results of previously cited clinical trials indicating that breast irradiation reduces the frequency of invasive breast recurrences after lumpectomy. In this report, invasive breast recurrences were reduced from 4.9% to 2.5% by the addition of breast irradiation after lumpectomy.

The authors concluded that breast carcinoma mortality after treatment of DCIS was inversely related to the patient's age at diagnosis, with the highest mortality among those less than 35 years old. Scrutiny of the data presented reveals that most of this effect was related to 5,253 women less than 39 years of age who constituted only 4.9% of the entire study cohort of 108,196 women. At age 40 and above, age at diagnosis did not appear to

have an important effect on mortality after treatment.

The authors' interpretation of data on the effect of DCIS size, grade, and ER-status on breast carcinoma recurrence and mortality is questionable because of the significant numbers of cases recorded as "Unknown" in each category: (estrogen receptor status, 49.2%; grade, 26%; size, 30.6%). In fact, the *p*-value for the "Unknown" category in each of these parameters was statistically significant ($p < 0.001$). This is a consequence of the fact that a pathology review was not conducted.

The observation that breast irradiation after lumpectomy reduces the risk of invasive recurrences without a commensurate reduction in breast carcinoma mortality was previously recorded in the NSABP B-17 and B-24 trials (30). Although it might be expected that the rate of invasive breast recurrences would be directly related to breast carcinoma mortality, there are reasons why this effect might not be evident in the foregoing studies. One of these factors is the relatively small absolute number of patients with invasive recurrences and the small proportion of deaths attributable to breast carcinoma in each study. For example, in the NSABP B-17 trial, the lumpectomy arm had 79 invasive recurrences (19.6%) compared with 44 in the lumpectomy plus breast irradiation arm (10.7%).

A noteworthy aspect of this epidemiologic study was the data on contralateral invasive carcinoma. The mean annual rate at which invasive contralateral carcinomas occurred was 0.31%. Contralateral invasive breast carcinoma was associated with a significantly increased risk of breast carcinoma mortality (HR, 13.8 [95 CI: 11.5–16.6]; $p < 0.001$). Thus, subsequent fatal metastatic carcinoma could, in a significant number of cases, have arisen from a new contralateral carcinoma rather than from an ipsilateral invasive recurrence. Since this study did not include a pathologic review, it would not be possible to distinguish between an ipsilateral invasive recurrence and a new invasive contralateral carcinoma as the source of fatal metastatic carcinoma in any one case.

Does DCIS Have an Inherent Potential to Metastasize?

Despite the histologic similarity of the cells in DCIS and those of associated invasive duct carcinomas, it is clear that new properties are manifested by the invasive cells, including the ability to metastasize. Although it is possible that there are examples of DCIS that are inherently capable of metastatic spread, the actual occurrence of metastases seeming to arise from DCIS is so exceedingly rare in clinical practice in the absence of an accompanying detectable invasive carcinoma as to make this possibility an insufficient basis for treating the more than 99% of DCIS patients for whom