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Heterogeneity of Ductal Carcinoma *In Situ* of the Breast

Michael D. Lagios, MD

California Pacific Medical Center, Department of Pathology, San Francisco, CA 94118

Abstract Ductal carcinoma *in situ* (DCIS) now accounts for 20–30% of all newly diagnosed breast cancers in centers which use mammographic surveillance as a standard part of the examination. The majority of these DCIS lesions, at least in the United States, are of very limited size, with mean estimated extents of 8–20 mm, based on pathological examination. A small fraction of these are incidental microscopic features of the biopsy; the majority are detected on the basis of mammographic microcalcifications.

These mammographically detected DCIS lesions are biologically heterogeneous, and this is reflected by their histology. Moreover, a number of recent independent studies have shown that the clinical outcome of patients, particularly those treated by breast conservation, is related to the presence of reproducible and identifiable histologic features, and possibly to certain immunohistochemically demonstrable gene markers as well.

Regardless of the type of therapy, local recurrence in the breast is the most common and often the only site of failure after breast conservation therapy for DCIS. Although individual studies show some variation in the proportion of invasive to non-invasive recurrence, equal numbers of invasive and non-invasive recurrences are most commonly noted.

Key words: Breast cancer, ductal carcinoma *in situ*, lumpectomy, mammography

In situ or non-invasive carcinomas of the breast are an arbitrarily defined, biologically and morphologically heterogenous group of lesions, which originate within and are limited to the ducts of the breast and the contiguous epidermis of the nipple-areola complex. Their importance relates to the degree of risk for subsequent invasive growth. Risks of subsequent invasion vary markedly among the lesions defined as *in situ* carcinomas of the breast. Some lesions, such as lobular carcinoma *in situ*, do not predict risk for a specific breast, and are associated with a cumulative risk of 1% or less per year. Others behave more like pre-invasive lesions in that the risk of subsequent invasion is limited to the ipsilateral breast, generally in the same quadrant, and may approximate 4% yearly for the initial five years.

Address correspondence to Michael Lagios, MD, Senior Surgical Pathologist, California Pacific Medical Center, Department of Pathology, 4th Floor, 3700 California Street, San Francisco, CA 94118.

DUCTAL CARCINOMA *IN SITU*

The majority of ductal carcinomas *in situ* (DCIS) are now identified on the basis of mammographically detected microcalcification and represent entirely occult lesions with a very limited distribution in the breast. Currently such lesions comprise 25% of all new breast cancer diagnoses at our hospital. Similar accession rates are reported by other institutions which employ mammographic surveillance as a routine part of breast patient evaluation.

Clinical experience with treatment options other than mastectomy for this group of patients is very recent. Prior to 1982, there was virtually no published literature on small, mammographically detected foci of DCIS, yet clinical concerns

have continued to dwell on questions of multicentricity and occult invasion, features generally associated with the type of DCIS encountered prior to the introduction of high quality mammography.

We first reported on a small series of patients whose DCIS was treated by planed lumpectomy without irradiation in 1982 [1]; the first reports of lumpectomy and irradiation for this disease appeared the following year. Since that time a small number of studies [2–5] have shown a variable success rate in terms of local control, without demonstrating an adverse effect on survival by the choice of breast conservation without irradiation.

Our own experience with DCIS of limited extent [1,4,6] has shown that mammographically detected lesions, adequately excised and documented to be less than 25 mm in extent, are not associated with occult invasion or axillary metastasis at mastectomy.

Seventy-nine patients with DCIS of 25 mm or less who were offered the option of adequate excision with follow-up alone (without irradiation), demonstrated a recurrence rate of 16.6% at 100 months of mean follow-up. When this group of patients is censored to include only those patients who meet present entry criteria and have an ipsilateral breast at risk (n = 75), the recurrence rate is 12.7% at 5 years and 15.9% at 10 years (Kaplan-Meier estimate). The uncensored recurrences include two which would not meet current entry criteria, and one at nine months almost certainly represents unrecognized residual disease. Censoring two of these cases should result in a Kaplan-Meier estimated recurrence rate of 11.4% at 10 years. All recurrences were ipsilateral, within the same quadrant and often at the biopsy site. Half of the recurrences were T1b invasive cancers, the remainder were DCIS and/or Paget's disease.

A group of 20 patients initially reported in 1982 [1] now has a minimum follow-up of 10 years (mean 14.25 years). There were 2 recurrences amongst the 7 high-grade DCIS included in this group (28%) at 14 years of follow-up.

Three patients with high-grade DCIS of 5–8 mm extent are still living with an ipsilateral breast at risk, and without evidence of local or distant recurrence. Follow-ups for these patients with non-recurrent, high-grade DCIS are presently 12, 14.3, and 14.5 years.

There have been five deaths due to heart disease, including one patient with high-grade DCIS of comedo type after five years of follow-up without clinical or mammographic recurrence. No patient has developed metastatic disease or died of carcinoma.

Factors which affect local control after lumpectomy alone for DCIS are extent of disease, adequacy of excision, and grade. Lumpectomy alone for DCIS is generally possible for small mammographic lesions which are closely associated with microcalcifications, and which are amenable to adequate excision. Generally lesions 20–25 mm in extent have been considered suitable for an attempt at breast conservation, although larger lesions which are adequately excised in patients with generous breasts, have also been treated conservatively. Complete mammographic-pathologic correlation, identification of margins, and processing of the entire biopsy material are requisites for entry in our study. Complete evaluation of the biopsy avoids misidentifying a microinvasive lesion for an *in situ* process.

The nuclear grade of the DCIS, as opposed to the conventional pathologic classification which is largely based on histologic architecture, appears to be strongly correlated with the risk of a local breast recurrence after lumpectomy alone and in conjunction with comedo type necrosis, is the most significant factor affecting local recurrence rate among patients with an adequate excision. Risks of local recurrence after lumpectomy alone at 106 months of follow-up in the high-grade group (high nuclear grade and comedo type necrosis) were 30.5% (n = 36); intermediate grade, 10% (n = 10); low grade, 0% (n = 33). In our series of 67 living, post-lumpectomy patients with an ipsilateral breast at risk, the local failure rate is 14.9% at mean follow-up of 106 months. Half of the recurrences are minimally invasive carcinomas (T1b), the remainder DCIS. Twelve of thirteen patients with a recurrence had an initial high-grade DCIS; one had an intermediate-grade lesion. A similar propensity for high-grade lesions to recur after lumpectomy and irradiation was noted by Silverstein *et al.* [7] and Solin *et al.* [8].

High-grade DCIS is associated with aneuploidy, the HER-2/*neu* oncogene, and a generally higher S-phase fraction. However, it is important to note that this high-grade DCIS group is heterogeneous, and that some aneuploid lesions are

low S-phase and estrogen receptor-positive. The extent to which these biochemical markers may help discern which of the high-grade DCIS subgroup is more likely to recur after a lumpectomy procedure remains to be demonstrated.

Breast conserving options for the patient with mammographically detected DCIS are dependent on a closely coordinated team approach requiring excellent mammography and substantial experience with localization procedure; an attempt at an *en bloc* excision of a clinically occult lesion by the surgeon; and meticulous evaluation of the entire specimen by the pathologist. Although the mammographic microcalcification may closely correspond with the actual pathologically documented extent of the *in situ* lesion, in many cases the microscopic lesion is more extensive. Meticulous mammographic/pathologic correlation is required if the extent of disease is to be determined accurately. Adequately excised lesions, those in which the excision is complete both in terms of the mammographic and the microscopic lesion, are candidates for breast conservation. Patients with DCIS of limited extent but microscopically involved margins may be re-excised with localization.

The benefits of radiation therapy in reducing the number of local recurrences after excision biopsy for DCIS have been well-documented in numerous studies. However, this benefit appears to decrease with greater follow-up. In those studies with follow-up in excess of five years [8–10, Silverstein, personal communication, 1993] recurrences appear to double between five and eight years and are greater still at ten years of follow-up. Solin *et al.* [10] reported an overall local recurrence rate of 16% at ten years of follow-up.

In a subsequent analysis of the influence of histologic grade on local recurrence, Solin *et al.* [8] noted recurrence rates of 20% for high-grade DCIS as compared to 5% for low grade lesions at 87 months of follow-up. These results are not dissimilar from our results of lumpectomy alone in which Kaplan-Meyer estimates of recurrence rates are projected to be 28% for similarly defined high-grade DCIS and 6% for low grade DCIS at 120 months of follow-up.

Patients who undergo radiation therapy for DCIS after a complete excision are being treated prophylactically. Given the recurrence rates available from the published literature at 8 and 10 years, it may be more appropriate to reserve radiation therapy for invasive recurrences.

The post-irradiation local recurrence reported by Fisher *et al.* [11] at 43 months of mean follow-up (7%) is not substantially different from studies employing surgery alone but with careful evaluation of margins and thorough specimen examination at a comparable follow-up period [3].

MICROINVASION

Microinvasion, as used in this laboratory, refers to foci of invasive cancer with maximum diameters of 1 mm or less. Larger areas of invasive growth are termed minimal invasive carcinoma. These comprise the original minimal invasive group as defined by Steven Gallagher; lesions 1–5 mm in maximum diameter (T1a), and the more loosely defined invasive carcinomas which may measure up to 10 mm in maximum diameter (T1b).

A diagnosis of microinvasion requires all the features of invasive growth, *i.e.*, extension of the lesion beyond the confines of a ductolobular unit, the development of a desmoplastic stroma and an appropriate histology.

Unfortunately, microinvasion can be mimicked by artifact, ductal sclerosis and entrapment, *etc.*, and represents one of the most commonly revised diagnoses on review. A number of pathologists report an equivocal focus of microinvasion as such rather than define the process as DCIS and comment on the equivocal areas. Our own standard requires definitive evidence of invasion; equivocal foci of microinvasion are not defined as invasive disease.

Common processes which have led to a misdiagnosis of microinvasion include crush and electrocautery artifact at the edge of a biopsy specimen, colonization of areas of sclerosing adenosis by DCIS, ductal sclerosis with entrapment of neoplastic epithelium within the area of the pre-existing ductal or ductolobular unit, "cancerization of lobules" with an associated, very striking lymphocytic host reaction, and larger ducts showing desquamation of ductal epithelium misinterpreted as "vascular" invasion.

Diagnosis of microinvasion has serious implications for the usual treatment patients may receive. Patients with DCIS are not candidates for adjuvant chemotherapy or radiation therapy after

mastectomy, and certainly for the majority of currently detected cases, are not candidates for axillary dissection.

An awareness of the possible pitfalls in interpreting artifact and other benign distorting processes as microinvasion may permit the pathologist to avoid misdiagnosis. Additionally, appropriate use of levels, and occasionally simple special stains, may permit clarification of an equivocal focus.

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