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Classification of Duct Carcinoma In Situ (DCIS) With a Characterization of High Grade Lesions: Defining Cohorts for Chemoprevention Trials

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Abstract In the last 6 years a number of non-randomized, predominantly single institutional trials of breast conservation therapy (BCT) with DCIS, have demonstrated that it constitutes a very heterogeneous group of diseases with markedly different risks of local recurrence and invasive transformation. There has been a consensus that DCIS, which exhibits a "comedo" morphology, generally defines a high risk group. Most studies, moreover, have identified the same two features, nuclear grade and necrosis, as contributing most significantly to prognosis [4–6]. Nuclear grade and necrosis have been identified as independent prognostic variables in several studies [5,6]. High nuclear grade DCIS which exhibits comedo necrosis defines the majority of all DCIS which will result in local recurrence and invasive transformation after BCT.

Studies utilizing image cytometry, to determine ploidy and S-phase fraction and immunohistochemical studies of proliferation and oncogene distribution have shown a significant association with morphologically identified high nuclear grade and aneuploidy, high S-phase fraction or proliferation rate, presence of HER-2/neu and P53 oncogenes and absence of estrogen receptors. Generally the inverse of this association is seen with low nuclear grade DCIS. However, initial hopes that these adjunctive studies would identify subsets within the high nuclear grade group which might be more likely to recur have not been fulfilled. J. Cell. Biochem. 25S:108–111.

Key words: duct carcinoma in situ; nuclear grade necrosis; prognostic features; local recurrence; invasive transformation

As recently as 1979, subtype classification of duct carcinoma in situ (DCIS) was not thought to contribute any prognostic information [1]. This was true for the time and circumstances when most DCIS were detected clinically as large palpable masses and were treated by some form of total mastectomy [2]. Since then the continuing impact of mammographic technology and the growing acceptance of breast conservation therapy (BCT), have created a large population of DCIS patients with an ipsilateral breast at risk. Within a few short years it became apparent that local recurrences, both recurrent or residual noninvasive as well as invasive disease, were markedly higher in the conservatively treated breast [3]—generally 20 to 30% versus 2% for mastectomy at 8 years of follow-up in various single institutional trials with or without irradiation [4–6]. This is exemplified by NSABP B17 which exhibited a 22% local recurrence rate in the nonirradiated treatment arm at a mean 43 months of follow-up [7].

Evaluation of patients with local recurrence has shown several significant factors that contribute prognostically. These include the subtype (i.e., grade) of the DCIS, the extent of disease in the breast (size) and the status of margins. Although, investigators have ranked these prognostic descriminants differently, the most significant is the subtype independent of extent of disease and margin status. The vast majority of published local recurrences, whether following treatment by total mastectomy or breast conservation with or without irradiation, reflect the biology of high-grade DCIS subtypes [4–6].

We introduced nuclear grade and necrosis in a classification of DCIS [4] based on a retrospective analysis of local recurrences in our series in which high-grade subtypes have accounted for all but one recurrence. Current updated follow-up of these patients has shown that high-

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grade subtypes continue to contribute most of the local recurrences with 124 months of mean follow-up [8]. Subsequently, these findings have been corroborated by several independent studies which have utilized nuclear grade and necrosis as the major prognostic indicators for conservatively treated DCIS [5,6,9,10]. This consensus is all the more striking if it is recalled that the separate studies utilized their own independent schemes of subtype classification based on nuclear grade and/or necrosis. The majority of the high-grade DCIS subtypes would fall into the conventional classification of "comedo" DCIS. Several studies, not utilizing nuclear grade or necrosis as specified criteria, also demonstrated that most recurrences were associated with the largely equivalent conventionally defined comedo subtype [11,12].

Patchefsky et al. [13] had shown that DCIS of comedo type was more often associated with invasive foci at mastectomy. In our own series of mastectomies studied by the serial subgross technique of Robert Egan, 75% of extensive DCIS which were associated with occult invasive foci were high-grade [14] and amongst the patients with occult invasion who subsequently recurred after modified radical mastectomy, all were high-grade, as were two patients who exhibited single axillary metastases [4].

High-grade DCIS is defined as cells containing grade III nuclei and comedo necrosis, i.e., an area of coagulative necrosis of tumor cells associated with karyorrhexis (nuclear fragmentation) [4, 8]. Solin et al. [5] independently evaluated nuclear grade III DCIS alone and in conjunction with necrosis. In their analysis nuclear grade III lesions were more likely to recur locally at 5 years, but not in numbers sufficient to indicate significance. Defining lesions with grade three nuclei and comedo necrosis, however, dramatically improved the prognostic power of the classification, dividing DCIS into high-grade lesions and non-high-grade DCIS. Silverstein et al. [6] have shown that nuclear grade and necrosis are independent prognostic variables in multivariate analysis.

Extent of necrosis has been shown to have a prognostic effect alone, and in a setting of high-grade nuclei separates a group with high Ki67 and HER-2/neu markers and reduced receptor content from a group with substantially lower Ki67, HER-2/neu and significant increases in the frequency of estrogen and progesterone receptor [5,15,16]. Necrosis had some prognostic effect in NSABP-B17 in which DCIS were divided into those having necrosis in 0 to 33% of ducts and those with 33% or more ducts involved with necrosis [17]. Unfortunately, this separation means that there will be significant numbers of DCIS defined as high-grade by others [4, 6] in either group and this will reduce the prognostic power of the feature. Silverstein et al. [6] have utilized necrosis to define an intermediate group of DCIS patients whereas we had based our intermediate category on the presence of grade II nuclei with or without necrosis. In the Van Nuys classification nuclear grade I and II lesions are classified as intermediate if necrosis is present and low grade if necrosis is absent (see Table I).

An intermediate risk group, variously defined by non high-grade nuclear morphology, with or without necrosis, identifies a patient population with local recurrence rates which are intermediate between high- and low-grade DCIS with BCT [4,6,21].

Quantitative criteria are pertinent for the lowest nuclear grade group (small cell, micropapillary/cribriform without necrosis) and distinguish between morphologically identical groups. Smaller lesions have a biology akin to risk markers, i.e., with risk equally distributed to either breast (cf. ADH, LCIS, ALH), while in larger lesions risk is limited to the ipsilateral breast [20].

The EORTC classification [18] identifies three grades of DCIS as well-intermediately and poorly differentiated. Although subtypes identified by their scheme largely correspond to the subtypes identified by Lagios et al., Solin et al., and Silverstein et al., [4–6] there are some interesting differences; neither nuclear size nor

TABLE 1. DCIS Classifications Based on Nuclear Grade and Necrosis*

		Nuclear Grade		
Necrosis		I	II	III
Lagios et al. 89	+	Low	Int.	High
	−			
Silverstein	+	Group II		Group
et al. 95	−	Group I		III
Solin et al. 93	+	Non-Comedo		Comedo
	−			

*Low = low-grade DCIS; Int. = intermediate grade DCIS; High = high-grade DCIS. Silverstein et al. [1995] refer to DCIS with nuclear grade I and II with necrosis as intermediate (group 2) and without necrosis (Group 3). (Adapted from Solin et al. [1993] and Silverstein et al. [1995]).

necrosis are specified diagnostic criteria in their published scheme, whereas these are features of the other classifications. Retrospective analysis of multiinstitutional studies of mammographically detected DCIS treated by BCT using the EORTC classification, essentially produces a very similar separation, however.

In evaluating published series of BCT for DCIS, one is struck by the great variation evident in pathologic handling and definition of the materials. This variation is most evident in recording the size or extent of diseases, the margins status and the degree of tissue sampling, all of which impact on the ability to identify prognostically significant features of the biopsy or resection in our experience. Probably the most important of these prognostic features for local recurrence is microinvasion. Microinvasion (invasion less than 1 mm) and larger but minimal foci of invasion are frequently overlooked in routine pathologic examination of breast biopsy material, not only because a lesion of small size can be overlooked even in well prepared tissue sections, but because the volume of tissue containing DCIS available from the biopsy is often considered too large to do anything more than sample. Such sampling can represent 10% or less of the volume of the mammographically directed biopsy. Obviously in a biopsy 40 × 35 × 20 mm, a 2 mm focus of invasion can be overlooked even if 50% of the tissue is sampled. The presence of microinvasion in a DCIS usually predicts for recurrence in the absence of radiation therapy, and so it is not surprising that studies which included cases with variable if not minimal sampling might produce a significant increase in local recurrence rates in a short period of time in the nonirradiated arm [7,17].

There is a clear association between high nuclear grade DCIS, comedo type necrosis and a specific pattern of oncogenes, receptors and ploidy. High-grade DCIS, characterized by grade III nuclei and necrosis, is predominantly HER-2/neu and p53 positive, estrogen and progesterone receptor negative, almost entirely aneuploid or tetraploid, and may exhibit a higher S-phase fraction and/or higher frequency of Ki67 positivity. Morphologically low-grade DCIS, in contrast, rarely demonstrates necrosis and is associated with a complimentary pattern of findings with the same markers. It is characteristically HER-2/neu and p53 negative, estrogen and progesterone receptor positive, and almost entirely diploid and low S-phase [19]. Recently morphologically identical low-grade lesions have been separated on the basis of quantitative criteria into a group of larger lesions which predict risk for the ipsilateral breast at a rate similar to that of lobular carcinoma in situ, and smaller lesions which behave in follow-up studies as a risk marker with risk equally distributed to either breast [20].

Because of the short interval to local recurrence, and the frequency of invasive transformation, high-grade DCIS would make an ideal subject for initial chemoprevention trials. Moreover it accounts for 35–40% of all newly detected DCIS [4,6,21]. The majority of current DCIS is detected mammographically, and at small size, and an increasing proportion of such patients are choosing BCT with or without irradiation. In actual practice the initial attempt at mammographically directed excision is successful in terms of adequate margins in only 50–60% of cases. The remainder are left with variable amounts of residual disease. It is standard practice in California to permit an adequate period for healing to take place, generally 8–12 weeks, before subjecting the patient to postoperative mammography and a repeat attempt at localization and excision. This would provide a large block of time to test chemopreventive agents, with a subsequent planned re-excision providing the opportunity to evaluate surrogate endpoints. It is my experience that women with biopsy proven DCIS for whom mastectomy is recommended never the less delay definitive surgery for an equal period of time. Some of these might also choose to participate in a chemopreventive trial during the interval.

In summary, high-grade DCIS, which represents 35 to 45% of all mammographically detected lesions, can be reproducibly identified on the basis of nuclear grade and necrosis, features which are both amenable to quantitative image analysis. The high-grade subset accounts for the majority of local and loco-regional recurrences in patients treated with breast conservation, and exhibits a characteristic pattern of oncogene markers and ploidy. The mean interval to local recurrence varies from 24 months without irradiation to 48–60 months with irradiation for this high-grade subset. Given the short interval to recurrence, half of which represent invasive events, high-grade subsets of DCIS are an ideal initial subject for chemoprevention trials employing short term

surrogate endpoints. Some 40–50% of such patients will have potential residual disease in the breast after initial attempts at excision, and these can provide a sizeable pool of candidates during the 2–5-month interval between biopsy and planned re-excision which is standard practice for DCIS patients preparing for BCT in California.

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