Prognostic classification of breast ductal carcinoma-in-situ

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Summary
We present a new prognostic classification designated the Van Nuys classification for ductal carcinoma-in-situ (DCIS). The classification combines high nuclear grade and comedo-type necrosis to predict clinical recurrence.

Three groups of DCIS patients were defined by the presence or absence of high nuclear grade and comedo-type necrosis: 1—non-high-grade DCIS without comedo-type necrosis, 2—non-high-grade DCIS with comedo-type necrosis, 3—high-grade DCIS with or without comedo-type necrosis. There were 31 local recurrences in 238 patients after breast-conservation surgery 3·8% (3/80) in group 1, 11·1% (10/90) in group 2, and 26·5% (18/68) in group 3. The 8-year actuarial disease-free survivals were 93%, 84%, and 61%, respectively (all p < 0·05).

The Van Nuys classification defines three distinct and easily recognisable groups, each of which has a different likelihood of local recurrence if treated with breast conservation.

Lancet 1995; 345: 1154–57

Introduction
Ductal carcinoma-in-situ (DCIS) is not a single entity but rather, a spectrum of diseases. The spectrum concept is based on molecular and cytogenetic findings,1 2 as well as on clinical evidence,3 4 showing a higher rate of local recurrence in DCIS with high nuclear grade5–7 or comedo-type necrosis.5–10 A classification that subdivides DCIS by risk of local recurrence would be useful to clinicians.

Classifications of DCIS have been attempted by nuclear grade,1 differentiation,11 architecture,12 the presence or absence of comedo-type necrosis,6 or by various combinations of factors. Although these systems can be used by most pathologists, discordance is common, even among experts,4 and the classifications do not always generate prognostically different subgroups.

We present a new classification, based on the presence or absence of high nuclear grade and comedo-type necrosis, which yields three subgroups with different outcomes, as measured by disease-free survival.

Patients and methods
3 groups of DCIS patients were defined by use of the presence of high nuclear grade (nuclear grade 3) to select the most aggressive group (group 3). The remaining non-high-grade lesions (nuclear grades 1 or 2) were then divided by the presence (group 2) or absence (group 1) of comedo-type necrosis (figure 1). Nuclear grade was scored by previously described methods.12 Essentially, low grade nuclei (grade 1) were defined as nuclei 1–1·5 red blood cells in diameter with diffuse chromatin and inapparent nucleoli. Intermediate grade nuclei (grade 2) were defined as nuclei 1·5–2 red blood cells in diameter with coarse chromatin and infrequent nucleoli. High grade nuclei (grade 3) were defined as nuclei with a diameter greater than two red blood cells, with vesicular chromatin, and one or more nucleoli.

Figure 1: Van Nuys DCIS classification

DCIS traditionally recognised by pathologists as comedo-type DCIS with central lumina containing necrotic debris surrounded by large pleomorphic viable cells in solid masses was classified as showing comedo-type necrosis.5 Other architectural patterns of DCIS, such as cribriform or micropapillary, with substantial amounts of necrotic neoplastic cells of duct origin within duct lumina were also classified as showing comedo-type necrosis. No requirement was made for a specific amount of high nuclear grade DCIS, nor was there any requirement for a minimum amount of comedo-type necrosis. Occasional desquamated or individually necrotic cells were ignored and were not scored as comedo-type necrosis.

The classification was applied to 425 consecutive patients with histologically confirmed DCIS, without evidence of microinvasion, treated at the Breast Center, Van Nuys, California, USA, between 1979 and 1994. All patients were prospectively entered into the Center’s computerised database: 187 patients were treated by mastectomy; 238 were treated with breast preservation (99 by excision alone and 139 by excision plus radiotherapy). Treatment was not randomised. Patients with large lesions (greater than 4 cm), multicentricity, or involved margins not amenable to re-excision were treated with mastectomy (usually with immediate breast reconstruction). Patients with smaller lesions (4 cm or less) and microscopically clear surgical margins were treated with excision alone or excision and radiotherapy.

Until 1998, all patients who elected to have breast conservation were advised to have radiotherapy; most accepted this recommendation. From 1989, patients treated with breast conservation who had clear biopsy margins were offered the option of follow-up without radiotherapy; most accepted this option.

Because the decision not to recommend radiotherapy bore no relation to clinical features, patients treated by excision with radiotherapy or excision alone were clinically similar. Mean

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tumour diameter was 18 mm for patients treated with excision and radiation therapy and 17 mm for patients treated with excision only. 88% of excision plus radiotherapy patients had non-palpable lesions compared with 87% of excision only patients.

Immunostaining for HER-2/neu and p53 in formalin-fixed, paraffin-embedded tissue was done on 4 μm sections with the R-60 anti-HER-2/neu antibody or DO-1 anti-p53 antibody (Santa Cruz Biotechnology Inc, Santa Cruz, California, USA) by an avidin biotin complex procedure with the Vectastain ABC kit (Vector Laboratories, Burlingame, California, USA). Samples were processed in batches of 40 sections with a positive and negative control run in parallel. Scoring for HER-2/neu overexpression was either negative or positive immunostaining. Scoring for p53 was negative or positive based on nuclear staining of more than 50% of the tumour cells in the section. Immunostaining was done at the laboratory of one author (DJS).

Level 1 and 2 axillary dissections were done routinely until 1988; thereafter, lower axillary sampling was done in some patients treated with mastectomy. Whole breast external beam irradiation (40–50 Gy) was carried out on a 4 or 6 MeV linear accelerator with a boost of 16–20 Gy to the tumour bed by iridium-192 implant or linear accelerator. Disease-free survival rates for each group were estimated by the Kaplan-Meier method. The statistical significance between survival curves was determined by log-rank test.

Results

Patient and tumour characteristics for the groups are shown in the table. Size, nuclear grade, and HER-2/neu were statistically different for all groups; differences for p53 were not significant.

33 patients had local and/or distant recurrences: 2 treated with mastectomy and 31 with breast conservation. 30 of 31 (97%) breast-conservation patients had recurrences at or near the primary lesion; 3 of these (all of whom had radiotherapy) developed inflammatory type recurrences (48%) were invasive; 2 of 3 (67%) in group 1, 3 of 10 (30%) in group 2, and 11 of 20 (55%) in group 3. Both patients were treated with excision plus radiotherapy.

Discussion

There is growing evidence that DCIS is a heterogeneous disease, ranging from atypical ductal hyperplasia to high-nuclear-grade DCIS with comedo-type necrosis. After breast-conservation treatment, DCIS without comedo-type necrosis shows a lower rate of local recurrence than DCIS with comedo-type necrosis, as does low nuclear-grade DCIS when compared with high nuclear grade DCIS. Evidence for DCIS as a spectrum of disease is further confirmed by the identification of similar allelic imbalances or chromosomal aneuploidy in both atypical hyperplasia of the breast and DCIS. There have been 2 deaths; 1 in group 2 and 1 in group 3. Both patients were treated with excision plus radiotherapy and both developed inflammatory type recurrences with dermal lymphatic involvement. There was no statistical difference in breast-cancer-specific survival among the 3 groups.
lesion had to be comedo DCIS. In our medical group, there were inter-observer differences in assessment of the amount of comedo-type necrosis. Since nuclear grade was not included, high-grade lesions such as large-cell solid DCIS without comedo-type necrosis were classified as DCIS without necrosis. There were 8 high nuclear grade lesions without necrosis in our series, 1 of whom had a recurrence. With the Nottingham classification, these 8 cases would be in the most favourable prognostic group (DCIS without necrosis); in our classification, they are in the least favourable group (group 3). We devised the Van Nuys classification to select all high nuclear grade lesions first, placing them in the worst prognostic group, before sorting the remaining cases by the presence or absence of comedo-type necrosis. 16

Although there is discordance among pathologists in subtypes of DCIS recognition of the lower-grade end of the spectrum,14 there is good agreement on the presence or absence of comedo-type necrosis.10 There is also evidence that comedo-type necrosis or high nuclear grade in DCIS is associated with HER-2/neu gene amplification or HER-2/neu protein overexpression19-21 and with p53 protein expression or p53 gene mutation,22,23 both of which are thought to be markers of adverse prognosis. In addition, DCIS with comedo-type necrosis and/or high nuclear grade is more likely to lack oestrogen-receptor24,25 or progesterone-receptor expression. Molecular analysis on the specimens used to devise our classification demonstrated that HER-2/neu protein overexpression correlated with increasing risk of recurrence.

We chose high nuclear grade as the most important factor in our classification because of general agreement that patients with high nuclear grade lesions are likely to do worse than patients with low nuclear grade lesions,10,14 and comedo-type necrosis because it is easy to recognise10 and its presence likewise suggests a poor prognosis.10 In addition, it has been suggested that there is an association between the differentiation of DCIS and the histological grade of coexistent invasive cancer;19 this proposal could imply that nuclear grade is a factor in progression of in-situ breast cancers to invasive disease, although proof is lacking. The hardest part of most classifications is nuclear grading,10 particularly for intermediate-grade lesions. The subtypes of grading are not important to our classification; only nuclear grade 3 need be recognised. The cells must be large and pleomorphic, lack architectural differentiation and polarity, have prominent nucleoli and coarse clumped chromatin, and generally show mitoses.1,5,8,12,13

The proposed classification is useful because it divides DCIS into three groups with profoundly different risks of local recurrence after breast conservation therapy. The disease-free survival curves by treatment (figure 3) suggest that non-high-grade DCIS (groups 1 and 2) can be effectively treated with breast preservation with or without radiotherapy. For group 3 DCIS, even with radiation therapy, the local recurrence rate is estimated to be 30% at 7 years, and for many patients in this subgroup, breast preservation may not be a good option.

The amount of normal tissue required for truly clear margins may differ for different lesions. Faverly et al,14 using an alternative DCIS classification devised by the European Pathologists’ Working Group, have recently shown that low-grade DCIS has skip lesions more often than high-grade DCIS; this observation suggests wider margins may be required for complete clearance of low-grade lesions. We used 1 mm as the definition of a clear margin, which may be insufficient. At re-excision, 43% of patients whose margins were thought to be clear by at least 1 mm had residual DCIS.29 The fact that 30 of 31 local recurrences in breast preservation patients in this series were at or near the site of the primary DCIS suggests that the recurrences were really persistences of the inadequately excised original lesion.

Most local recurrences in patients with DCIS are detected by mammography. The most common mammographic finding is microcalcifications, which are commonly associated with tumour necrosis. The low rates of local recurrence in patients with group 1 DCIS may be due to the fact that these lesions do not have microcalcifications. When they recur, if they do not develop microcalcifications, their detection is likely to be delayed.

Because all conservatively treated patients are included in figure 2, projected recurrence rates at 8 years will probably be no worse than those estimated here—7% for group 1, 16% for group 2, and 39% for group 3. With wider excision margins, recurrence rates will probably be less. Since adopting a wide excision policy (>10 mm) for DCIS with detailed assessment of margins and margin distance coupled with re-excision of cavity walls for lesions with margins less than 10 mm, the Nottingham
Group have not so far experienced any local recurrences in 48 cases of localised DCIS less than 4 cm in size with 38 months of median follow-up (Ellis IO, Blamey RW, personal communication).

If radiotherapy is used, recurrence rates are also likely to be lower.6,30 The National Adjuvant Breast and Bowel Project has suggested that radiotherapy is appropriate for all patients with DCIS treated with breast preservation.30 Our results suggest that pathological subset analysis in DCIS is important, that different forms of DCIS may require different treatment, and that not all breast conservation patients with DCIS require radiation therapy.

This work was supported in part by USPHS grant CA 36827 and a grant from the Revlon Foundation.

References