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Original Paper

Ductal Carcinoma *In Situ* of the Breast from a Population-defined Cohort: an Evaluation of New Histopathological Classification Systems

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The increased incidence of ductal carcinoma *in situ* of the breast (DCIS) in the era of mammography screening requires a deeper knowledge of the biology of the disease and calls for a suitable classification system to optimise therapy. Our aim was to evaluate the correlation to prognosis for two new classification systems of DCIS. The histopathological specimens from 195 women consecutively diagnosed between 1986 and 1994 with a primary DCIS were re-classified by two separate observers using the system proposed by an European Organization for Research and Treatment of Cancer (EORTC) working group and the Van Nuys system. The relapse-free survival (RFS) by histopathological subgroup and by nuclear grade only was estimated for women treated with breast conserving surgery ($n = 149$). Thirty-two local recurrences occurred among 149 women (mean follow-up time 59 months). No distant recurrences or breast cancer deaths were reported. The women in the group with the highest differentiation according to the EORTC classification had no recurrences. RFS did not differ appreciably between the two other groups. This was true also after stratification for radiotherapy. We found no statistically significant difference in RFS between the three groups in the Van Nuys classification. There was an overall agreement between the observers in 79% and 64% of the cases, according to the EORTC and Van Nuys systems, respectively. We were able to define one group with highly differentiated lesions and an excellent prognosis with the EORTC classification. Further classification into intermediate and low differentiated lesions did not help predict RFS.

Key words: carcinoma *in situ*, breast neoplasm, histopathology, classification, prognosis
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INTRODUCTION

DUCTAL CARCINOMA *in situ* of the breast (DCIS) was described at the beginning of the century [1, 2]. Despite this, there is still no classification system that is unanimously accepted to be clinically useful [3]. The most often used classification system [4] is based on the architectural growth pattern. The main disadvantages of this classification system are the lack of clear criteria for the different subgroups and the fact that within the same lesion there may be a mixture of different growth patterns. This leads to low reproducibility [3, 5–8].

It is claimed that subgroups of DCIS differ in their biological behaviour, e.g. the comedo-type lesion is reported to have a higher risk to progress to invasive cancer [6, 9]. The comedo-type lesion presents with a higher thymidine labelling index, a higher grade of Stromelysin-3 and it is more often c-erbB2 positive than the other subgroups [10–13]. After a primary diagnosis of DCIS there is an up to 11 times increased risk of developing invasive breast cancer compared with the normal population, but it is not clear whether this risk pertains especially to any subgroup [14–21]. It would be beneficial for patient information, choice of treatment and follow-up policies, and classification in clinical research if subgroups of patients with a worse or better prognosis could be reliably defined.

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In accordance with this, new proposals for classification systems of DCIS have been presented [22–24]. The system proposed by Holland and co-workers within a working group of the European Organization for Research and Treatment of Cancer (EORTC) [22] is based upon the cytonuclear differentiation and the architectural differentiation with special reference to cellular polarisation. To our knowledge, there is currently no study where the relation to prognosis is evaluated according to this classification system. The Van Nuys system proposed by Silverstein and colleagues is based upon nuclear grade and the presence or absence of comedo-type necrosis, and there are indications that the subgroups have a different likelihood of local recurrence after breast conserving surgery (BCS) [23].

The aim of the present investigation was to evaluate whether the EORTC and the Van Nuys classification systems could distinguish prognostic subgroups in a population-based cohort of women treated with BCS after a primary diagnosis of DCIS. We also evaluated the correlation between nuclear grade only and prognosis, and determined whether it was easy to learn these new classification systems.

PATIENTS AND METHODS

Patients

We re-evaluated the histopathology for 210 women from the catchment area of Uppsala and Västerås hospitals, Sweden reported to the Regional Cancer Registry (RCR) as having a primary DCIS. RCR is a part of the Swedish Cancer Registry (SCR). It is mandatory by law in Sweden to report all cancer events to the SCR including carcinoma *in situ* of the breast. The SCR has a high degree of completeness, with 90–99% of all diagnosed cancer cases reported [25–27]. In a validity control of the register in the south of Sweden, the correctness of registration of breast carcinoma *in situ* was found to be 93.8% and completeness was 78.0% during the period 1982–1988. Correctness and completeness were improved during the period 1989–1991, to 95.9% and 94.6%, respectively [27].

Seven women of the 210 were found to have invasive cancer upon histopathological re-examination. Another seven lesions were re-classified as benign and one lesion as a lobular carcinoma *in situ* (LCIS). These 15 women were excluded from further study and our study cohort then consisted of 195 consecutive women diagnosed with primary DCIS between 1987 and 1994 at the University Hospital of Uppsala (102 women) and between 1986 and 1994 at the hospital of Västerås (93 women). There has been a population-based mammography screening programme for women aged 40–69 years since 1986 in Västerås and for women aged 40–74 years since 1988 in Uppsala. Both hospitals have their own mammography unit and the two pathology departments are the only two existing in this region with socialised medical care.

Methods

All medical records from the surgical and oncological departments were studied from the time of primary diagnosis onwards. If a woman was discharged from further follow-up but alive and living in the region, and not registered in any hospital file or in the Regional Cancer Registry for a new breast cancer, she was considered to be relapse-free. One woman had moved to another region and her records were collected from this hospital. Any cancer event in the ipsilateral breast was considered a local relapse and thus qualified as an event in the analysis of local relapse-free survival (RFS). Ipsilateral new events occurring synchronous or metachronous to a contralateral breast cancer (2 women) were also included in the analyses. Death certificates were collected for all women who died during the follow-up.

Tumour size and assessment of radicality were obtained from the original pathology report. The pathologists did not use a standard protocol during this period and the size was only included in the analysis if it was described in millimetres in the original pathology report. If the pathologist reported clear margins we defined this as radicality. Only a minority of the tumours had been analysed for hormone–receptor status and DNA-profile (42 and 11, respectively). The re-evaluation of the histopathological slides was blinded in relation to prognostic information.

Treatment during the studied period was routinely mastectomy for lesions affecting more than one quadrant of the breast. Smaller lesions were usually treated with breast conserving surgery. In 1989, a Swedish nationwide randomised study was initiated with the aim of evaluating the eventual effect by postoperative radiotherapy to the ipsilateral breast after the treatment with BCS in patients with DCIS.

All histopathological specimens, stained according to van Gieson, were re-classified according to the system proposed by the EORTC working group. Six months later we did a re-classification according to the Van Nuys system, blinded to the earlier classification results. The classification system by the EORTC working group divides DCIS into three different categories; well differentiated, intermediately and poorly differentiated, which we in this study denoted R1–R3. The first category R1 consists of well differentiated lesions with monomorphic, equally sized nuclei evenly spaced, inconspicuous nucleoli, few mitosis, no individual cell necrosis, and polarisation with well defined apex and luminal orientation. The third category R3 consists of lesions poorly differentiated with pleomorphic, irregularly spaced nuclei with marked variation in size, irregular nuclear contours, coarse chromatin and prominent nucleoli, frequent mitosis, individual cell necrosis and autophagocytosis and no polarisation. The second and intermediate category R2 consists of lesions in-between the two other groups, with moderate pleomorphism and a tendency to polarisation which results in pseudocribriform and papillary patterns, sometimes in predominantly solid areas.

The Van Nuys system also divides DCIS into three categories. Firstly, between high and non-high nuclear grade and secondly the non-high-grade lesions are divided by the presence or absence of comedo-type necrosis. In this study we denoted these categories N1–N3. N1 included the lesions with non-high nuclear grade and absence of necrosis, N2 included the lesions with non-high-grade and necrosis and N3 included all high-grade lesions. In a separate analysis, we studied nuclear grade only, which is the accepted system for classification of DCIS by a European Union Work Group on Breast Cancer Screening Pathology in 1996 [24]. The categories low-, intermediate- and high nuclear grade were denoted K1–K3 in this study.

The re-classification was first performed separately by two independent observers and then by the two observers together, in order to reach consensus. One observer was an experienced breast pathologist (HN) and the other was a surgeon (FW) with a special interest in breast cancer. If there

Table 1. *Patient and tumour characteristics including all* 195 *women with ductal carcinoma* in situ *of the breast*

	EORTC			Van Nuys			Nuclear grade		
	R1	R2	R3	N1	N2	N3	K1	K2	K3
Number*	13 (7%)	99 (51%)	83 (43%)	61 (31%)	26 (13%)	107 (55%)	16 (8%)	71 (37%)	107 (55%)
Mean age (standard deviation)	60.2 (8.0) yrs	61.1 (12.4) yrs	58.0 (10.4) yrs	64.1 (11.2) yrs	57.0 (11.2) yrs	57.8 (11.0) yrs	59.1 (9.7) yrs	62.7 (12.0) yrs	57.8 (11.0) yrs
Mean follow-up (standard deviation)	65.2 (31.9) mo	60.0 (27.7) mo	56.0 (26.5) mo	59.6 (28.8) mo	57.3 (25.3) mo	56.5 (27.2) mo	73.9 (23.7) mo	65.0 (27.2) mo	56.5 (27.2) mo
Mean size (standard deviation)†	9.9 (7.0) mm (7)	13.2 (10.1) mm (66)	17.7 (13.7) mm (49)	13.3 (9.9) mm (39)	14.4 (12.9) mm (17)	15.7 (12.5) mm (66)	11.8 (7.7) mm (9)	14.0 (11.3) mm (47)	15.7 (12.5) (66)
Multifocal	1 (8%)	16 (16%)	11 (13%)	6 (7%)	5 (19%)	16 (15%)	1 (6%)	10 (14%)	16 (15%)
Mammography detected	12 (92%)	64 (65%)	71 (86%)	36 (59%)	22 (85%)	89 (83%)	13 (81%)	45 (63%)	89 (83%)
Breast conserving surgery (BCS)	13 (100%)	72 (73%)	64 (77%)	50 (82%)	21 (81%)	78 (73%)	15 (94%)	56 (79%)	78 (73%)

*One histopathological specimen was lost in the analysis according to the Van Nuys and nuclear grade classification systems; †Number of lesions available for evaluation. R1–R3 and N1–N3 according to the EORTC and the Van Nuys classification systems, respectively. K1–K3 according to nuclear grade only.

Table 2. Patients with ductal carcinoma in situ *of the breast treated with breast conserving surgery (BCS) (*n = 149*)*

	EORTC			Van Nuys			Nuclear grade		
	R1	R2	R3	N1	N2	N3	K1	K2	K3
Number	13	72	64	50	21	78	15	56	78
Radicality									
No	0	1	0	1	0	0	0	1	0
Doubtful	1	8	7	5	4	7	1	8	7
Unknown	0	0	1	0	0	1	0	0	1
Postoperative radiotherapy	3 (23%)	13 (18%)	26 (41%)	9 (18%)	6 (29%)	27 (35%)	1 (6%)	14 (25%)	27 (35%)

The different subgroups according to the EORTC and the Van Nuys classification systems (R1–R3 and N1–N3) and nuclear grade (K1–K3).

was a dominating pattern and only a small foci of another pattern the lesion was classified according to the dominating pattern when we used the EORTC system. We defined a ''small'' focus as being a maximum of 25% of the total tumour area. According to the Van Nuys system, a few per cent of high-grade cells were acceptable in a lesion classified as a non-high-grade lesion. The architectural pattern was determined from the original pathological report.

Statistical methods

Kaplan–Meier estimations were made for RFS for each category, R1–R3, N1–N3 and K1–K3, including only the patients treated with breast conserving surgery. For comparison of the Kaplan–Meier estimates, a log-rank test was used and when comparing proportions and mean values we used the Chi-squared test and the *t*-test, respectively. Statistical significance was set at $P < 0.05$. The Microsoft Statistica software was used for all statistical calculations.

RESULTS

Mean and median follow-up times for all 195 women were 58.6 and 58 months, respectively. Patient and tumour characteristics by histopathological subgroup are shown in Table 1. 149 women (76%) were treated with a breast conserving surgical technique; 145 with a sector resection (i.e., removal of all breast tissue in a sector from behind the mamilla and all the way to the periphery with the aim of a free margin of at least 10 mm) and four with a local excision. 148 women (76%) were diagnosed via the population-based mammography screening programme. In 45 women the lesions were found clinically (i.e., a symptomatic lesion or a lesion detected by clinical mammography other than screening) and two lesions were found ''en passant'' when the woman was operated on for a different primary reason.

In Table 2, the number of women treated with BCS by histopathological subgroup is presented. The proportion of women who received radiotherapy and the proportion of lesions with doubtful or lack of radicality after BCS are also shown. There was a tendency that after BCS the proportion of women who received radiotherapy was higher in the R3, N3 and K3 groups than in the other groups, R1–R2, N1–N2 and K1–K2 together (20%).

The architectural patterns were compared according to the pathological reports with the histopathological subgroups of the EORTC and Van Nuys systems. Seventy-seven per cent ($n = 64$) of the R3 lesions were comedo-type or mixed, and these mixed lesions mostly had comedo-type elements; 71% ($n = 70$) of the R2 subgroup were cribriform-type or mixed lesions; and 92% ($n = 12$) of the R1 subgroup were papillary/micropapillary or cribriform-type. Eighty-five per cent of the N1 subgroup and 77% of the N2 subgroup were micropapillary/papillary, cribriform and mixed-type lesions; whilst 66% of the N3 subgroup were comedo-type or mixed-type lesions.

There was an agreement between the two observers in the categorisation of R1–R3 in 66 of the first 100 cases (66%). After a consensus meeting about the first 100 lesions, there was an agreement in 88 of the remaining 95 cases (93%) with an overall agreement in 79% of the cases. Interobserver discrepancies were found between R2 and R3 lesions in 32 of the 41 women with dissimilar results.

In evaluating the interobserver agreement of the Van Nuys classification system, one histopathological slide was lost and in two cases only one observer made the classification. There was overall agreement in 64% of cases. In 26 of the 69 cases there was a different opinion between the two observers between a N2 and a N3 lesion. Twenty-nine lesions were classified as either N1 or N3 and in 14 cases the opinion differed between N1 and N2. For nuclear grade, the interobserver agreement was 66%.

The relapses and the new breast cancer events among the 149 women treated with BCS are characterised in Table 3. There were 32 local events (19 *in situ*- and 13 invasive cancers) and during the follow-up period 6 women had a

Table 3. Site and type of new cancer events in 149 *women treated with breast conserving therapy after a primary ductal carcinoma* in situ *of the breast*

	EORTC			Van Nuys			Nuclear grade		
New cancer event	R1	R2	R3	N1	N2	N3	K1	K2	K3
Total number at risk	13	72	64	50	21	78	15	56	78
Ipsilateral ($n = 32$): invasive/*in situ*	0/0	9/10	4/9	6/6	0/2	7/11	1/1	5/7	7/11
Contralateral ($n = 6$): invasive/*in situ*	2/1	2/0	1/0	3/1	0/0	2/0	2/0	1/1	2/0

The different subgroups according to the EORTC and the Van Nuys classification systems (R1–R3 and N1–N3) and nuclear grade (K1–K3).

diagnosis of a contralateral breast cancer. No woman had distant metastases or died from breast cancer during the follow-up. 10 of 195 women died from other causes, with no reports of breast cancer relapse, 5 of these women underwent an autopsy. Among the women who were treated with mastectomy, there was only one local relapse; an *in situ* carcinoma in the scar. Of 17 women with no or doubtful radicality at operation, four had a local relapse (24%) during the follow-up period.

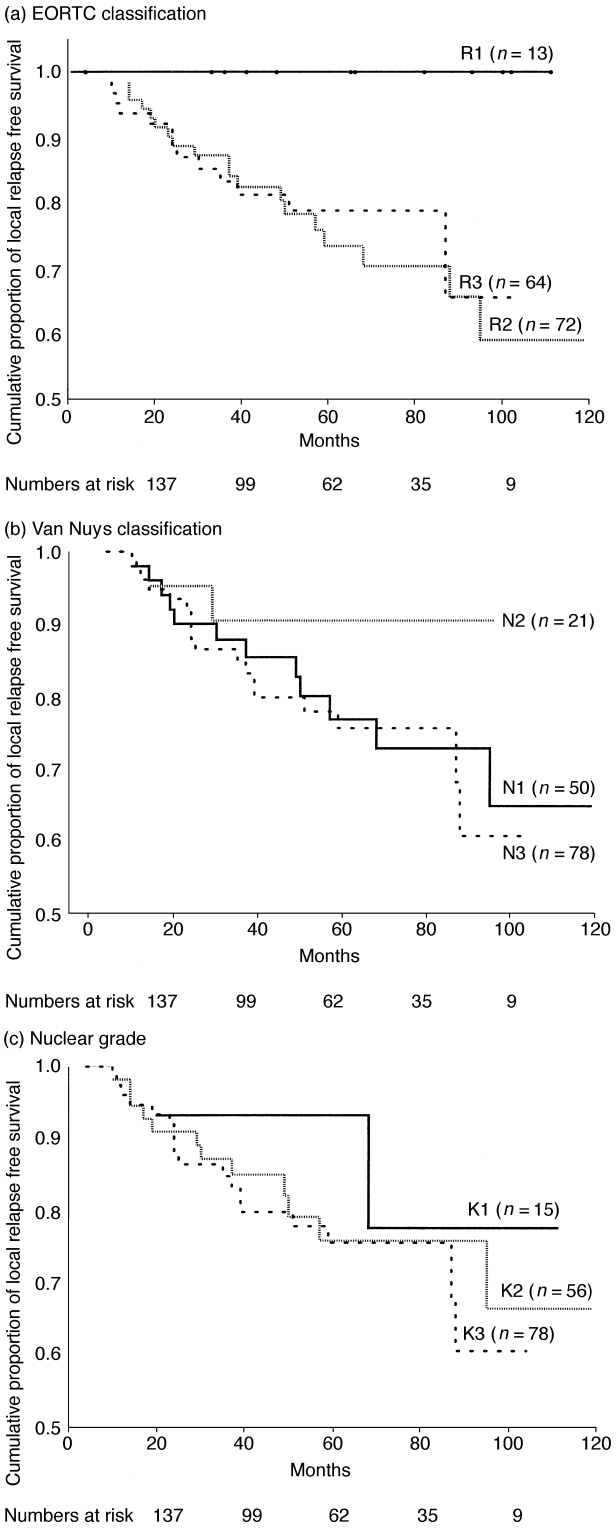

Figure 1. The cumulative probability of relapse-free survival (Kaplan–Meier method) by histopathological subgroup, in patients with a ductal carcinoma *in situ* of the breast and treated with breast conserving surgery. (a) EORTC classification (log-rank test between R2 and R3, $P = 0.75$). (b) Van Nuys system (log-rank test $P = 0.53$). (c) Nuclear grade (log-rank test $P = 0.52$).

In the analysis of RFS in patients treated with BCS, the Kaplan–Meier survival curves of R2 and R3 did not differ significantly (log-rank test $P = 0.75$) (Figure 1a) but they clearly differed in outcome as compared with R1. Postoperative irradiation may have confounded the comparison and therefore the R2 and R3 subgroups were analysed according to radiotherapy treatment. However, neither analysis indicated a significant difference (log-rank test $P = 0.96$, both with and without postoperative radiotherapy). The Kaplan–Meier survival curves of N1–N3 in women treated with BCS did not differ significantly (log-rank test $P = 0.53$; Figure 1b), nor was there a statistically significant difference between any of the groups after stratification for radiotherapy (data not shown). In the analysis of subgroups K1–K3, the Kaplan–Meier survival curves were not significantly different (Figure 1c).

DISCUSSION

We found that the classification of DCIS according to the EORTC working group was easy to learn with an interobserver agreement in more than 90% after a short learning period. One group with well differentiated lesions, constituting less than 10%, was easily discernible and this group had no local relapses during the follow-up period. We were not able to show any difference in the prognosis between the two other groups of this classification. Within the Van Nuys classification, there was overall interobserver agreement in 64% of the cases. There was no statistically significant difference regarding local RFS between the subgroups using this classification system. When necrosis was excluded and only nuclear grade considered, a pattern in the survival curves was noted which resembled the pattern in the EORTC classification system. This study design did not investigate the reproducibility of the classification systems. Only one clinically experienced pathologist participated and the interobserver agreement should be regarded as a test of whether these systems are easy to learn.

The cohort was population based and the follow-up was complete. The cohort consisted of women consecutively diagnosed in the population of approximately 540,000 inhabitants in the catchment areas of the two hospitals. A mammography screening programme served both areas during the period studied. All medical reports and all histopathological sections were available and the mean follow-up time was almost 5 years. During the study period, the treatment policies have mainly been unchanged. Altogether, this makes it probable that the results are generalisable to women with DCIS in a mammography screened population. The study is comparatively large given that DCIS is studied, but subgroups are still small limiting the possibility of studying interactions between different determinants in e.g. multivariate analyses.

Two reports using the EORTC classification have been published [28, 29], and both showed a larger proportion of highly differentiated lesions than our study (Table 4). We found a larger proportion of intermediately differentiated lesions. Prognosis was not reported in these studies so we cannot determine if their well differentiated groups had a

Table 4. Proportion of the different subgroups according to EORTC classification system and mode of detection in patients with a primary ductal carcinoma in situ *of the breast*

Study [ref]	No. of cases	Well differentiated (%)	Intermediately differentiated (%)	Poorly differentiated (%)	Mammography detected (%)
Bobrov [28]	105	21	25	54	23
Zafrani [29]	127	30	31	39	100
Current study	195	7	51	43	76

prognosis similar to that in our study. A group with a good prognosis was identified in our study using the EORTC system which may have implications for therapy selection and follow-up. However, this group only consisted of 13 women and thus the results have to be interpreted with caution. One may argue that we classified too few patients into the well differentiated group. Lesions with good prognosis could theoretically be selected from the papillary/micropapillary and cribriform-type lesions, since our R1 group consisted of such lesions according to the architectural growth pattern. However, in our R2 group, we had 11 local relapses among the 54 women with papillary/micropapillary or cribriform-type lesions. Also, we could not see any statistically significant difference in local RFS between the micropapillary/papillary, the cribriform- and the comedo-type lesions within the R2 and R3 categories (data not shown).

Another possibility as to why we had comparatively few lesions in our R1 group is that we may have had a more strict definition of DCIS, not including in our study some lesions classified as atypical hyperplasia by us, but that would have been classified as DCIS by other pathologists.

There was no difference in prognosis between the R2 and R3 groups. This may have been due to misclassification. However, we did not see proportionally more local relapses among the women in the R2 group where one of the observers had classified the lesion as R3 before consensus, nor among the R3 lesions were there proportionally fewer relapses in women where one of the observers had classified the lesion as R2 before consensus.

The pattern within this and two other studies is not consistent with the notion that the mode of detection should have an influence on the distribution of the lesions into the different subgroups. In Bobrov's study [28] 23% of the lesions were screening detected. Their cohort consisted of 105 cases with pure DCIS diagnosed between 1975 and 1991 in one breast unit. In Zafrani's series [29] all patients had mammographically detected lesions and they were diagnosed between 1990 and 1993. In our study 76% of the lesions were detected by mammography as a result of the population-based screening programme.

In our hands the Van Nuys classification system did not show any value for predicting prognosis. If we excluded necrosis as a criteria and only classified the lesions according to nuclear grade, then there was better separation between the survival curves, although not to a statistically significant degree. When necrosis was used as a criterion, there were a large number of lesions ($n = 45$) with intermediate nuclear grade but no necrosis and which therefore were classified into the subgroup N1, according to the Van Nuys system. Among these 45 women there were ten local relapses, explaining the difference in RFS between the N1–N2 and K1–K2 subgroups.

It is difficult to find a straightforward explanation for the difference in results between our study and the Van Nuys paper. In the presentation of the Van Nuys classification system [23] the mode of detection was not presented. The DCIS lesions were divided according to their system into three almost equally sized subgroups; N1 = 32.7, N2 = 36.9 and N3 = 30.4%. In our study the corresponding groups consisted of 31, 13 and 55%. This may represent a true difference between the study populations, probably due to the mode of detection. The comparison between the studies could be hampered if mode of detection influences both distribution by subgroup and prognosis. Another possibility is that we differed in our way of classifying the lesions. Although, our N2 group was smaller and the N3 was larger, it was not a general phenomena to classify "possible" N2 lesions as N3: out of 26 lesions where there was disagreement between N2 and N3 before consensus, ten ended up as N2 and 16 as N3.

If the histopathological pattern was used as one factor in choosing mastectomy—and used differently in Silverstein's study and ours—this could also bias the overall comparison between the two studies regarding prognosis. However, for rate of mastectomy to confound the internal comparisons of the association between subgroup and prognosis, the indications for mastectomy also need to be coupled to another risk factor for local recurrence, for example if mastectomy is more often recommended for doubtful margins in the N3 group. There were no indications of this in our study and a strong correlation between management choices and the Van Nuys classification is unlikely in our study where the classification was done retrospectively and blinded to the outcome. Not unexpectedly, there was a tendency to use radiotherapy more often in the high-grade lesions in our study. However, both according to our results and those from Van Nuys, controlling for radiotherapy did not appreciably change the results.

We did not specifically study the treatment efficacy of radiotherapy, since confounding by indication here would be a large problem. Several, large randomised studies are underway to address treatment issues in DCIS and it seems appropriate to take the opportunity to study prognostic classification systems within those. In the randomised setting, there should be opportunities to assess critically these systems' ability to predict treatment response. In our hands, the classification proposed by the EORTC working group seems to be the most promising, but mainly for discerning a minority subset of women with very good prognosis.

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