“Women who have undergone a breast biopsy for benign disease have an increased risk of breast cancer”

Dupont and Page

NEJM 1985
## Borderline Lesions - Risk Assessment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Risk Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slight</td>
<td>1.5-2.0</td>
<td>Hyperplasia</td>
</tr>
<tr>
<td>Moderate</td>
<td>4-5</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>High</td>
<td>10</td>
<td>ADH + FH, LCIS, Non comedo DCIS</td>
</tr>
<tr>
<td>Lesion</td>
<td>Risk</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Florid UEH</td>
<td>1.5 - 2</td>
<td>Minimal risk</td>
</tr>
<tr>
<td>ALH</td>
<td>4x</td>
<td></td>
</tr>
<tr>
<td>ALH + family history</td>
<td>8 - 10x</td>
<td>Bilateral risk</td>
</tr>
<tr>
<td>ADH</td>
<td>4x</td>
<td></td>
</tr>
<tr>
<td>LCIS</td>
<td>10x</td>
<td></td>
</tr>
<tr>
<td>LCIS + family history</td>
<td>10x</td>
<td></td>
</tr>
<tr>
<td>DCIS low grade</td>
<td>10x</td>
<td>Ipsilateral risk</td>
</tr>
</tbody>
</table>

Lobular neoplasia risk most relevant in 5th decade
Slight preponderance of cancer in the ipsilateral breast for LN
Borderline Lesions

Markers of risk - ADH, ALH, LCIS

Determinant lesion - Low grade DCIS

Largely committed lesion - High Grade DCIS

Page 1992
Florid Ductal Hyperplasia
Without Atypia

- Streaming patterns
- Intracellular borders ill defined
- Irregularity of nuclear shape, chromasia and position
- Irregular slit-like secondary spaces

Page + Rogers Human Path 1992, 23, 1095
Ductal Carcinoma In Situ - Non Comedo

- Evenly spaced uniform cells
- Oval or rounded nuclear features
- Sole population of two duct spaces
- Pale cytoplasm with distinct borders
- Secondary spaces rounded/punched out
- Rigid non tapering bars
- Usually over 3mm

*Page + Rogers Human Path 1992, 23, 1095*
Atypical Ductal Hyperplasia

- Partial involvement of duct space
- Cell population same as non comedo DCIS (usually hyperchromatic nuclei)
- Second population of polarised basal cells
- At least one non tapering bar (>6 cells across)

NB  DCIS v ADH - if in doubt = ADH

Page + Rogers Human Path 1992, 23, 1095
Borderline Epithelial Lesions of the Breast

Borderline Epithelial Lesions

- 5 experienced pathologists
- 10 ductal, 7 lobular cases
- “Usual practice” criteria

Borderline Epithelial Lesions

Agreement

- No cases with complete agreement
- 5/6 3 cases (18%)
- all diagnosis proffered H - CIS
  6 cases (33%)

Inter Observer Reproducibility :-

The Diagnosis of Ductal Proliferative Breast Lesions using Standardized Criteria

Proliferative Breast Disease - Ductal

- Six experienced breast pathologists
- 24 cases
- Standard criteria (Page)
- Teaching illustrations and slides

*Schnitt Am J Surg Pathol 16, 1133, 1992*
## Proliferative Breast Disease - Ductal

<table>
<thead>
<tr>
<th>Agreement</th>
<th>Complete</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>58%</td>
</tr>
<tr>
<td>5/6</td>
<td></td>
<td>17</td>
<td>71%</td>
</tr>
<tr>
<td>4/6</td>
<td></td>
<td>22</td>
<td>92%</td>
</tr>
</tbody>
</table>

No “Hawks” or “Doves”

*Schnitt Am J Surg Pathol 16, 1133, 1992*
K:  
0.00 – 0.20 slight
0.21 – 0.40 fair
0.41 – 0.60 moderate
0.61 – 0.80 substantial
0.81 – 1.00 almost perfect
<table>
<thead>
<tr>
<th>Circulation (No of cases)</th>
<th>Benign (54)</th>
<th>Atypical hyperplasia</th>
<th>In situ / Micro-invasive (103)</th>
<th>Invasive</th>
<th>Overall (216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>902,911,912</td>
<td>0.72</td>
<td>0.19</td>
<td>0.71</td>
<td>0.81</td>
<td>0.68</td>
</tr>
<tr>
<td>921,922,931</td>
<td>0.75</td>
<td>0.16</td>
<td>0.71</td>
<td>0.86</td>
<td>0.72</td>
</tr>
<tr>
<td>932,941,942</td>
<td>0.81</td>
<td>0.15</td>
<td>0.75</td>
<td>0.88</td>
<td>0.77</td>
</tr>
<tr>
<td>951,952,961</td>
<td>0.75</td>
<td>0.17</td>
<td>0.77</td>
<td>0.86</td>
<td>0.77</td>
</tr>
<tr>
<td>962,971,972</td>
<td>0.79</td>
<td>0.26</td>
<td>0.81</td>
<td>0.91</td>
<td>0.82</td>
</tr>
<tr>
<td>981,982,991</td>
<td>0.84</td>
<td>0.13</td>
<td>0.69</td>
<td>0.90</td>
<td>0.79</td>
</tr>
<tr>
<td>All</td>
<td>0.79</td>
<td>0.18</td>
<td>0.75</td>
<td>0.88</td>
<td>0.77</td>
</tr>
</tbody>
</table>
LOH Studies

14 cases of ADH

Ch 16q  5 of 9 informative cases
Ch 17p  2 of 8 informative cases

Lakhani *J Pathol.* 1995
## Diagnosis of epithelial proliferative lesions

<table>
<thead>
<tr>
<th>Hyperplasia</th>
<th>Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK 5, 6, 14</td>
<td>+</td>
</tr>
<tr>
<td>ER</td>
<td>-</td>
</tr>
</tbody>
</table>

Bocker et al. *Virchow Arch A Pathol Anat* 421 315 & 323, 1992
Shoker et al. *J Pathol* 188; 237, 1999
DCIS
Relationship to invasive carcinoma

Summary

- Morphological and molecular similarities
- Clonal process
- Analogous to epithelial in situ lesions elsewhere
- High frequency of progression to invasive carcinoma if incompletely excised
## DCIS local recurrence

<table>
<thead>
<tr>
<th>DCIS Type</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Intermediately Differ</td>
<td>9</td>
<td>41</td>
<td>2</td>
<td>52 (24)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>3</td>
<td>73</td>
<td>73</td>
<td>149 (69)</td>
</tr>
<tr>
<td>Total %</td>
<td>23 (11)</td>
<td>117 (54)</td>
<td>75 (35)</td>
<td>215</td>
</tr>
</tbody>
</table>

$\chi^2=110.0$, P=0.0001

Lampejo et al. Seminars in Diagnostic Pathology 1994; 11:215-222
DCIS

LOH Studies

46 pure DCIS
86 DCIS + invasive (micro dissection)

Ch 16q allelic imbalance in 50% informative cases
Ch 17p allelic imbalance in 10% informative cases
Ch 17q allelic imbalance in 10% informative cases

Stratton *J Pathol.* 1995;175;195-201
DCIS
Relationship to invasive carcinoma

Summary

- Morphological and molecular similarities
- Clonal process
- Analogous to epithelial in situ lesions elsewhere
- High frequency of progression to invasive carcinoma if incompletely excised
DCIS

Prevalence in normal female population

- Kramer and Rush 1973 >70 years
  6% (4 / 70) DCIS
  50% bilateral

- Alpers and Wellings 1985 20 to >60 years
  9% (9 / 100) DCIS

- Nielson et al 1987 20 to 54 years
  14% (16 / 110) DCIS
  50% detectable
## DCIS

### Natural history - biopsy alone

<table>
<thead>
<tr>
<th>Year</th>
<th>No. patients</th>
<th>Subsequent cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis</td>
<td>1938</td>
<td>8</td>
</tr>
<tr>
<td>Farrow</td>
<td>1970</td>
<td>25</td>
</tr>
<tr>
<td>Haagensen</td>
<td>1971</td>
<td>11</td>
</tr>
<tr>
<td>Millis</td>
<td>1975</td>
<td>8</td>
</tr>
<tr>
<td>Rosen</td>
<td>1985</td>
<td>15</td>
</tr>
<tr>
<td>Page</td>
<td>1982</td>
<td>25</td>
</tr>
<tr>
<td>Eusebi</td>
<td>1994</td>
<td>80</td>
</tr>
</tbody>
</table>

172       47 (28%)
Natural History DCIS

- 28 patients - breast biopsy
- Original benign diagnosis
- Low grade DCIS diagnosed on review
- 30 years follow up
- 40% recurrence with invasive carcinoma
- Same site as previous biopsy

## DCIS - Grade and Recurrence

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Nuclear grade</th>
<th>Necrosis</th>
<th>Architecture</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Comedo</td>
<td>High</td>
<td>+++</td>
<td>Solid</td>
<td>7/31</td>
<td>(23)</td>
</tr>
<tr>
<td>II Crib/pap with necrosis</td>
<td>High</td>
<td>+++</td>
<td>Crib/pap</td>
<td>2/5</td>
<td>(40)</td>
</tr>
<tr>
<td>Sub total</td>
<td></td>
<td></td>
<td></td>
<td>9/36</td>
<td>(25)</td>
</tr>
<tr>
<td>III Cribriform/intermediate</td>
<td>Intermediate</td>
<td>+/-</td>
<td>Crib</td>
<td>1/10</td>
<td>(10)</td>
</tr>
<tr>
<td>IV Micropapillary/non necrotic cribriform</td>
<td>Low</td>
<td>0</td>
<td>Micropap/crib</td>
<td>0/33</td>
<td>(0)</td>
</tr>
</tbody>
</table>

Classification of DCIS

High Nuclear Grade

Nuclei pleomorphic, irregularly spaced, usually large
Irregular nuclear contours
Coarse chromatin
Prominent nucleoli
Mitoses frequent and may be abnormal
Growth pattern often solid but may be micropapillary or cribriform
Frequently central necrosis
Rarely any polarisation of cells

NHS BSP Pathology Reporting Guidelines 1995
Classification of DCIS
Low Nuclear Grade

Monomorphemic, evenly-spaced cells
Nuclei usually small, spherical and centrally-placed
Inconspicuous nucleoli
Few mitoses
Rarely any individual cell necrosis
Generally micropapillary and cribriform patterns 
(frequently both). Solid architecture rare.

Usually polarisation around lumina or micropapillae

NHS BSP Pathology Reporting Guidelines 1995
**Classification of DCIS**

**Intermediate Grade DCIS**

Mild to moderate pleomorphism, less than high grade DCIS but lacking monotony of low grade

Nuclear to cytoplasmic ratio often high

One or 2 nucleoli present

Growth pattern may be solid, cribriform or micropapillary

Some degree of polarisation (not as marked as low grade DCIS)

NHS BSP Pathology Reporting Guidelines 1995
Classification of DCIS

Mixed Type

Variations in growth pattern frequent

Rarely cells of different nuclear grade identified; usually a dominant type

Record different nuclear grades seen, but classify case according to highest nuclear grade present

NHS BSP Pathology Reporting Guidelines 1995
Classification of DCIS

Other (Rare) Variants

May be classified separately and include:

Signet ring DCIS
Apocrine DCIS
Cystic hypersecretory DCIS
Neuroendocrine DCIS

NHS BSP Pathology Reporting Guidelines 1995
Nottingham DCIS series Summary

• 9% of cases in this series of 372 cases of DCIS recurred
• High grade DCIS was more likely to recur; 85% of recurrences arose from high grade DCIS
• 62% of recurrences were as invasive disease
• Both recurrent DCIS and invasive recurrence were frequently of the same grade as the original DCIS
DCIS

Recurrence in remote quadrants

- 5% (2/43)

Adesson Fisher Zafrani
DCIS

Recurrence

A determinant of local failure in the conserved breast is the extent of DCIS, with or without an invasive component

Connolly JL et al. Mod Pathol 11; 134, 1998
DCIS

Nottingham & Silverstein Studies

Local cure of DCIS by surgery alone is possible and requires:

Good surgical technique with wide margins

Detailed pathological examination of margins
What is an appropriate surgical excision margin?

- Nottingham: 10 mm
- Silverstein: 10 mm
- Boston: 1 mm
- NSABP: 1 mm
DCIS

Definitions

Unicentric (1 duct system)
- Focal continuous
- Multifocal discontinuous

Multicentric (>1 duct system)

Holland
DCIS

81 cases - 1 duct system

1 cases - multiple ducts systems

\ Unicentric process

Holland Lancet 335, 519, 1990
DCIS

Growth Pattern

The growth of DCIS is 2x faster towards the nipple than the periphery

Evans In Press
DCIS

Breast Screening

• What is the effect of DCIS diagnosis and treatment?

• Will incident invasive cancer rate fall?
DCIS

Dilemmas of Breast Screening

- How to treat localised DCIS
- Overdiagnosis?
- Effect of detection
DCIS

Mammographic screening

It is likely that much of the survival advantage attributed to screening mammography in young women is due to the detection of DCIS.

If left in place these would evolve into invasive cancer in 5 to 8 years.

DCIS

Needs:

• Better understanding of natural history

• Clear treatment protocols
DCIS

Key Facts

- Biopsy alone (low grade)
  40% invasive cancers 30 years

- Conservation treatment
  50% recurrences invasive
Summary

Progression is NOT invariable

Risk of progression related to type and grade of DCIS
LCIS

- LCIS described in 1941 as a histological entity by Foote and Stewart - only 2 cases of pure LCIS, 12 LCIS + invasive carcinoma

- A “rare form of mammary carcinoma”
LCIS

- Detection increased in recent years, found in approximately 1% (0.5 - 3.6%) of all breast biopsy specimens but reported as accounting for up to 9.8% of mammographically detected lesions classified as malignancies.
- True incidence unclear; the absence of clinical or mammographic features makes detection random.
- May be widespread, with high rates of multicentricity (60-80%) and bilaterality (23-35%).
LCIS

• Up to a 12 x increased risk of subsequent invasive carcinoma (most studies 7 - 10 x)
• Marker of risk in both breasts rather than true premalignant lesion
• Most subsequent malignancies occur >15 years after diagnosis
• Most ductal rather than lobular although there is a particular increase in lobular morphology over expected - lobular 18 x c.f. ductal 4 x expected rate
NSABP B-17: LCIS

- 182 women with LCIS in NSABP Protocol B-17 treated by lumpectomy only
- 13 ipsilateral recurrences (7%)
- All occurred in same quadrant as the index LCIS

_Fisher ER et al. Cancer. 1996; 78; 1403-1416_
LCIS with Microinvasion

• 6 patients with LCIS with microinvasion described
• Rare but raises some questions re LCIS as a risk factor only

## Apocrine lesions

### Categorisation of difficult apocrine lesions

<table>
<thead>
<tr>
<th>Size</th>
<th>Usual Nuclei</th>
<th>Borderline Nuclei</th>
<th>As in DCIS Nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4mm</td>
<td>AA or PAC</td>
<td>AA or PAC with atypia</td>
<td>Limited Apo DCIS</td>
</tr>
<tr>
<td>4 - 8 mm</td>
<td>AA or PAC</td>
<td>Borderline Apo DCIS</td>
<td>Apo DCIS</td>
</tr>
<tr>
<td>&gt;8mm</td>
<td>Rare</td>
<td>Borderline Apo DCIS</td>
<td>Apo DCIS</td>
</tr>
</tbody>
</table>

O’Malley et al. Hum Pathol 25; 164, 1994
## Apocrine lesions

### Nuclear features of apocrine lesions

<table>
<thead>
<tr>
<th>Nuclear Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual apocrine</td>
<td>Regular, round vesicular nuclei; single large nucleolus usually present</td>
</tr>
<tr>
<td>Borderline</td>
<td></td>
</tr>
<tr>
<td>Type a</td>
<td>Markedly enlarged nuclei in at least 25%</td>
</tr>
<tr>
<td>Type b</td>
<td>Majority of cells showing nuclei 2-3 times usual apocrine nuclei, irreg nuc membranes 2-3 small nucleoli</td>
</tr>
<tr>
<td>Non comedo</td>
<td>Irregular nuclear membrane, coarse chromatin pattern, multiple nucleoli</td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
</tr>
</tbody>
</table>

O’Malley et al Hum Pathol 25; 164, 1994
Columnar cell hyperplasia is associated with lobular carcinoma in situ and tubular carcinoma
Rosen PP Am J Surg Pathol 1999; 23; 1561
Breast Cancer Carcinogenesis

Multistep Model

Normal

Usual hyperplasia
Atypical hyperplasia

Carcinoma in situ
Invasive carcinoma

Metastasis
Allele Loss in Breast Carcinoma

- 1p
- 1q
- 3p
- 6q
- 7q
- 8p
- 11p
- 11q
- 13q
- 16q
- 17p
- 17q
- 18q
Allele Loss in Tubular Carcinoma

High LOH:

- 3p   FHIT
- 11q  ATM?
- 13q
- 16q

Man et al Cancer Research 1996, 56: 5484
## Breast Cancer Carcinogenesis

<table>
<thead>
<tr>
<th>DCIS type</th>
<th>Ave no genetic imbalances</th>
</tr>
</thead>
<tbody>
<tr>
<td>low grade</td>
<td>2.5</td>
</tr>
<tr>
<td>Int. grade</td>
<td>5.5</td>
</tr>
<tr>
<td>High grade</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Buerger et al. *J Pathol* 187; 396, 2000
Breast Cancer Carcinogenesis

CGH studies in DCIS

Low & Int grade
- 16q loss
- 11q gain
- 1q gain

High grade
- 17q gain
- 11q gain

Buerger et al. J Pathol 187; 396, 2000
E Cadherin → Lobular Carcinoma

?Common Precursor → LOH 16q → Low Grade DCIS

C-erbB-2 & p53 → High Grade Carcinoma

Other candidates: BRCA 1 17q
BRCA 2 13q
1q 3p 11q 13q 17q

Medullary
Tub & Lob
Tubular
# Breast Cancer Carcinogenesis

## Progression models

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Insitu</th>
<th>Invasive</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALH</td>
<td>LCIS</td>
<td>Inv Lobular</td>
<td>E Cadherin</td>
</tr>
<tr>
<td>Mucinous Hyperplasia</td>
<td>Mucinous</td>
<td>Mucinous</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>DCIS</td>
<td>Carinoma</td>
<td></td>
</tr>
<tr>
<td>Columnar Alteration</td>
<td>Columnar</td>
<td>Tubular</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>atypia/DCIS</td>
<td>Carcinoma</td>
<td></td>
</tr>
</tbody>
</table>
## Breast Cancer Carcinogenesis

### Progression models

<table>
<thead>
<tr>
<th>Precursor</th>
<th>In situ</th>
<th>Invasive</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>Low grade</td>
<td>Low grade Carcinoma</td>
<td>16q loss</td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>?</td>
<td>High grade</td>
<td>High grade</td>
<td>17q gain</td>
</tr>
<tr>
<td>Apocrine Hyperplasia</td>
<td>Apocrine</td>
<td>Apocrine Carcinoma</td>
<td>?</td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Ductal Intraepithelial Neoplasia (DIN)

<table>
<thead>
<tr>
<th>DIN Classification</th>
<th>Current Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIN 1a</td>
<td>IDH</td>
</tr>
<tr>
<td>DIN 1b</td>
<td>AIDH flat monomorphous</td>
</tr>
<tr>
<td>DIN 1c &lt;2mm</td>
<td>AIDH</td>
</tr>
<tr>
<td>DIN 1c &gt;2mm</td>
<td>DCIS grade 1 (crib/micropap)</td>
</tr>
<tr>
<td>DIN 2</td>
<td>DCIS grade 2 (crib/micropap + necrosis or atypia)</td>
</tr>
<tr>
<td>DIN 3</td>
<td>DCIS grade 3 (anaplastic DCIS +/- necrosis)</td>
</tr>
</tbody>
</table>

*Virchows Arch (2001) 438:221-227*
Ductal Intraepithelial Neoplasia (DIN)

Advantages

• Reduced impact of dichotomous Ca versus B9 separation for pathologists

• Improved reproducibility of diagnosis

• Incorporates flat monomorphous/columnar/clinging lesions

• Allows for different management approaches based on size of low and high grade lesions

• Avoids use of the term Cancer for these lesion reducing patient stress and risk of unnecessary surgery

• Flexible allowing modification easily
Ductal Intraepithelial Neoplasia (DIN)

Disadvantages

- Inclusion of usual ductal hyperplasia
- Does not reflect recent understanding of molecular biology
- Not applicable to rarer subtypes
- Reproducibility unproven
- Not fundamentally different from previous classifications
- Not being used in many major centres
## Borderland Lesions of the Breast

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelial hyperplasia</strong></td>
<td></td>
</tr>
<tr>
<td>Usual type</td>
<td>Follow up not appropriate</td>
</tr>
<tr>
<td><strong>Lobular neoplasia</strong></td>
<td></td>
</tr>
<tr>
<td>Atypical ductal hyperplasia</td>
<td>Risk factor - follow up only required - no specific therapy</td>
</tr>
<tr>
<td><strong>Ductal Ca in situ</strong></td>
<td></td>
</tr>
<tr>
<td>Low grade &lt; 3mm</td>
<td></td>
</tr>
</tbody>
</table>
**Tamoxifen - Prevention Studies**

- The American Cancer Society estimation > 180,000 women in the USA develop breast cancer/year and > 40,000 women die

- By National Cancer Institute model, 5 years of preventive tamoxifen reduces the risk of invasive breast cancer by 49% in women at increased risk

- Reduction in risk greatest in women with a history of LCIS (56% relative risk reduction) or atypical hyperplasia (86% relative risk reduction)

- But no benefit found in 2 European studies (using different risk evaluation models and entry criteria)
## Borderland Lesions of the Breast

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ductal Ca in situ</strong></td>
<td></td>
</tr>
<tr>
<td>Low grade &gt; 3 mm</td>
<td>Excellent prognosis lesions - complete</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td>excision required</td>
</tr>
<tr>
<td>High grade</td>
<td>± axillary dissection</td>
</tr>
<tr>
<td>(Microinvasive Ca)</td>
<td></td>
</tr>
<tr>
<td>‘Small’ invasive Ca</td>
<td>± local irradiation</td>
</tr>
<tr>
<td>&lt; 15mm</td>
<td>- no systemic therapy</td>
</tr>
<tr>
<td>special type</td>
<td></td>
</tr>
<tr>
<td>grade 1</td>
<td></td>
</tr>
<tr>
<td><strong>Invasive carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local + systemic therapy based on prognostic factors</td>
</tr>
</tbody>
</table>