Why can't we grade DCIS?

IAP Breast Update Meeting
London Fri 24th November 2017

Dr Jeremy Thomas
Consultant Pathologist, Edinburgh

The Sloane Project
Understanding non-invasive breast disease

West Midlands Cancer Intelligence Uni

BCRT breast cancer research trust

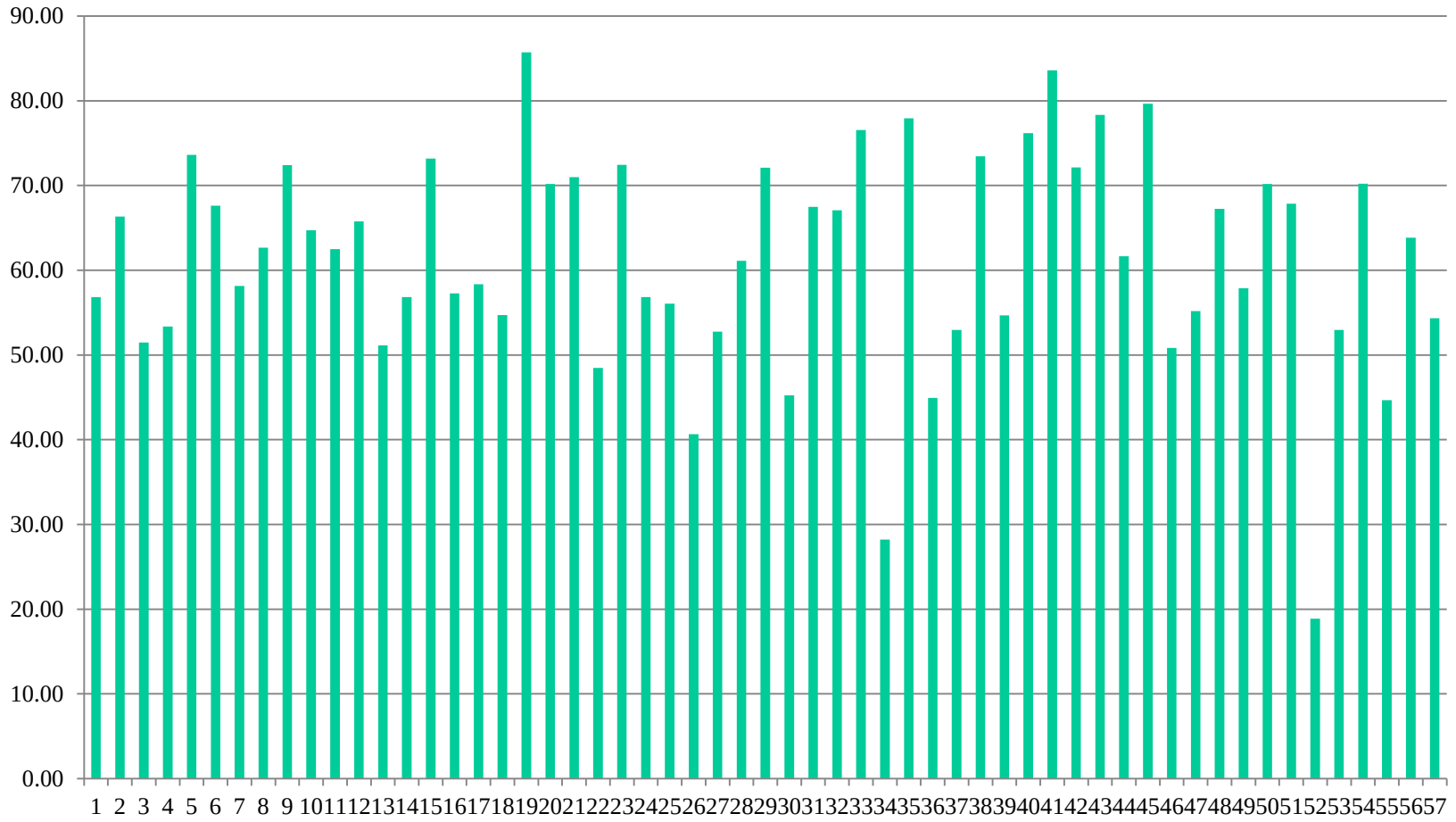
NHS Breast Screening Programme

Why do we grade?

- Prognosis:
  - Natural history
  - Invasive relapse
- Treatment:
  - Whether to treat at all – The LORIS Trial
  - Surgery +/- radiotherapy

Pathology Practice Variation

% High Grade DCIS by Hospital



Grading DCIS
NHS BSP Guidelines

Feature	**Low**	**Intermediate**	**High**
Pleomorphism	Monotonous	Intermediate	Marked
Size	1.0 - 2x size of RBC	Intermediate	>3x size of RBC
Chromatin	Diffuse; finely dispersed	Intermediate	Vesicular; Irregular distribution
Nucleoli	Only occasional	Intermediate	Prominent; Often multiple
Mitoses	Only occasional	Intermediate	*Usually* frequent
Orientation	Polarised towards luminal spaces	Intermediate	*Rarely* polarised

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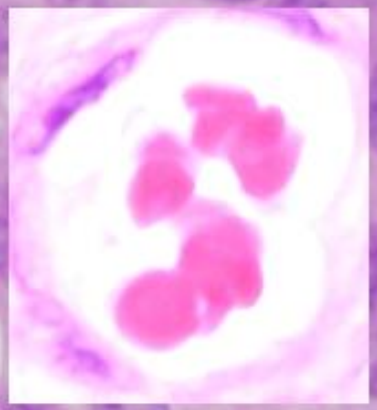
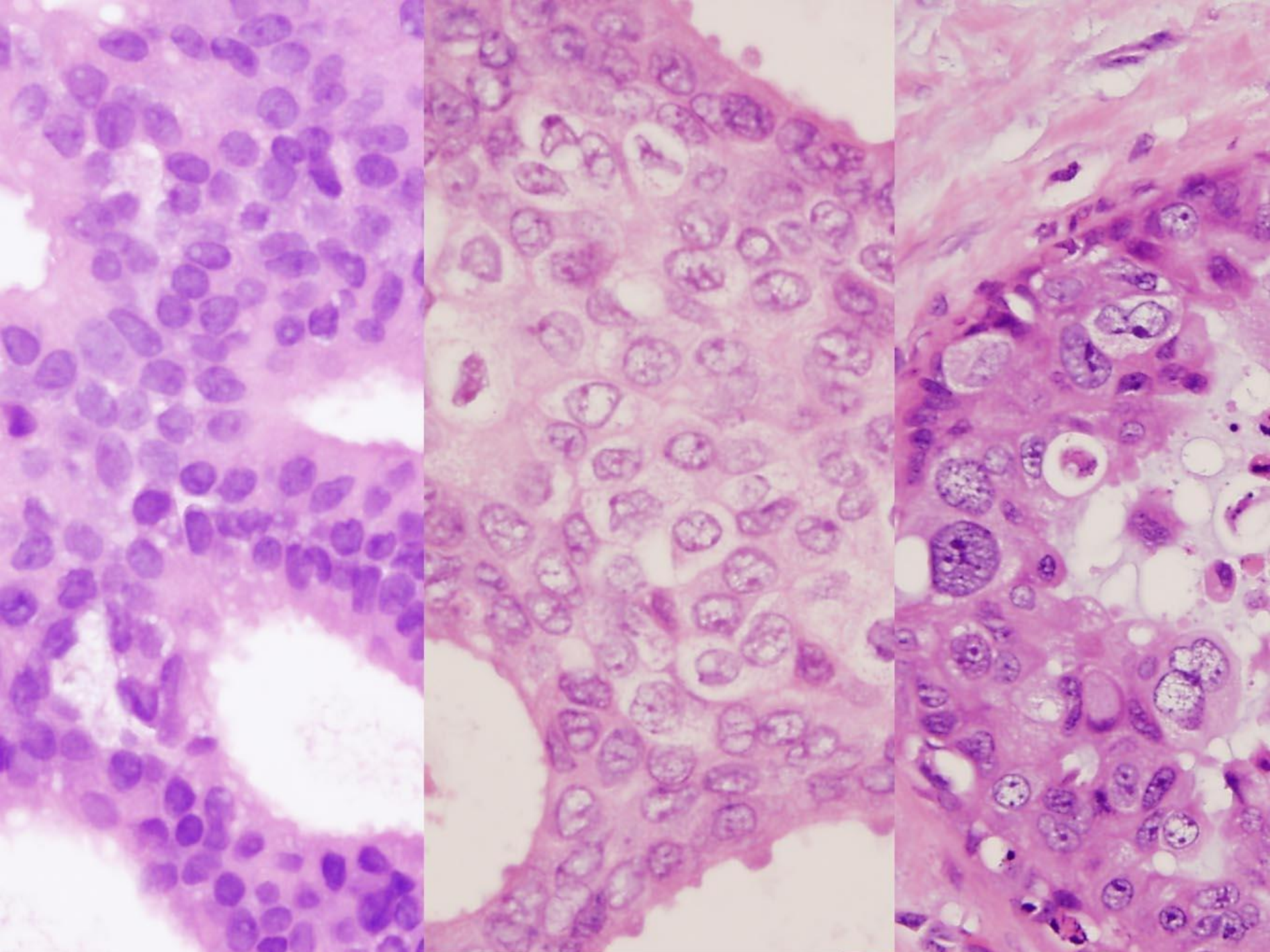
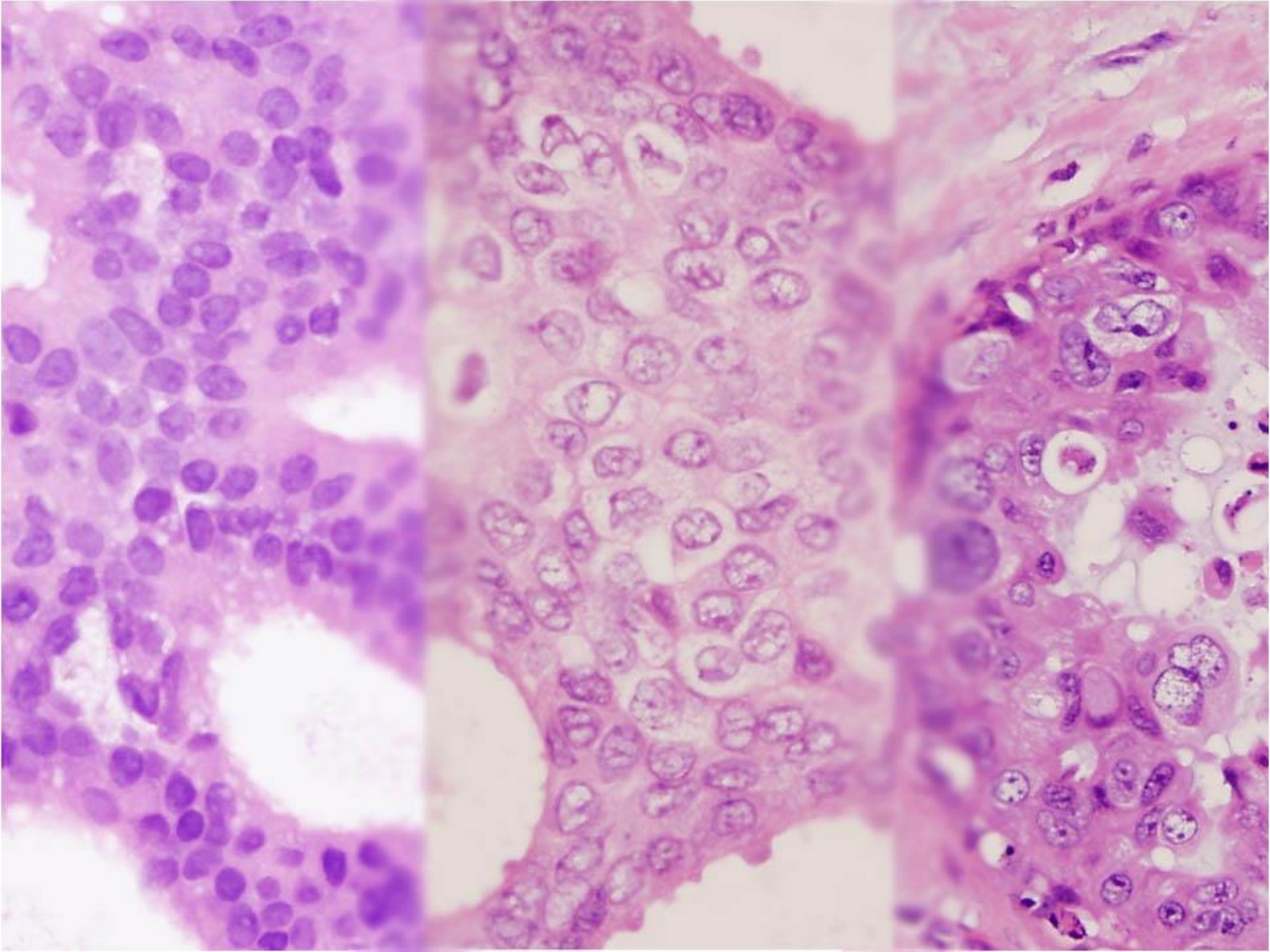
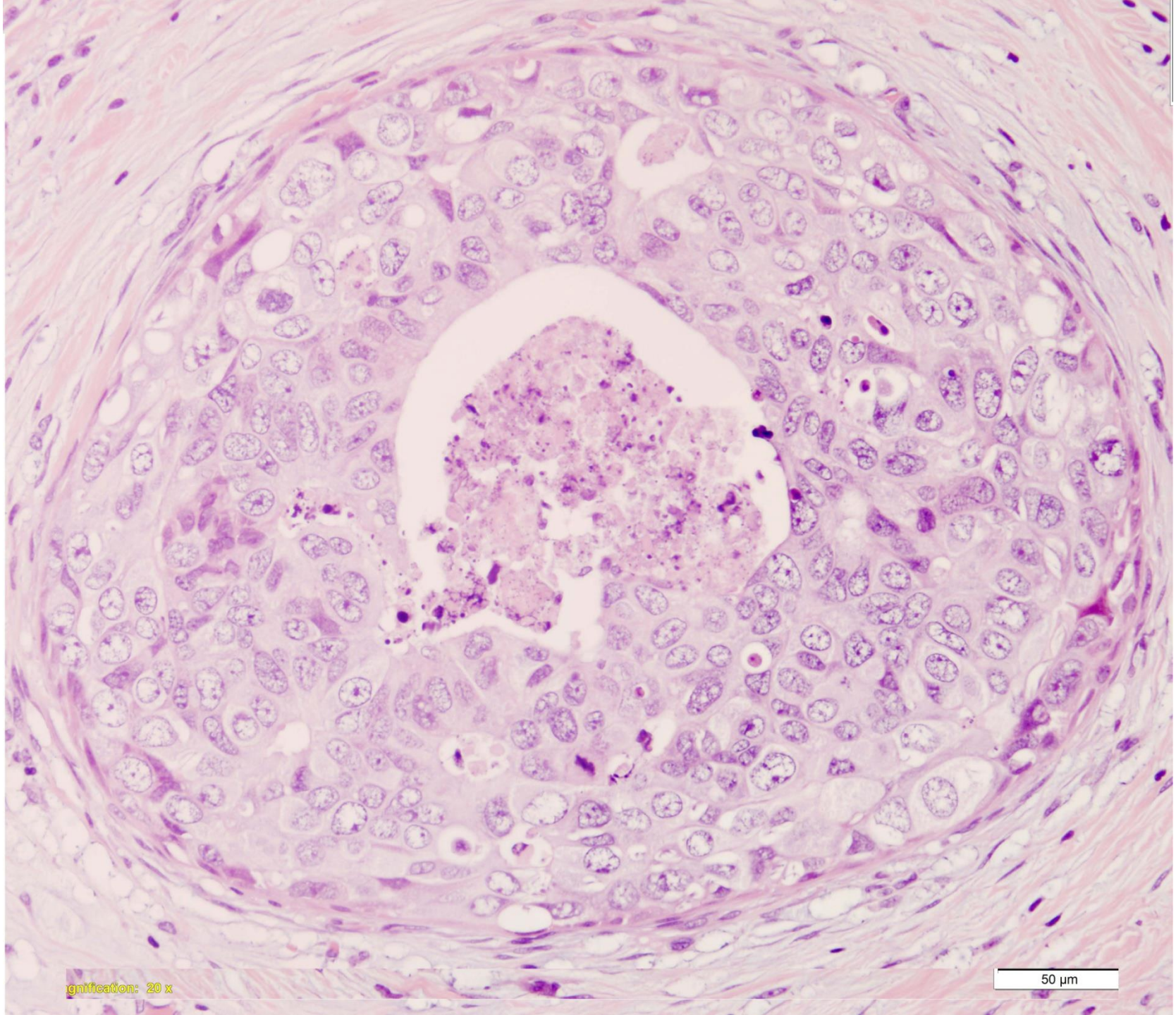
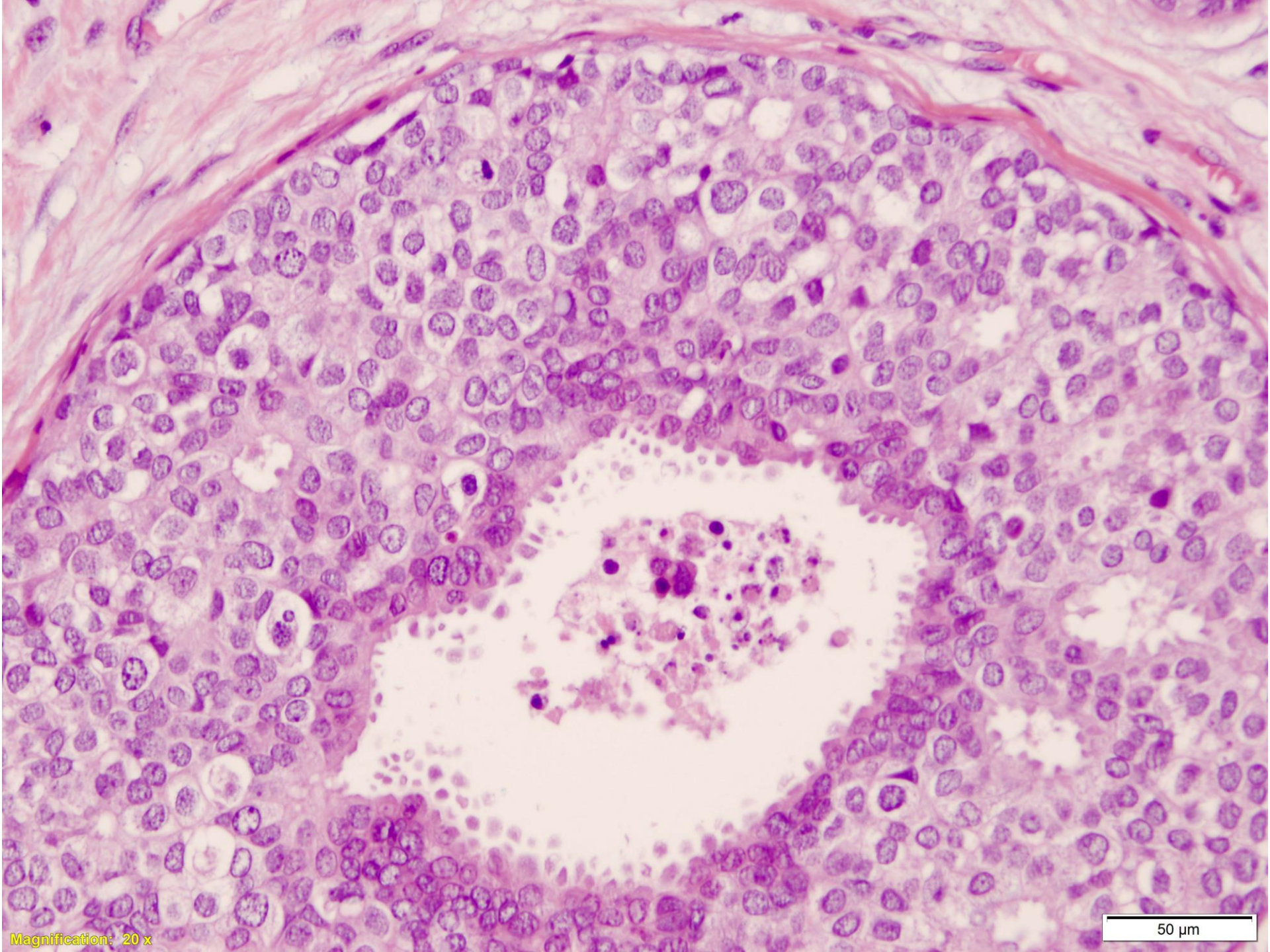
<2 RBCs or >3 RBCs








gnification: 20 x
50 µm


Magnification: 20 x
50 µm

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17. Schuh F, Biazús JV, Resetkova E, et al. Reproducibility of three classification systems of ductal carcinoma in situ of the breast using a web-based survey. Pathol Res and Pract. 2010;206:705–11.
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PERGAMON

European Journal of Cancer 36 (2000) 1769–1772

European Journal of Cancer

www.ejconline.com

Causes of inconsistency in diagnosing and classifying intraductal proliferations of the breast

European Commission Working Group on Breast Screening Pathology: C.W. Elston [a,*], J.P. Sloane [b*], I. Amendoeira [c], N. Apostolikas [d], J.P. Bellocq [e], S. Bianchi [f], W. Boecker [g], G. Bussolati [h], D. Coleman [i], C.E. Connolly [j], P. Dervan [k], M. Drijkoningen [l], V. Eusebi [m], D. Faverly [n], R. Holland [o], J. Jacquemier [p], M. Lacerda [q], J. Martinez-Penuela [r], C. de Miguel [s], S. Moss [i], C. Munt [i], J.L. Peterse [t], F. Rank [u], A. Reiner [v], M. Sylvan [w], C.A. Wells [x], B. Zafrani [y]

[a] *Department of Pathology, City Hospital, Nottingham NG5 1PB, UK*

	UEH	ADH	DCIS
Slides	0.54	0.35	0.78
Images	0.47	0.29	0.78

Even with digitised images of DCIS kappa of 0.47 for growth pattern & 0.49 for nuclear grade.

“Most of the differences due to morphological interpretation”

“Improvements ... only if diagnostic criteria or methods changed”

“More rigorous assessment of the proportions of the different nuclear grades could lead to improvements”

Van Nuys Scoring of DCIS

VNPI scoring system	**1**	**2**	**3**
Tumor size (diamter in mm)	less or equal to 15	16-40	greater or equal to 41
Margin width (in mm)	less or equal to 10	1-9	< 1
Pathologic Classification	non-high grade, (nuclear grades 1 and 2) no necrosis	non-high grade, (nucelar grades 1 and 2)with necrosis	high grade(nuclear grade 3) with or without necrosis
Overall VNPI score	3 or 4	5-7	8 or 9
8 year local recurrence-free survival rate.(statistics from the original study, not a prediction)	97%	77%	20%
8 year breast-cancer specific survival rate.(statistics from the original study, not a prediction)	100%	97%	100%

Schuh *et al. Diagnostic Pathology* (2015) 10:93
DOI 10.1186/s13000-015-0320-2

DIAGNOSTIC PATHOLOGY

RESEARCH Open Access

Histopathological grading of breast ductal carcinoma *In Situ*: validation of a web-based survey through intra-observer reproducibility analysis

Kappa statistics:

- ➢0.81 – 1.00 = Excellent
- ➢0.61 – 0.80 = Good
- ➢0.41 – 0.60 = Moderate
- ➢0.21 – 0.40 = Acceptable
- ➢ < 0.21 = Poor

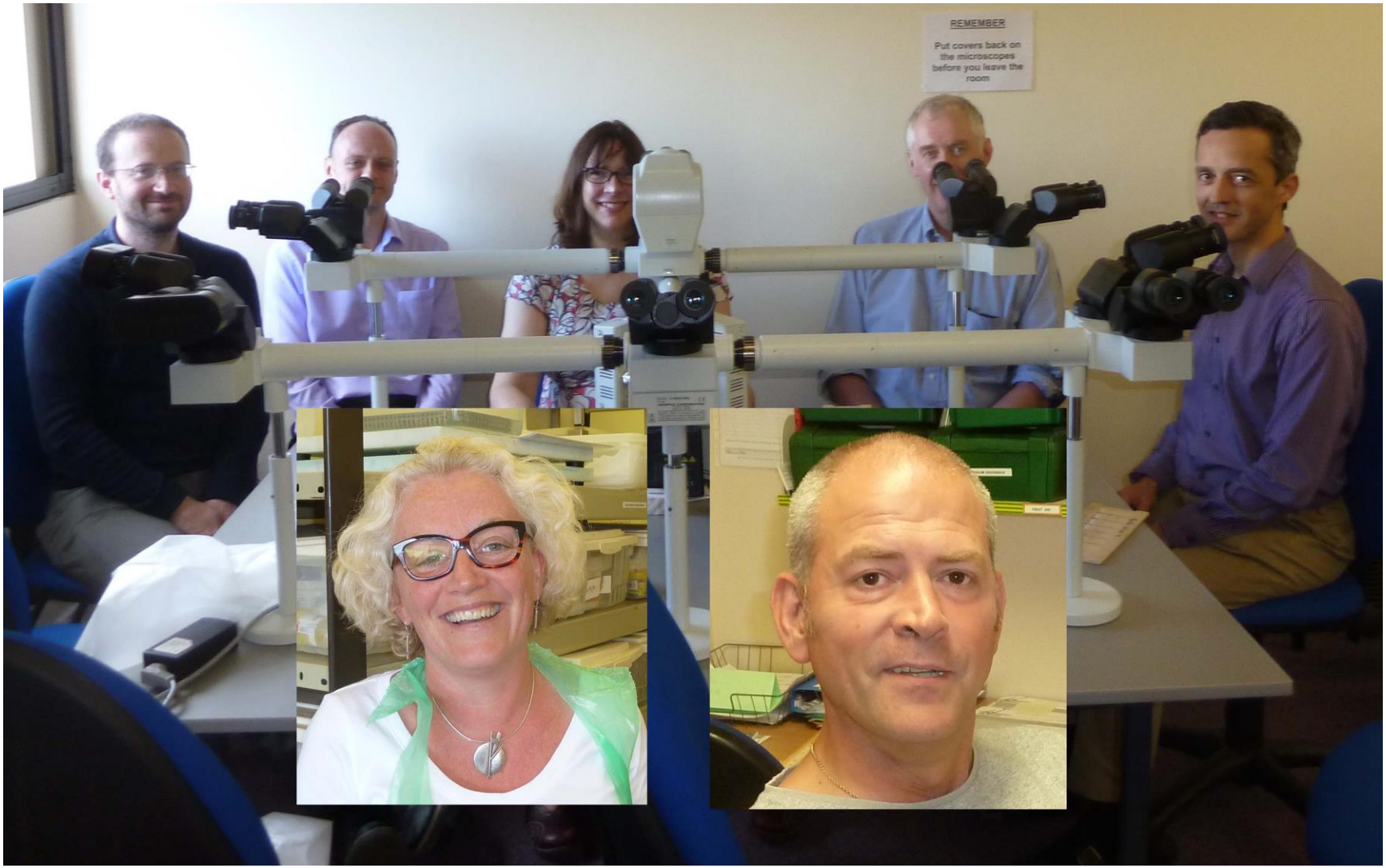
Table 3 Proportion of cases found in each histological grade in the three classification systems studied

Systems	Nuclear grade	Diagnostic scoring system n (%)	Subjective reading n (%)
Black	Grade 1	12 (27.9)	11 (25.6)
	Grade 2	10 (23.3)	13 (30.2)
	Grade 3	21 (48.8)	19 (44.2)
Holland	Grade 1	2 (4.7)	8 (18.6)
	Grade 2	19 (44.2)	15 (34.9)
	Grade 3	22 (51.2)	20 (46.5)
Van Nuys	Group 1	17 (39.5)	17 (39.5)
	Group 2	5 (11.6)	9 (20.9)
	Group 3	21 (48.8)	17 (39.5)

Table 5 Degree of disagreements between the web-based survey and the subjective reading in the three classification systems studied

	1-step disagreement			2-step disagreement		
	Super-estimated[a] n (%)	Sub-estimated[a] n (%)	Total n (%)	Super-estimated[a] n (%)	Sub-estimated[a] n (%)	Total n (%)
Holland	8 (18.6)	2 (4.6)	10 (23.2)	1 (2.3)	0 (0.0)	1 (2.3)
Van Nuys	5 (11.6)	3 (7.0)	8 (18.6)	1 (2.3)	0 (0.0)	1 (2.3)
Black	5 (11.6)	4 (9.3)	9 (20.9)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Superestimated and Subestimated by the web-based survey vs the subjective reading


REMEMBER
Put covers back on the microscopes before you leave the room

Digital Pathology

Overdiagnosis/Overtreatment

The NEW ENGLAND JOURNAL of MEDICINE

From the Dartmouth Institute for Health Policy and Clinical Practice, Lebanon (H.G.W., A.J.O.), and the Departments of Medicine (H.G.W.) and Biomedical Data Science (A.J.O.), Geisel School of Medicine, Hanover — both in New Hampshire; and the Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (P.C.P., B.S.K.). Address reprint requests to Dr. Welch at the Dartmouth Institute for Health Policy and Clinical Practice, 35 Centerra Pkwy., HB 7251, Lebanon, NH 03766, or at h.gilbert.welch@dartmouth.edu.

N Engl J Med 2016;375:1438-47.
DOI: 10.1056/NEJMoa1600249

ORIGINAL ARTICLE

Breast-Cancer Tumor Size, Overdiagnosis, and Mammography Screening Effectiveness

H. Gilbert Welch, M.D., M.P.H., Philip C. Prorok, Ph.D., A. James O'Malley, Ph.D., and Barnett S. Kramer, M.D., M.P.H.

ABSTRACT

Kyoto Breast Cancer Consensus Conference 2

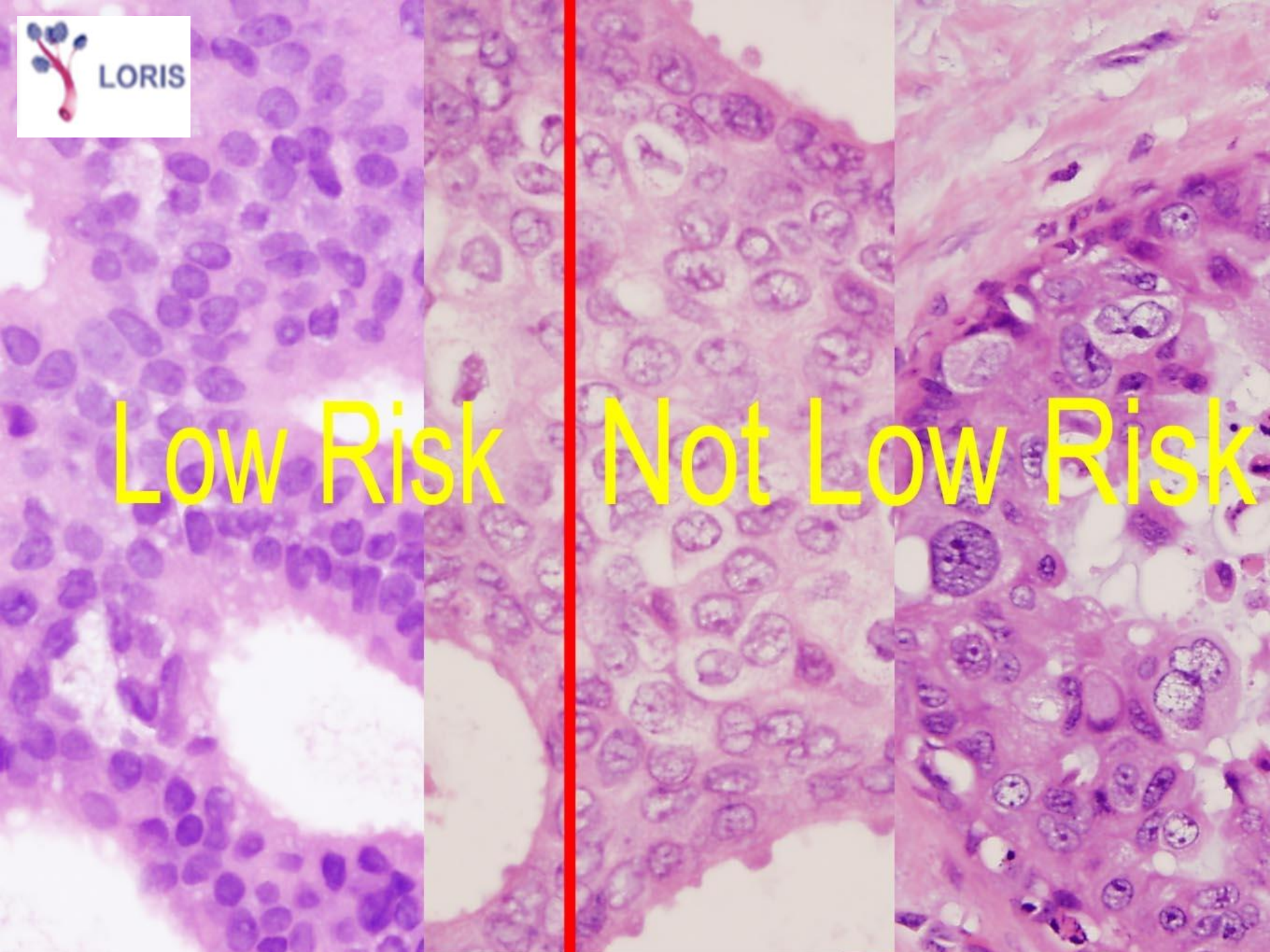
Treatment of low-risk ductal carcinoma in situ: is nothing better than something?

John R Benson, Ismail Jatoi, Masakazu Toi

The heterogeneous nature of ductal carcinoma in situ has been emphasised by data for breast-cancer screening that show substantial increases in the detection of early-stage non-invasive breast cancer but no noteworthy change in the incidence of invasive and distant metastatic disease. Indolent non-progressive forms of ductal carcinoma in situ are managed according to similar surgical strategies as high-risk disease, with extent of resection dictated by radiological

Lancet Oncol 2016; 17: e442–51

This is the second in a Series of two papers about the 2016 Kyoto Breast Cancer Consensus Conference


LORIS
Low Risk
Not Low Risk

Big Questions for the LORIS Trial

- In the surgery arm what is the upgrade rate?
- In the no surgery arm:
  - How many go on to surgery anyway
  - Psychological issues

Can we refine the grading?

- Additional clinical/morphology?
- Biomarkers

Ann Surg Oncol (2017) 24:2999–3003
DOI 10.1245/s10434-017-5941-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Evaluating the Risk of Upstaging HER2-Positive DCIS to Invasive Breast Cancer

Rose E. Mustafa, MD[1], Lauren M. DeStefano, MD[2], Joey Bahng, MS[1], Kahyun Yoon-Flannery, DO MPH[1], Carla S. Fisher, MD[1], Paul J. Zhang, MD[1], Julia Tchou, MD PhD[1], Brian J. Czerniecki, MD PhD[3], and Lucy M. De La Cruz, MD[4]

Single institution
272 pts CNB Δ DCIS

27% upstage rate on excision:
$HER2^{pos}/ER^{pos}/PGR^{pos}$ –OR 2.5
$HER2^{pos}$ v $HER2^{neg}$ –OR 1.89
$HER^{neg}/ER^{pos}/PGR^{pos}$ –OR 0.5

DOI: 10.1093/jnci/djq101
Advance Access publication on April 28, 2010.

ARTICLE

Biomarker Expression and Risk of Subsequent Tumors After Initial Ductal Carcinoma In Situ Diagnosis

Karla Kerlikowske, Annette M. Molinaro, Mona L. Gauthier, Hal K. Berman, Fred Waldman, James Bennington, Henry Sanchez, Cynthia Jimenez, Kim Stewart, Karen Chew, Britt-Marie Ljung, Thea D. Tlsty

1162 pts 1983 -1994 ~ 8yrs f/up

Histopathology and Biomarkers:

Subsequent invasive carcinoma:
$P16^{pos}/COX\text{-}2^{pos}/Ki67^{pos}$
Subsequent DCIS:
$ER^{neg}/HER2^{pos}/Ki67^{pos}$

AIMM Applied Immunohistochemistry & Molecular Morphology
OFFICIAL PUBLICATION OF THE INTERNATIONAL SOCIETY FOR IMMUNOHISTOCHEMISTRY & MOLECULAR MORPHOLOGY

Her2 and Ki67 Biomarkers Predict Recurrence of Ductal Carcinoma in Situ

Davis, James E. MD; Nemesure, Barbara PhD; Mehmood, Saira MD; Nayi, Vipul MD; Burke, Stephanie B. [illegible], Sabrina R. MD, PhD; Singh, Meenakshi MD

	Recurrent (%)	Non-Recurrent (%)
Necrosis	83	46
HER2 pos	50	14
Ki67 <10%	50	87

Applied Immunohistochemistry & Molecular Morphology: January 2016 - Volume 24 - Issue 1 - p 20–25

DOI:10.1093/jnci/djt067
Advance Access publication May 2, 2013

ARTICLE

A Multigene Expression Assay to Predict Local Recurrence Risk for Ductal Carcinoma In Situ of the Breast

Lawrence J. Solin, Robert Gray, Frederick L. Baehner, Steven M. Butler, Lorie L. Hughes, Carl Yoshizawa, Diana B. Cherbavaz, Steven Shak, David L. Page, George W. Sledge Jr, Nancy E. Davidson, James N. Ingle, Edith A. Perez, William C. Wood, Joseph A. Sparano, Sunil Badve

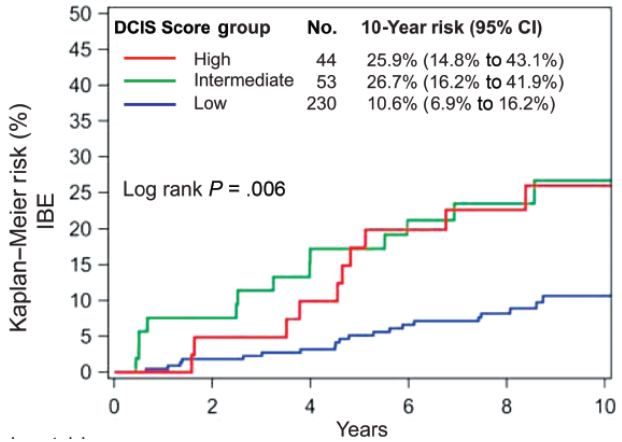
Proliferation group
Ki67
STK15
Survivin
CCNB1 (cyclin B1)
MYBL2

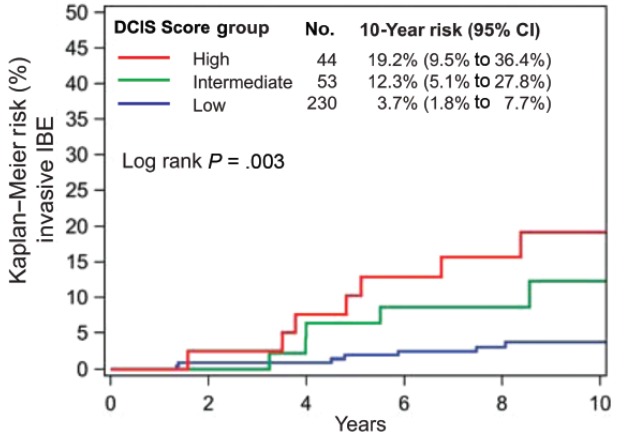
Hormone receptor group
PR

GSTM1

Reference group
ACTB (β-actin)
GAPDH
RPLPO
GUS
TFRC

DCIS Score and 10 year recurrence risk (%)			
	Low	**Int**	**High**
IBE	10.6	26.7	25.9
Inv $_{event}$	3.7	12.3	19.2





Risk independent of:

- Grade (Local or central review)
- Adjustment for endocrine therapy
- 21 Gene assay (for invasive disease)

Significant associations:

- Age
- Tumour size
- Premenopausal HR 0.49

Solin LJ et al JNCI 2013; **105**: 701-710

DOI 10.1007/s10549-015-3464-6

CLINICAL TRIAL

A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone

Eileen Rakovitch[1,2,3] · Sharon Nofech-Mozes[3,4] · Wedad Hanna[3,4] · Frederick L. Baehner[5,6] · Refik Saskin[2] · Steven M. Butler[5] · Alan Tuck[7] · Sandip Sengupta[8] · Leela Elavathil[9] · Prashant A. Jani[10,11] · Michel Bonin[12] · Martin C. Chang[3,13] · Susan J. Robertson[14] · Elzbieta Slodkowska[4] · Cindy Fong[2] · Joseph M. Anderson[5] · Farid Jamshidian[5] · Dave P. Miller[5] · Diana B. Cherbavaz[5] · Steven Shak[5] · Lawrence Paszat[1,2,3]

Received: 20 April 2015 / Accepted: 8 June 2015 / Published online: 29 June 2015

571 DCIS patients – BCS alone
Median follow up 9.6 years
100 cases had local recurrence
DCIS Score gave independent prog info beyond traditional clin-path variables

Conclusions

- DCIS is very difficult to grade consistently
- Strong impetus to define low risk disease
- Histopathology alone is probably not enough
- Role of digital Pathology
- Combination of biomarkers likely to be helpful

Acknowledgements

- Colleagues and friends:
  - Pathology
    - Drs Joe Loane
    - Ashley Graham
    - Catriona Cowan
    - Marie O'Donnell
    - Sarah Pinder
    - Andy Hanby
    - Emad Rakha
    - Ian Ellis
    - Colin Purdie
    - Liz Mallon
    - Ian Miller
    - Elena Provenzano
    - Abeer Shaaban
  - Oncology
    - David Cameron
    - Larry Hayward
    - Frances Yuill
  - International
    - Fraser Symmans
    - David Rimm
    - Stuart Schnitt
  - Surgery
    - Mike Dixon
    - Matthew Barber
  - Lab
    - Scott Maxwell
    - Tim Ingman
    - John Bartlett