Personalized Treatment of DCIS

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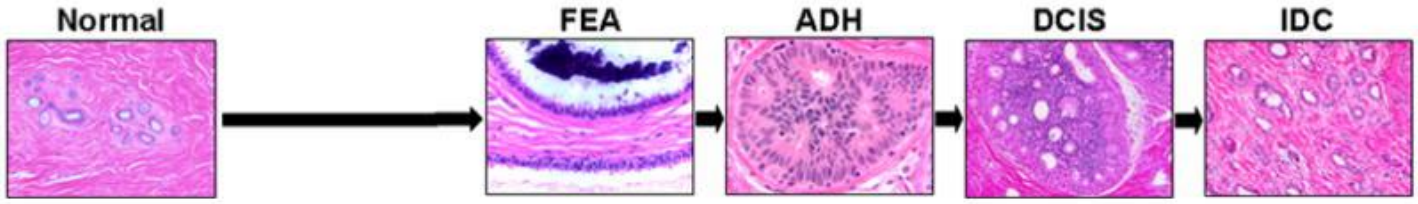
No Disclosure

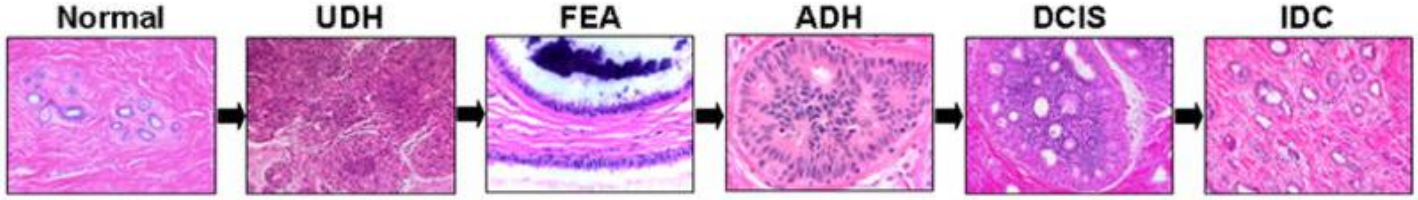
Models of ductal cancer progression

Model A (O)



- ✓ Immunohistochemical, genomic and transcriptomic data strongly support the evidence of a continuum from FEA to ADH, DCIS and IDC.
- ✓ FEA to ADH, DCIS are the non-obligate precursors of invasive ductal carcinoma.

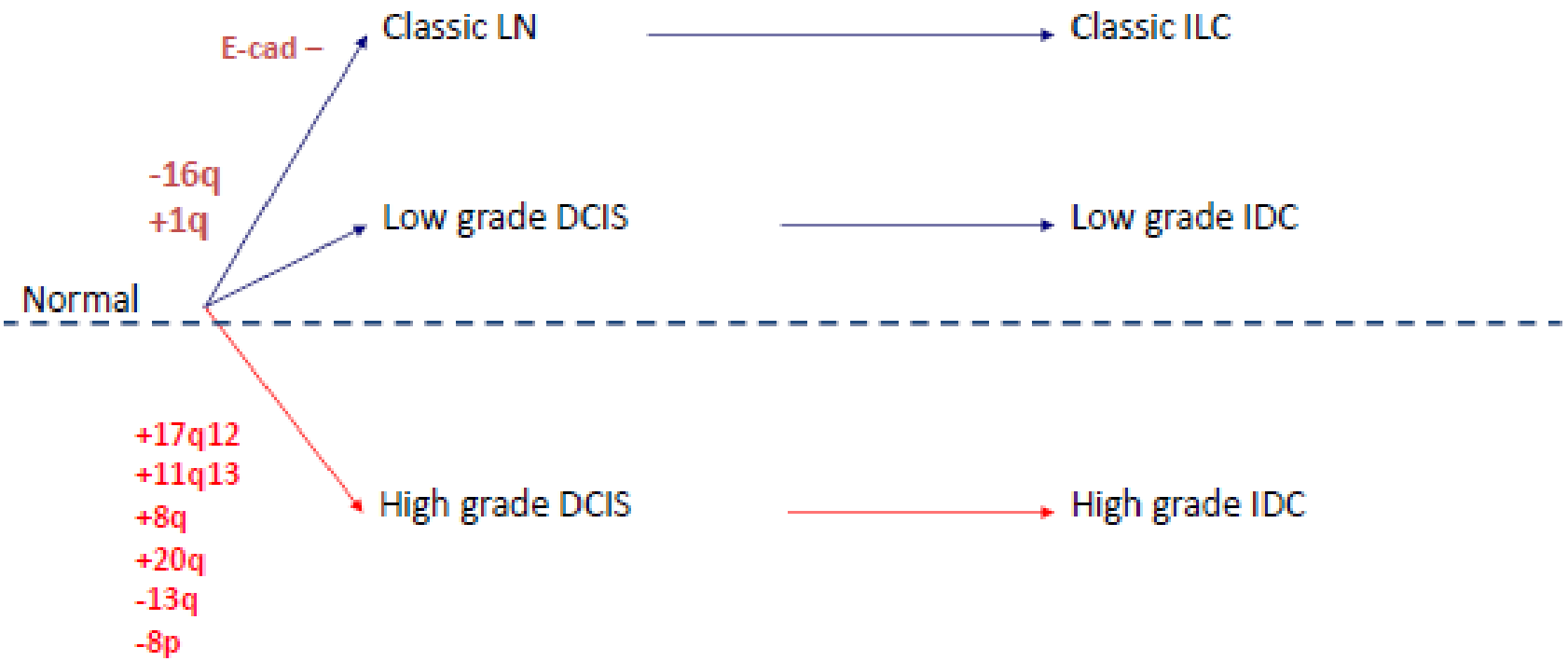
Model B (X)



- ✓ Based on epidemiologic and morphologic observations, proposes UDH instead of FEA as direct precursor to ADH.
- ✓ Recent studies have shown that UDH has a distinct immunohistochemical and molecular profile from FEA and probably represents a biologic dead end.

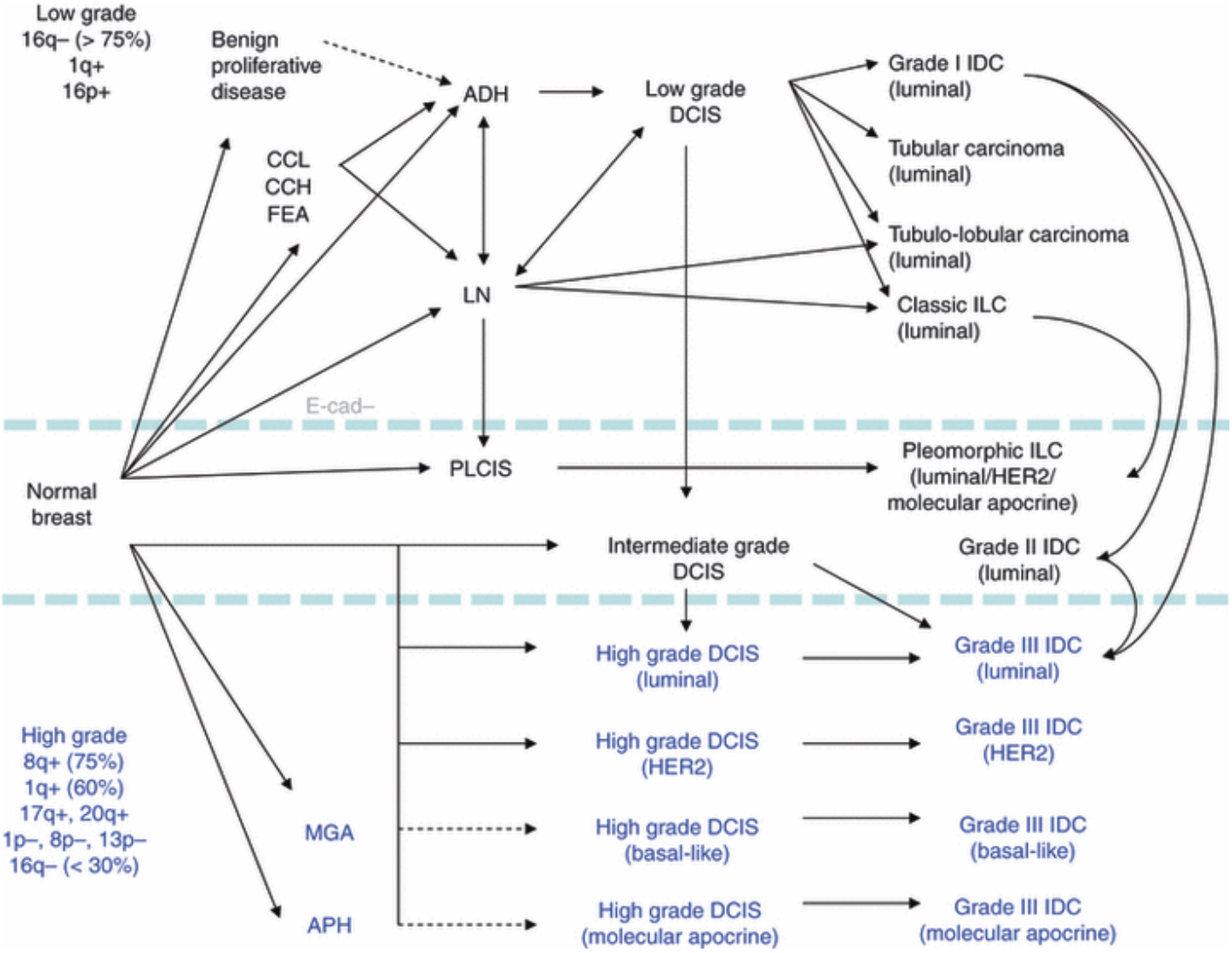
J Pathol. 2011 Jan;223(2):307-17. The molecular pathology of breast cancer progression. Bombonati A, Sgroi DC.

Distinct genomic profiles b/t H/G & L/G lesions



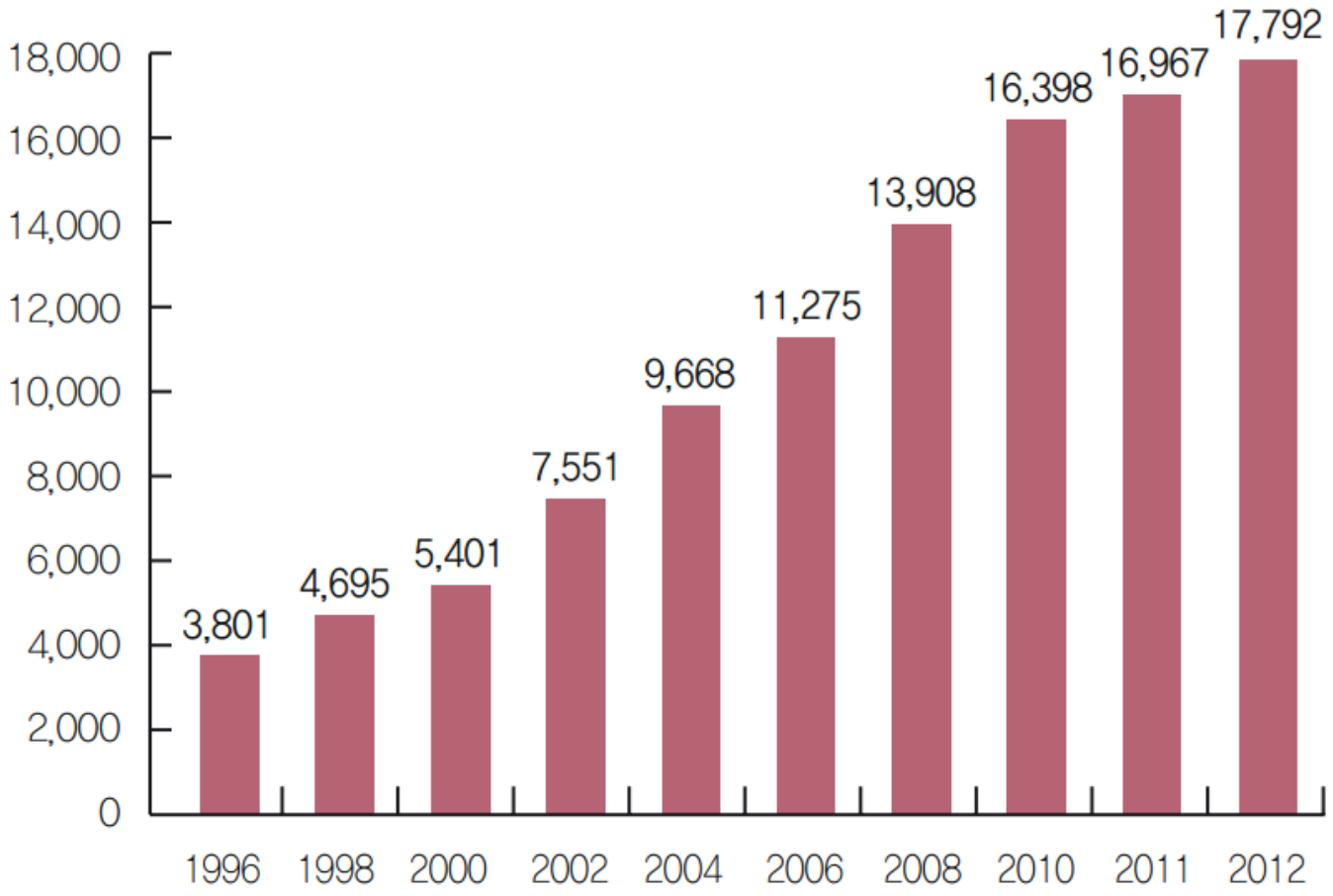
ASBS 2015. Molecular Subtypes of DCIS. Melissa Murray, Department of Pathology, Memorial Sloan Kettering Cancer Center

Distinct genomic profiles b/t H/G & L/G lesions



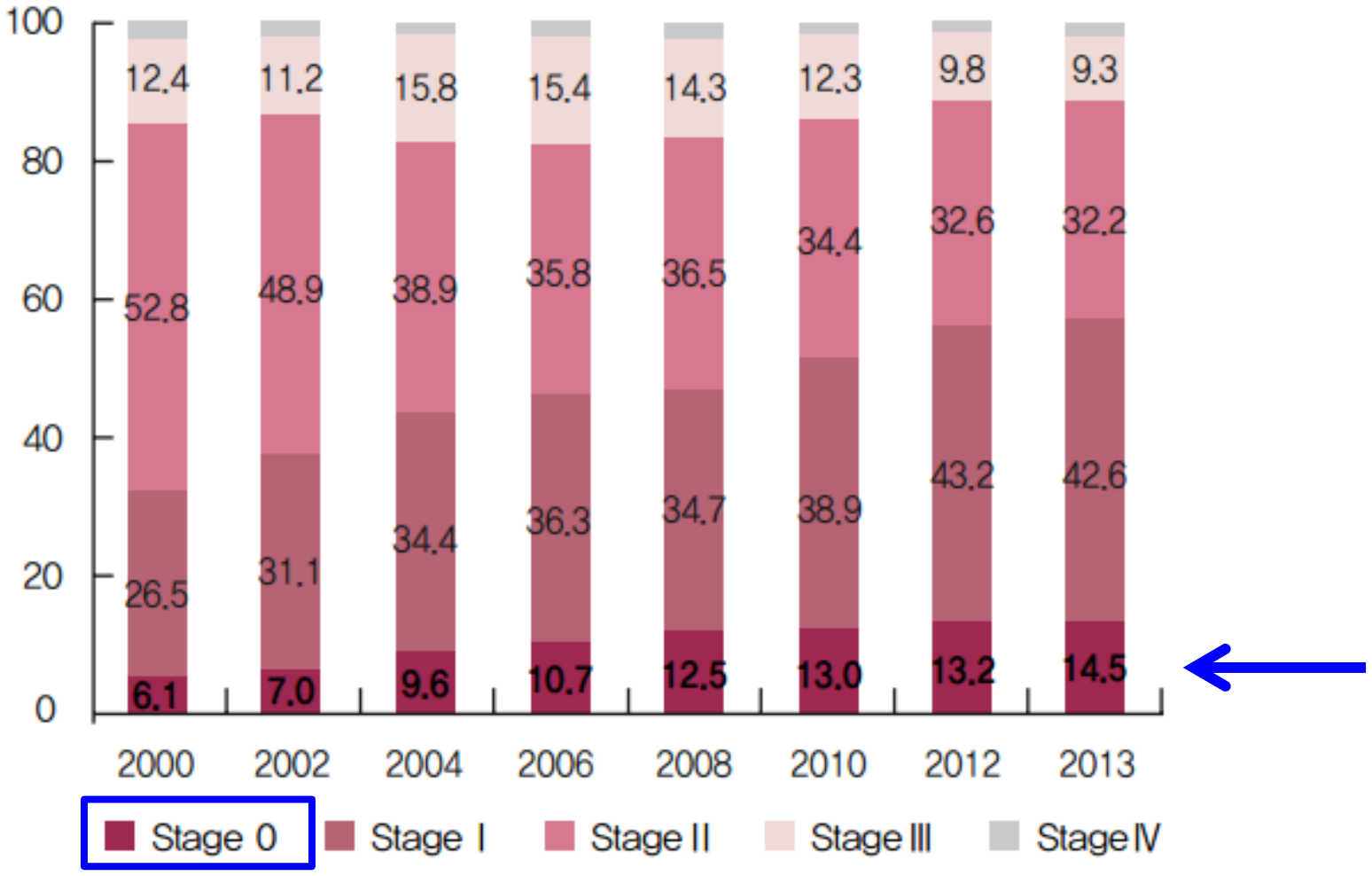
GBCC 2013. Recurrence Predictive Markers for DCIS.
Dr. Gary Tse, Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, Hong Kong

Annual number of breast cancer cases (South Korea)



2015 white book of the Korean Breast Cancer Society

Increasing early detection rate (South Korea)



2015 white book of the Korean Breast Cancer Society

Ductal carcinoma in situ

- neoplastic proliferation of epithelial cells confined to ductal lobular units
- non-obligate precursor to invasive carcinoma
- Low / Intermediate / High grades

- Breast cancer specific mortality among women with DCIS
  : 1.0-2.6% dying 8-10 years after initial diagnosis

- 10%-20% of DCIS lesions recurred by 10 years
- Once it recurs, 50% is invasive and 50% is DCIS.

SEER cancer statistics review 2012

Current treatment guidelines to DCIS

- Treatment goals

  (1) prevent local recurrence & progression to invasive cancer

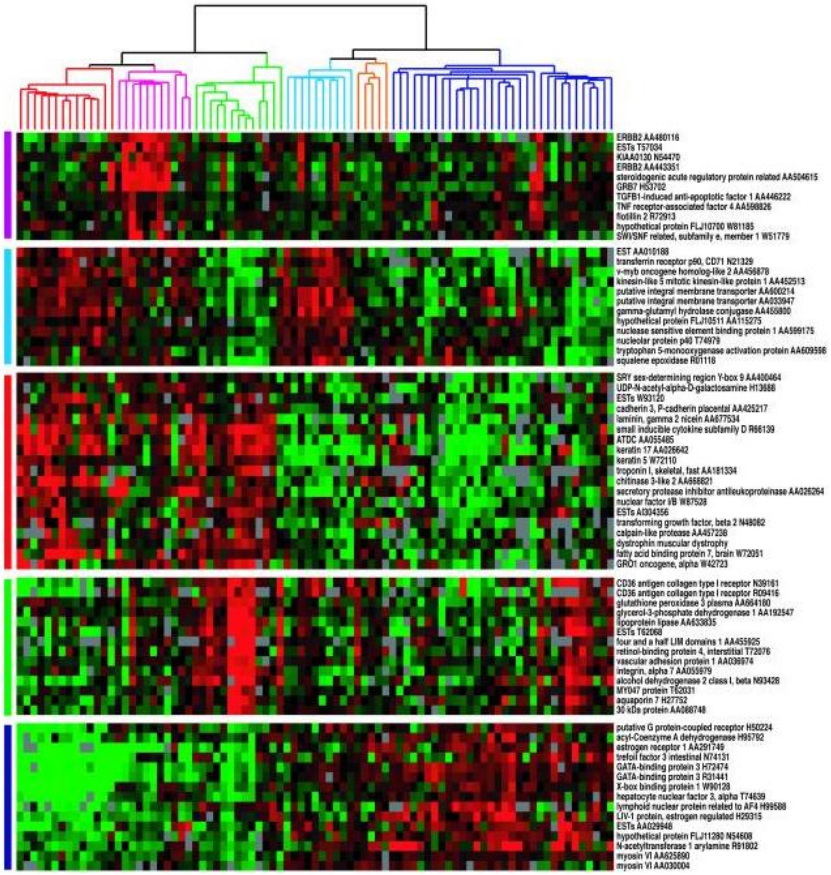
  (2) decrease risk of contralateral breast

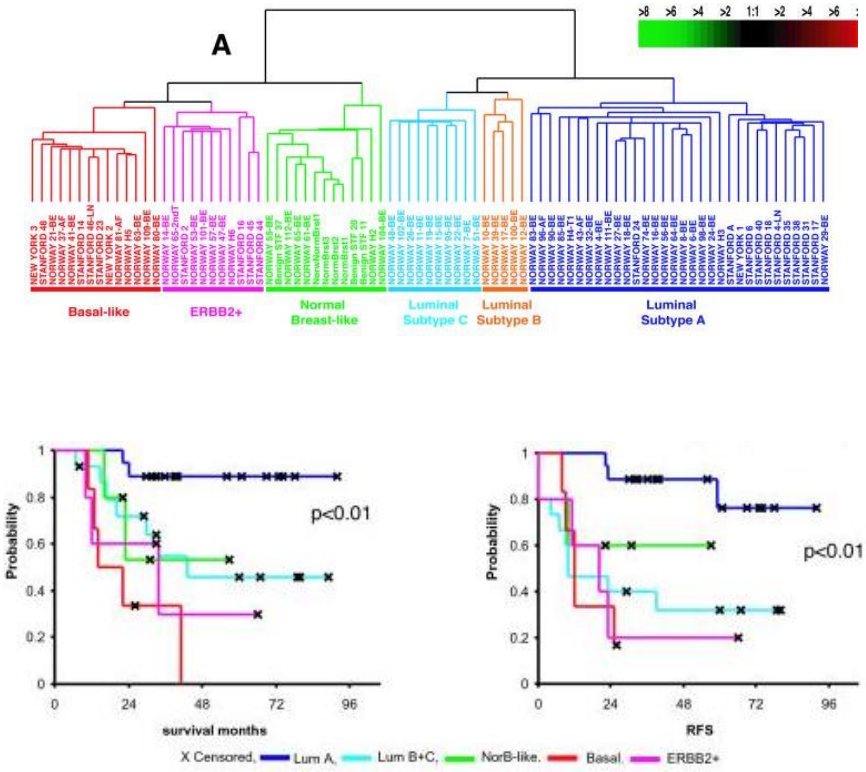
- ✓ Surgery (BCS or mastectomy) are standard treatment options.
- ✓ Radiation therapy reduces about 50% of the risk of IBTR after BCS.
- ✓ Tamoxifen & AI can be considered for women with ER+ DCIS.

- women can die with asymptomatic DCIS without progression to invasive disease. (DCIS present in up to 15% autopsy)

- Some DCIS being <u>over-diagnosed</u> and <u>over-treated</u>

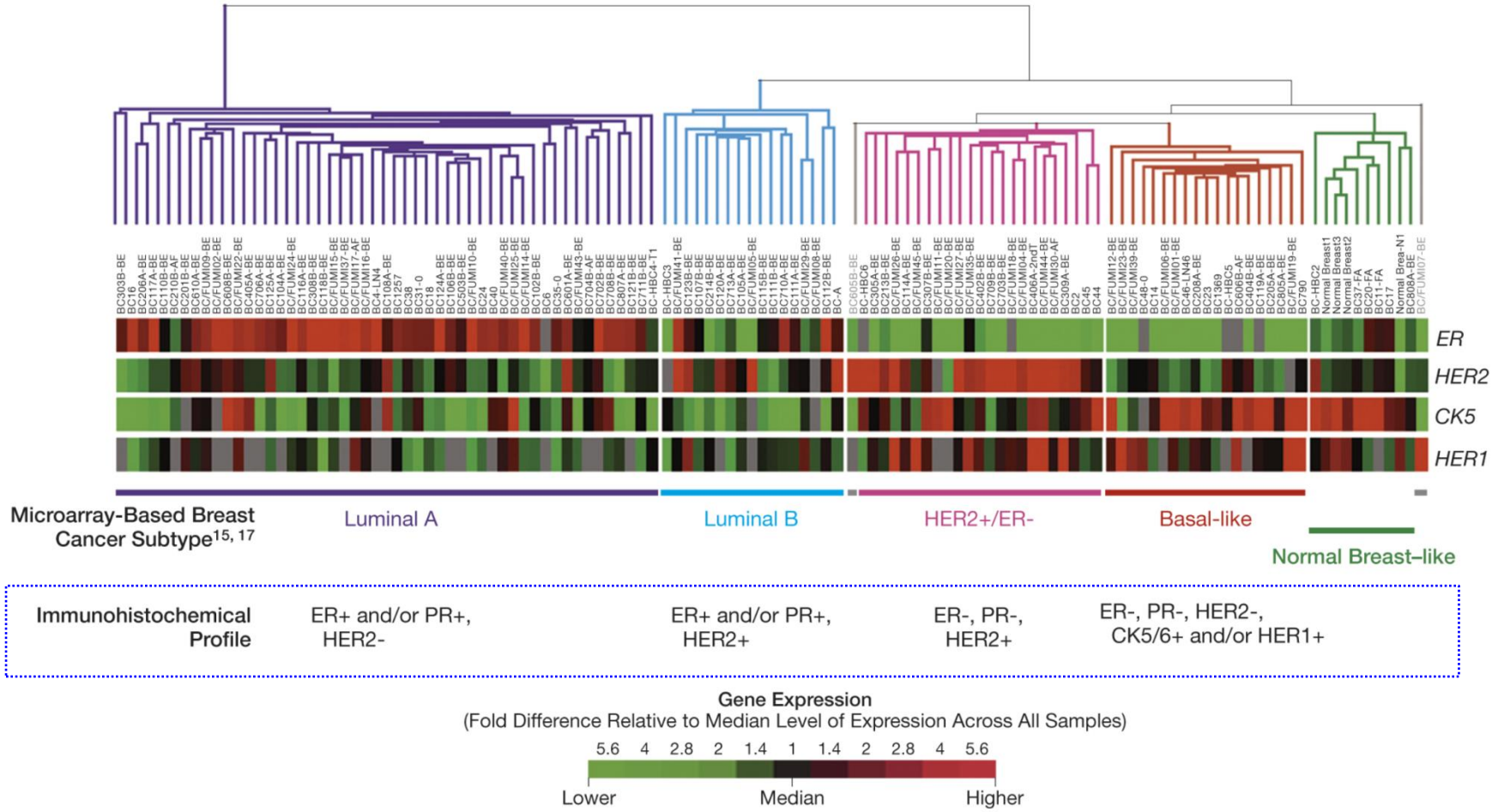
Subtypes of IDC with gene expression





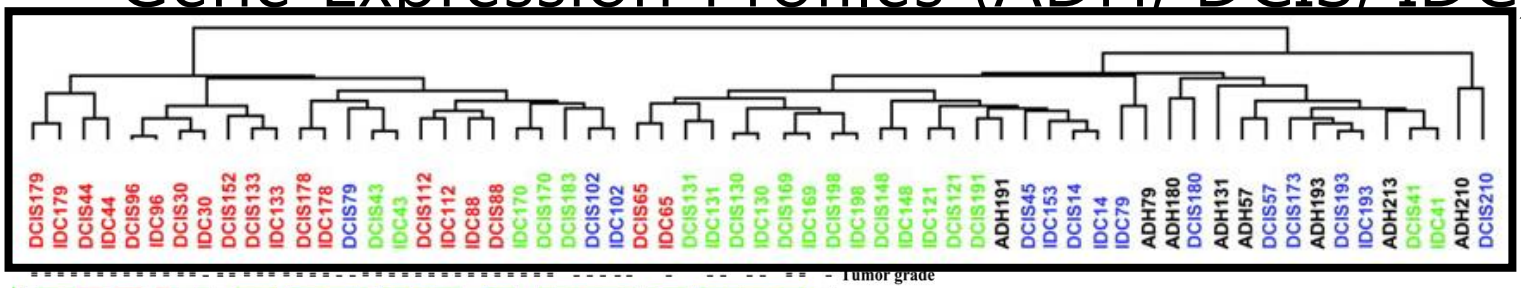
Nature. 2000 Aug 17;406(6797):747-52. Molecular portraits of human breast tumours. Perou CM, et al.
Proc Natl Acad Sci U S A. 2001 Sep 11;98(19):10869-74. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Sørlie T, et al.

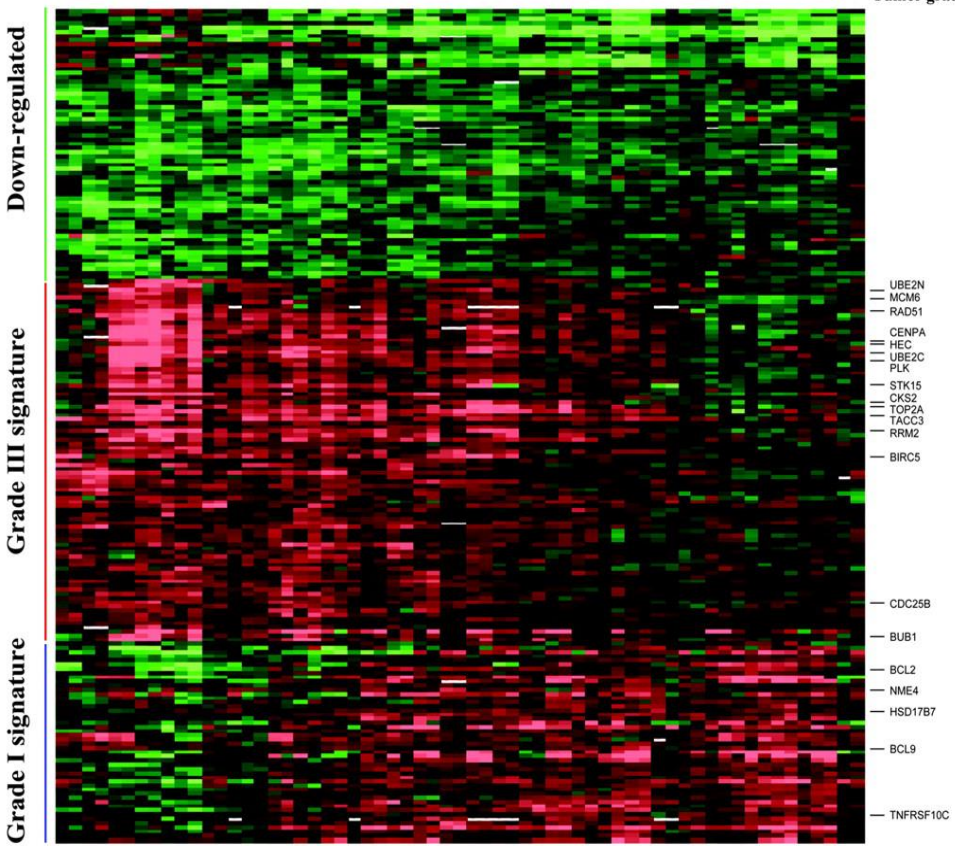
Subtypes of IDC with IHC surrogates



JAMA. 2006 Jun 7;295(21):2492-502. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. Carey LA, et al.

Gene Expression Profiles (ADH, DCIS, IDC)



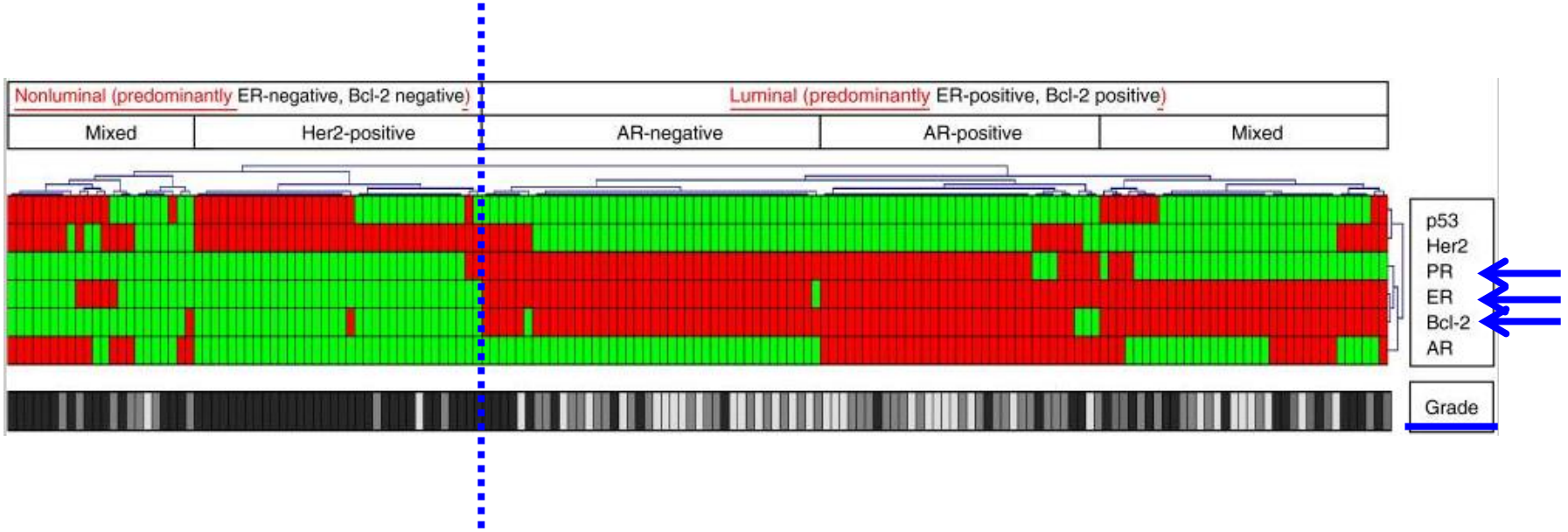


- L/G and H/G DCIS exhibit reciprocal expression patterns.
- I/G DCIS are in the mixture.
- Expression signatures characteristic of lesion grade but not stage of Progression.
- L/G DCIS signature more like L/G IBC signature than H/G DCIS signature

Proc Natl Acad Sci USA 2003 May 13; 100(10): 5974–5979. Gene expression profiles of human breast cancer progression. Xiao-Jun Ma, et al.

Subtyping of DCIS with IHC surrogates

- Unsupervised hierarchical cluster analysis categorized DCIS into *two* major groups that could be further subdivided into subgroups based on the expression of six markers (ER, PR, AR, Bcl-2, p53, and Her2).
- I/G DCIS shared a comparable IHC staining pattern with L/G DCIS that was distinct from H/G DCIS (P<0.001).



Br J Cancer. 2008 Jan 15;98(1):137-42. Immunohistochemical categorisation of ductal carcinoma in situ of the breast. Meijnen P, et al.

Prevalence of IHC phenotypes in DCIS & IDC

- TMA slides of 272 DCIS & 1550 IDC cases were grouped into molecularly defined subtypes by using the IHC results for ER, PR, HER2, CK5/6 and EGFR.

- Frequency of molecular phenotypes

Immunophenotype	DCIS ($n = 272$)	Infiltrating ductal, NOS only ($n = 1550$)	p value[b]
	n (%)	N (%)	
Luminal A	170 (62.5)	1053 (67.9)	0.08
Luminal B	36 (13.2)	90 (5.8)	<0.0001
HER2+	37 (13.6)	107 (6.9)	<0.0001
Basal-like	21 (7.7)	223 (14.4)	0.005
Unclassified	8 (2.9)	77 (5.0)	0.14

- according to tumor grade

Tumour type	Luminal A	Luminal B	Her2 type	Basal
DCIS				
DCIS, low nuclear grade	26 (92.9)	1 (3.6)	0	1 (3.6)
DCIS, intermediate grade	109 (79.0)	15 (10.9)	6 (4.4)	6 (4.4)
DCIS, high nuclear grade	35 (33.0)	20 (18.9)	31 (29.3)	14 (13.2)
Invasive tumours				
Well-differentiated	134 (95.7)	2 (1.4)	0	2 (1.4)
Moderately differentiated	344 (79.3)	24 (5.5)	21 (4.8)	31 (7.1)
Poorly differentiated	252 (56.8)	20 (4.5)	43 (9.7)	99 (22.3)

type	Lum A		Lum B		Her2		Basal	
L/G DCIS	26	**15.3%**	1	2.8%	0	0.0%	1	4.8%
I/G DCIS	109	**64.1%**	15	41.7%	6	16.2%	6	28.6%
H/G DCIS	35	20.6%	20	**55.6%**	31	**83.8%**	14	**66.7%**
total	170	100.0%	36	100.0%	37	100.0%	21	100.0%

Breast Cancer Res. 2008;10(4):R67. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. Tamimi RM, et al.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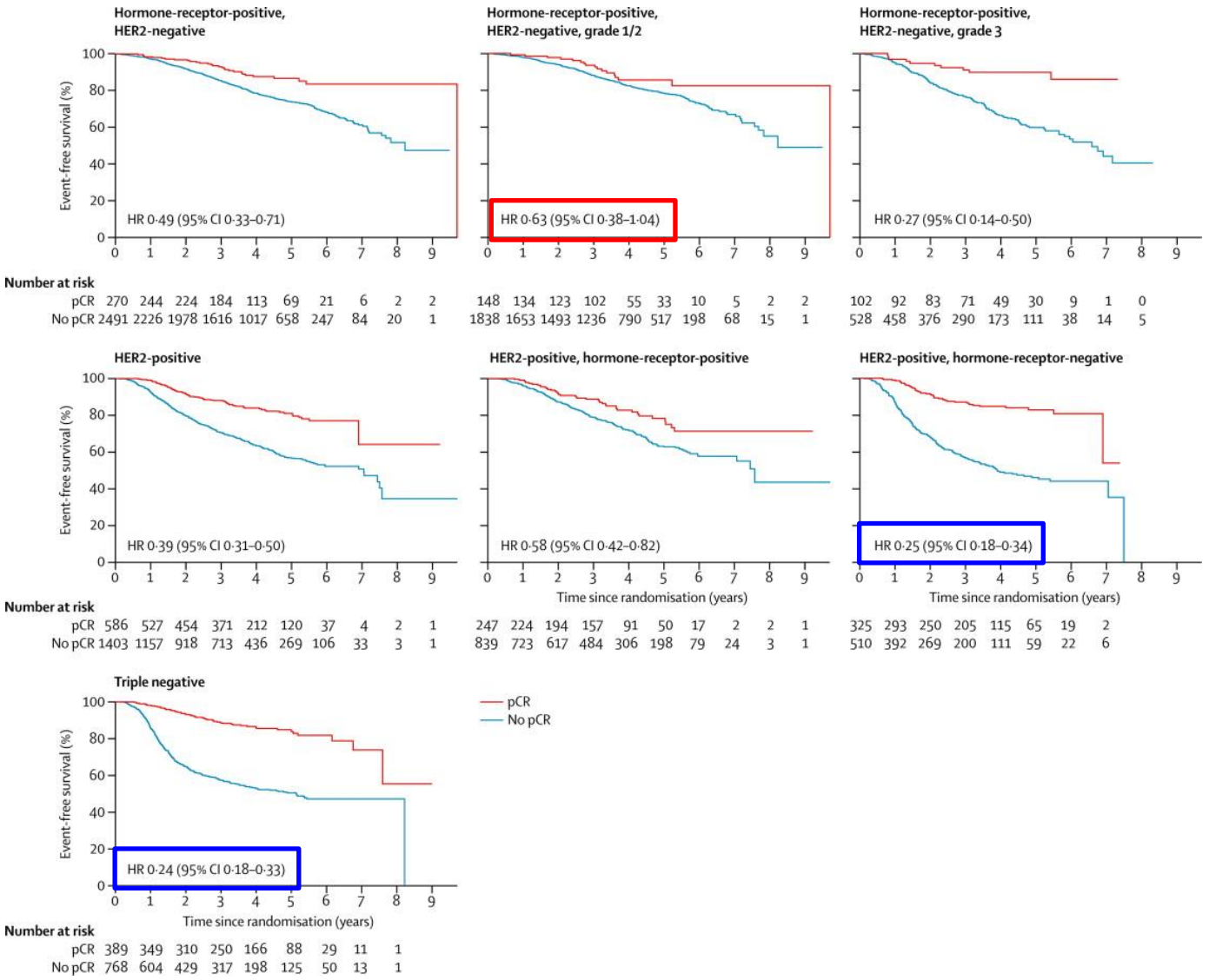
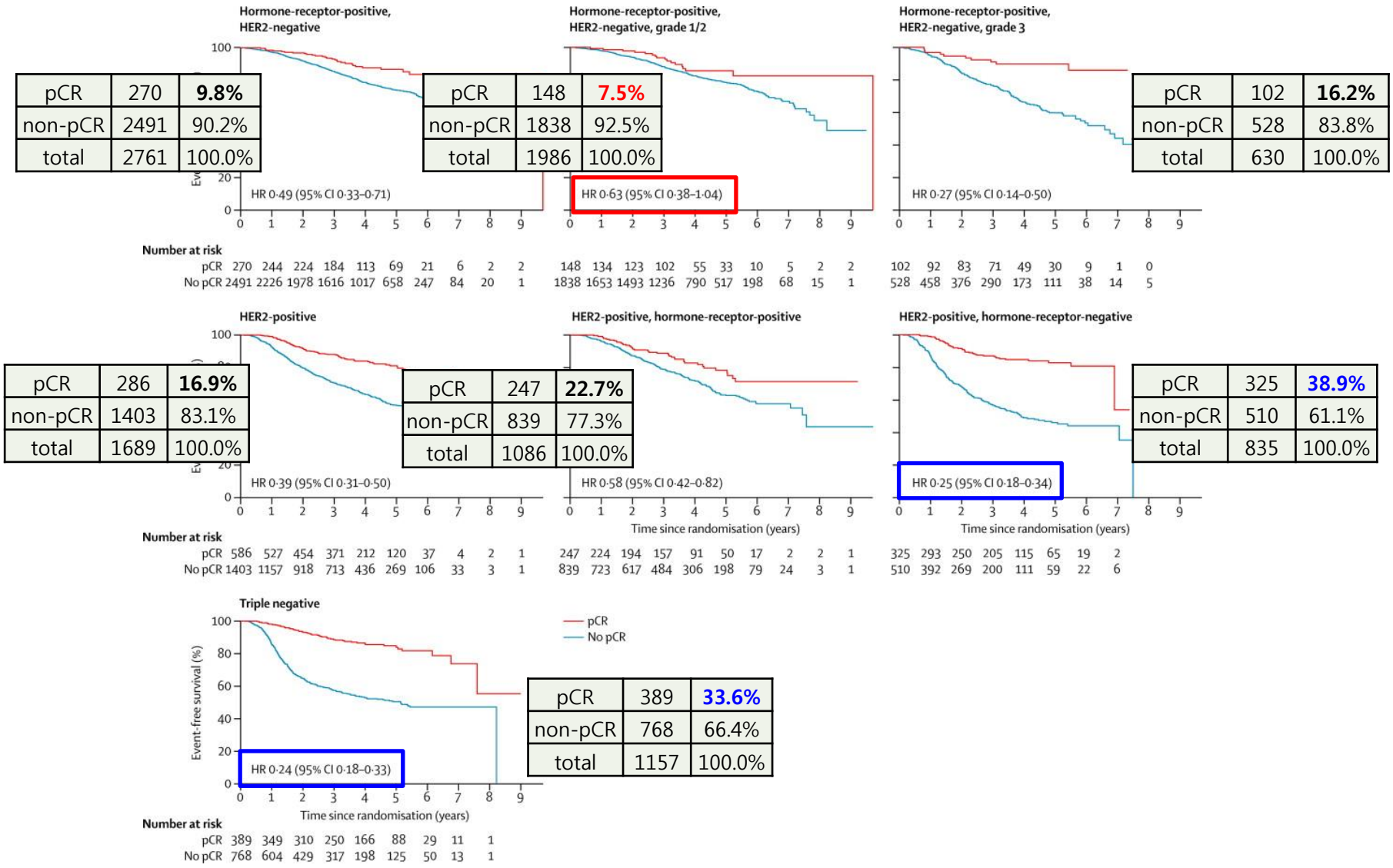
Subtypes in IDC related to pCR & prognosis



Lancet. 2014 Jul 12;384(9938):164-72. pCR and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Cortazar P, et al.

Subtypes in IDC related to pCR & prognosis



pCR	270	**9.8%**
non-pCR	2491	90.2%
total	2761	100.0%

pCR	148	**7.5%**
non-pCR	1838	92.5%
total	1986	100.0%

pCR	102	**16.2%**
non-pCR	528	83.8%
total	630	100.0%

pCR	286	**16.9%**
non-pCR	1403	83.1%
total	1689	100.0%

pCR	247	**22.7%**
non-pCR	839	77.3%
total	1086	100.0%

pCR	325	**38.9%**
non-pCR	510	61.1%
total	835	100.0%

pCR	389	**33.6%**
non-pCR	768	66.4%
total	1157	100.0%

Lancet. 2014 Jul 12;384(9938):164-72. pCR and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Cortazar P, et al.

IHC-based subtypes of DCIS & prognosis

- IHC expression of ER, PR, Ki-67, HER2
- 314 women (median age 57.7 years) with primary DCIS (1990-2010)
- Recurrence by molecular phenotype: 57 (18.2%) patients recurred
- median follow-up time: 60.5 months (12-240 months)

ER/PR+HER2-

ER/PR+/HER2+

ER-/PR-/HER2+

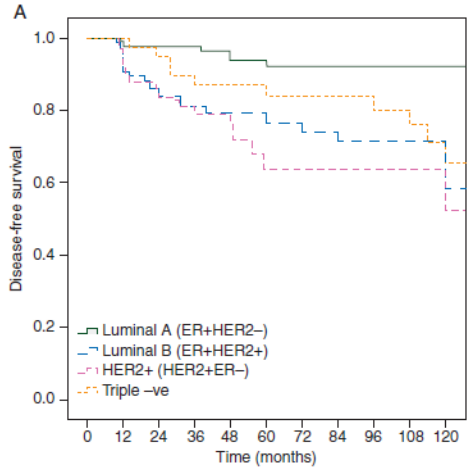
ER-/PR-/HER2-

	Overall recurrence			Invasive recurrence		
	No.	5-year rate (%)	10-year rate (%)	No.	5-year rate (%)	10-year rate (%)
Luminal A ($n = 134$)	7	7.6	7.6	1	1.3	1.3
Luminal B ($n = 88$)	24	23.2	41.5	9	12.1	16.1
HER2 type ($n = 51$)	16	36.1	47.7	6	13.8	29.5
Triple negative ($n = 41$)	10	15.8	34.3	6	12.1	23.1

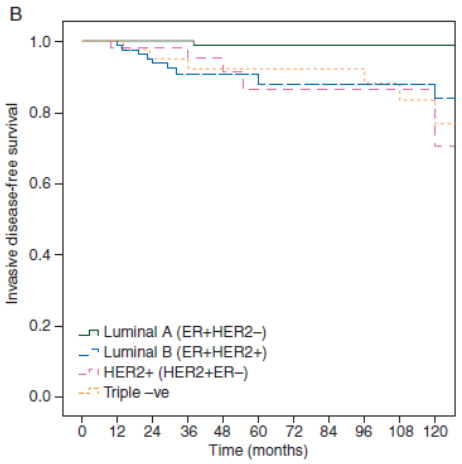
Recurrence rates derived from a Kaplan–Meier analysis.

Ann Oncol. 2015 May;26(5):1019-25. Molecular phenotypes of DCIS predict overall and invasive recurrence. Williams KE, et al. (UK)

IHC-based subtypes of DCIS & recurrence



Overall



Invasive

	Adjusted[a] model HR (95% CI)	*P*-value
Age (per year)	–	–
Tumour size (versus <15 mm)		
15–25 mm	–	–
>25 mm	–	–
High grade (versus lower grade)	2.28 (1.11, 4.66)	0.024*
Ki67 (per %)[b]	–	–
Microinvasion present (versus absent)	–	–
Surgery type Mx (versus BCS)	0.35 (0.16, 0.73)	0.005*
Margin status involved (versus clear)	4.31 (2.40, 7.74)	<0.001*
Molecular phenotype (versus Luminal A)		
Luminal B	5.14 (2.04, 13.0)	0.001*
HER2 type	6.46 (2.40, 17.3)	<0.001*
Triple negative	3.27 (1.13, 9.44)	0.028*

	Adjusted[a] model HR (95% CI)	*P*-value
Age (per year)	–	–
Tumour size (versus <15 mm)		
15–25 mm	–	–
>25 mm	–	–
High grade (versus lower grade)	–	–
Ki67 (per %)[b]	1.04 (1.01, 1.08)	0.021*
Microinvasion present (versus absent)	–	–
Surgery type Mx (versus BCS)	–	–
Margin status involved (versus clear)	–	–
Molecular phenotype (versus Luminal A)		
Luminal B	13.4 (1.70, 106)	0.014*
HER2 type	11.4 (1.31, 99)	0.027*
Triple negative	10.3 (1.24, 86)	0.031*

Ann Oncol. 2015 May;26(5):1019-25. Molecular phenotypes of DCIS predict overall and invasive recurrence. Williams KE, et al. (UK)

Intrinsic subtype: helpful !

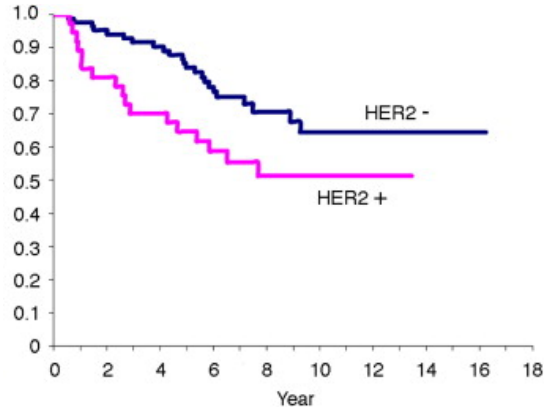
- DCIS molecular phenotype predicts for both overall and invasive recurrence.
- HER2 testing of DCIS could help clinicians individualize the treatment of patients with DCIS.

	Total	All recurrences (DCIS/ invasive)	Invasive recurrence
ER+ HER2-	106 (38.8%)	6 (5%)	2 (2%)
ER+ HER2+	85 (31%)	25 (29%)	6 (7%)
ER- HER2+	45 (16.5%)	15 (33%)	7 (16%)
ER- HER2-	37 (13.5%)	9 (14%)	5 (13.5%)
Total number	273	55	20
P-value		<0.01	<0.016

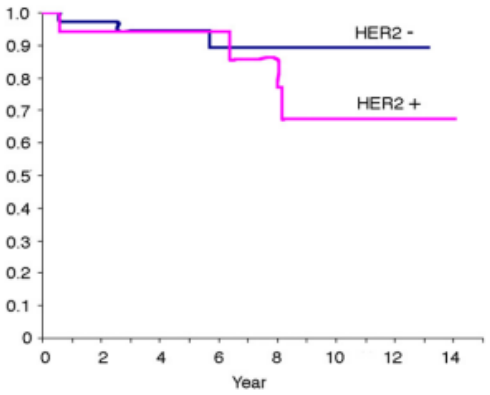
Ann Oncol. 2015 May;26(5):1019-25. Molecular phenotypes of DCIS predict overall and invasive recurrence. Williams KE, et al. (UK)

Intrinsic subtype: helpful !

- IHC expression of ER, PR, HER2
- 180 BCS women with primary DCIS (1987-2000)
- BCS alone (n=125) & BCS+RTx (n=55)
- IHC-based molecular subtyping
  - ✓ Luminal A (ER and/or PR (+), HER2(-))
  - ✓ Luminal B (ER and/or PR (+), HER2(+))
  - ✓ HER2+ (ER (-) and PR (-) and HER2(+))
  - ✓ Triple Negative (ER, PR and HER2 (-))
- median follow-up time: 8.7 years



Local recurrence-free survival in BCS alone



Local recurrence-free survival in BCS+RTx

Clin Oncol 2012 Apr;24(3):183-9. Expression of HER2neu in ductal carcinoma in situ is associated with local recurrence. Han K, et al. (Canada)

Intrinsic subtype: helpful ?

- 230 consecutive patients with DCIS (2005-2012)
- lumpectomy with/without radiation or mastectomy
- Recurrence: 17.8%, median F/U: 44 months
- IHC expression of ER, PR, Ki-67, HER2
  - ✓ ER positivity: 70.4%
  - ✓ PR positivity: 52.6%
  - ✓ HER2 positivity: **77.8%**
  - ✓ low, intermediate and high Ki-67 expression: 38.7%, 26.1% and 35.2%

Lumpectomy	61 (26.5)
Lumpectomy plus radiotherapy	92 (40.0)
Mastectomy	77 (33.5)

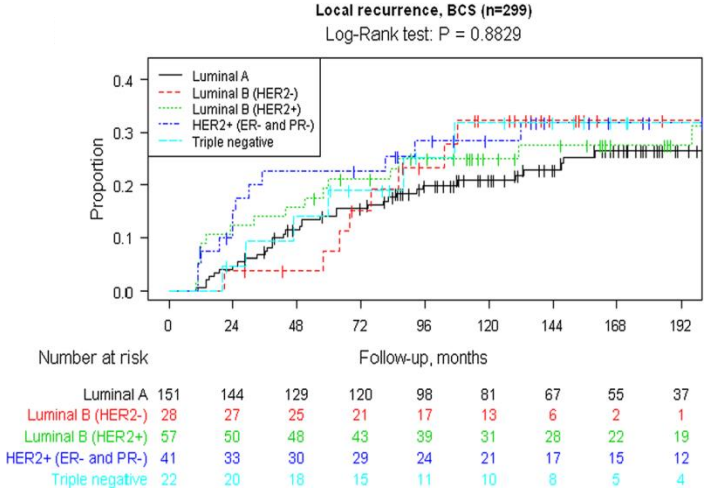
- Recurrence rates were not significantly associated with ER, PR status or HER2 expression.

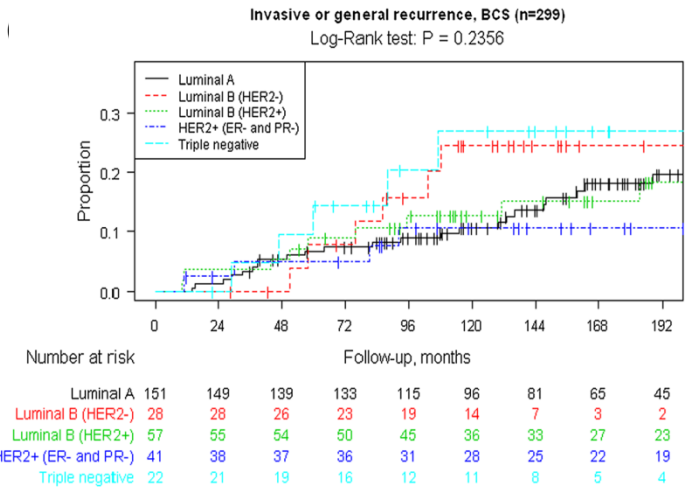
Variables	Category or increment	Multivariable analysis	
		Multivariable HR (95%CI)	p
Age at diagnosis	10 years increase	**0.60 (0.43–0.83)**	**0.002**
Grade	1 level increase	**1.72 (1.06–2.78)**	**0.028**
ER expression	Positive vs. Negative	1.13 (0.51–2.53)	0.764
PR expression	Positive vs. Negative	1.42 (0.70–2.89)	0.331
HER2 expression	Positive vs. Negative	1.04 (0.48–2.24)	0.930
Ki-67 expression	Intermediate/High vs. Low	**1.78 (1.11–2.88)**	**0.017**
Treatment	Lumpectomy plus radiotherapy vs. Lumpectomy alone	**0.34 (0.16–0.73)**	**0.005**
	Mastectomy vs. Lumpectomy alone	**0.38 (0.24–0.61)**	**<0.001**

Breast. 2016 Feb;25:57-61. Hormonal receptor status, Ki-67 and HER2 expression: Prognostic value in the recurrence of ductal carcinoma in situ of the breast? Poulakaki N, et al. (Greece)

Intrinsic subtype: helpful ?

- 458 primary DCIS patients (1986-2004) (mean F/U: 164 months)
- IHC-based molecular subtyping & SISH
  - ✓ Luminal A (ER and/or PR (+), HER2(-) and Ki67 <14%) n=186, 40.6%
  - ✓ Luminal B/HER2- (ER and/or PR (+), HER2(-) and Ki67 ≥14%) n=33, 7.2%
  - ✓ Luminal B/HER2+ (ER and/or PR (+), HER2(+)) n=74, **16.2%**
  - ✓ HER2+/ER- (non luminal) (ER and PR (-) and HER2(+)) n=61, **13.3%**
  - ✓ Triple Negative (ductal), (ER, PR and HER2 (-)) n=27, 5.9%
- 359 (78.4%) had BCS and less than half of them (44.8%, 161) had RTx.





→ failed to find the molecular subtyping is a prognostic useful tool in DCIS

BMC Cancer. 2013 Oct 30;13:512. Molecular subtypes in ductal carcinoma in situ of the breast and their relation to prognosis: a population-based cohort study. Zhou W, et al. (Swedish)

Multiple IHC markers in DCIS

- 213 patients with DCIS (1982-2000)
- median F/U
  - ✓ BCS+RTx: 7.7 years (0.32-14.1 years)
  - ✓ BCS alone: 8.7 years (0-16.2 years)
- IHC of molecular markers
  - ✓ ER, PR, Her2/neu, Ki67
  - ✓ p53, p21, cyclin D1, etc.
  - ✓ CISH for equivocal Her2
- Rate of recurrence at 5, 10 years
  - ✓ BCS alone: 20%, 36%
  - ✓ BCS+RTx: 6%, 18%

	Breast-conserving surgery+ radiotherapy (N = 72)	Breast-conserving surgery (N = 141)	P-value
Age mean (range) (years)	54.4 (33.4, 81.6)	58.1 (27, 86)	0.04
Tumour size (cm)			
Mean (range)	1.2 (0.09, 5.0)	0.8 (0.02, 2.5)	<0.001
Comedo necrosis			
Yes	48 (67%)	87 (62%)	0.48
No	20 (28%)	53 (37%)	
Missing	4 (5%)	1 (1%)	
Nuclear grade			
Low	5 (7%)	20 (14%)	0.034
Moderate	27 (38%)	65 (46%)	
High	38 (53%)	56 (40%)	
Missing	2 (2%)		
Molecular markers			
HER2/neu+	19 (26.4%)	39 (27.8%)	0.84
Psoriasin *continuous*	7.9 (0 ,100)	5.2 (0, 90)	0.27
Psoriasin (⩾10%)	18 (25.0%)	20 (14.2%)	0.051
Calgranulin *continuous*	5.2 (0, 75)	11.1 (0, 100)	0.06
Calgranulin (⩾10%)	11 (15.3%)	31 (22.0%)	0.24
Ki67 *continuos*	12.9 (0, 80)	13.4 (0, 80)	0.82
Ki67 (⩾10%)	49 (68.1%)	91 (64.5%)	0.61
p53–*continuous*	41.9 (0, 100)	15.1 (0, 100)	<0.001
p53+(⩾10%)	44 (61.1%)	39 (27.7%)	<0.001
ER positive	59 (81.9%)	94 (66.7%)	0.02
PR positive	52 (72.2%)	83 (58.9%)	0.06
Cyclin D1	71.5 (0, 100)	78.8 (0, 100)	0.047
p21–*continuous*	20.1 (0, 100)	20.1 (0, 100)	0.99
p21+(⩾10%)	41 (57.0%)	74 (52.4%)	0.54

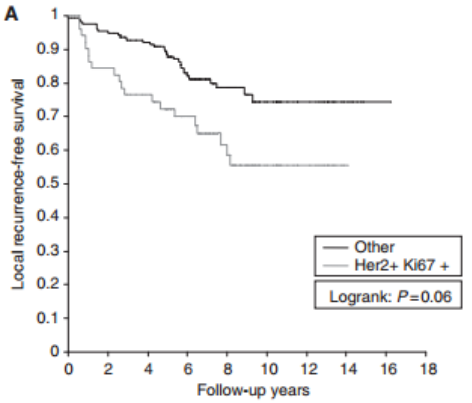
Br J Cancer. 2012 Mar 13;106(6):1160-5. HER2/neu and Ki-67 expression predict non-invasive recurrence following breast-conserving therapy for ductal carcinoma in situ. Rakovitch E, et al. (Canada)

Multiple IHC markers in DCIS

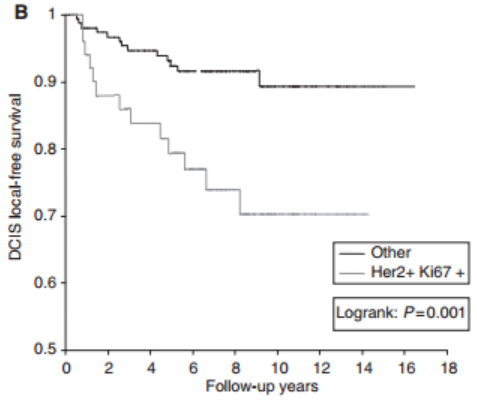
Molecular predictors of any local recurrence

Variables	N	No of LR	Hazard ratio (95% CI)	P-value
Univariable analysis				
HER2/neu+			2.11 (1.21, 3.68)	0.01
Psoriasin (⩾10%)			0.81 (0.38, 1.72)	0.58
Calgranulin			1.35 (0.72, 2.54)	0.35
Ki67 (⩾10%)			0.91 (0.51, 1.61)	0.75
p53+(⩾10%)			0.89 (0.49, 1.59)	0.68
ER positive			0.85 (0.47, 1.53)	0.59
PR positive			0.94 (0.53, 1.65)	0.82
Cyclin D1			1.00 (0.99, 1.01)	0.74
p21+(⩾10%)			1.04 (0.59, 1.81)	0.90
Multivariable analysis (adjusted for age and XRT)				
Her2/neu positive (*vs* other)	58	22	2.10 (1.19, 3.69)	0.01
HER2/neu+/Ki67+ (*vs* other)	51	16	2.15 (1.20, 3.83)	0.01
HER2/neu+/Ki67− (*vs* other)	7	2	1.22 (0.29, 5.06)	0.79
HER2/neu+/p53+(*vs* other)	35	8	1.29 (0.64, 2.62)	0.48
Ki67+/p53+ (*vs* other)	63	12	1.23 (0.65, 2.33)	0.53
HER2/neu+/Ki67+/p53+ (*vs* other)	31	8	1.50 (0.73, 3.07)	0.27
ER−/HER2/neu+/Ki67+ (*vs* other)	31	11	1.52 (0.77, 2.99)	0.23

Her2/neu and Ki67 & local recurrence



Her2/neu and Ki67 & non-invasive recurrence



Br J Cancer. 2012 Mar 13;106(6):1160-5. HER2/neu and Ki-67 expression predict non-invasive recurrence following breast-conserving therapy for ductal carcinoma in situ. Rakovitch E, et al.

Her-2, a bad guy in DCIS?

Table 4 Molecular predictors of non-invasive (DCIS) local recurrence

	N	No of DCIS LR	Hazard ratio (95% CI)	P-value
Univariable analysis				
HER2/neu+			2.72 (1.26, 5.88)	0.01
Psoriasin (⩾10%)			1.30 (0.52, 3.24)	0.57
Calgranulin (⩾10%)			1.47 (0.62, 3.49)	0.39
Ki67 (⩾10%)			1.05 (0.47, 2.35)	0.91
p53 (⩾10%)			0.89 (0.40, 1.99)	0.77
ER positive			1.14 (0.48, 2.71)	0.77
PR positive			0.71 (0.33, 1.53)	0.37
Cyclin D1 (⩾10%)			1.01 (0.99, 1.02)	0.52
p21 (⩾10%)			1.24 (0.57, 2.71)	0.58
Multivariable analysis (adjusted for age and XRT)				
Her2/neu+	58	13	2.67 (1.23, 5.79)	0.01
HER2/neu+/Ki67+ (vs other)	51	10	3.22 (1.47, 7.03)	0.003
HER2/neu+/Ki67− (vs other)	7	0	Not calculable	
HER2/neu+/p53+(vs other)	35	5	1.54 (0.61, 3.91)	0.36
Ki67+/p53+ (vs other)	63	6	1.09 (0.44, 2.67)	0.86
HER2/neu+/Ki67+/p53+ (vs other)	31	5	1.79 (0.70, 4.57)	0.22
ER−/HER2/neu+/Ki67+ (vs other)	31	6	1.65 (0.66, 4.15)	0.28

Table 5 Molecular predictors of invasive recurrence

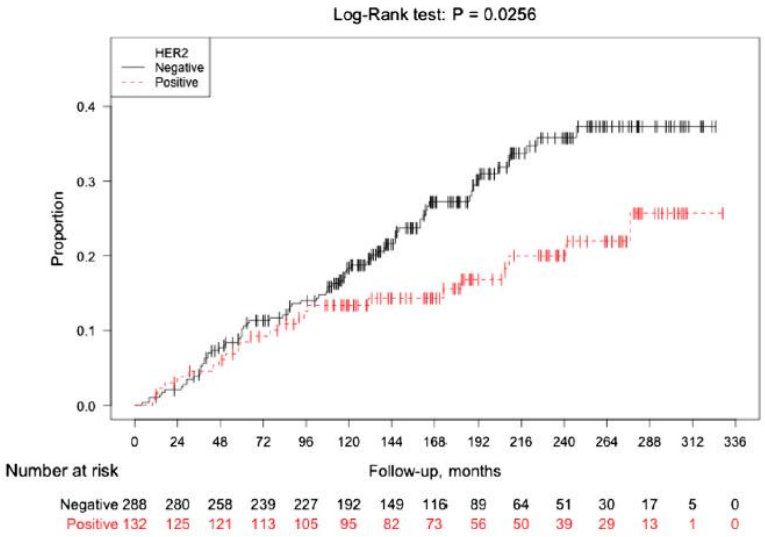
Univariable analysis	N	No of Inv LR	Hazard ratio (95% CI)	P-value
HER2/neu+			1.58 (0.69, 3.62)	0.28
Psoriasin (⩾10%)			0.38 (0.09, 1.60)	0.19
Calgranulin (⩾10%)			1.24 (0.49, 3.12)	0.65
Ki67 (⩾10%)			0.79 (0.35, 1.77)	0.56
p53 (⩾10%)			0.88 (0.38, 2.06)	0.77
ER positive			0.64 (0.29, 1.45)	0.29
PR positive			1.30 (0.55, 3.03)	0.55
Cyclin D1 (⩾10%)			0.99 (0.98, 1.01)	0.85
p21 (⩾10%)			0.85 (0.38, 1.90)	0.69
Multivariable analysis (adjusted for age and XRT)				
HER2/neu/neu+	58	9	1.61 (0.70, 3.73)	0.26
HER2/neu+/Ki67+ (vs other)	51	6	1.33 (0.54, 3.28)	0.54
HER2/neu+/Ki67− (vs other)	7	2	1.22 (0.29, 5.06)	0.79
HER2/neu+/p53+(vs other)	35	3	1.04 (0.35, 3.11)	0.94
Ki67+/p53+ (vs other)	63	6	1.41 (0.57, 3.52)	0.46
HER2/neu+/Ki67+/p53+ (vs other)	31	3	1.22 (0.40, 3.69)	0.73
ER−/HER2/neu+/Ki67+ (vs other)	31	5	1.39 (0.51, 3.78)	0.52

→ Her2/Ki67 is bad in non-invasive local recurrence, but not in invasive recurrence.

Br J Cancer. 2012 Mar 13;106(6):1160-5. HER2/neu and Ki-67 expression predict non-invasive recurrence following breast-conserving therapy for ductal carcinoma in situ. Rakovitch E, et al.

Her-2, a good guy in DCIS?

- 458 primary DCIS patients (1986-2004) → TMA with IHC & SISH
- BCS in 78.6%. Radiation in 44.8% of BCS patients.
- 132 Her2 positive (31%) and 288 Her2 negative (69%)
- mean follow-up: 184 months



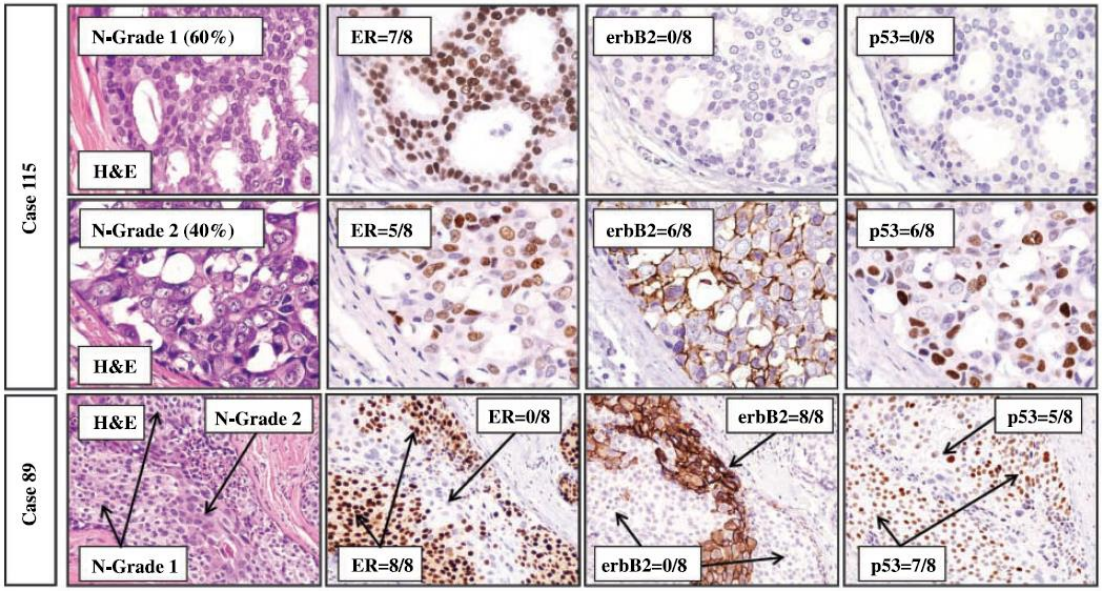
Invasive recurrence-free-survival according to Her2 status

→ significantly improved long-term invasive disease-free survival for patients with Her2(+) disease in the primary DCIS

BMC Cancer. 2015 Jun 11;15:468. The prognostic role of HER2 expression in ductal breast carcinoma in situ (DCIS); a population-based cohort study. Borgquist S, et al. (Swedish)

Molecular diversity in DCIS and IDC

- Histologic and biological diversity within cases of DCIS (nuclear grades)
  - ✓ H&E-stained slides from 120 recent consecutive cases of pure DCIS
  - ✓ no diversity (54.2%) → grade 1 (29.2%), 2 (22.5%), 3 (2.5%)
  - ✓ with diversity (45.8%) → grades 1&2 (30.0%), 2&3 (6.6%), 1&2&3 (9.2%)
- examples of intratumoral diversity



Clin Cancer Res. 2008 Jan 15;14(2):370-8. Ductal carcinoma in situ and the emergence of diversity during breast cancer evolution. Allred DC, et al.

Intrinsic subtype changes during progression

- 90 patients with DCIS, IDC, and lymph node metastasis lesion
- IHC staining for ER, PR, HER2 and Ki67 & HER2 SISH
  - ✓ Luminal A (ER+ and/or PR+, HER2-, Ki67 low (<14%))
  - ✓ Luminal B (ER+ and/or PR+ and HER2-, Ki67 high or HER2+, Ki67 any)
  - ✓ HER2 type (ER-/PR-/HER2+)
  - ✓ triple negative (ER-/PR-/HER2-)
- <u>changes intrinsic subtype throughout tumor progression</u>

Subtype in DCIS		Subtype in IDC				Subtype in Metastasis			
		Luminal A	Luminal B	HER2	Basal like	Luminal A	Luminal B	HER2	Basal like
Luminal A	39 (43.3)	30	7	0	2	25	5	0	1
Luminal B	24 (26.7)	1	19	4	0	3	22	1	0
HER2	19 (21.1)	0	0	18	1	0	2	20	1
Basal like	8 (8.9)	0	0	1	7	0	0	0	10

Int J Clin Exp Pathol. 2015 Nov 1;8(11):15184-90. Changes in intrinsic subtype of breast cancer during tumor progression in the same patient. Kim C, et al.

Intrinsic subtype: really helpful?

factors related to recurrence in DCIS

- Age
- Margin
- Tumor size
- clinical presentation
- Family history
- Nuclear grade / necrosis
- Radiation
- Endocrine therapy
- year of surgery

+ Molecular subtype (?)

Scoring System for USC/VNPI

- prospective data base
- 1,704 patients with pure DCIS (1979-2014)
  - ✓ Mastectomy: 556 (32.8%)
  - ✓ excision and radiation therapy: 442 (26.1%)
  - ✓ excision alone: 696 (41.1%)
- Based on 5 measurable prognostic factors
  : tumor size, margin width, nuclear grade, comedo necrosis, age

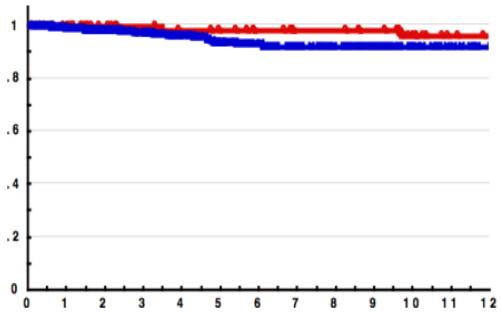
Score	1	2	3
Size	≤15 mm	16–40	≥40
Margin	≥10 mm	1–9	<1
VN class	Grade 1/2 without necrosis	Grade 1/2 with necrosis	Grade 3
Age	>60	40–60	<40

Lancet. 1995 May 6;345(8958):1154-7. Prognostic classification of breast ductal carcinoma-in-situ. Silverstein MJ, et al.
Breast J. 2015 Mar-Apr;21(2):127-32. Treatment selection for patients with ductal carcinoma in situ (DCIS) of the breast using the University of Southern California/Van Nuys (USC/VNPI) prognostic index. Silverstein MJ, Lagios MD.

USC/VNPI score & Prognosis

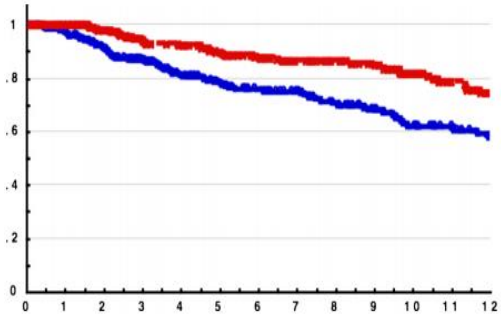
excision plus radiation therapy
excision alone

4, 5, 6



→ Excision alone

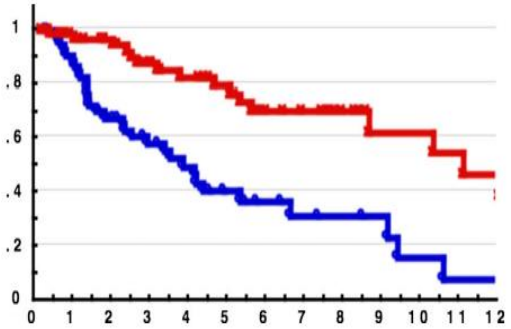
7, 8, 9



→

7 & margins ≥3 mm → Excision alone
7 & margins <3 mm → Radiation
8 & margins ≥3 mm → Radiation
8 & margins <3 mm → Mastectomy
9 & margins ≥5 mm → Radiation
9 & margins <5 mm → Mastectomy

10, 11, 12



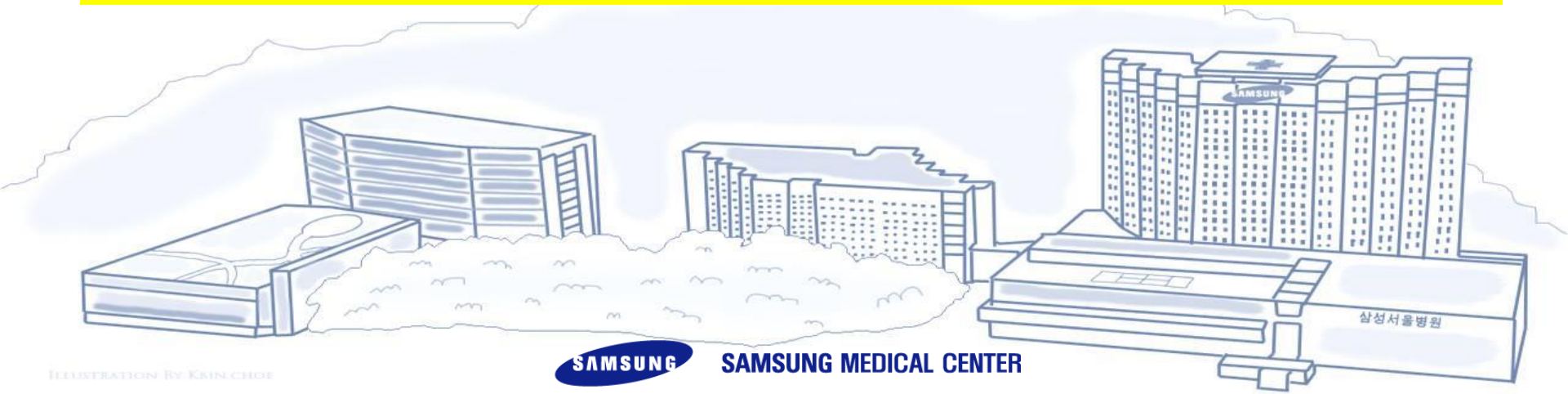
→ Mastectomy

Breast J. 2015 Mar-Apr;21(2):127-32. Treatment selection for patients with ductal carcinoma in situ (DCIS) of the breast using the University of Southern California/Van Nuys (USC/VNPI) prognostic index. Silverstein MJ, Lagios MD.

Personalized Treatment of DCIS

- 5 measurable prognostic factors of VNPI
  : margin width, nuclear grade, tumor size, comedo necrosis, age

  → Factors for Personalized Treatment???



Margin width in IDC

Relationship between IBTR and margin status

	No. of studies	No. of participants	Adjusted OR of IBTR[a]	95% CI	*P* (association)
Margin category (model one)		28,162			<0.001
Close/positive	33	6,178	1.96	1.72–2.24	
Negative	33	21,984	1.0	—	
Margin category (model two)		13,081			<0.001
Positive	19	1,641	2.44	1.97–3.03	
Close	19	2,407	1.74	1.42–2.15	
Negative	19	9,033	1.0	—	—
Threshold distance (model two)[b]					0.90
1 mm	6	2,376	1.0	—	—
2 mm	10	8,350	0.91	0.46–1.80	—
5 mm	3	2,355	0.77	0.32–1.87	—

Impact of margin width on IBTR adjusted for individual covariates and follow-up

Covariate	No. of studies	Threshold distance negative margin: adjusted OR (mm)			*P* (association)
		1	2	5	
Age	18	1.0	0.53	0.77	0.53
Endocrine therapy	16	1.0	0.95	0.90	0.95
Radiation boost	18	1.0	0.86	0.92	0.86

→ "No DCIS or invasive tumor cells on the inked margin"

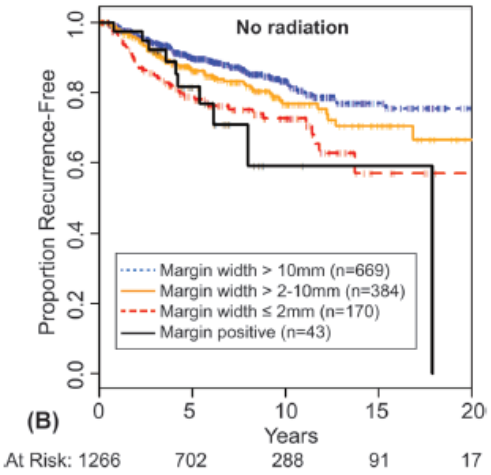
Ann Surg Oncol. 2014 Mar;21(3):704-16 Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins forbreast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Moran MS, et al.

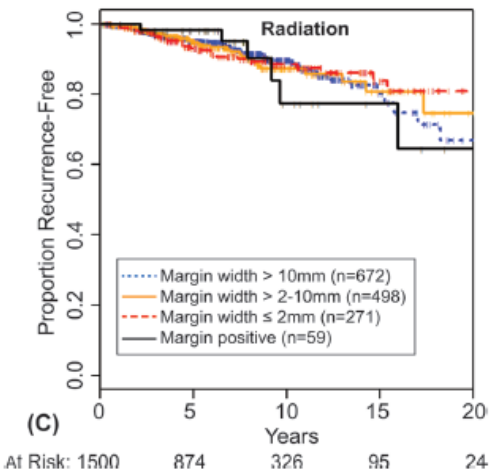
Margin width in DCIS

- 2996 DCIS pts treated with BCS (1978-2010) → 363 recurrence (12.1%)
- BCS with RTx (1588; 53.6%) & BCS alone (1374; 46.4%)

* Crude Recurrences by Margin Width and Use of Radiation

	No Radiation (N = 1374)*		Radiation (N = 1588)*	
Margin Width	**Events/ N**	**%**	**Events/ N**	**%**
Positive	10/43	23.3	6/59	10.2
Close (≤2 mm)	42/170	24.7	27/271	10.0
>2–10 mm	63/384	16.4	35/498	7.0
>10 mm	87/669	13.0	58/672	8.6
Unknown	21/108	19.4	14/88	15.9

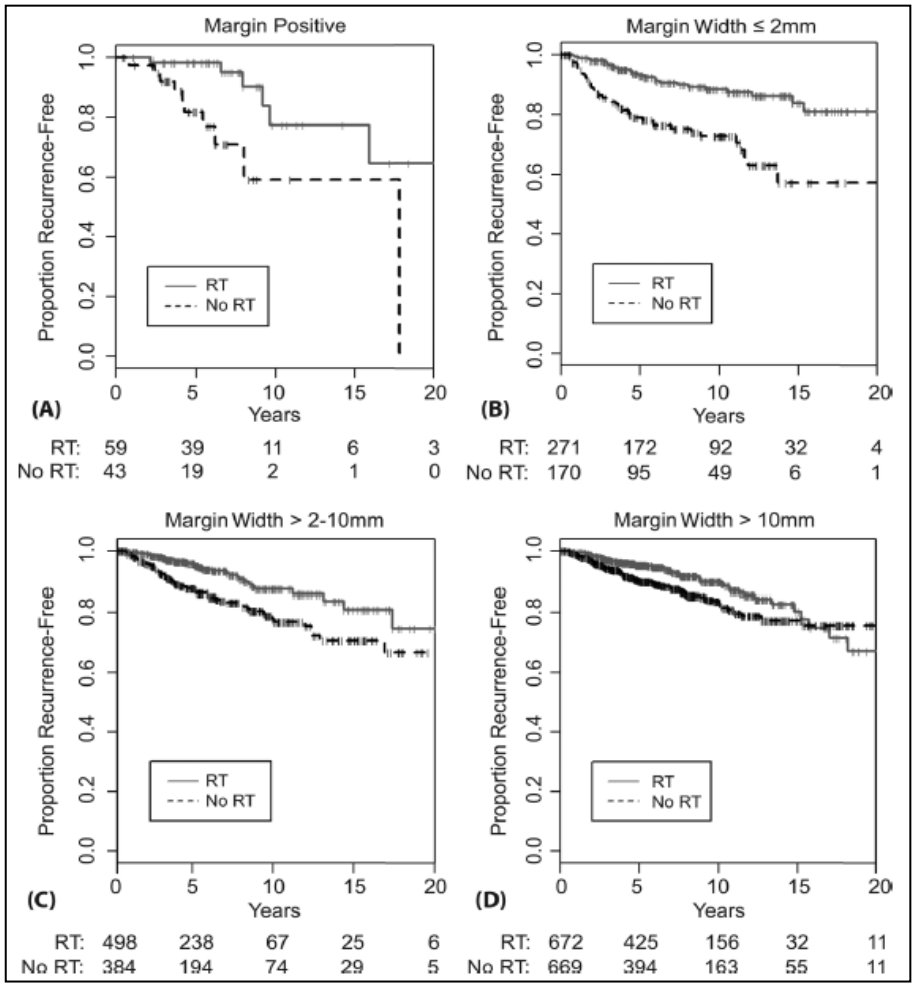




→ "Obtaining wider negative margins may not be necessary in BCS with RTx."

Ann Surg. 2015 Oct;262(4):623-31. Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years. Van Zee KJ, et al. (Memorial Sloan Kettering Cancer Center)

Margin width in DCIS



→ "RT was associated with a statistically significant reduction in recurrence for each margin width."

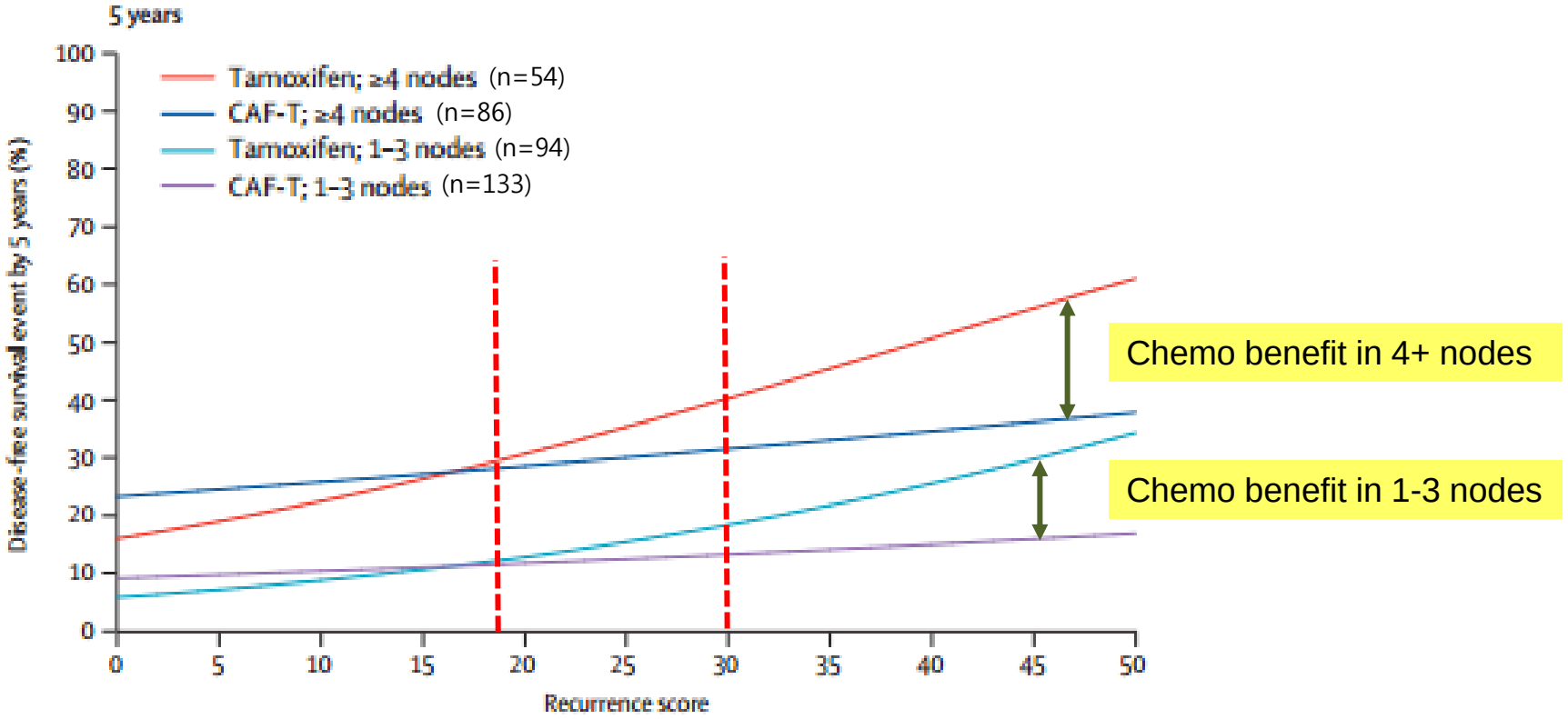
→ "Greater proportional and absolute risk reduction of RT is associated with positive or close margins."

→ "the association of recurrence with margin width was significant in those without RT (P<0.0001), but not in those with RT (P=0.95)."

Ann Surg. 2015 Oct;262(4):623-31. Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years. Van Zee KJ, et al. (Memorial Sloan Kettering Cancer Center)

Oncotype Dx in personalized medicine for postmenopausal ER(+) Her2(-) N(+)

- Risks of a disease-free survival event by linear recurrence score, treatment, and number of positive nodes



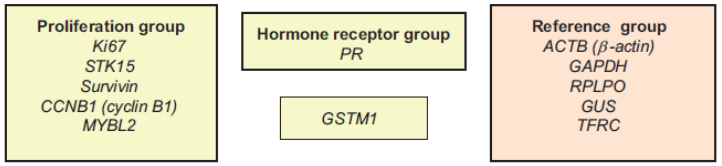
Lancet Oncol. 2010 Jan;11(1):55-65. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Albain KS, et al.
Slide modified from the courtesy of Soonmyung Paik, MD

12-gene Oncotype DX DCIS Score

- Oncotype DX breast cancer assay for 327 DCIS patients treated with surgical excision *without radiation* in the Eastern Cooperative Oncology Group (ECOG) E5194 study

- enrollment criteria for E5194: non-palpable DCIS and margins ≥3 mm
  1) L/G to I/G DCIS: 0.3~2.5 cm or 2) H/G DCIS: <1 cm
- Hormone receptor (+) in 97.9% & HER2 (-) in 85.6% (by RT-PCR)

- Calculation of the DCIS Score
  - ✓ five reference genes: ACTB, GAPDH, RPLPO, GUS, TFRC
  - ✓ proliferation group score = (Ki67+STK15+Survivin+CCNB1+MYBL2)/5
- DCIS Score$_{\mu}$ = +0.31×proliferation group score –0.08×*PR* – 0.09×*GSTM1*

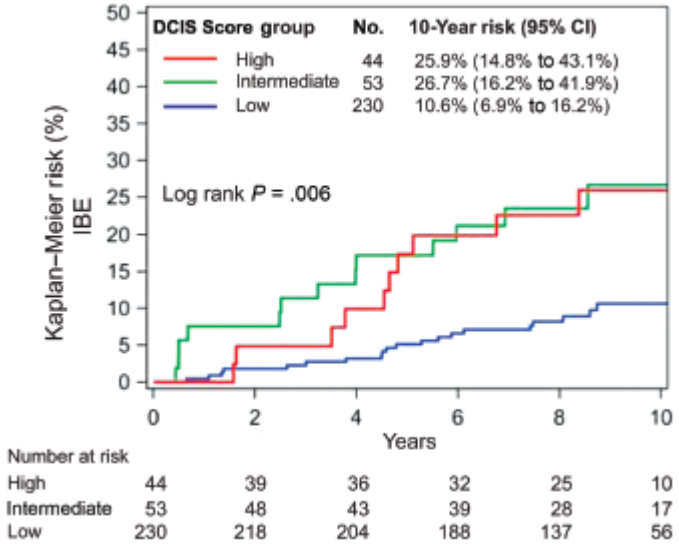


J Natl Cancer Inst. 2013 May 15;105(10):701-10. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. Solin LJ, et al.

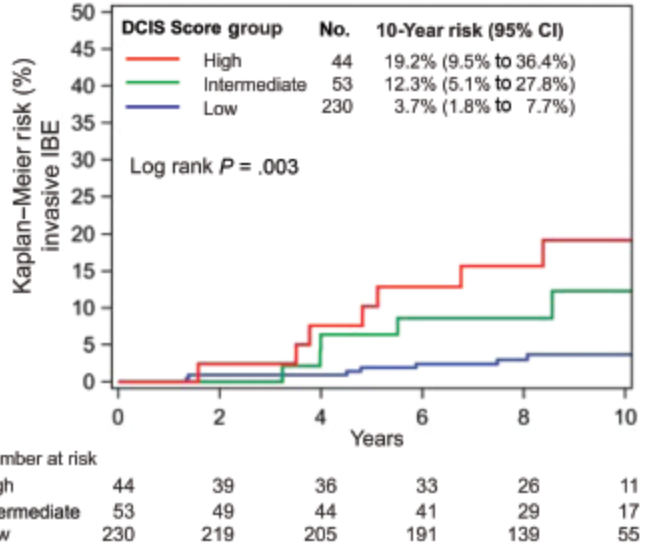
DCIS Score

- For the pre-specified low, intermediate, and high DCIS risk groups
  - ✓ 10-year risks of developing IBR: 10.6%, 26.7%, 25.9%,
  - ✓ 10-year risks of developing invasive IBR: 3.7%, 12.3%, 19.2%

IBR

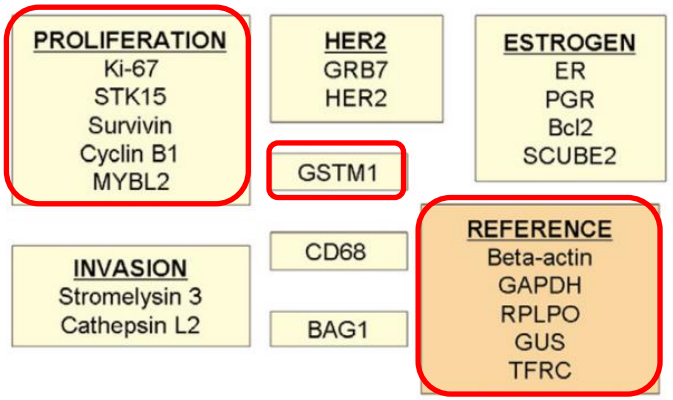


invasive IBR



Mod Pathol. 2015 Sep;28(9):1167-73. Correlation of histopathologic features of ductal carcinoma in situ of the breast with the oncotypeDX DCIS score. Knopfelmacher A, et al.

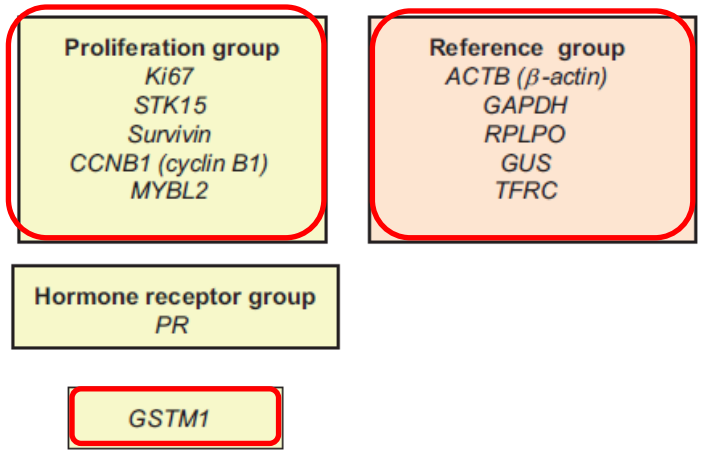
21-gene Oncotype Dx score & 12-gene DCIS score



$RS_U =$

+ 0.47 × HER2 Group Thresholded Score
− 0.34 × ER Group Score
+ 1.04 × Proliferation Group Thresholded Score
+ 0.10 × Invasion Group Score
+ 0.05 × CD68
− 0.08 × GSTM1
− 0.07 × BAG1

proliferation group score = (Ki67+STK15+Survivin+CCNB1+MYBL2)/5



$DCIS\ Score_{\mu} = +0.31 \times$ proliferation group score $-0.08 \times PR - 0.09 \times GSTM1.$

Breast Cancer Res. 2006;8(3):R25. A population-based study of tumor gene expression and risk of breast cancer death among LN(-) patients. Habel LA, et al.
J Natl Cancer Inst. 2013 May 15;105(10):701-10. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. Solin LJ, et al.

molecular-based, "patient–tailored" treatment planning for DCIS

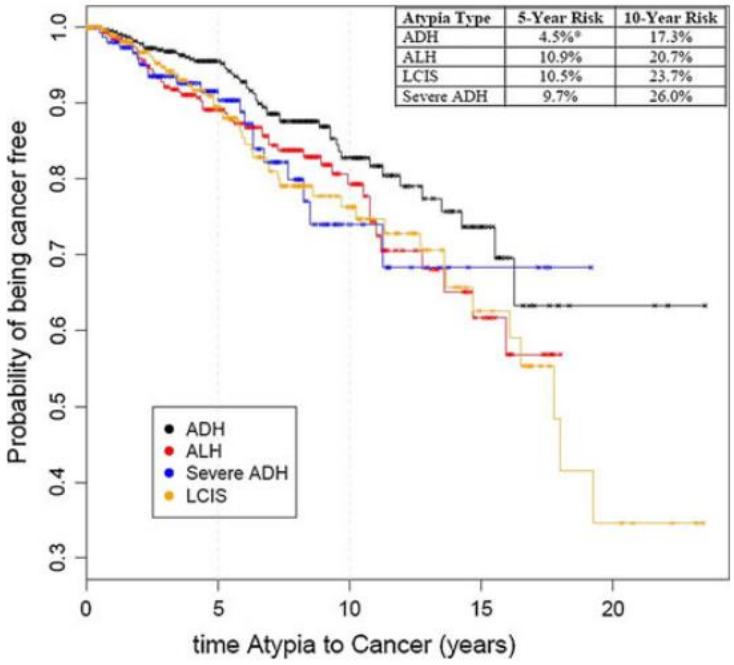
- "More aggressive treatments could be applied to the women with DCIS with higher risk of progressing to invasive cancer."
- "Identifying patients curable by local surgical excision from those who have more aggressive biology and require additional treatment is important to spare low-risk patients from mastectomy and adjuvant treatments such as radiotherapy and hormonal blockade."
- "Studies have identified multiple genomic changes and revealed the degree of intra-tumoral heterogeneity in DCIS."

→ So far, none of the molecular-based treatment is feasible to prevent a DCIS lesion from in situ recurrence or invasive progression.

Other considerations?

Cancer risk of atypia without chemoprevention

Estimated 5- and 10-year breast cancer risks



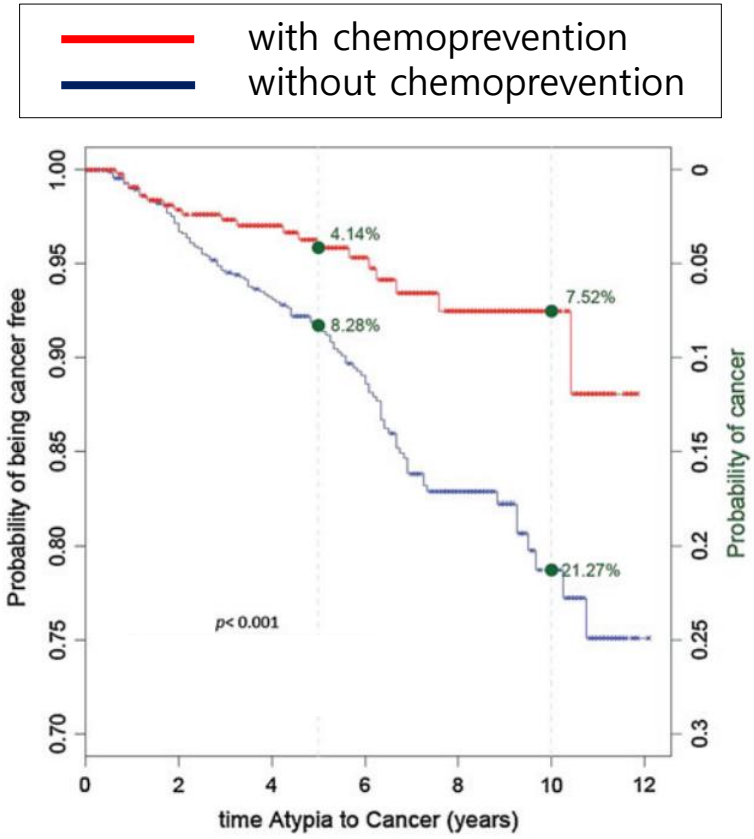
Laterality and type of cancer

	ADH (%) ($n = 57$)	ALH (%) ($n = 61$)	LCIS (%) ($n = 45$)	Severe ADH (%) ($n = 21$)
Laterality of cancer				
Ipsilateral[a]	34 (59.6)	37 (60.7)	25 (55.6)	10 (47.6)
Contralateral	22 (38.6)	23 (37.7)	17 (37.8)	9 (42.8)
Bilateral	1 (1.8)	0 (0.0)	2 (4.4)	1 (4.8)
Side unknown	0 (0.0)	1 (1.6)	1 (2.2)	1 (4.8)
Type of cancer				
Invasive[b]				
IDC	15 (26.3)	24 (39.3)	13 (28.9)	9 (42.9)
ILC	6 (10.5)	11 (18.0)	14 (31.1)	0 (0.0)
Invasive NOS	6 (10.5)	7 (11.5)	5 (11.1)	3 (14.3)
Non-invasive				
DCIS	29 (50.9)	18 (29.5)	12 (26.7)	9 (42.9)
In situ NOS	1 (1.8)	1 (1.6)	1 (2.2)	0 (0.0)

Breast Cancer Res Treat. 2012 Dec;136(3):627-33. The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. Coopey SB, et al. (Boston)

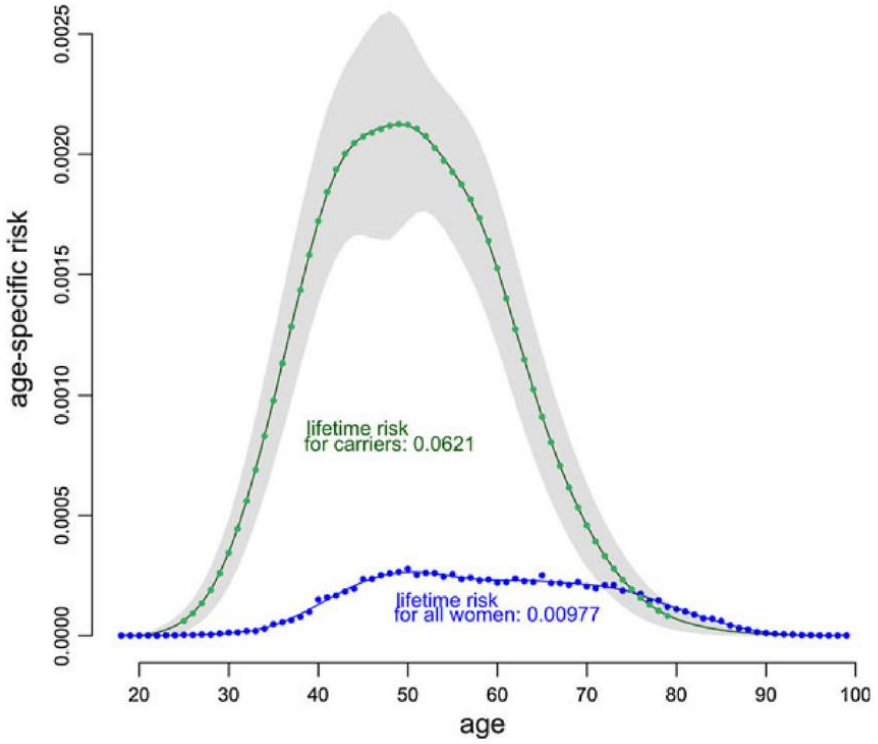
chemoprevention to modify the risk

	Chemoprevention group (%) (n = 466)
Type	
Tamoxifen alone	307 (65.9)
Raloxifene alone	102 (21.9)
Exemestane alone	7 (1.5)
Tamoxifen + Raloxifene	45 (9.6)
Tamoxifen + Exemestane	5 (1.1)
Raloxifene + Exemestane	0 (0.0)
Duration	
<1 year	59 (12.7)
1–3 years	122 (26.2)
3–4.5 years	85 (18.2)
4.5–5.5 years	148 (31.7)
>5.5 years	34 (7.3)
n/a	18 (3.9)
Use by atypia type	
ADH (n = 786)	145 (18.4)
ALH (n = 540)	99 (18.3)
LCIS (n = 374)	125 (33.4)[a]
Severe ADH (n = 238)	97 (40.8)[a]



Breast Cancer Res Treat. 2012 Dec;136(3):627-33. The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. Coopey SB ,et al. (Boston)

Risk for DCIS in BRCA carriers

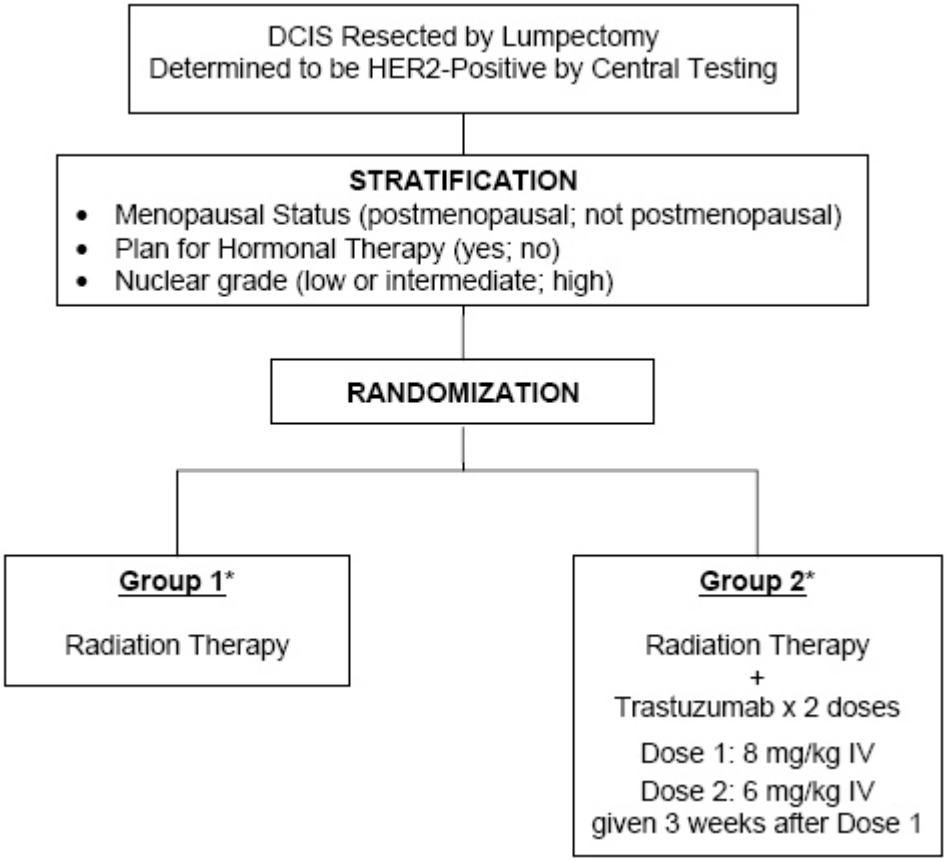


- BRCA carrier lifetime risk:
  DCIS: 6.21%
  (95% CI: 6.09-6.33%)

- Non-carrier lifetime risks:
  DCIS: 0.98%
  IBC: 12.5%

Breast Cancer Res Treat. 2013 Jan;137(1):315-8. The penetrance of ductal carcinoma in situ among BRCA1 and BRCA2 mutation carriers. Mazzola E, et al. (Joint re-analyze of SEER9 database (1973~2006) and a Claus study (1994~1998))

NSABP B-43 clinical trial (ongoing)



* Patients with ER-positive and/or PgR-positive DCIS should receive a minimum of 5 years of hormonal therapy.

http://www.nsabp.pitt.edu/B-43.asp

Questions still remained…

- fundamental natural history of untreated DCIS: 'genomic alterations+α' may determine prognosis in DCIS
- 'Tumor biology-tailored' as well as 'tailored surgical control' decision making: margin, radiation
- Stratified risk calculation: BRCA, and other genomic analysis
- Early detection before DCIS: chemoprevention
- De-escalation: not-doing-surgery trial (?)

Thank you very much for your attention!