World Congress on Breast Cancer

August 1-3, 2015, Birmingham, UK

Multiparameter characterization of breast carcinoma: subgross, microscopy, proteins, and genes

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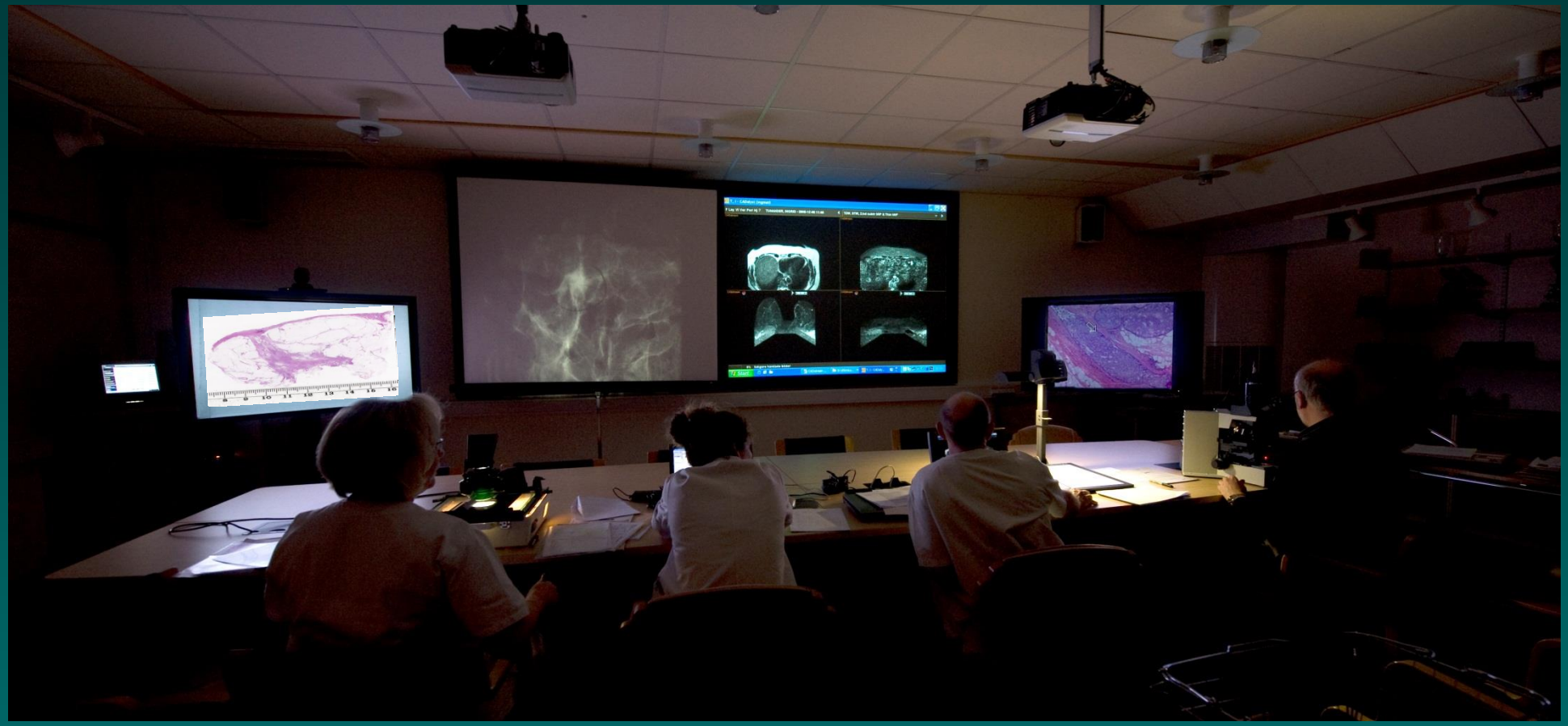
Falun, Sweden

European Society of Pathology

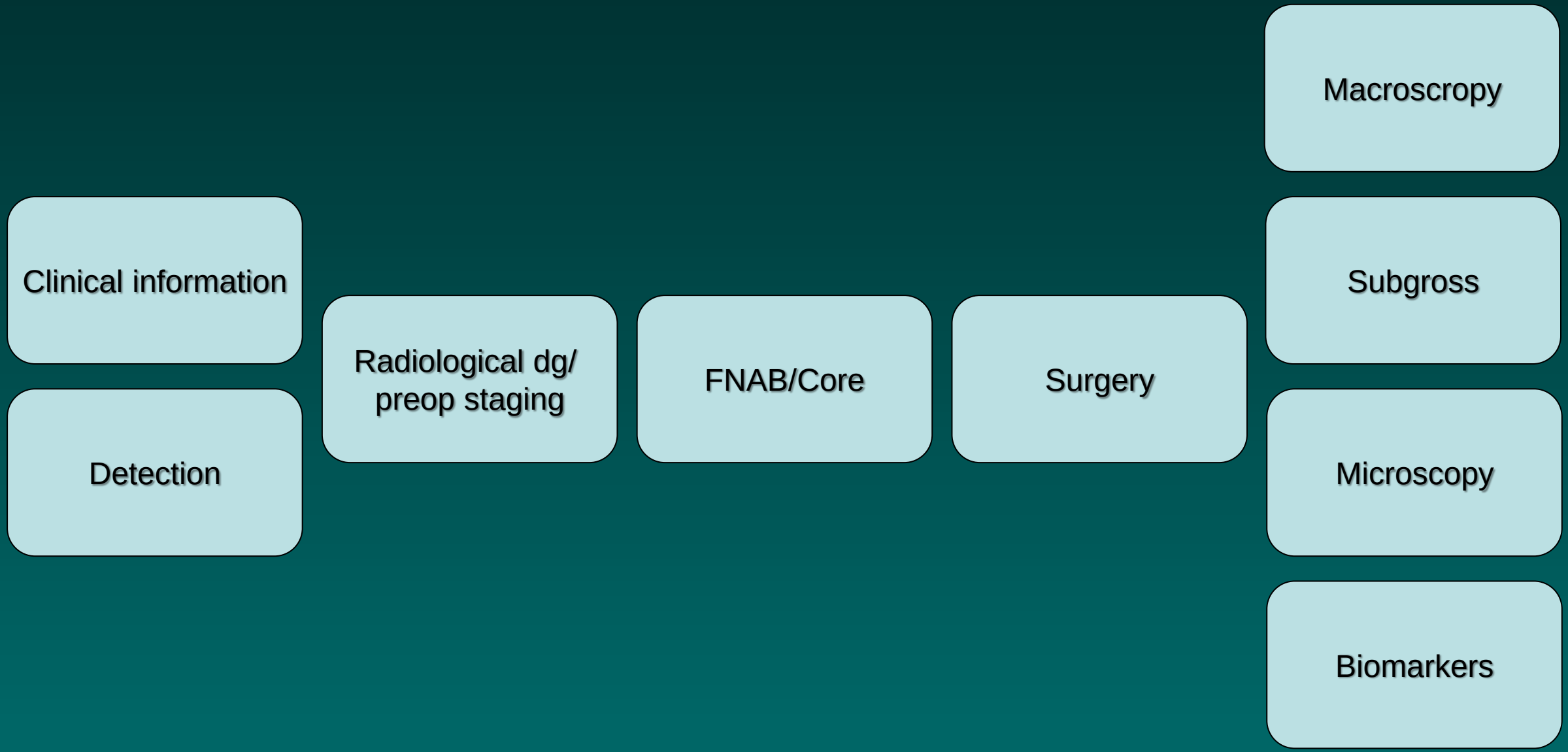
LmD

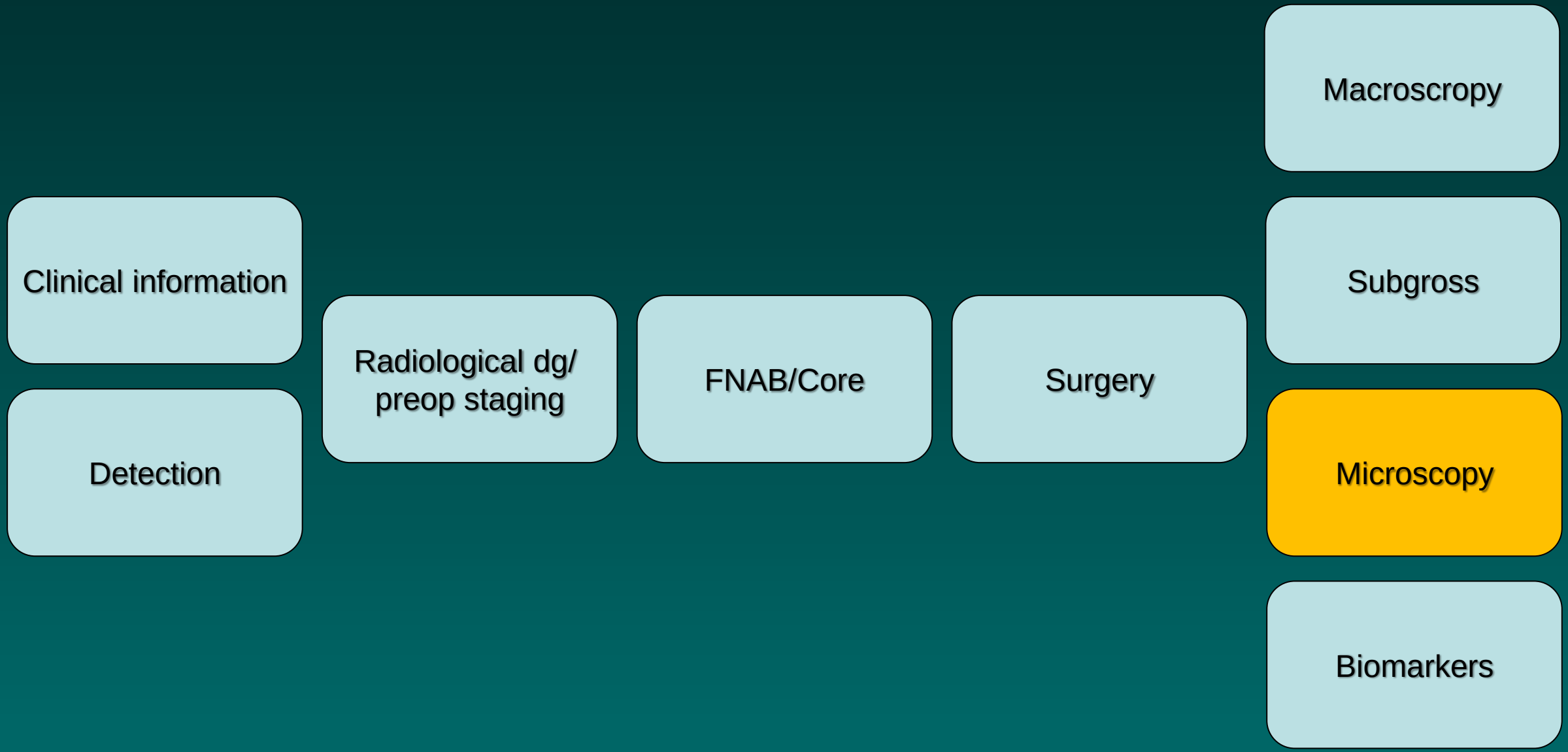
Laboratoriemedicin, Dalarna

Radiological – pathological correlation is essential in diagnosing breast carcinoma



The radiology images are courtesy of
Prof Laszlo Tabár, DRs Nadja Lindhe and Mats Ingvarsson


Clinical information
Detection
Radiological dg/ preop staging
FNAB/Core
Surgery
Macroscropy
Subgross
Microscopy
Biomarkers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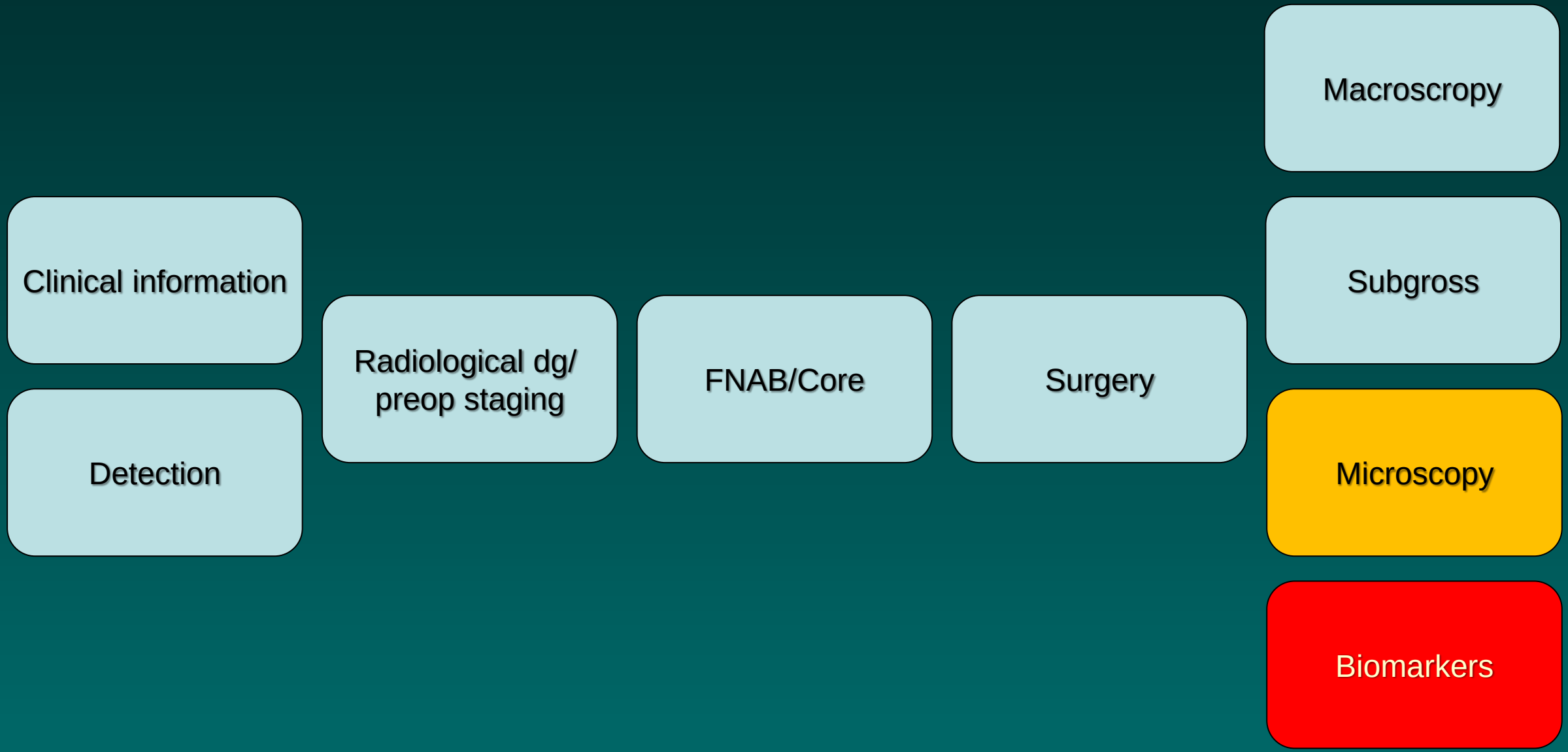
Clinical information
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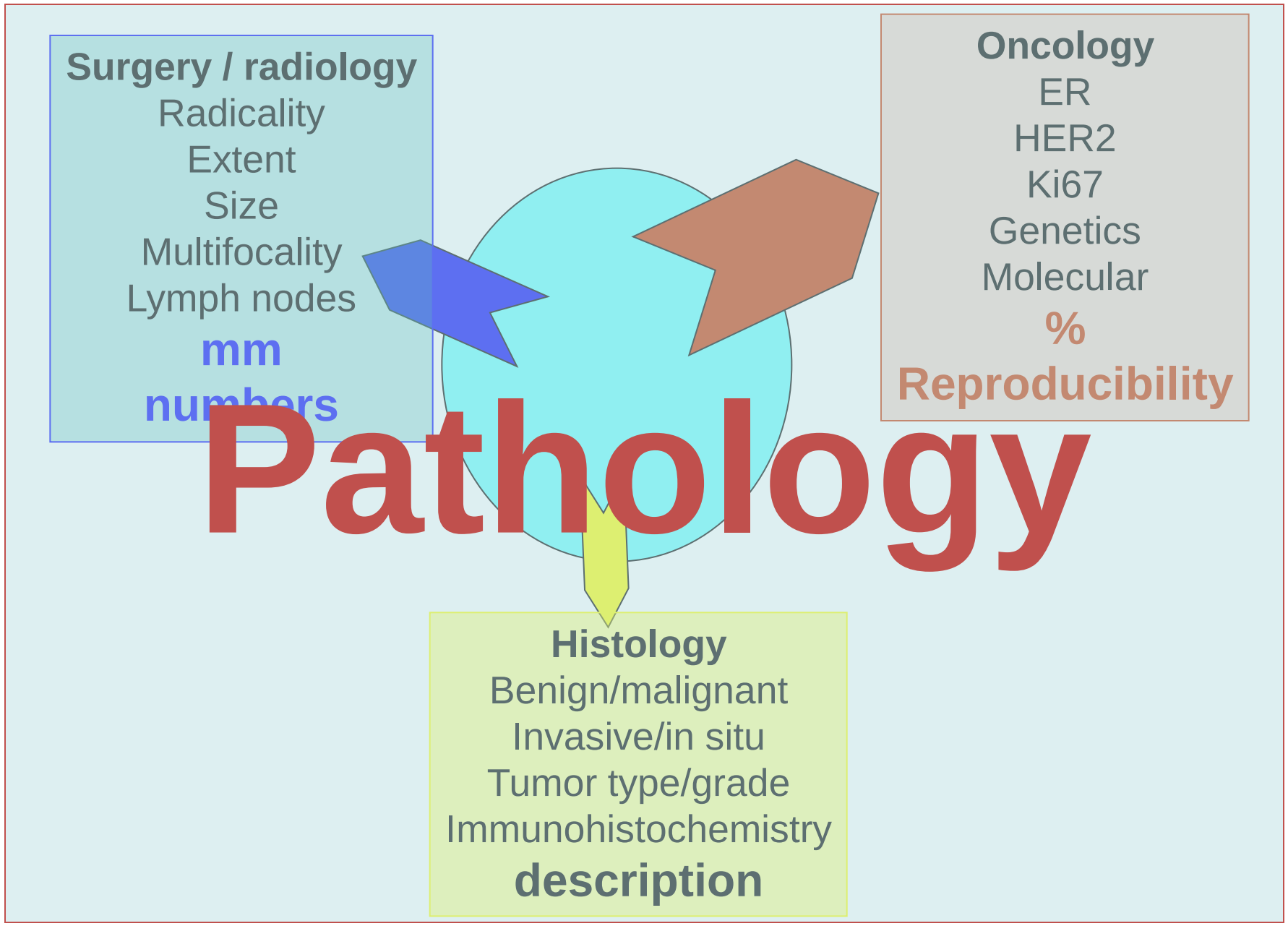
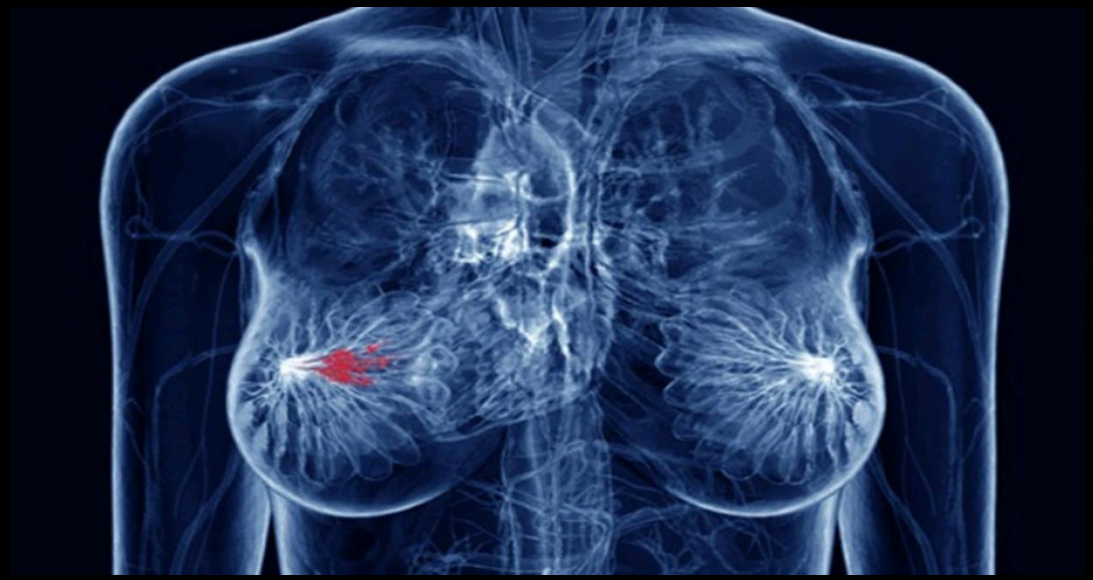

Surgery / radiology
Radicality
Extent
Size
Multifocality
Lymph nodes
mm
numbers
Oncology
ER
HER2
Ki67
Genetics
Molecular
%
Reproducibility
Pathology
Histology
Benign/malignant
Invasive/in situ
Tumor type/grade
Immunohistochemistry
description

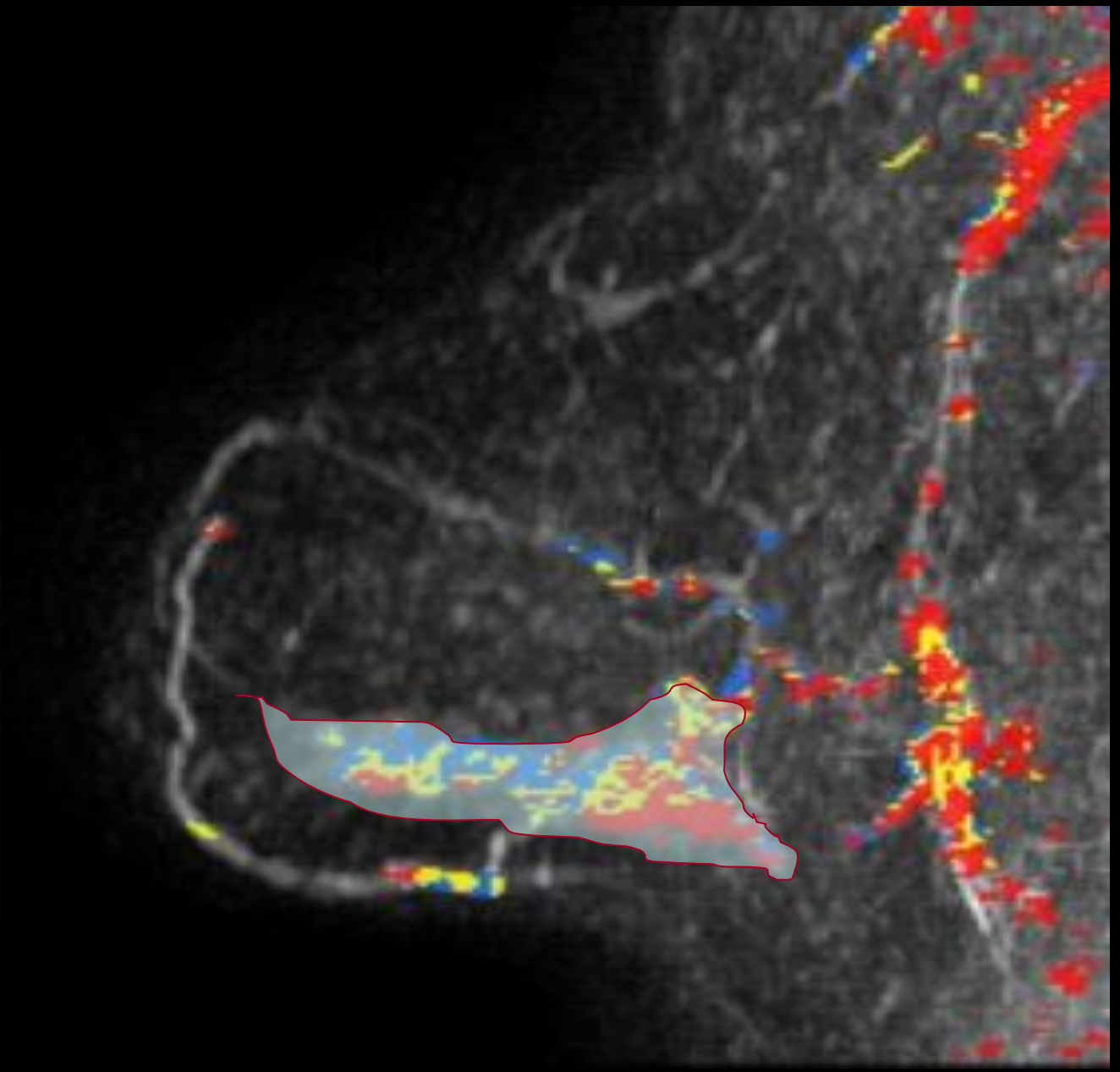
Large section histology

LN status
Margins
Additional lesions

Molecular phenotype (ER, PR, HER2, Ki67, CK5/6, CK14, EGFR)
+ E-cadherin
+D2-40

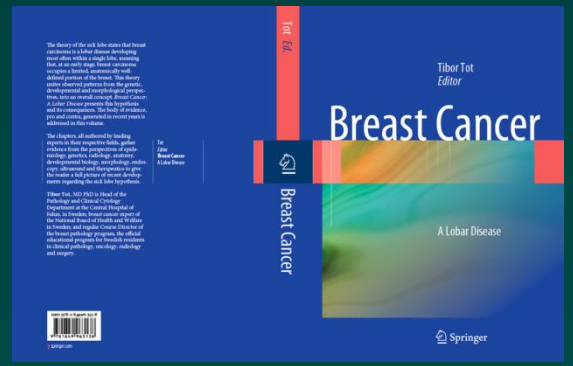
Extent
Distribution
Size
Heterogeneity
Margins
R-P correlation

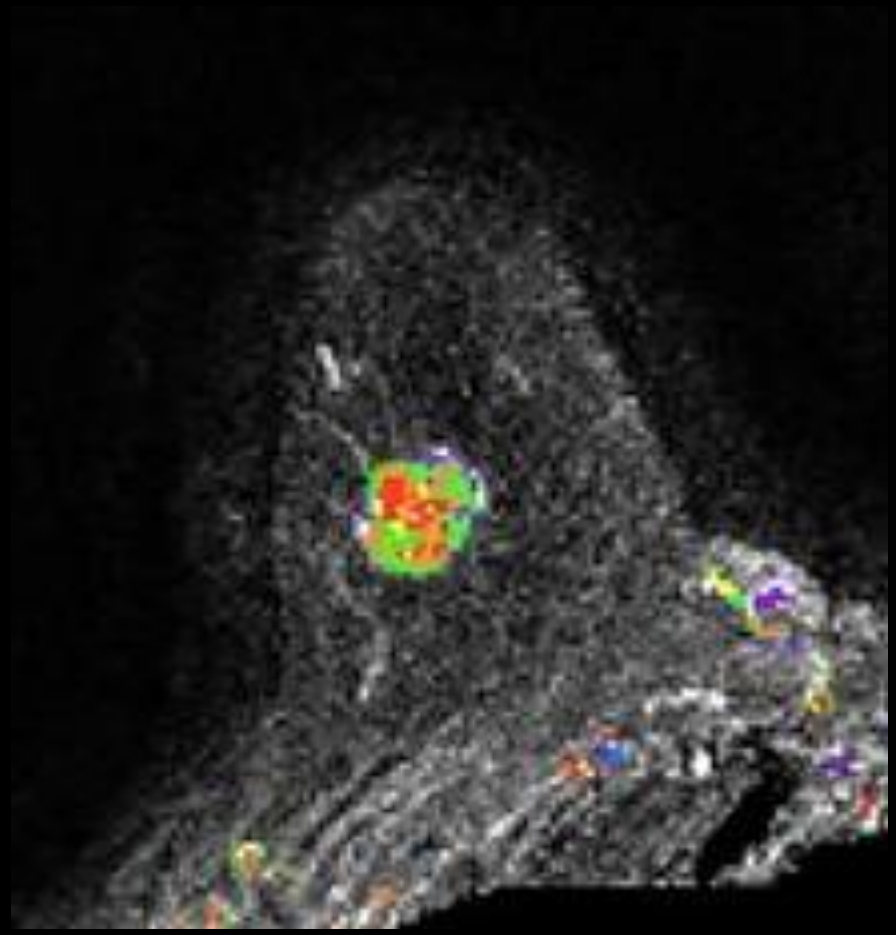




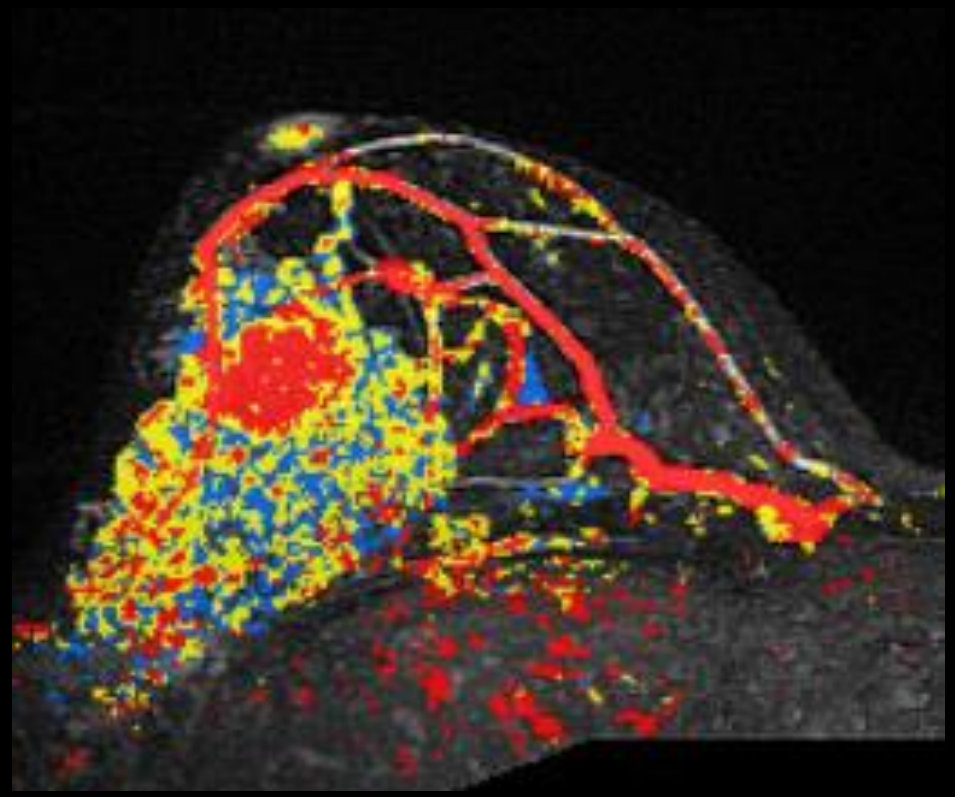
Breast carcinoma is a lobar disease in the meaning that the simultaneously or asynchronously appearing, often multiple, in situ and/or invasive tumor foci originate in a single lobe of one breast.
(The theory of the sick lobe)

- Tot T: Correlating the ground truth of mammographic histology with the success or failure of imaging. Technology In Cancer Research and Treatment, 4(1):23-8; 2005,
- Tot T: DCIS, cytokeratins and the theory of the sick lobe. Virchows Arch 447:1-8; 2005,
- Tot T: The theory of the sick lobe and the possible consequences. Int J Surg Pathol 15(4:) 369-75, 2007





Unifocal luminal B
invasive breast carcinoma
without diffuse lobar DCIS



Unifocal luminal B
invasive breast carcinoma
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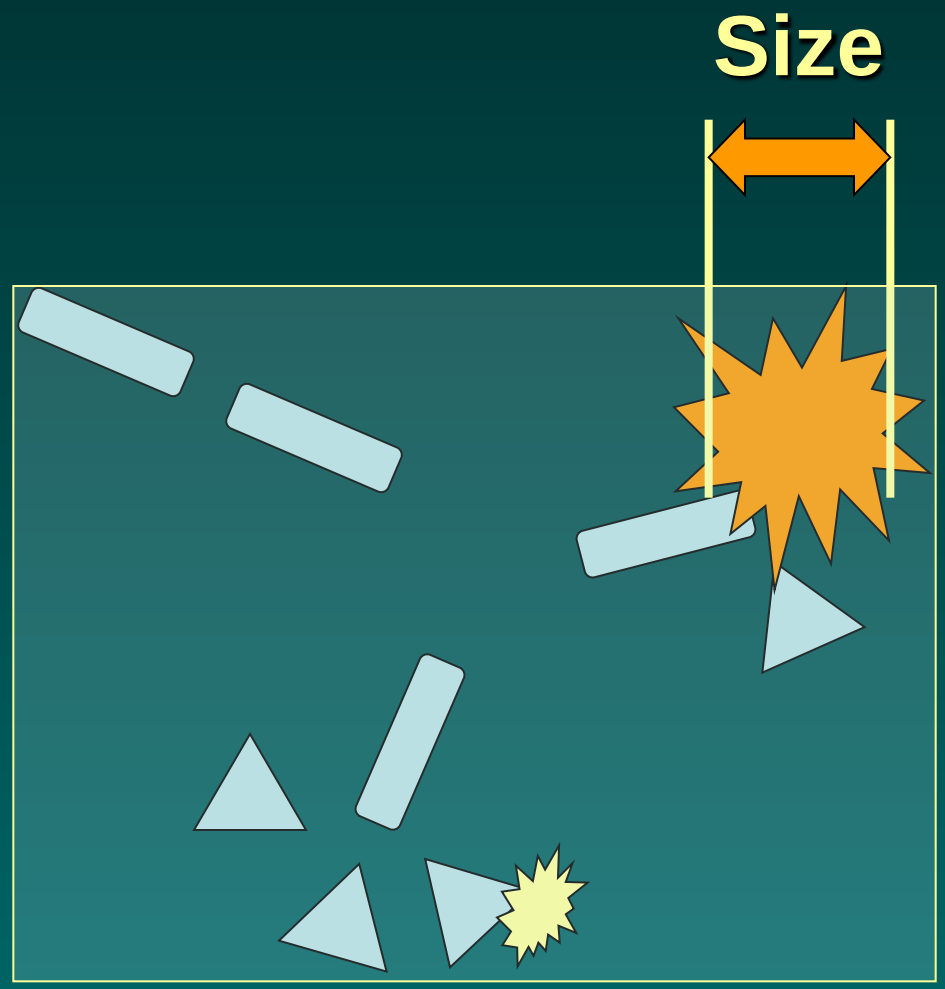
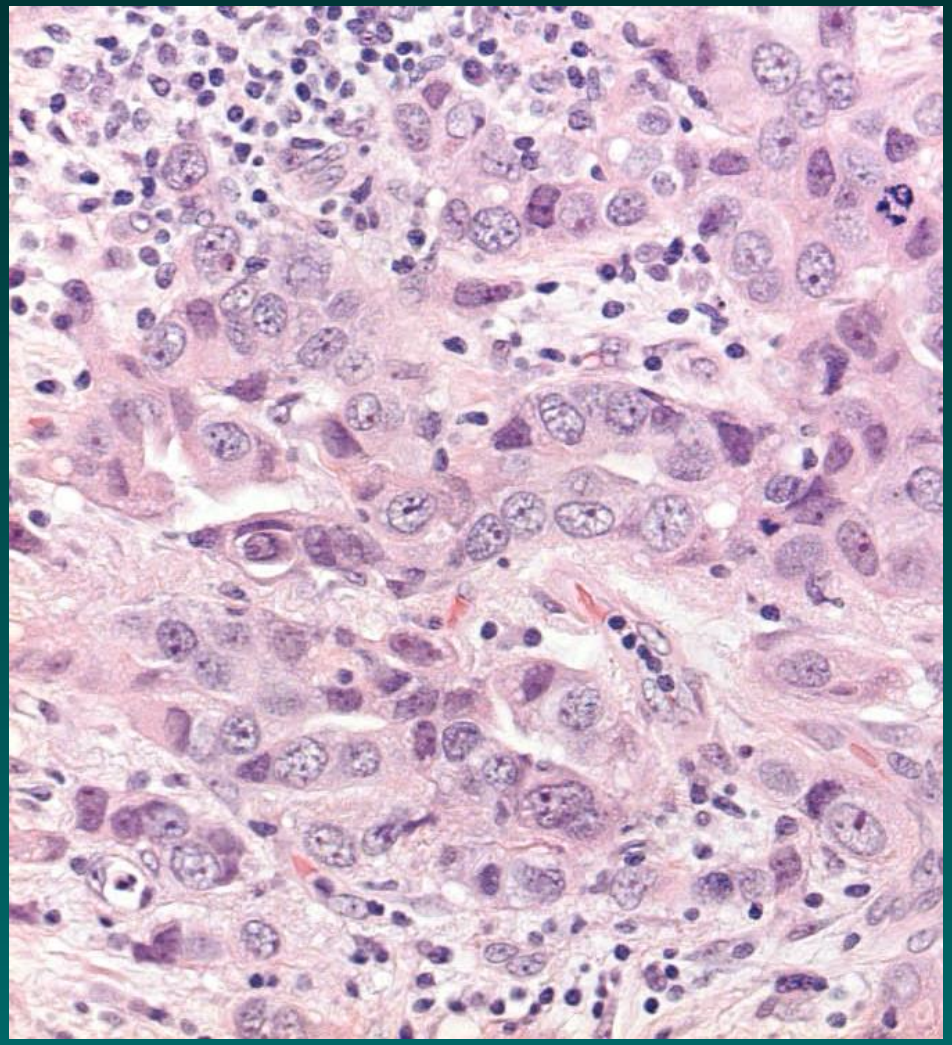
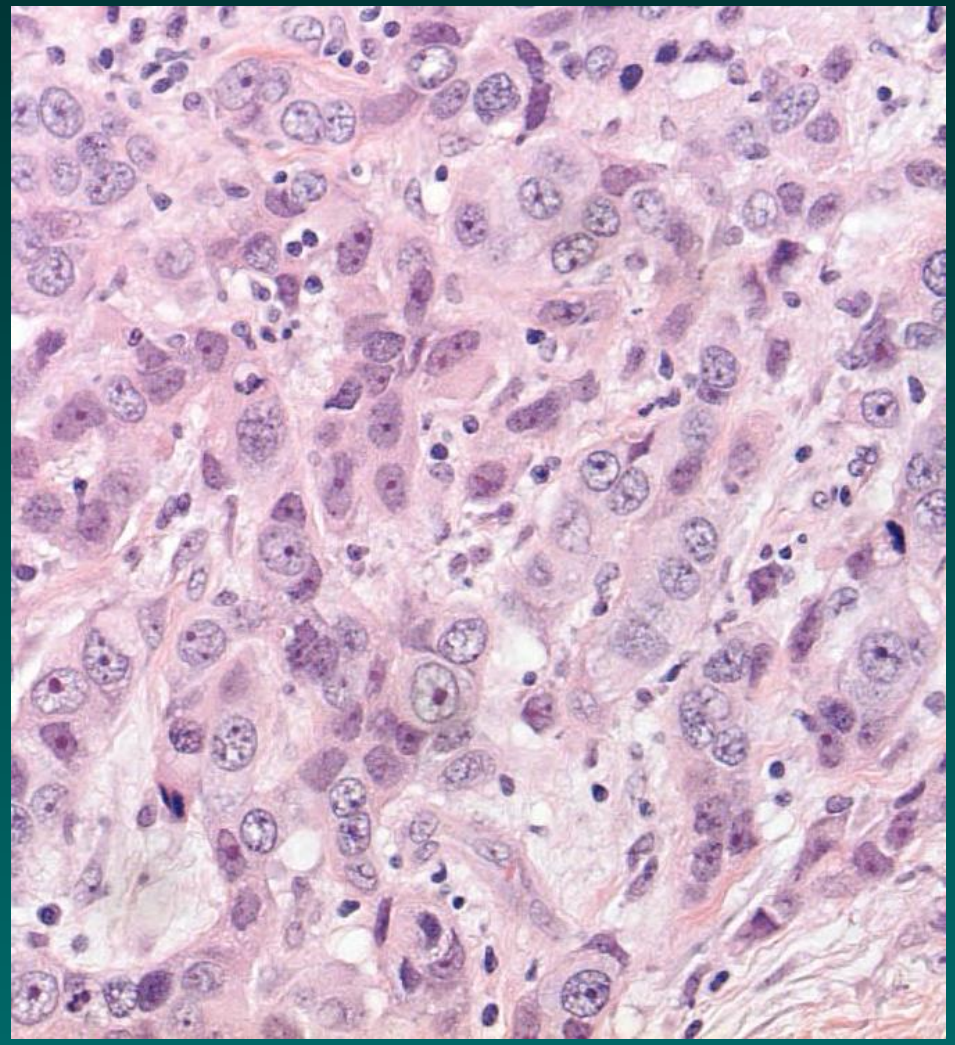

Size
E X T E N T

When describing malignant lesions in the breast, the following morphologic parameters should be listed (independent of the used imaging method):

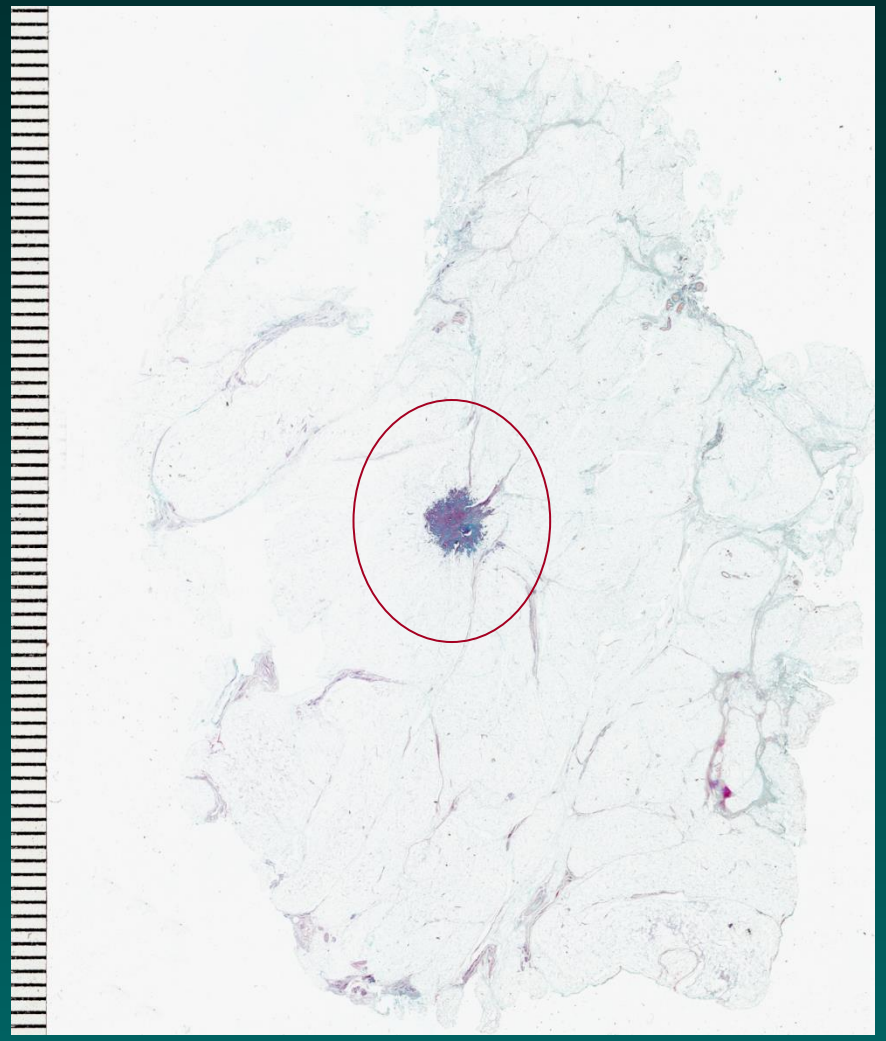
- **the distribution of the lesions (as unifocal, multifocal or diffuse) separately for invasive and in situ lesions,**
- **the extent of the disease (representing the whole area including all the invasive, in situ and intravascular malignant structures),**
- **the size of the tumor corresponding to the largest diameter of the lagest individual invasive tumor focus,**
- **evidence for intratumoral or intertumoral heterogeneity.**



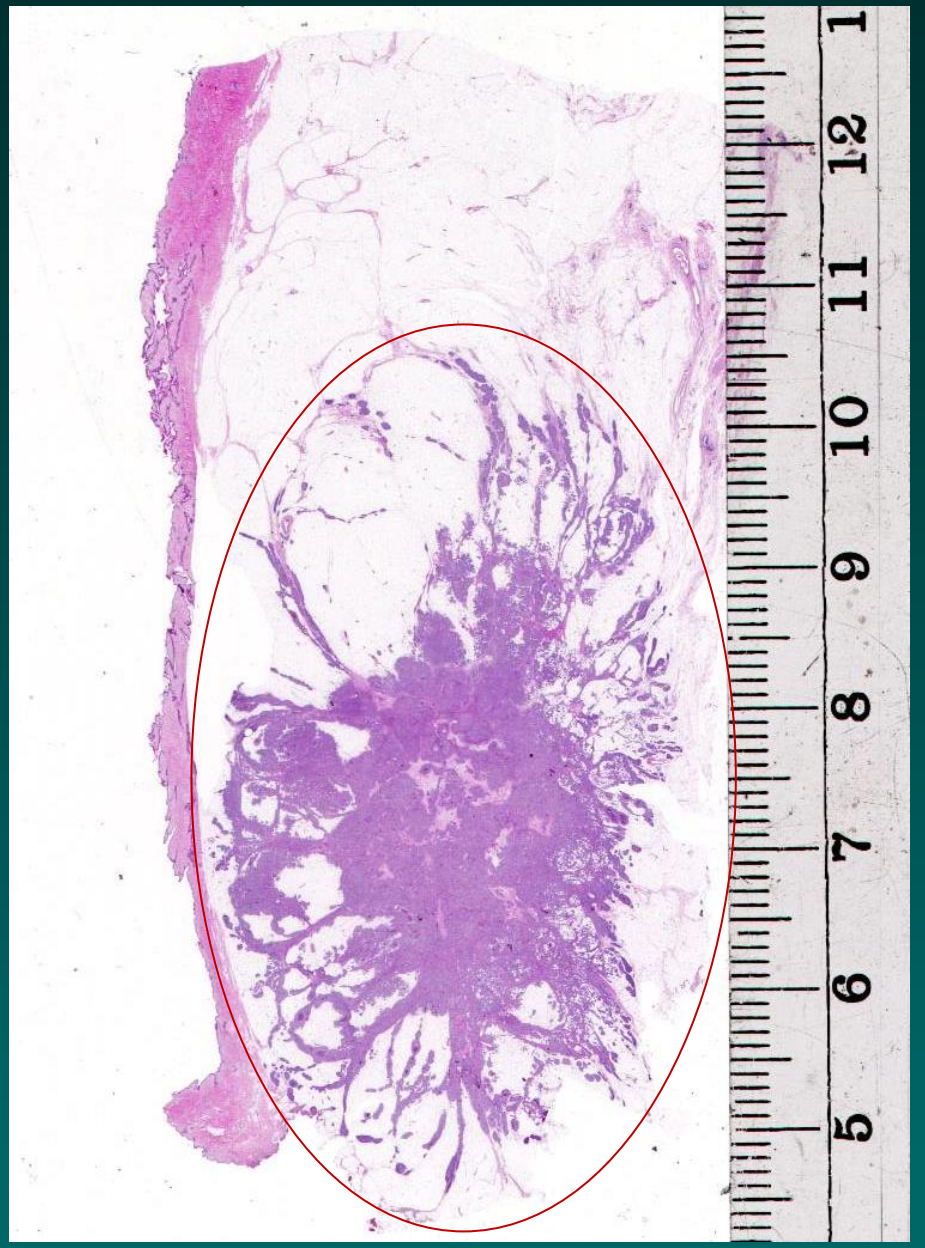
Invasive breast carcinoma NST



Invasive breast carcinoma NST

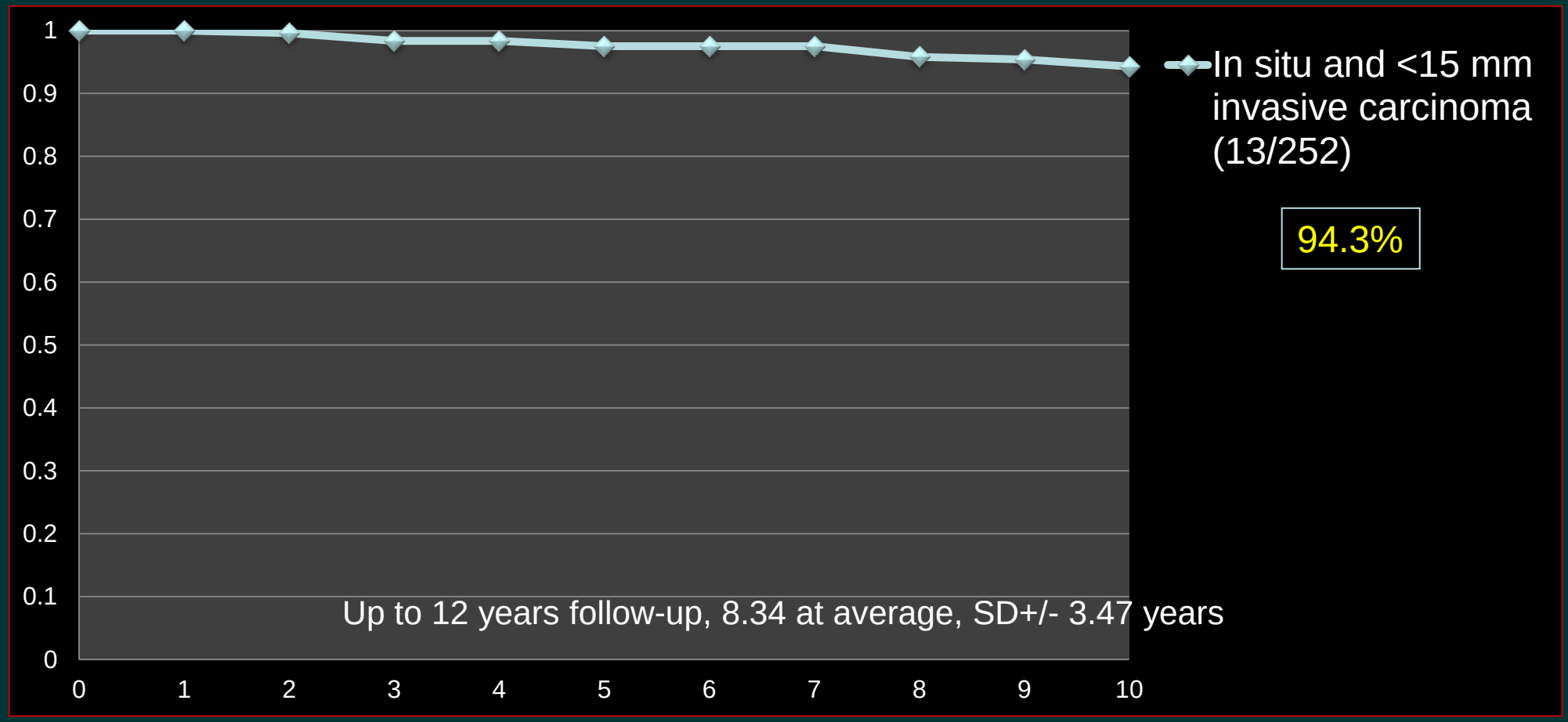


Early invasive breast carcinoma



Advanced invasive breast carcinoma

Cumulative survival in early (in situ and <15 mm invasive) breast carcinomas, Falun, 1996-1998



Kahán Z, Tot T. Breast Cancer, a Heterogeneous Disease Entity. The Very Early Stage, Springer 2011.

Life expectancy of screen-detected invasive breast cancer

- Age matched invited women with and without screen detected cancer (858)
- **6 year shorter survival in those with s.d.c.**
- **No difference in survival for those <15 mm comprising 40% of s.d.c.**
- **>=15 mm: 6 – 12 year shorter survival, depending on tumor size**

Otten JDM, Broeders MJM, Den Heeten GJ et al. Life expectancy of screen-detected invasive breast cancer patients compared with women invited to the Nijmegen Screening Program. Cancer 2010:116-586-91.

Carcinomas by detection mode and tumor size, Falun 1996-2003

	Screening	*Outside screening*	*Interval*	*Follow-up*	*Refusers*	*Sum*
In situ	**18%** (130)	**8%** (52)	**8%** (24)	**14%** (6)	**0%** (0)	**12%** (212)
1 – 9 mm	**26%** (203)	**8%** (51)	**14%** (42)	**35%** (15)	**14%** (2)	**18%** (313)
10 – 14 mm	**23%** (167)	**11%** (69)	**18%** (52)	**33%** (14)	**14%** (2)	**18%** (304)
15 – 19 mm	**16%** (123)	**17%** (106)	**18%** (55)	**2%** (1)	**14%** (2)	**17%** (287)
20-29 mm	**11%** (81)	**26%** (163)	**26%** (73)	**8%** (4)	**42%** (6)	**19%** (327)
30 + mm	**6%** (44)	**23%** (140)	**16%** (47)	**6%** (3)	**14%** (2)	**14%** (236)
Sum	**740 2unknown**	**620 41unknown**	**297 2unknown**	**43**	**14**	**1725 11unknown**

67%

50%

Screening + interval = 78%

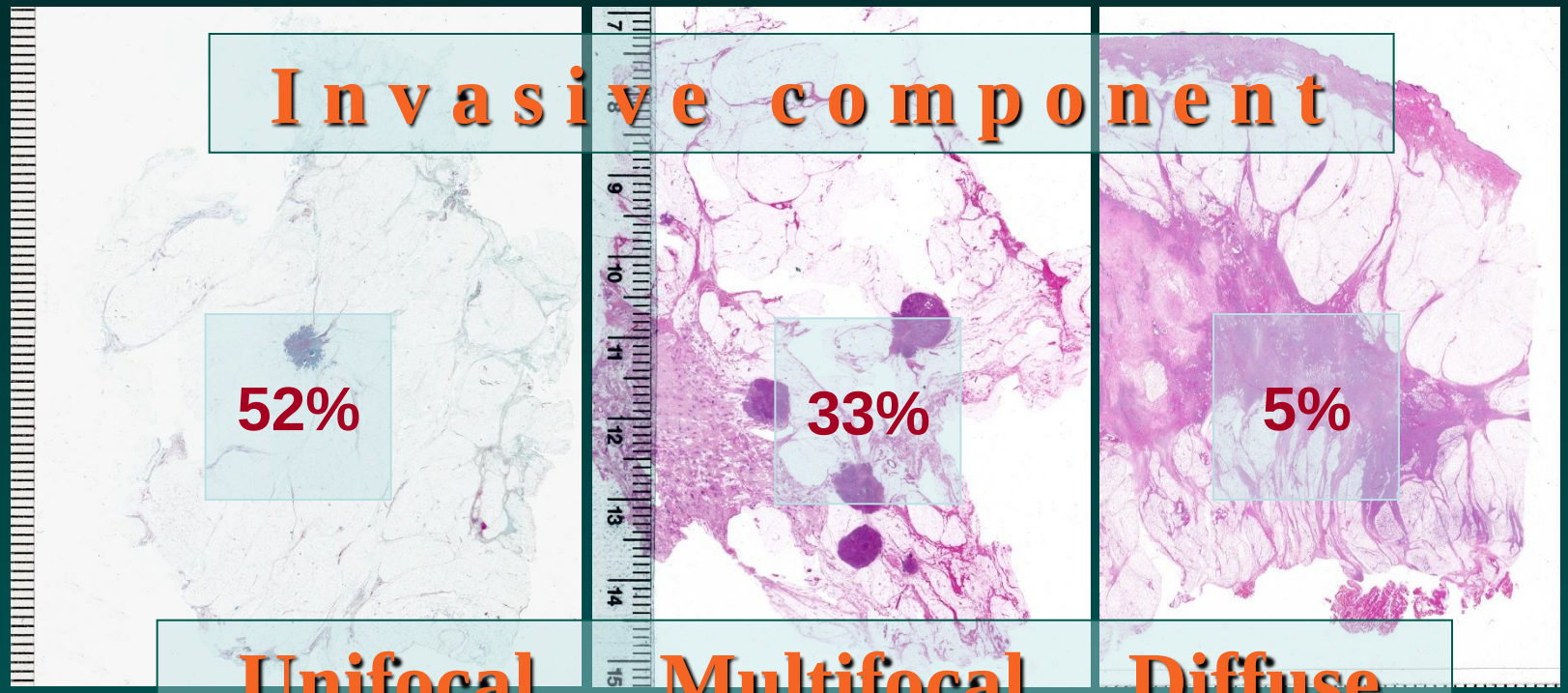
45 unknown size, 11 unknown detection mode

Molecular characteristics of early vs more advanced invasive breast carcinomas

	Early BC < 15 mm	Advanced BC >= 15 mm	Total	P-value
Basal-like	**5.9%** (12/203)	**15.1%** (48/317)	11.5% (60/520)	**= 0.0035**
ER negative*	**12.3%** (42/342)	**18.2%** (93/510)	15.8% (135/852)	= 0.0238
Tripple negative	**6.4%** (22/341)	**10.5%** (53/507)	8.8% (75/848)	= 0.0193
Her-2 positive	**8.9%** (31/347)	**13.3%** (68/511)	11.5% (99/858)	= 0.0917
Grade 3	**12.9%** (46/355)	**29,5%** (151/511)	22.0% (197/866)	**< 0.0005**
Total	41.5% (362/873)	58,5% (511/873)	100% (873/873)	

Kahán Zs., Tot T., eds. Breast Cancer, a Heterogeneous Disease Entity: The Very Early Stage. Springer 2011

Invasive component



52%

33%

5%

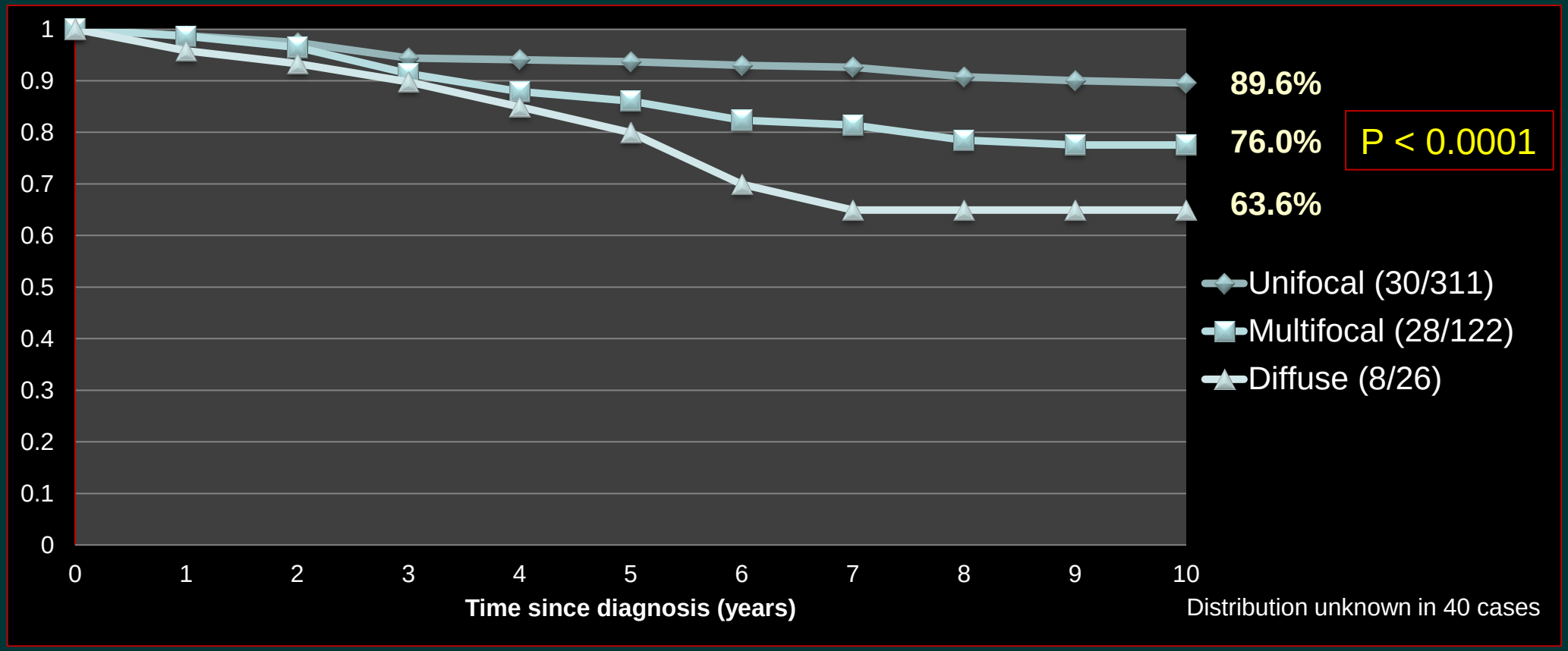
10%

Unifocal

Multifocal

Diffuse

Cumulative survival in 499 invasive breast carcinoma cases by distribution of the invasive component, Falun, 1996-1998



Tot et al. Breast cancer multifocality, disease extent, and survival. Hum Path 2011

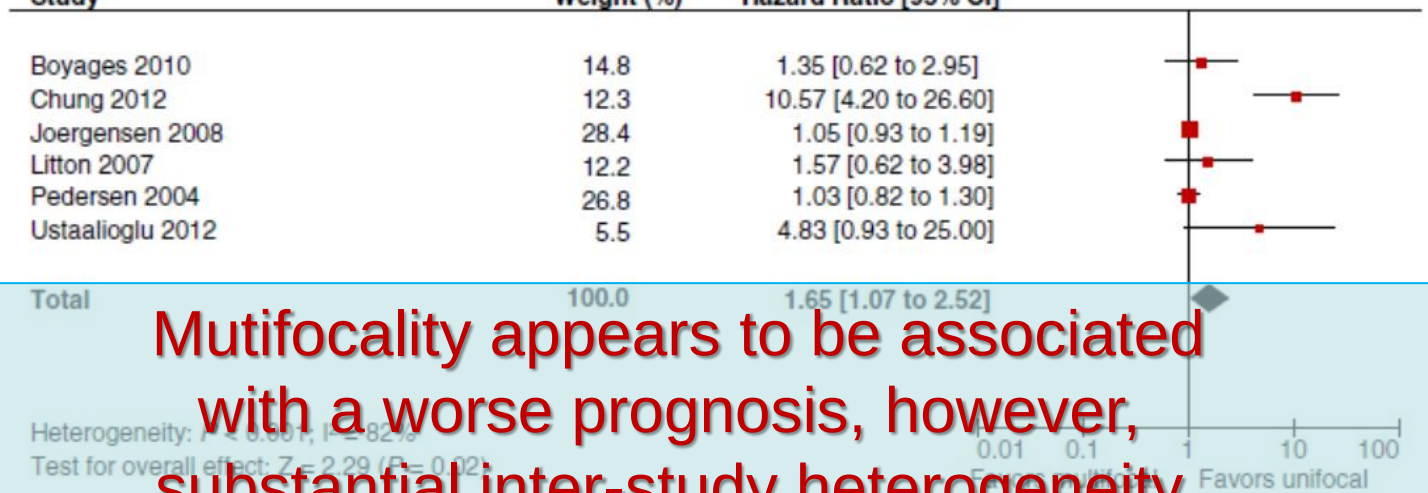
Alice P Chung, Kelly Huynh, Travis Kidner, Parisa Mirzadehgan, Myung-Shin Sim, Armando E Giuliano. **Comparison of Outcomes of Breast Conserving Therapy in Multifocal and Unifocal Invasive Breast Cancer**
(J Am Coll Surg 2012;215: 137–147. © 2012 by the American College of Surgeons)

164 MF tumors (”2 or more distinct tumors in a single incision or segmentectomy”)
Only breast conserving surgery. Median follow-up 112 months.

Results: patients in the MF group had

higher **10-year LR (0.6% vs 6.1%, p<0.001**)
and lower **10-year DFS (97.7% vs 89.3%, p<0.001)**
and **OS (98.4% vs 85.8%, p<0.001).**

On multivariable analysis, multifocality was independently significantly associated with local recurrence-free survival (LRFS), DFS, and OS.



Mutifocality appears to be associated with a worse prognosis, however, substantial inter-study heterogeneity limits the precise determination of increased risk.

Fig. 2 Forrest plot showing the association between multifocality and overall survival

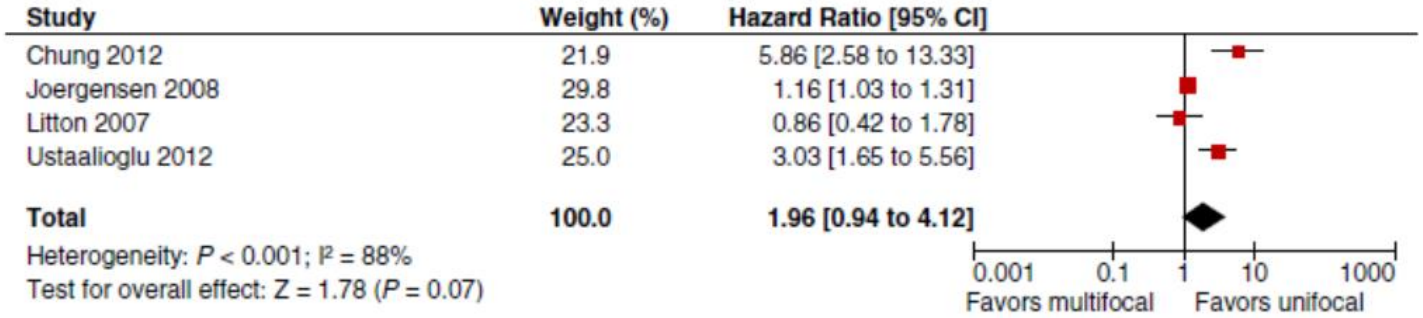


Fig. 3 Forrest plot showing the association between multifocality and disease-free survival

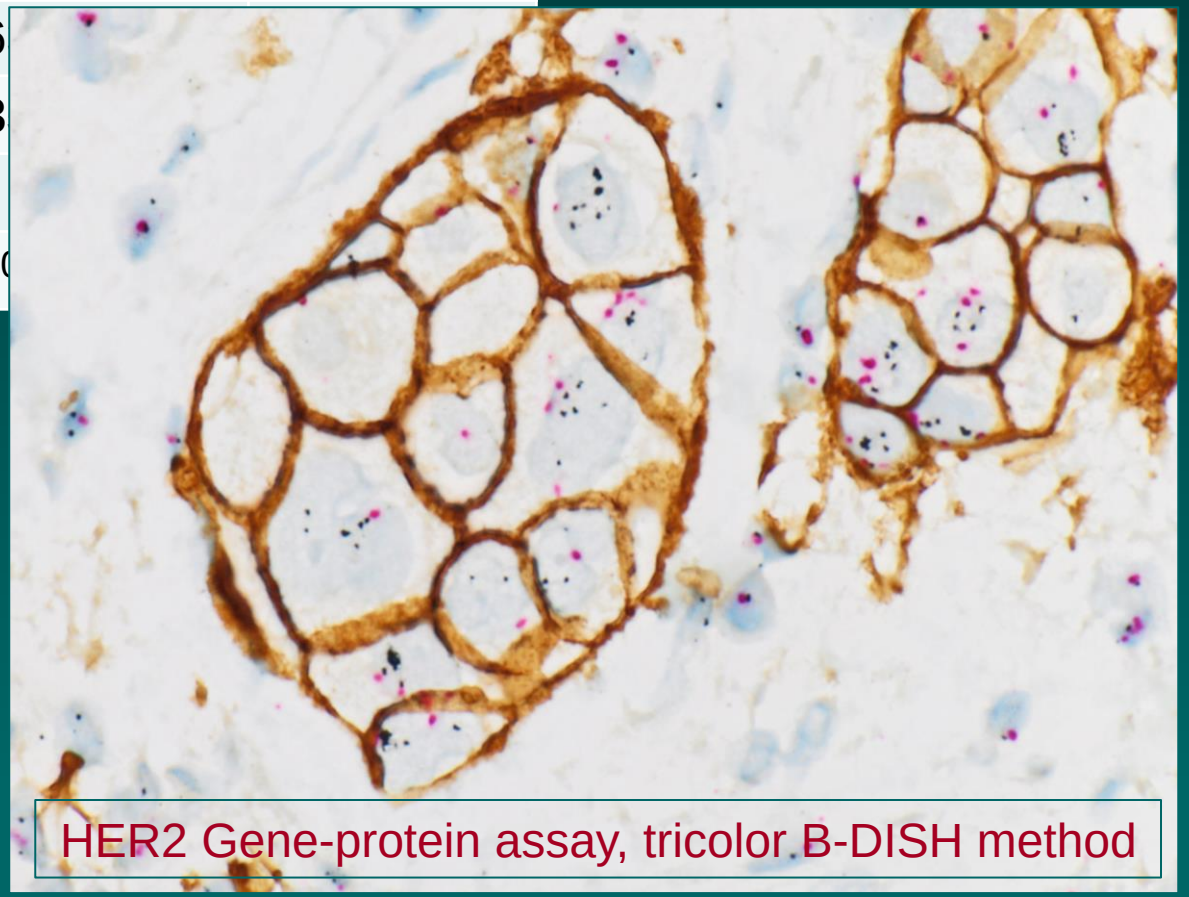
Francisco E et al. Effect of multifocality and multicentricity on outcome in early stage breast cancer: a systematic review and meta-analysis. Breast Cancer Res treat 2014

Invasive tumor focality by St Gallen 2013 molecular phenotypes, Dalarna County, 2008-13

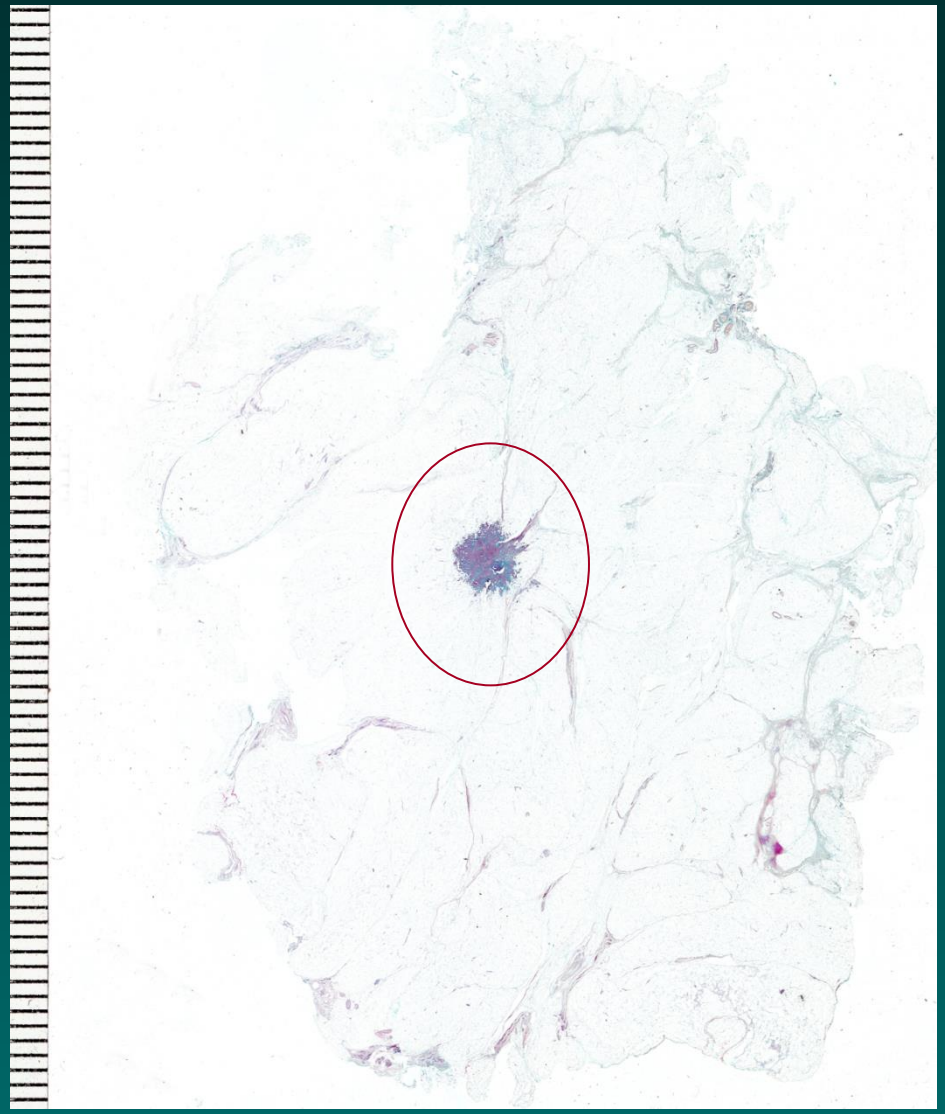
Tot T. Breast Cancer Subgross MorphologicalParameters and Their Relation to Molecular Phenotypes and Prognosis. TJOP 2014;00:1–8
DOI: 10.13032/tjop.2052-5931.100106.

	LA	LB	HER2	TN	Total
U	64.5% (267)	56.6% (294)	43.8% (14)	6	
MF	**30.4%** (126)	**36.3%** (189)	**56.2%** (18)	**3**	
D	5.1% (21)	7.1% (37)	0		
Total	100% (414)	100% (520)	100% (32)	1(	

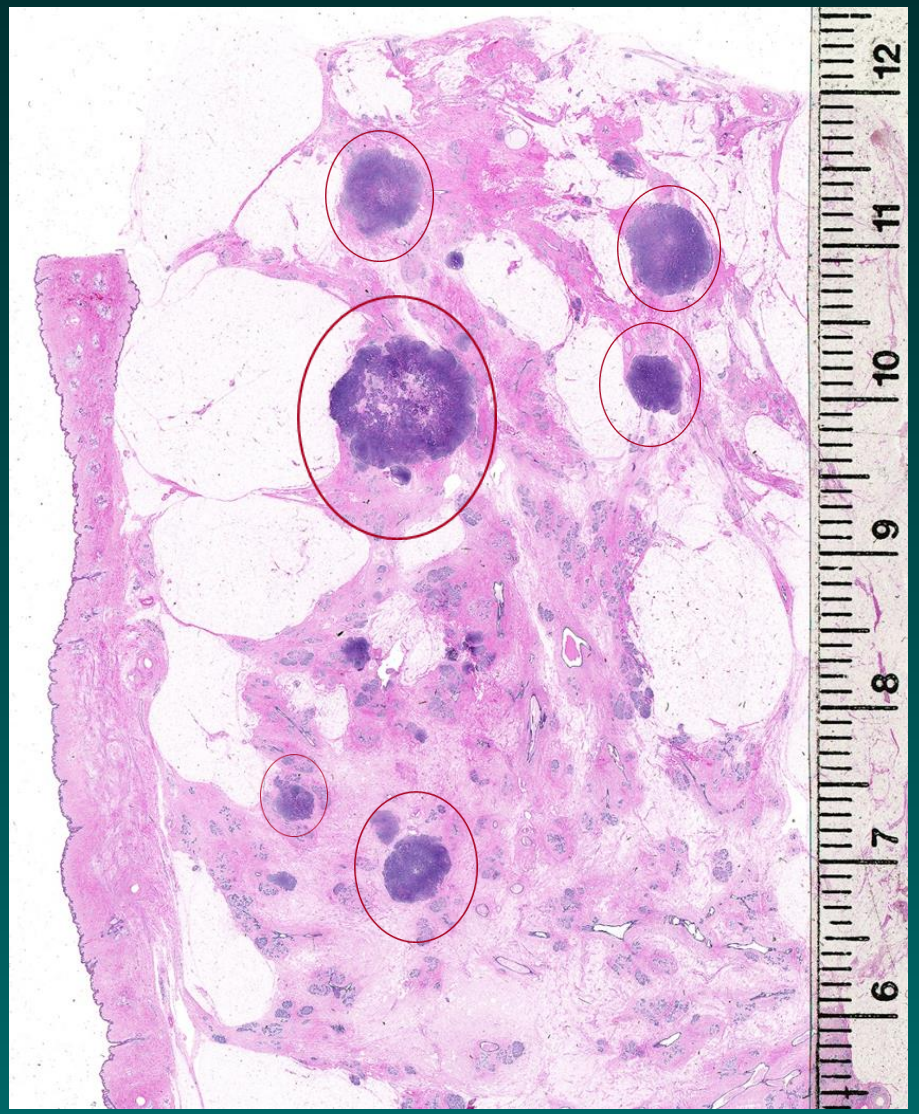
	LB HER2 -	LB HER2+	HER2
U	56.6% (249/440)	56.2% (45/80)	43.8% (14/32)
MF	**35.9%** (158/440)	**38.9%** (31/80)	**56.2%** (18/32)
D	7.5% (33/440)	5.0% (4/80)	0
Total	100% (440/440)	100% (80/80)	100% (32/32)



HER2 Gene-protein assay, tricolor B-DISH method

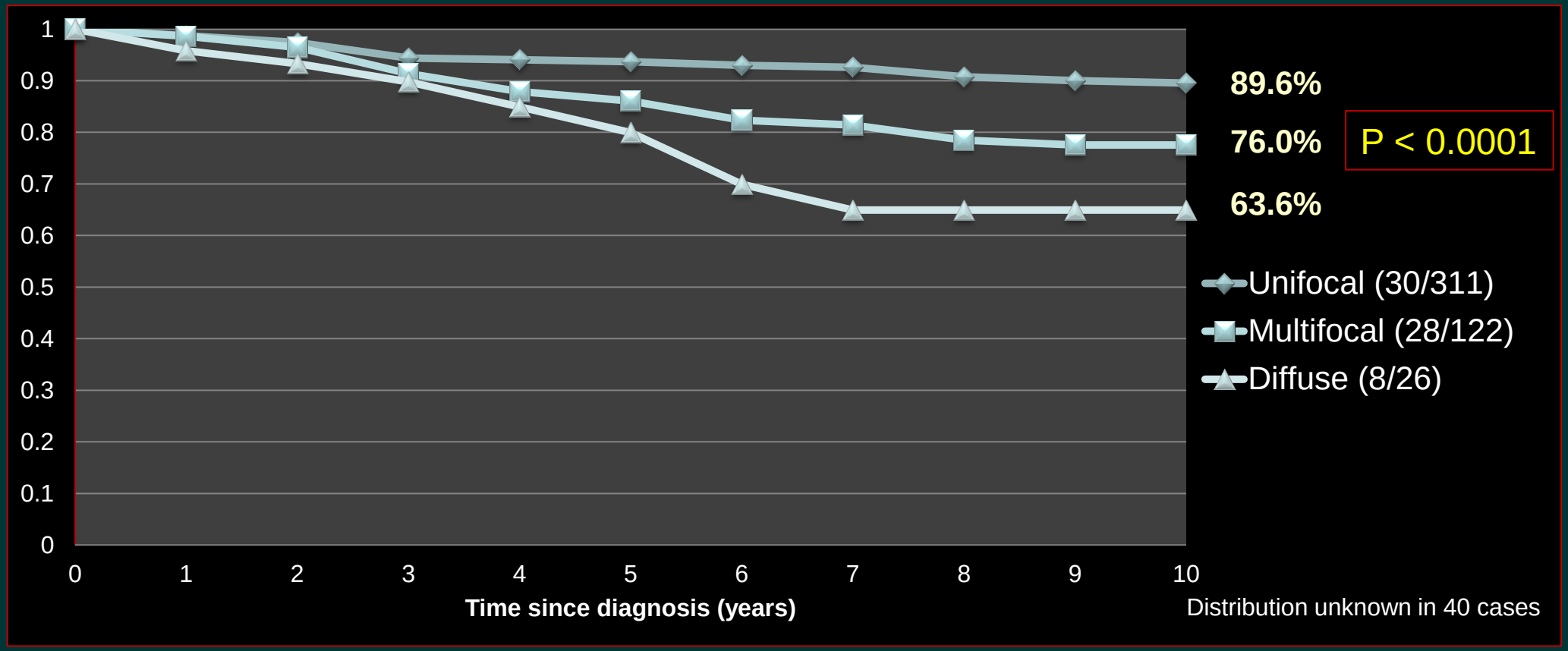


Unifocal invasive breast carcinoma



Multifocal invasive breast carcinoma

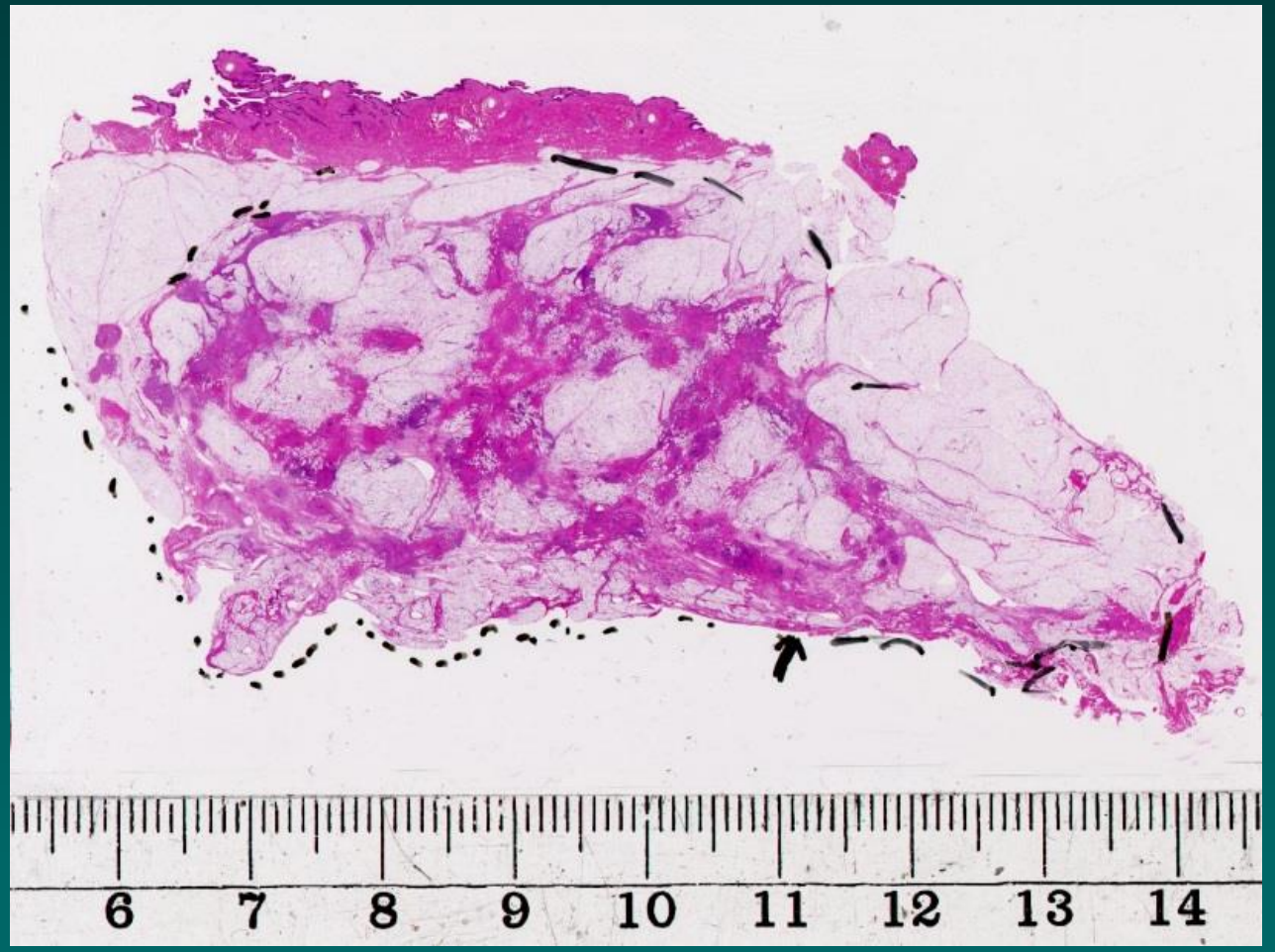
Cumulative survival in 499 invasive breast carcinoma cases by distribution of the invasive component, Falun, 1996-1998



Tot et al. Breast cancer multifocality, disease extent, and survival. Hum Path 2011

Diffuse invasive cancer

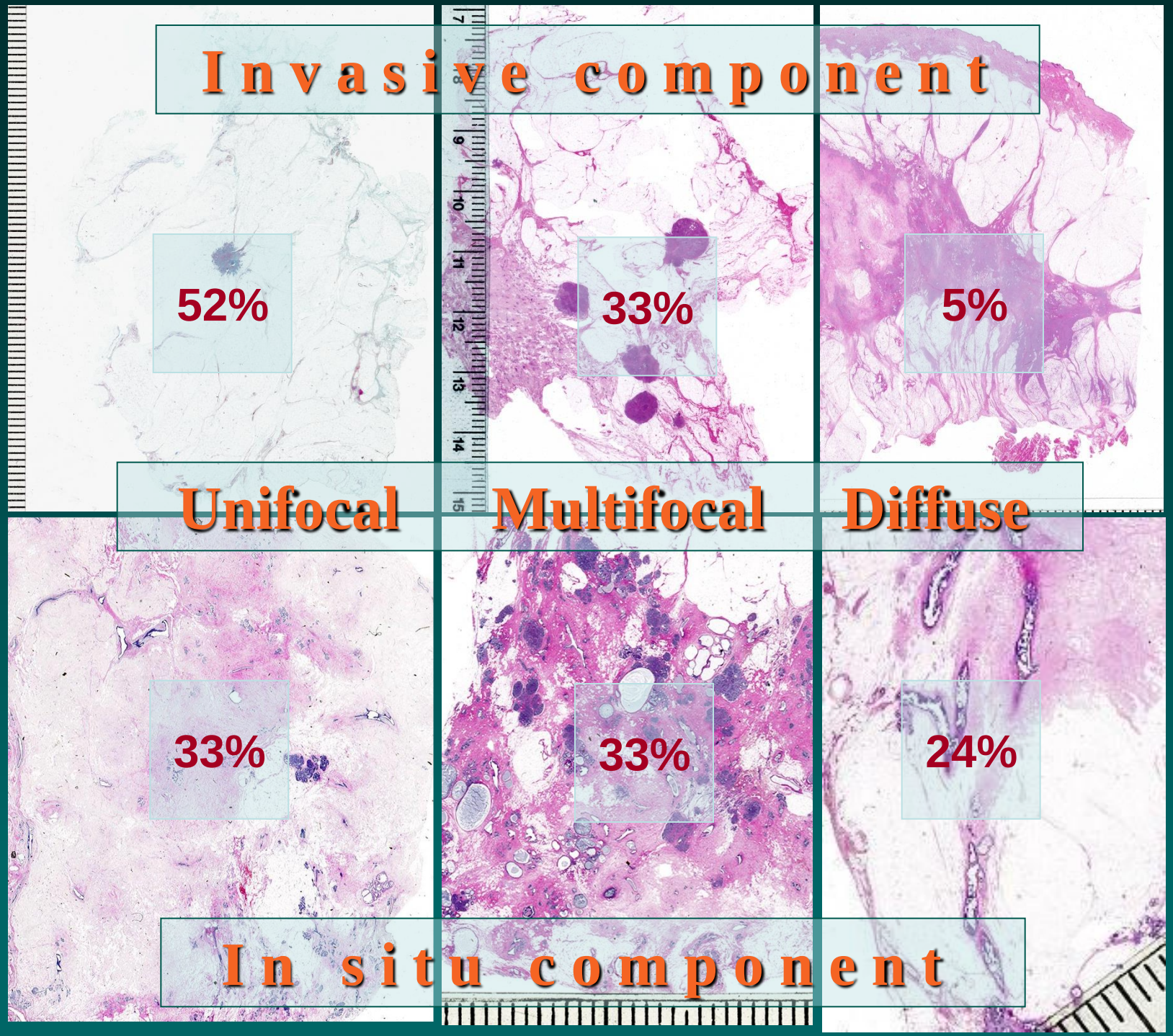
- **5%** of all BCs (5.6%, 59/1059 cases),
- **75%** gives clinical signs,
- **55%** are **architectural distortion on the mammogram** (55.9% 33/59 cases)

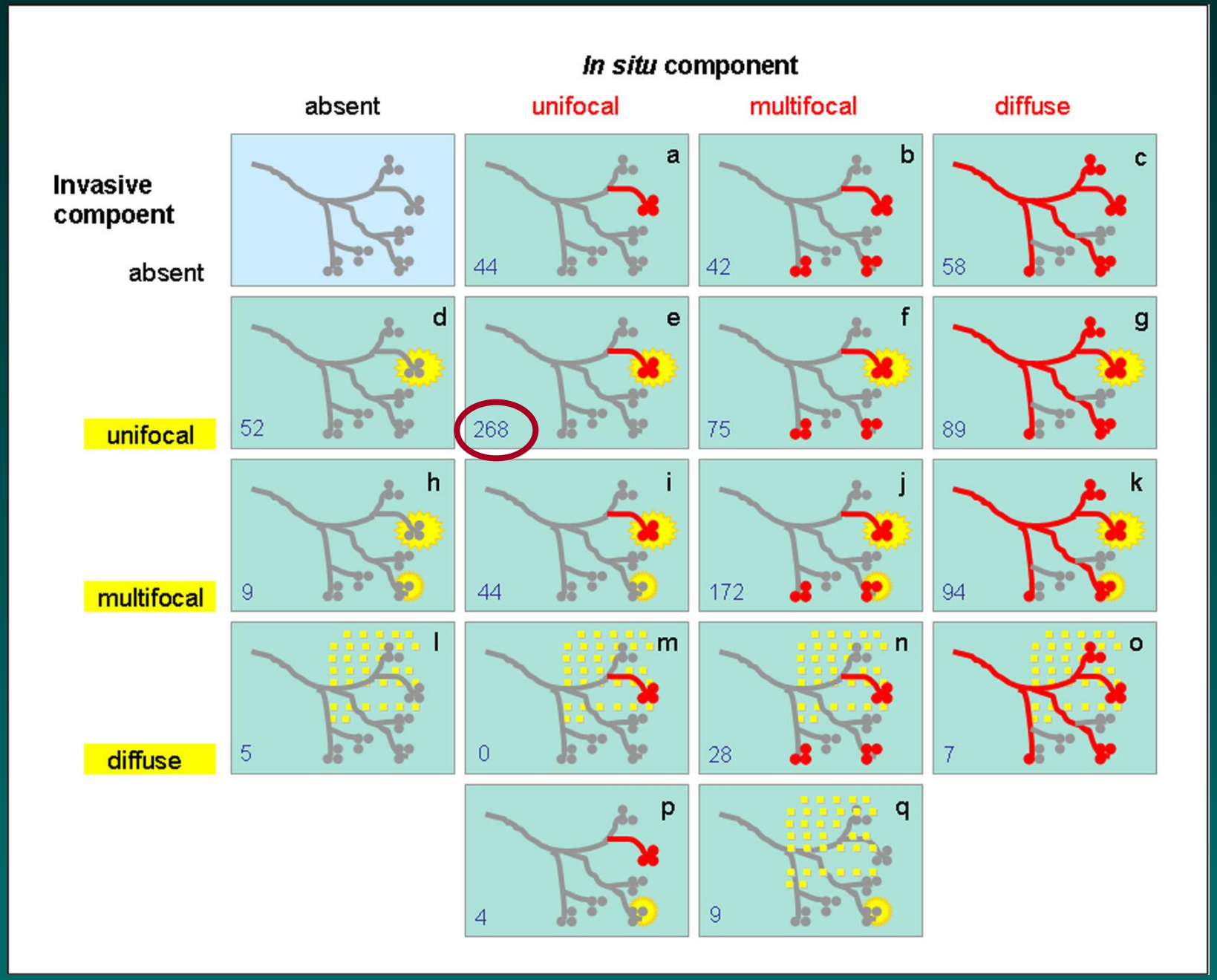


Diffuse invasive carcinomas

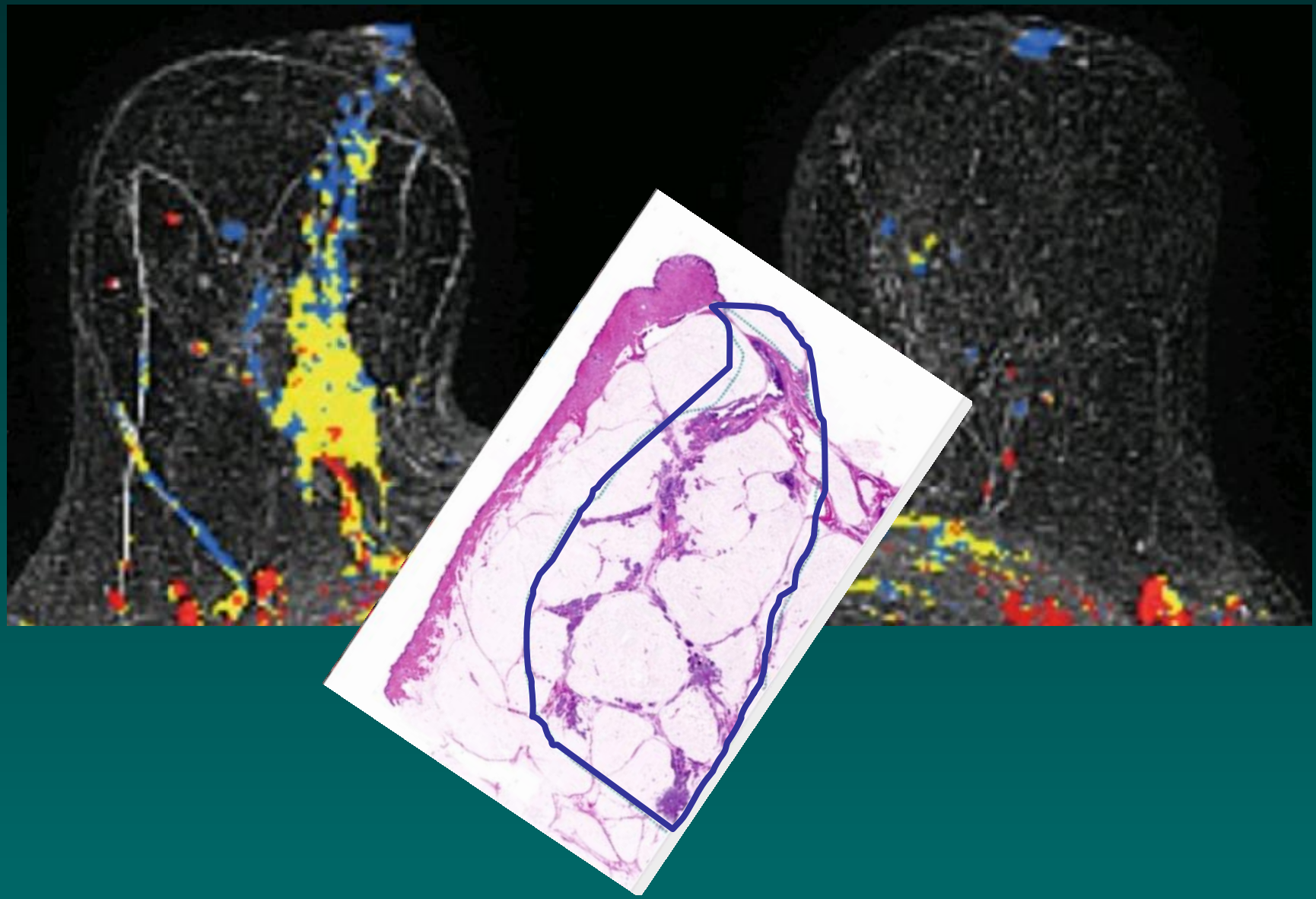
- **75% are lobular,**
- **98% are ER positive,**
- **Rarely HER2 positive** (6.7%, 4/59)
- 90% are grade 2, **10% grade 3**

- 25% of the patients with diffuse lobular cancer and 50% of those with diffus ductal cancer died of the disease (series 1996-98).


Invasive component
52%
33%
5%
10%
Unifocal
Multifocal
Diffuse
33%
33%
24%
10%
In situ component

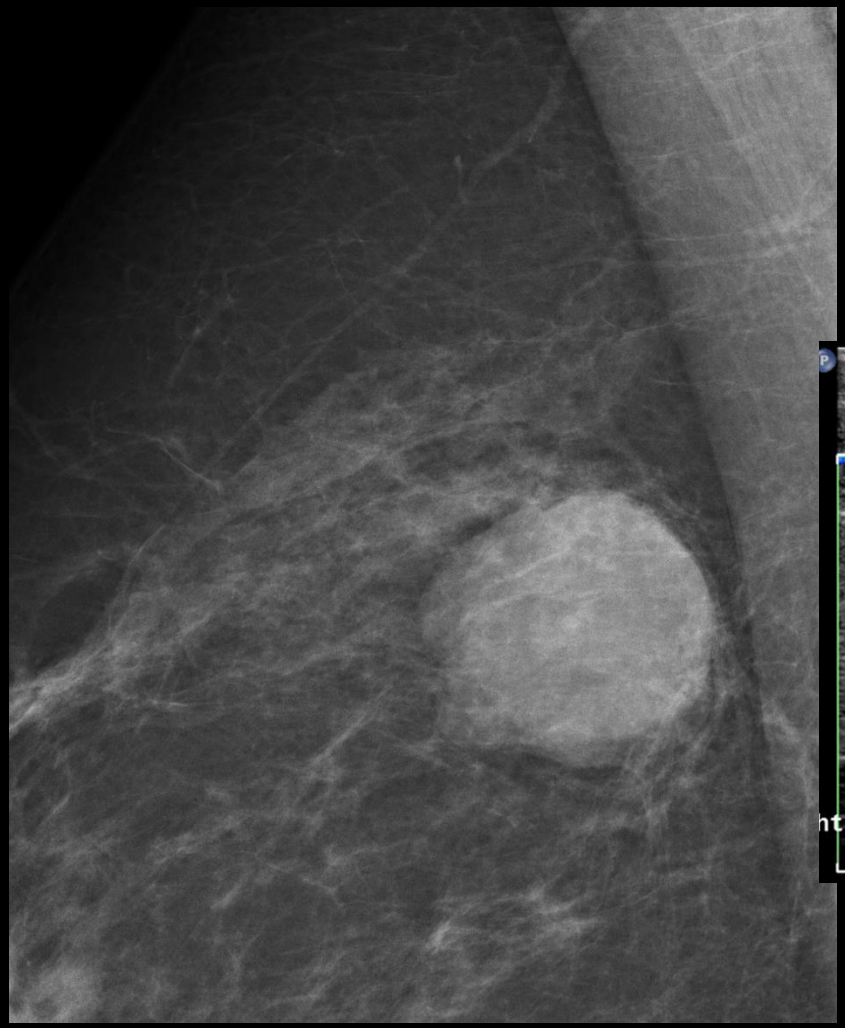


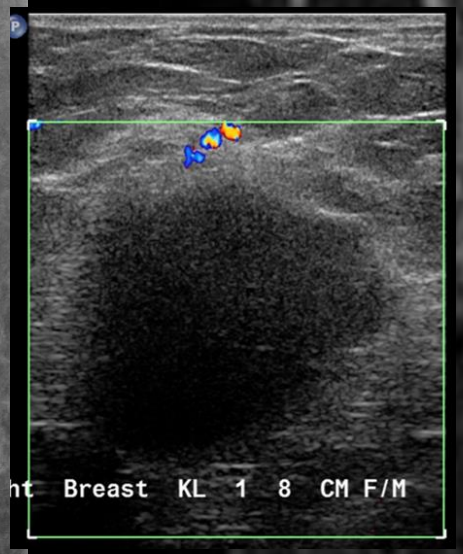
Tot T, Int J Breast Cancer, 2012

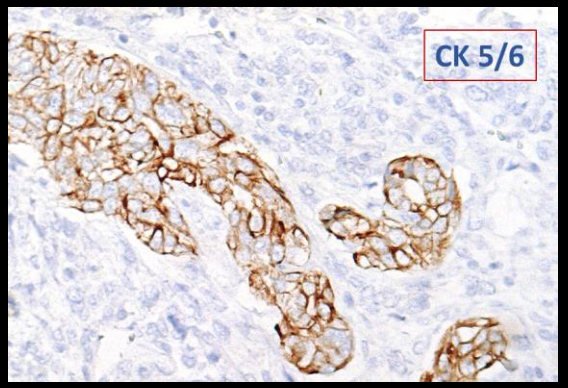


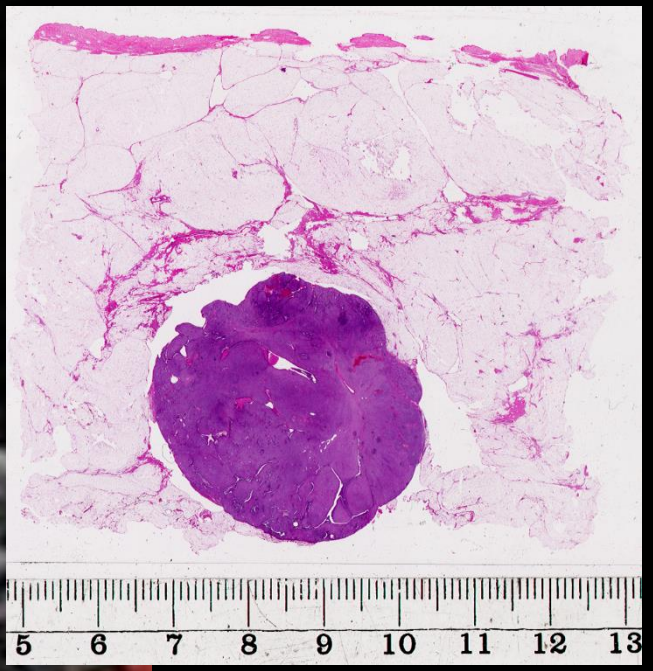
Diffuse *in situ* cancer

- **24% of all cancers**
- Large (**extensive**), > 40 mm
- **High grade**
- Occypying the large ducts
- A single lactiferous duct
- **Lobar**
- Contiguous









Mammographic – ultrasound – MRI – large-section correlation: basal – like cancer of the breast

Mammographic appearance	Basal phenotype	Histological lesion distribution	Tumor size	10-year risk of BC death
Architectural distortion 4.8% (62/1280)	+/-	**Diffuse invasive**		**42.3%**
Casting calcifications 6.1% (78/1280)	+/-	**Diffuse aggregate**		**27.7%**
Circular mass 30.9% (396/1280)	**Basal like** (22%)	**Multifocal** (36.0%)		**15.6%**
		Unifocal (64.0%)	**15 mm+** (83%)	**22.7%**
			<15 mm (17%)	**1.9%**
	Non-basal like (78%)	**Multifocal** (31.1%)		**19.1%**
		Unifocal (68.9%)	**15 mm+** (56.5%)	**5.2%**
			<15 mm (43.6%)	**1.9%**
Stellate mass 45.6% (583/1280)	+/-	**Multifocal** (34.5%)		**14.3%**
	+/-	**Unifocal** (65.5%)		**9.6%**
Powdery calcifications 2.1% (27/1280)				**5.9%**
Crushed stone like calcifications 10.5% (134/1280)				**3.9%**

Abstract P4-03-07: RA Smith, WY-Y Wu, L Tabar, SL-S Chen, AM-F Yen, SW Duffy, T Tot, SY-H Chiu, JC-Y Fann, TH-H Chen.
The contribution of mammographic appearance, basal-like phenotype, and disease extent to prediction of breast cancer death .
Cancer Research 12/2013; 73(24 Supplement):P4-03-07-P4-03-07. DOI:10.1158/0008-5472

Breast cancer pathology - a manifesto for optimal care

The 10 essential / obligatory parameters

- **Tumour type** (according to the actual WHO classification)
- **Tumour size / disease extent**
- **Tumour grade** (Nottingham histology grade by Elston and Ellis)
- **Lymph node status**
- **Operative margins**
- **Peritumoral vascular invasion**
- **Multifocality/centricity**
- **Hormone receptor status** (ER/PR)
- **HER2 status**
- **Ki67 labelling index**

In addition, these services are likely to be needed in future:

- **Gene profiling**
- **Biobanking**

T. Tot; G. Viale; E. Rutgers; E. Bergsten-Nordström; A. Costa
Optimal breast cancer pathology manifesto. EJC, in press

Conclusion:

Molecular classification of breast cancer is a powerful tool but gains in power when combined with conventional subgross morphological parameters.