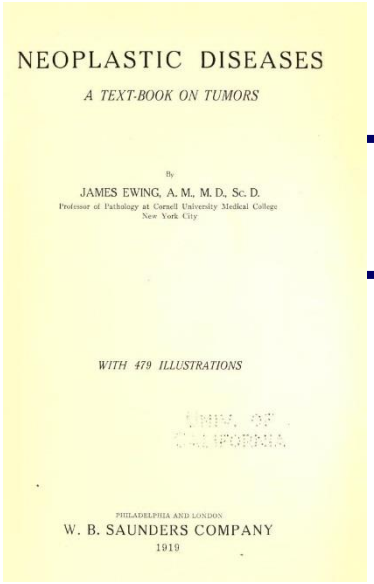
Histopatologi og molekylære subtyper

Anne-Vibeke Lænkholm

1977
40
2017
DBCG

16th ACTA ONCOLOGICA SYMPOSIUM

Klassifikation af brystkræfttumorer


NEOPLASTIC DISEASES

A TEXT-BOOK ON TUMORS

By

JAMES EWING, A. M., M. D., Sc. D.

Professor of Pathology at Cornell University Medical College
New York City

WITH 479 ILLUSTRATIONS

PHILADELPHIA AND LONDON
W. B. SAUNDERS COMPANY
1919

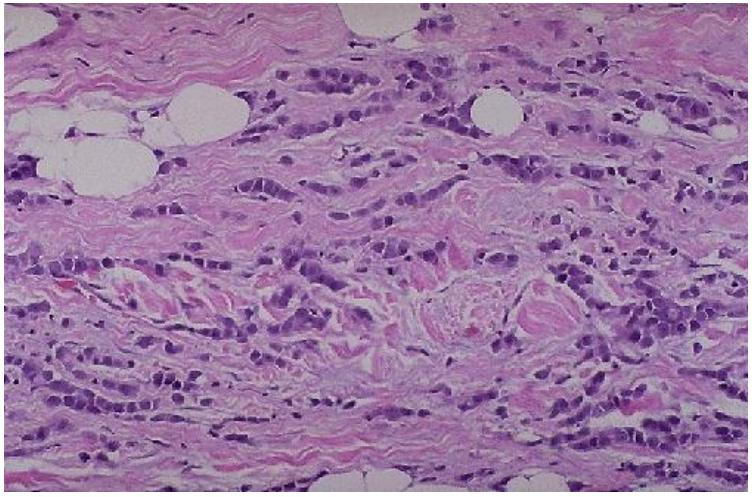
Haagensen C.D.
1933

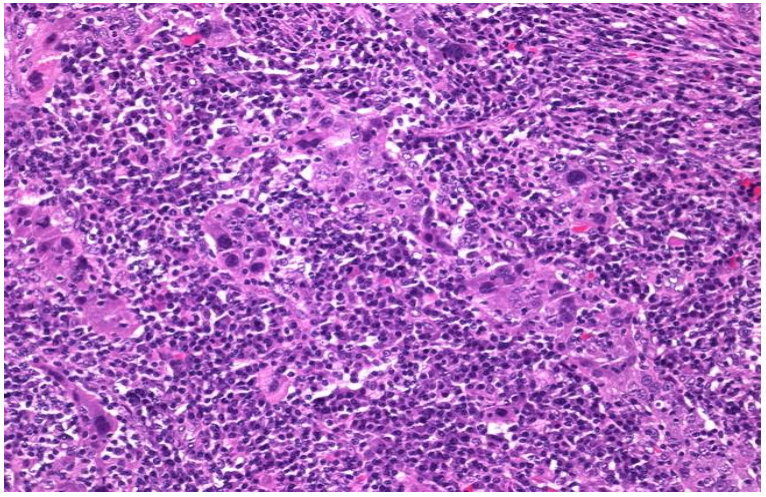
Stewart F. W.
1950

Hultborn A. and
Tornberg B. 1960

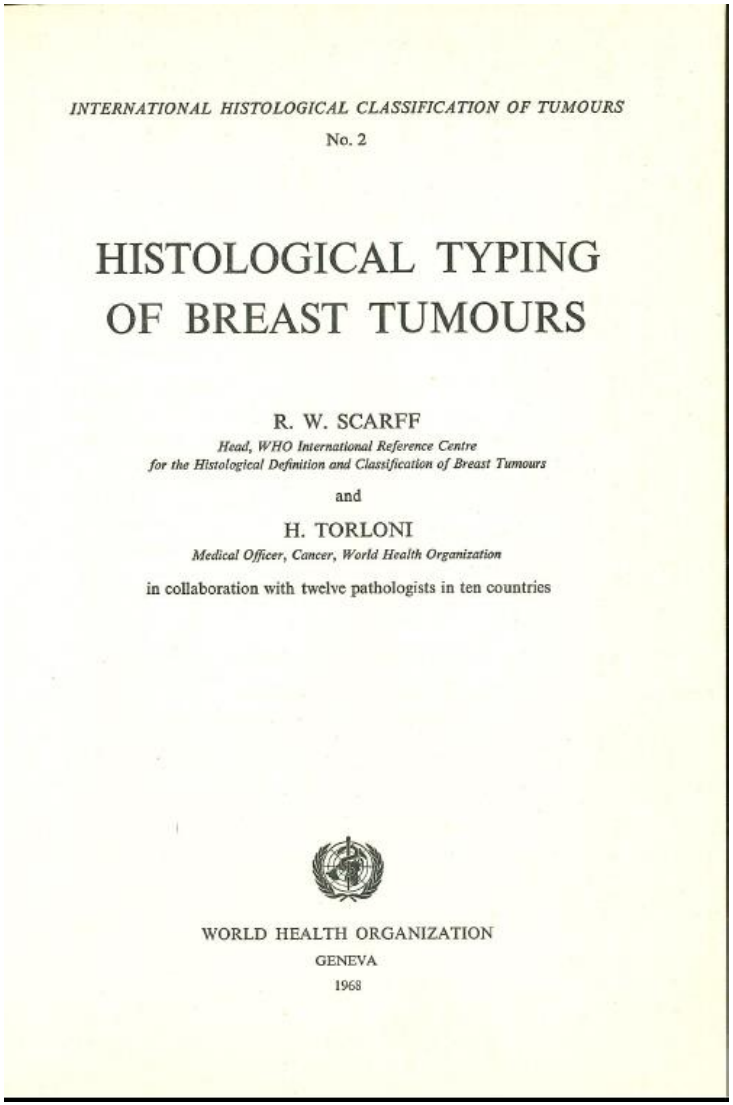
1941-43
Fred W Stewart og Frank W. Foote
Karakteristik af invasivt lobulært karcinom og lobulært karcinom in situ

1949 Cancer
Oliver S. Moore and Frank W. Foote
"The relatively favorable prognosis of medullary carcinoma of the breast"





Tumorklassifikation



INTERNATIONAL HISTOLOGICAL CLASSIFICATION OF TUMOURS

No. 2

HISTOLOGICAL TYPING OF BREAST TUMOURS

R. W. SCARFF
Head, WHO International Reference Centre for the Histological Definition and Classification of Breast Tumours

and

H. TORLONI
Medical Officer, Cancer, World Health Organization

in collaboration with twelve pathologists in ten countries

WORLD HEALTH ORGANIZATION
GENEVA
1968

HISTOLOGICAL TYPING OF PROLIFERATIVE CONDITIONS AND TUMOURS OF THE BREAS

A. BENIGN MAMMARY DYSPLASIAS

- I. Cyst
  - a. simple cyst
  - b. papillary cyst
- II. Adenosis
- III. Regular typical epithelial proliferation in ducts or lobules
- IV. Duct ectasia
- V. Fibrosclerosis
- VI. Gynaecomastia
- VII. Other non-neoplastic proliferative lesions

B. BENIGN OR APPARENTLY BENIGN TUMOURS

- I. Adenoma of breast
- II. Adenoma of nipple
- III. Duct papilloma
- IV. Fibroadenoma
  - a. pericanalicular fibroadenoma
  - b. intracanalicular fibroadenoma
    - 1. simple type
    - 2. cellular intracanalicular fibroadenoma
- V. Benign soft tissue tumours

C. CARCINOMA

- I. Intraduct and intralobular non-infiltrating carcinoma
- II. Infiltrating carcinoma

— 13 —

- III. Special histological variants of carcinoma
  - a. medullary carcinoma
  - b. papillary carcinoma
  - c. cribriform carcinoma
  - d. mucous carcinoma
  - e. lobular carcinoma
  - f. squamous cell carcinoma
  - g. Paget's disease of breast
  - h. carcinoma arising in B.IV.b.2 (cellular intracanalicular fibroadenoma)

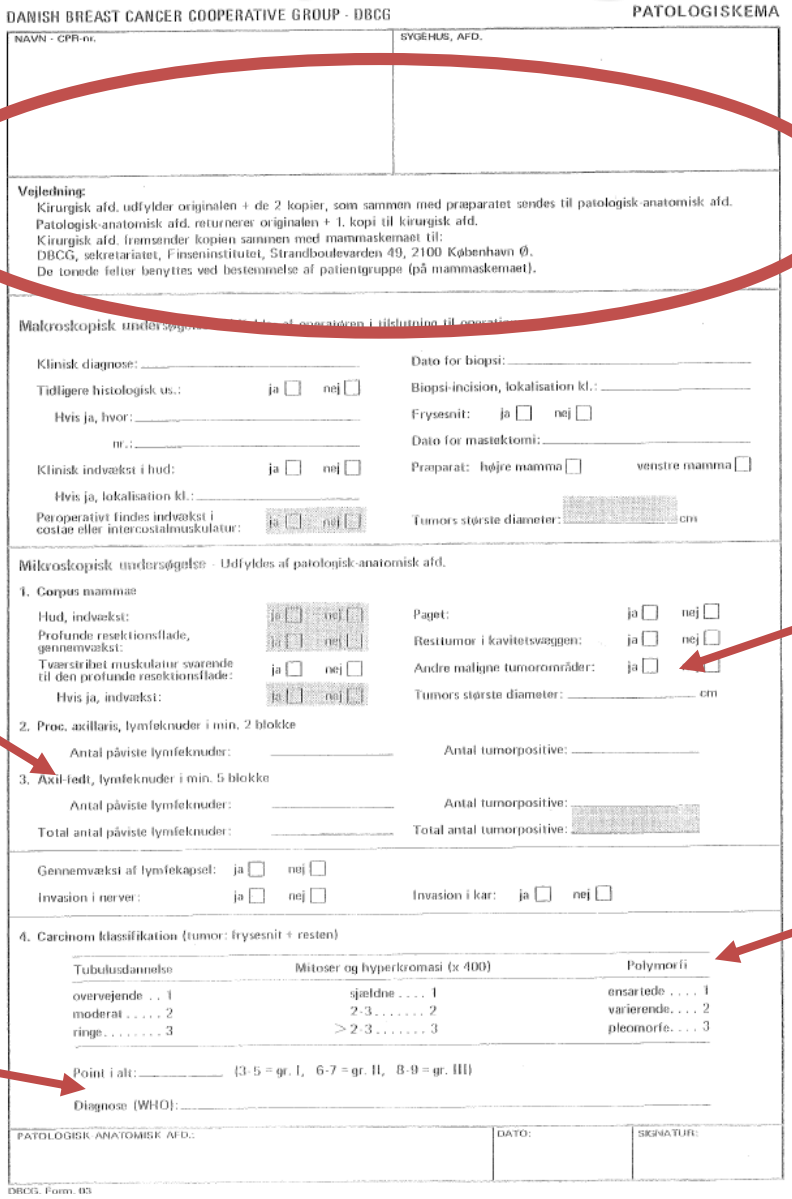
D. SARCOMA

- I. Sarcoma originating in B.IV.b.2 (cellular intracanalicular fibroadenoma)
- II. Other types of sarcoma

E. CARCINOSARCOMA

F. UNCLASSIFIED TUMOURS

DBCG77 patologiskema



DANISH BREAST CANCER COOPERATIVE GROUP - DBCG

PATOLOGISKEMA

NAVN - CPR-nr.

SYGEHUS, AFD.

Vejledning:
Kirurgisk afd. udfylder originalen + de 2 kopier, som sammen med præparatet sendes til patologisk-anatomisk afd.
Patologisk-anatomisk afd. returnerer originalen + 1. kopi til kirurgisk afd.
Kirurgisk afd. fremsender kopien sammen med mammaskemaet til:
DBCG, sekretariatet, Finseninstitutet, Strandboulevarden 49, 2100 København Ø.
De tonede felter benyttes ved bestemmelse af patientgruppe (på mammaskemaet).

Makroskopisk undersøgelse

Klinisk diagnose:

Dato for biopsi:

Tidligere histologisk us.: ja ☐ nej ☐

Biopsi-incision, lokalisation kl.:

Hvis ja, hvor:

Frysesnit: ja ☐ nej ☐

nr.:

Dato for mastektomi:

Klinisk indvækst i hud: ja ☐ nej ☐

Præparat: højre mamma ☐ venstre mamma ☐

Hvis ja, lokalisation kl.:

Peroperativt findes indvækst i costae eller intercostalmuskulatur: ja ☐ nej ☐

Tumors største diameter: cm

Mikroskopisk undersøgelse - Udfyldes af patologisk-anatomisk afd.

1. Corpus mammae

Hud, indvækst: ja ☐ nej ☐

Profunde resektionsflade, gennemvækst: ja ☐ nej ☐

Tværstribet muskulatur svarende til den profunde resektionsflade: ja ☐ nej ☐

Hvis ja, indvækst: ja ☐ nej ☐

Paget: ja ☐ nej ☐

Resttumor i kavitetsvæggen: ja ☐ nej ☐

Andre maligne tumorområder: ja ☐

Tumors største diameter: cm

2. Proc. axillaris, lymfeknuder i min. 2 blokke

Antal påviste lymfeknuder:

Antal tumorpositive:

3. Axil-ledt, lymfeknuder i min. 5 blokke

Antal påviste lymfeknuder:

Antal tumorpositive:

Total antal påviste lymfeknuder:

Total antal tumorpositive:

Gennemvækst af lymfekapsel: ja ☐ nej ☐

Invasion i nerver: ja ☐ nej ☐

Invasion i kar: ja ☐ nej ☐

4. Carcinom klassifikation (tumor: frysesnit + resten)

Tubulusdannelse	Mitoser og hyperkromasi (x 400)	Polymorfi
overvejende . . 1	sjældne 1	ensartede 1
moderat 2	2-3 2	varierende. . . . 2
ringe. 3	> 2-3 3	pleomorfe. . . . 3

Point i alt: (3-5 = gr. I, 6-7 = gr. II, 8-9 = gr. III)

Diagnose (WHO):

PATOLOGISK-ANATOMISK AFD.:

DATO:

SIGNATUR:

DBCG. Form. 03

Tumorstørrelse

Lymfeknudestatus

Malignitets-gradering

WHO diagnose

DBCG patologiskema 2017

PATO-ANATOMISK UNDERSØGELSE – UDFYLDES AF PATOLOGIAFDELINGEN. Vejledning se næste side.

Præparat nummer:

Nedfrosset tumorvæv (-80°C) ☐ Ja ☐ Nej

Hud på præparat ☐ Ja ☐ Nej

Mikroskopisk undersøgelse

Papil, Mb. Paget (PDN)

Invasivt karcinom — I profun. resektionsrand / I sideresektionsrand — Nej = 0, Ja = 1, Ikke us. = 9

Karinvasion

Antal karcinomer

Diameter af invasivt karcinom, mm

Diameter af inv. karc. + sammenhæng. DCIS, mm

DCIS udenfor tumor Nej = 0 Ja = 1 Ikke us. = 9

Afstand til nærmeste sideresektionsrand fra inv.karc. mm

Afstand til nærmeste sideresektionsrand fra DCIS,mm

Lokal fremskreden sygdom

Hudinvasion ☐ Ja ☐ Nej ☐ Uvis

Gennemvækst af bundfascie ☐ Ja ☐ Nej ☐ Uvis

Karcinomklassifikation

WHO-diagnose og SNOMED-koder:

Tubulusdannelse points (1-3)

Mitoser points (1-3)

Kernepolymorfi points (1-3)

Kun ved duktale NOS og lobulære

Malignitetsgrad 3-5 = I, 6-7 = II, 8-9 = III, uegnet =0

Aksilfedt

Aksilfedt, præparat foreligger ☐ Ja ☐ Nej ☐ Andet (ekstra LN uden aksilrømning)

Antal påviste lymfeknuder incl. sentinel node Uoplyst = 99

Antal uden spredning

Antal positive (beregnet)

Antal med makrometastaser, >2 mm

Antal med mikrometastaser, >200 celler og ≤2 mm

Antal med isolerede celler, små grupper (clusters) ≤ 0,2 mm eller ≤ 200 tumorceller

Perinodal vækst Nej = 0 Ja = 1 Ikke us. = 9

Sentinel node

Sentinel node teknik anvendt ☐ Ja ☐ Nej

Antal fundne sentinel nodes

Antal uden spredning

Antal positive (beregnet)

Antal med makrometastaser, > 2 mm

Antal med mikrometastaser, > 200 celler og ≤ 2 mm

Antal med isolerede celler, små grupper (clusters) ≤ 0,2 mm eller ≤ 200 tumorceller

Frys

Antal lymfeknuder til frys

Antal makrometastaser

Antal mikrometastaser

Antal isolerede celler

Biomarkørundersøgelse

	% pos.	Uopl.
ER-bestemmelse		
PgR-bestemmelse		
Ki67, % af celler		

	Neg.	1+	2+	3+	Uopl.	ISH ratio, 2 dec.
HER-2						

HER-2 status ☐ Pos. ☐ Neg. ☐ Uopl.

Antal HER-2 genkopier pr. celle, 2 dec.

TOP2A ISH ratio, 2 dec.

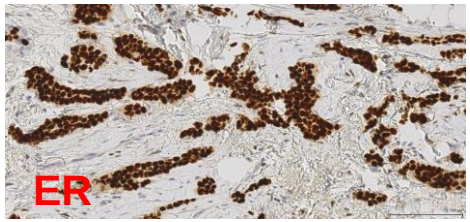
TOP2A status ☐ Normal ☐ Amplifikation ☐ Deleteret ☐ uoplyst

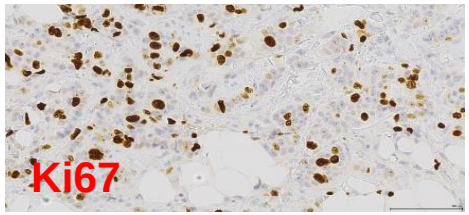
PAM 50 Klassifikation

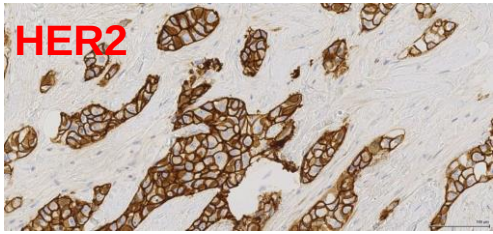
☐ Luminal A ☐ Luminal B ☐ HER2 enriched ☐ Basallike ☐ Ukendt

DATA SKAL SAMMENHOLDES MED PATOLOGIBESVARELSE

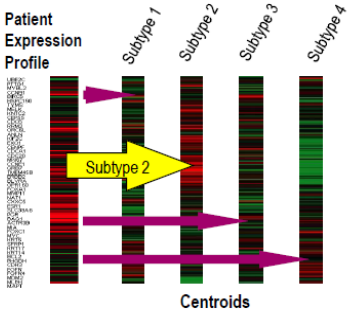
Patologiafdeling: Dato: Patologens navn (Blokbogstaver):







Determine correlation to molecular subtype centroids



DBCG: Behandlingsdatabase

C: PROGNOSE GRUPPE.

Alder	TUMOR STR	LK STATUS	HIST and GRAD	ER	HER2	DBCG gruppe
≥60 år	≤ 10 mm	0	Duktal I, ? Lobulær I-II, ? Anden type	≥10% / ukendt Medulær(neg)	Negativ / ukendt	☐ I
					Positiv	☐ II
				0-9%		☐ II
			Duktal II-III/Lobulær III			☐ II
		≥ 1				☐ II
	> 10 mm					☐ II
< 60 år						☐ II

D: MEDICINSK BEHANDLING.

DBCG gruppe	HER2 status	ER status (%pos)	Alder	Menopause	Risiko-fakt.*	Behandl.	Beh.'s-program
I						Ingen	☐ 2010 – a
II	Positiv	0 %				KT+ Tras	☐ 2010 – d,t
		≥1%				KT + Tras + ET	☐ 2010 – b,t
	Negativ	0 %				KT	☐ 2010 – d
		1-9%				KT + ET	☐ 2010 – b
		≥10 %	<40 år			KT + ET	☐ 2010 – b
			40-49 år		Nej	ET	☐ 2010 – c
					Ja	KT + ET	☐ 2010 – b
			≥ 50	Præmeno.	Nej	ET	☐ 2010 – c
					Ja	KT + ET	☐ 2010 – b
				Postmeno.	Nej	ET	☐ 2010 – c
					Ja	KT + ET	☐ 2010 – b

*__RISIKOFAKTORER:__ For pt. ≥40 år med HER2 neg. og ER≥10% tilbydes KT når der er mindst én risikofaktor, er angivet med "Ja" nedenfor.

Alder 40-49 år	Ja: Størrelse > 10mm eller node positiv eller duktal grad 2-3 eller lobulær grad 3
Præmenopausal og alder ≥ 50 år	Ja: Størrelse > 20mm eller node positiv eller duktal grad 2-3 eller lobulær grad 3
Postmenopausal og alder ≥ 50 år	Ja: DBCG score Q2-Q4 eller N4+ (≥4 positive lymfeknuder)

Molekylær subtypeklassifikation PAM50

www.dbcg.dk

QUALITY CONTROL OF PATHO-ANATOMICAL DIAGNOSIS OF CARCINOMA OF THE BREAST

Acta Oncologica 27 (1988) Fasc. 6 a

H. KLÆR, J. A. ANDERSEN, F. RANK and B. V. PEDERSEN

Interobserver variation in the diagnosis infiltrating lobular carcinoma. Estimated kappa value ± estimated spread

	Pathologist 1	Pathologist 2	Pathologist 3
The whole country	0.346±0.093	0.311±0.095	0.330±0.096
Pathologist 1		0.743±0.053	0.666±0.059
Pathologist 2			0.753±0.051

QUALITY CONTROL OF PATHO-ANATOMICAL DIAGNOSIS OF CARCINOMA OF THE BREAST

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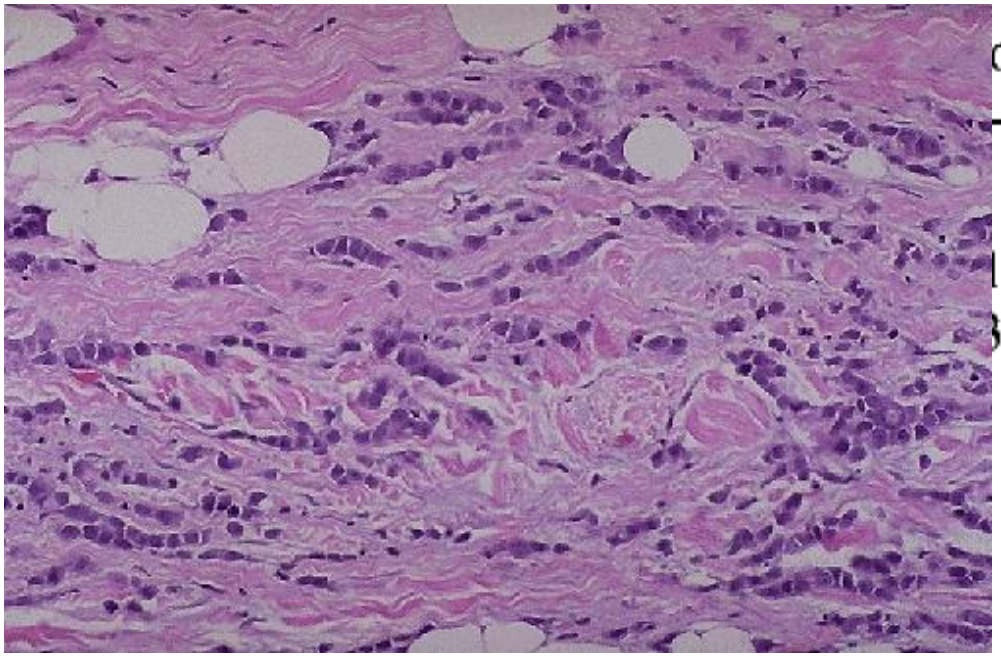
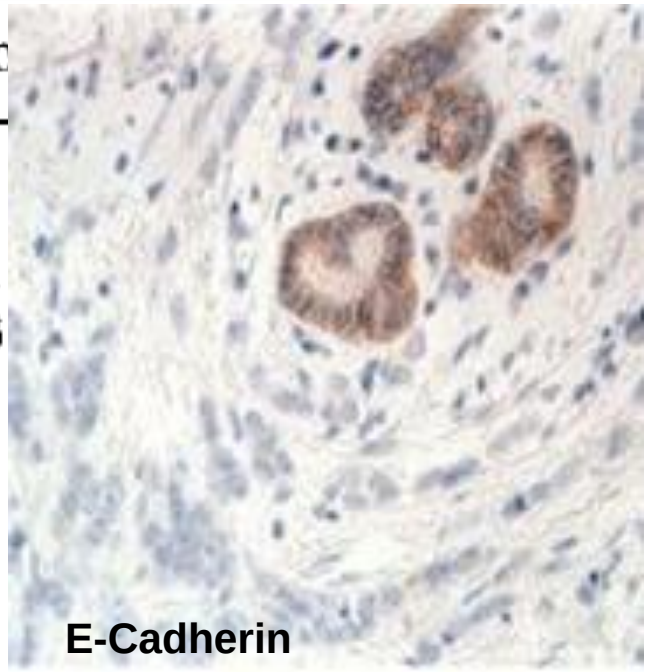




E-Cadherin

Vurdering af (bio-)markører
Evidensniveau
Standardisering og kvalitetssikring

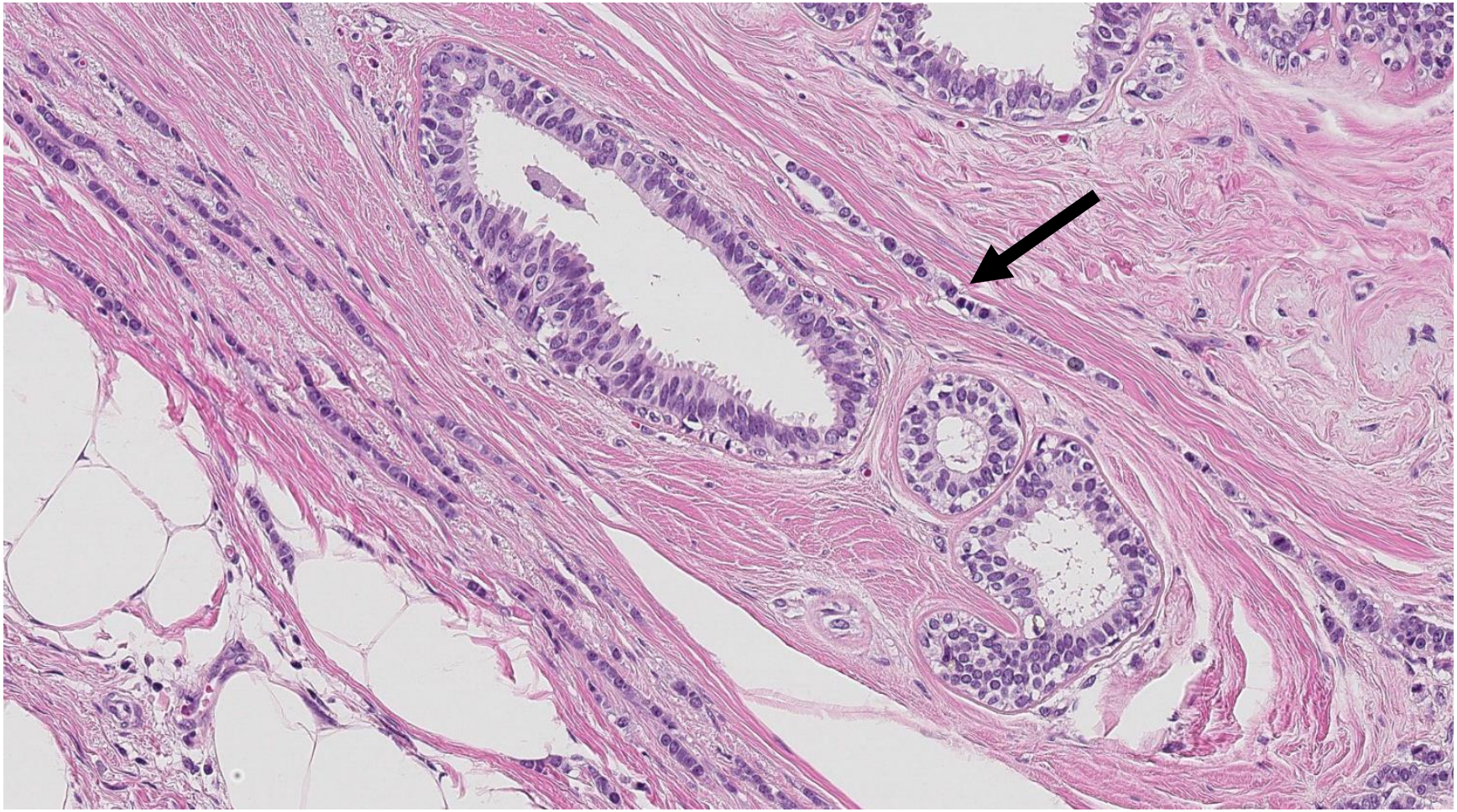
- Analytisk validitet
  - Sensitivitet, specificitet, reproducerbarhed
    - Preanalytisk fase
      - iskæmitid, fiksering, vævspræparation
    - Testfasen/Analyse
      - Antistofklon / probesæt – kontroller, metode
    - Postanalytisk fase
      - Fortolkning, Kvantitering

Vurdering af (bio-)markører
Evidensniveau
Standardisering og kvalitetssikring

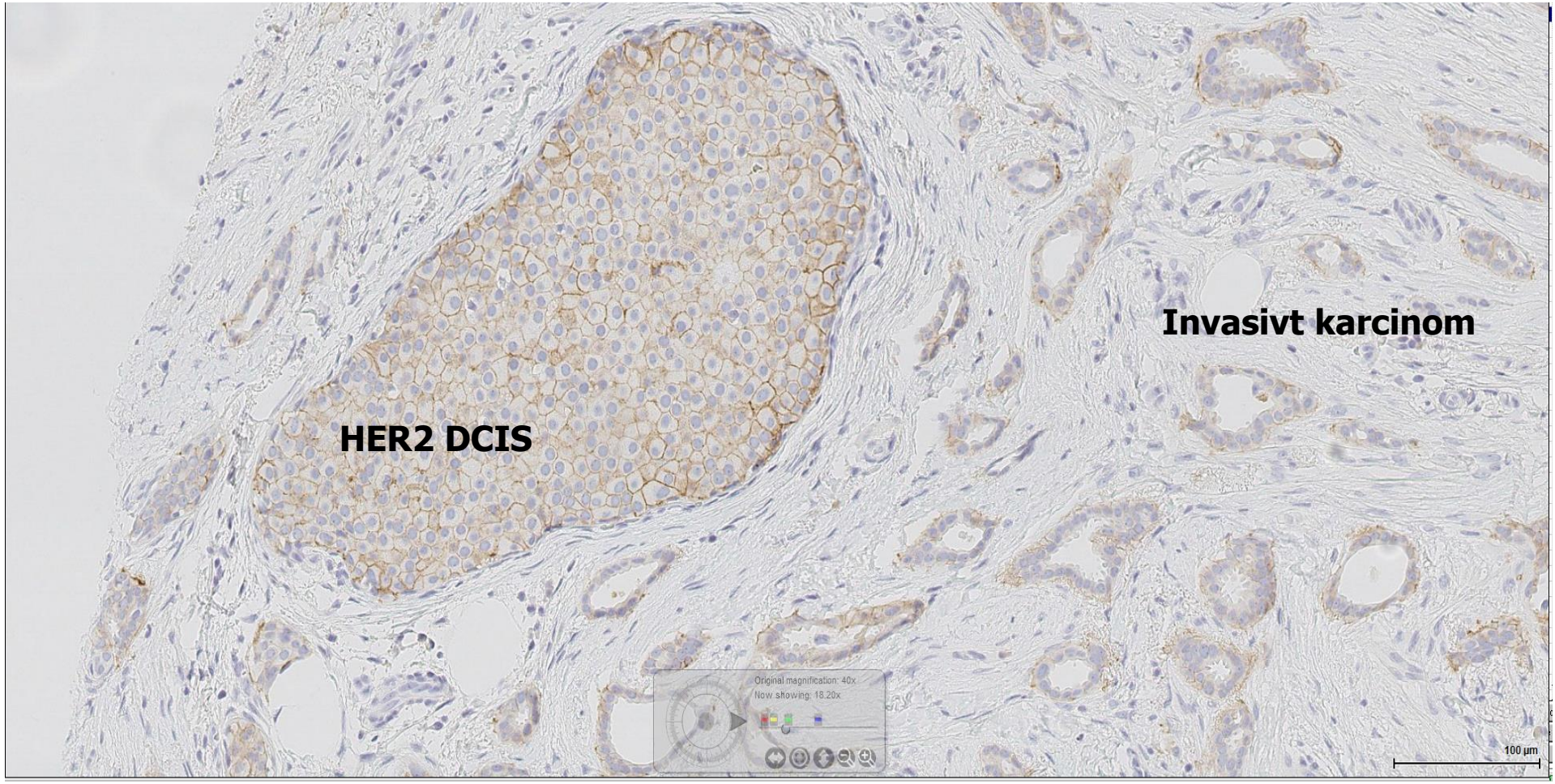
Patologiafdelingen, Aalborg Universitetshospital

Udvalg for Molekylærpatologi

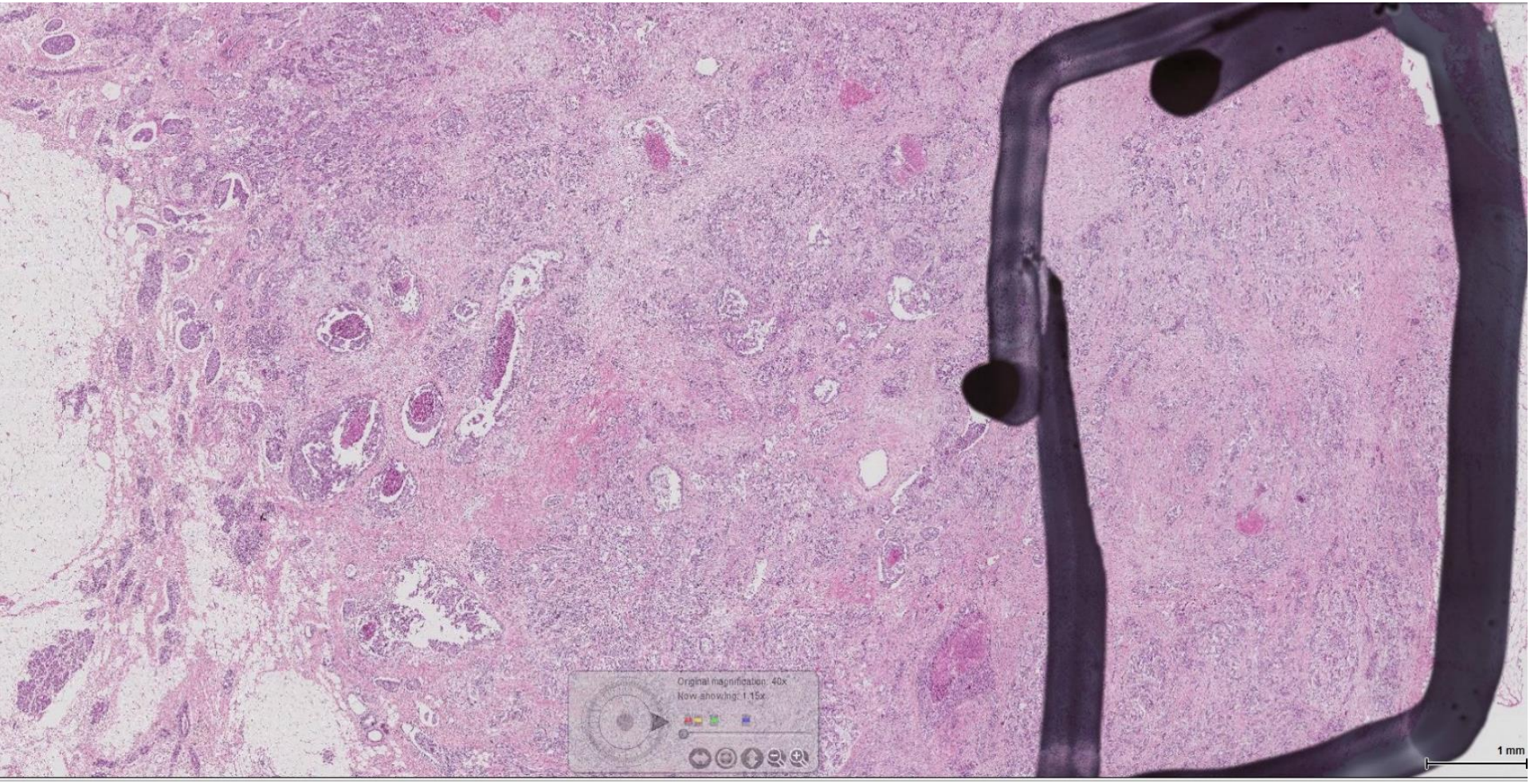
Tumor sampling og verifikation af den invasive tumorkomponent Heterogenitet



Tumor sampling og verifikation af den invasive tumorkomponent Heterogenitet



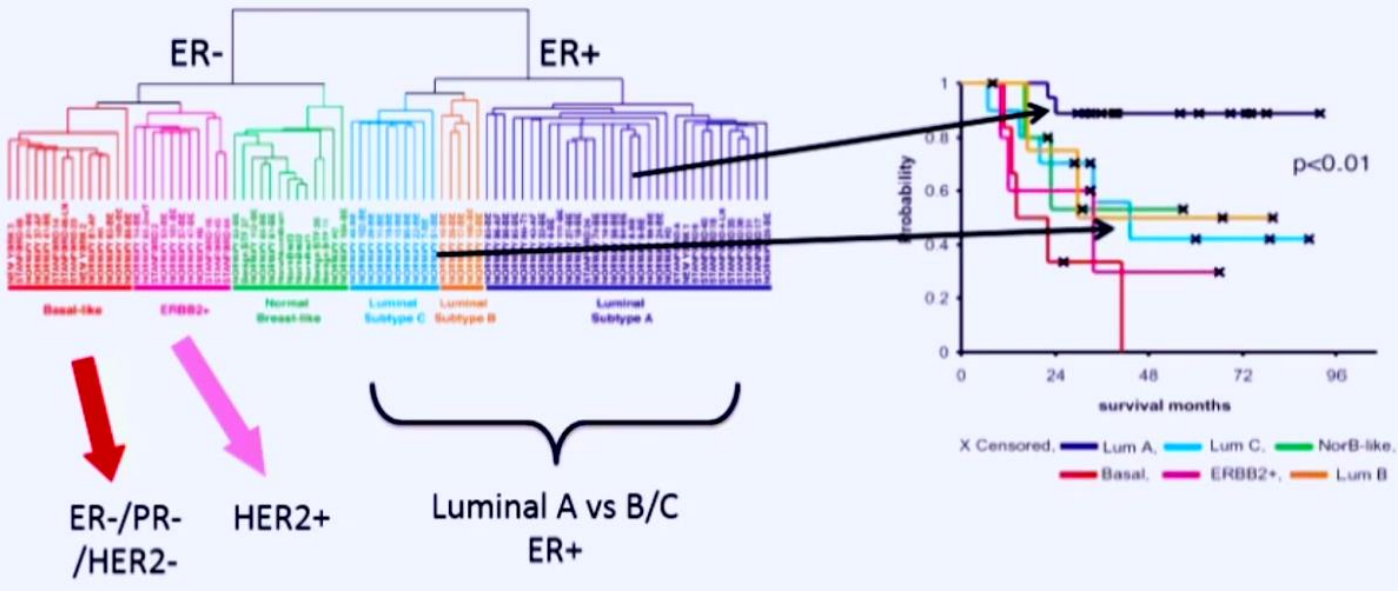
Tumor sampling og verifikation af den invasive tumorkomponent Heterogenitet



Genekspressionsprofiler / Prognostisk information

2000	2002	2003	2004	2005	2008….
Molekylære subtyper	70-gen signatur	76-gen signatur	Oncotype DX 21 gener	Genomic grade Index	Prosigna-PAM50: 50 gener, molekylær subtype, Risk of Recurrence score (ROR) BCIN: 11 gen assay EndoPredict: 12 gen assay

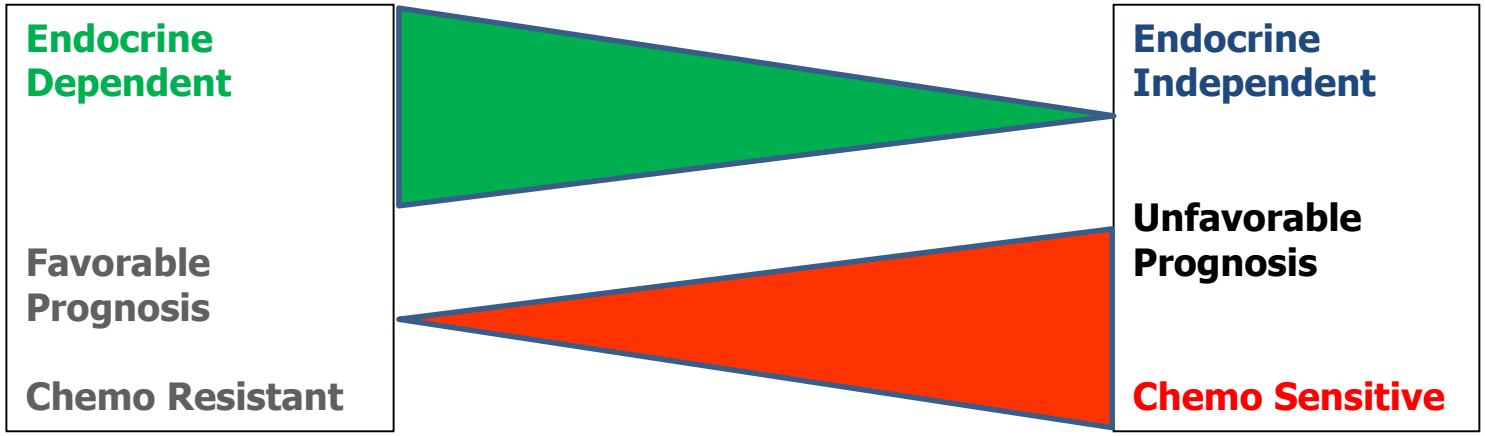
Perou et al., Nature 2000
Sorlie et al., PNAS 2001

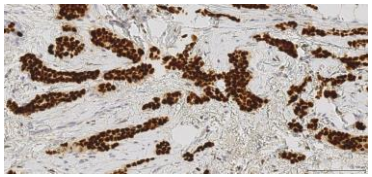
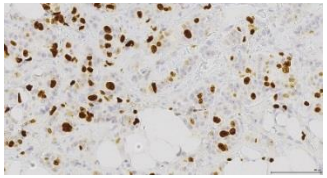
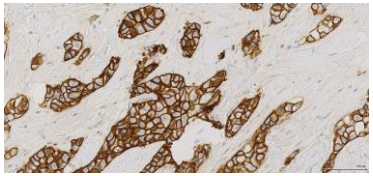
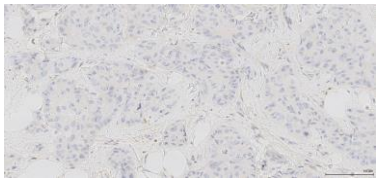
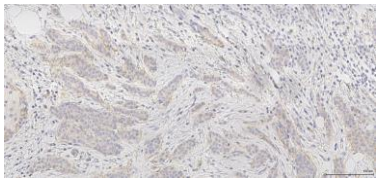


Prognostiske Genprofiler

	MammaPrint	Oncotype DX	EndoPredict	Prosigna	Breast Cancer Index
Assay	Agendia 70-gene assay	Genomic Health 21-gene recurrence score	Myriad (Sividon) 12-gene assay	Nanostring 50-gene assay Mol subtype / ROR score	Biotheranostics 11-gene assay
Methods	DNA microarray	RT-PCR	RT-PCR	NanoString nCounter	RT-PCR
Tissue	Frozen or FFPE	FFPE	FFPE	FFPE	FFPE
Central Analysis	Yes	Yes	No	No	Yes
Population	N0-1	N0-1, ER+	N0-1, ER+/HER2-	N0-1, ER+/HER2-	N0, ER+/HER2-
Analytical Validity	Yes	Yes	Yes	Yes	Yes
Clinical Validity	Yes	Yes	Yes	Yes	Yes
Clinical Utility	Yes	Yes	Yes	Yes	Yes
Level of Evidence	IA (5 years)	IA (5 years)	IB	IB	IB
Prospective Trials	MINDACT	TAILORx RxPONDER ADAPT	ADENDOM	OPTIMA PRECISION NEOPAL	Extended Endocrine Treatment

Brystkræft – Molekylære subtyper



Luminal A	Luminal B	HER2-enriched	Basal-like	
				ER negative
ER positive	Ki67 indeks ↑	HER2 positive		HER2 negative

"St Gallen international breast cancer conference" Skiftende forslag til Ki67 tærskelværdi gennem årene

2009: Ki67: 3 kategorier lav <15%, intermediær 16–30% og høj >30%

2011: Ki67: 14%

2013: Luminal A: ER+, PR ≥20% og Ki67<20%, HER2-
Luminal B: ER+ og PR<20% og/eller Ki67 ≥20%, HER2-

2015: Ki-67 interval :20%–29% (`luminal B-like` subtype).

2017: "lav" ki67 versus "høj" ki67.

Acta Oncologica, 2017;doi.org/10.1080/0284186X.2017.1404127

An inter-observer Ki67 reproducebility study applying two different assessment methods: on behalf of the Danish Scientific Committee of pathology, DBCG.

Anne-Vibeke Lænkholm, Dorthe Grabau†, Maj-Lis Møller Talman, Eva Balslev, Anne Marie Bak Jylling, Tomasz Piotr Tabor, Morten Johansen, Anja Brügmann, Giedrius Lelkaitis, Tina Di Caterino, Henrik Mygind, Thomas Poulsen, Henrik Mertz, Gorm Søndergaard & Birgitte Bruun Rasmussen.

ABSTRACT

Introduction: In 2011, the St. Gallen Consensus Conference introduced the use of pathology to define the intrinsic breast cancer subtypes by application of immunohistochemical (IHC) surrogate markers ER, PR, HER2 and Ki67 with a specified Ki67 cutoff (>14%) for luminal B-like definition. Reports concerning impaired reproducibility of Ki67 estimation and threshold inconsistency led to the initiation of this quality assurance study (2013–2015). The aim of the study was to investigate inter-observer variation for Ki67 estimation in malignant breast tumors by two different quantification methods (assessment method and count method) including measure of agreement between methods.

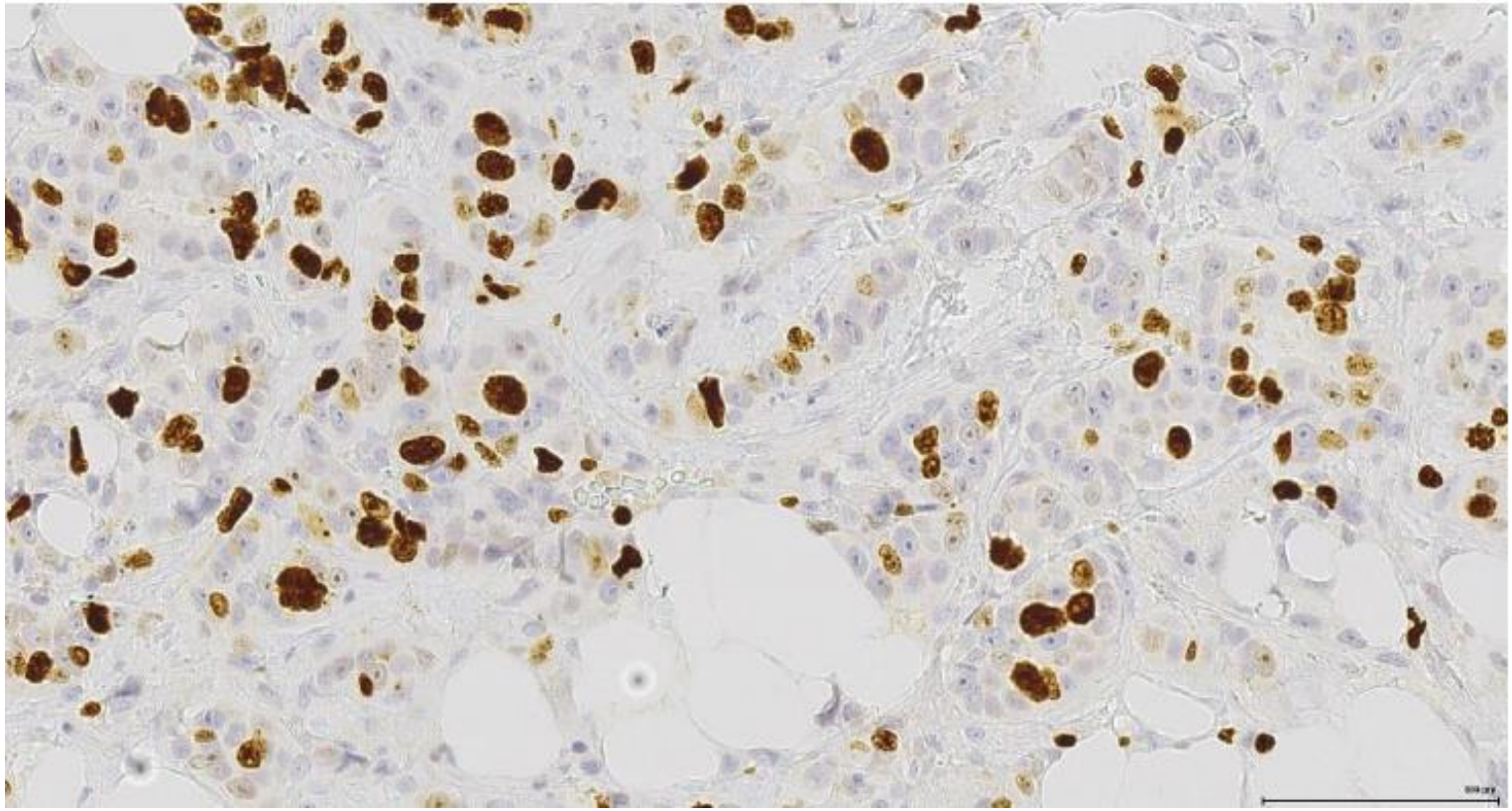
Material and methods: Fourteen experienced breast pathologists from 12 pathology departments evaluated 118 slides from a consecutive series of malignant breast tumors. The staining interpretation was performed according to both the Danish and Swedish guidelines. Reproducibility was quantified by intra-class correlation coefficient (ICC) and Lights Kappa with dichotomization of observations at the larger than (>) 20% threshold. The agreement between observations by the two quantification methods was evaluated by Bland–Altman plot.

Results: For the fourteen raters the median ranged from 20% to 40% by the assessment method and from 22.5% to 36.5% by the count method. Light's Kappa was 0.664 for observation by the assessment method and 0.649 by the count method. The ICC was 0.82 (95% CI: 0.77–0.86) by the assessment method vs. 0.84 (95% CI: 0.80–0.87) by the count method.

Conclusion: Although the study in general showed a moderate to good inter-observer agreement according to both ICC and Lights Kappa, still major discrepancies were identified in especially the mid-range of observations. Consequently, for now Ki67 estimation is not implemented in the DBCG treatment algorithm.

Ki67 IHC

14 observatører, 12 patologiafdelinger heraf 11 danske
118 vævssnit blev cirkuleret.

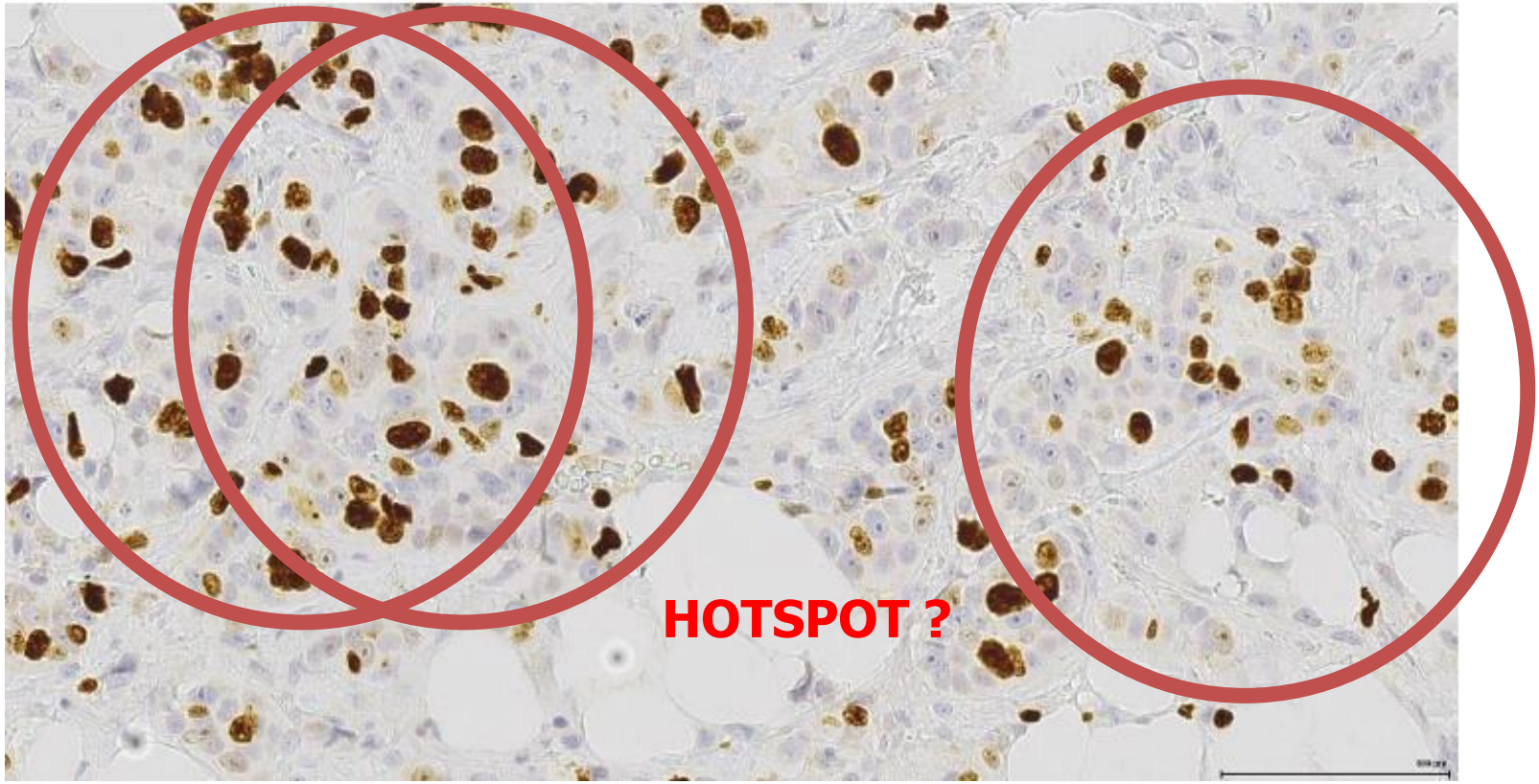


Mikroskopisk vurdering

1. Semikvantitativ: Ki67 positive tumorceller (%) i hotspot (DK)
2. Kvantitativ: andel Ki67 positive tumorceller (%) / 200 tumorceller (Sverige)

Ki67 IHC

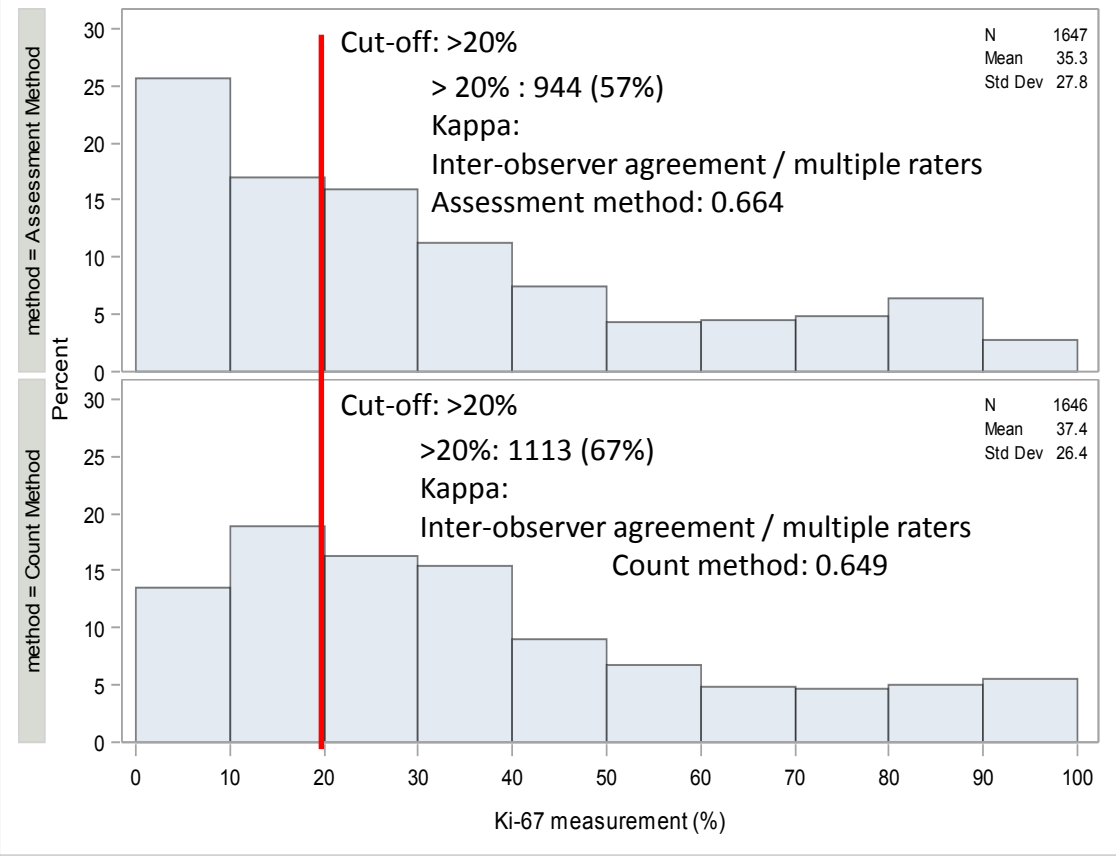
14 observatører, 12 patologiafdelinger heraf 11 danske
118 vævssnit blev cirkuleret.



Mikroskopisk vurdering

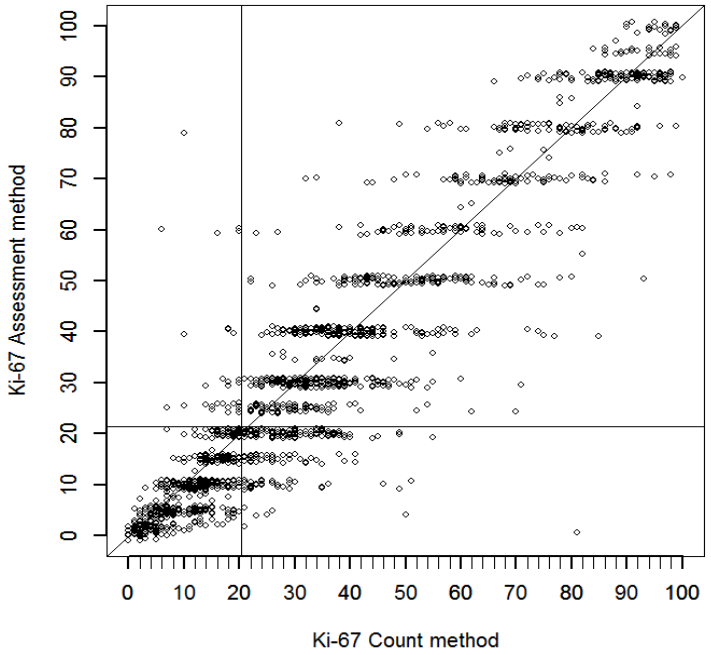
1. Semikvantitativ: Ki67 positive tumorceller (%) i hotspot (DK)
2. Kvantitativ: andel Ki67 positive tumorceller (%) / 200 tumorceller (Sverige)

Interobservatør overensstemmelse Kappa statistik



Acta Oncologica, 2017;doi.org/10.1080/0284186X.2017.1404127

Overensstemmelse observationer/metoder

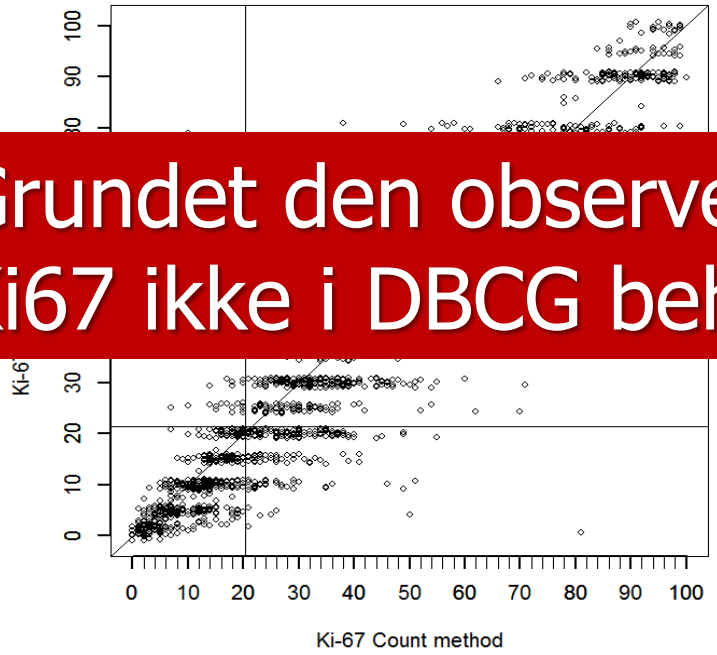


Assessment Method	Count Method		
	≤ 20%	> 20%	Total
≤ 20%	507 (72%)	195 (28%)	702
> 20%	26 (3%)	918 (97%)	944
Total	533	1113	1646
Observations missing = 6			

Proportion of agreement (observations ≤20%): 0.65 – 0.91, median 0.83
Proportion of agreement (observations >20%): 0.73 – 0.96, median 0.87

Acta Oncologica, 2017;doi.org/10.1080/0284186X.2017.1404127

Overensstemmelse observationer/metoder



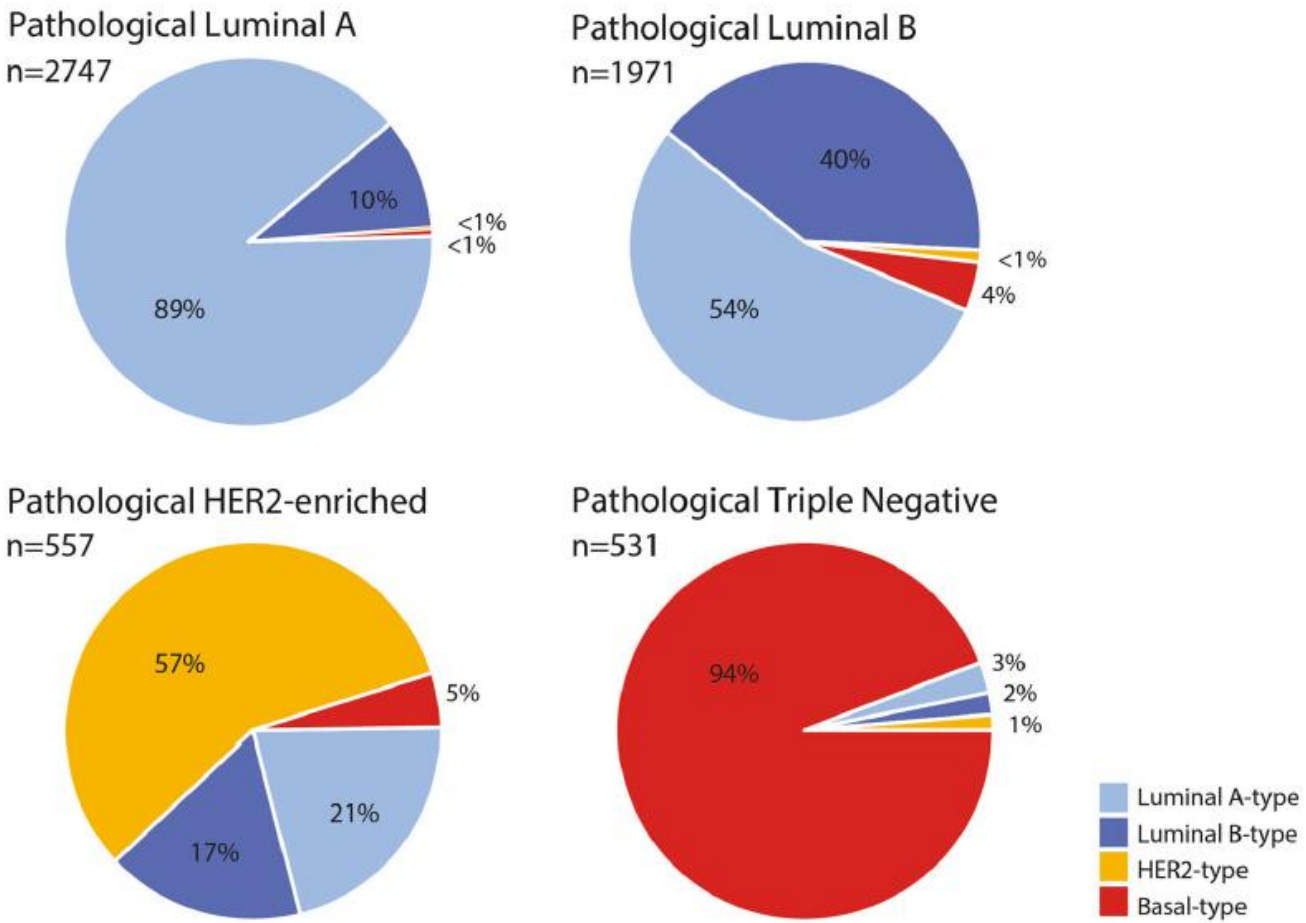
Assessment Method	Count Method		
> 20%	26 (3%)	918 (97%)	944
Total	533	1113	1646
Observations missing = 6			

Grundet den observerede diskrepans indgår Ki67 ikke i DBCG behandlingsalgoritme

Proportion of agreement (observations ≤20%): 0.65 – 0.91, median 0.83
Proportion of agreement (observations >20%): 0.73 – 0.96, median 0.87

Acta Oncologica, 2017;doi.org/10.1080/0284186X.2017.1404127

Ikke tilfredsstillende overensstemmelse mellem subtyper bestemt ved IHC markører sammenlignet med molekylær analyse



Viale G et al. Breast Cancer Res Treat 2017
DOI 10.1007/s10549-017-4509-9

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

PAM50 Risk of Recurrence Score Predicts 10-Year Distant Recurrence in a Comprehensive Danish Cohort of Postmenopausal Women Allocated to 5 Years of Endocrine Therapy for Hormone Receptor–Positive Early Breast Cancer

Anne-Vibeke Lænkholm, Maj-Britt Jensen, Jens Ole Eriksen, Birgitte Bruun Rasmussen, Ann S. Knoop, Wesley Buckingham, Sean Ferree, Carl Schaper, Torsten O. Nielsen, Taryn Haffner, Torben Kibøl, Maj-Lis Møller Talman,Anne Marie Bak Jylling, Tomasz Piotr Tabor, and Bent Ejlertsen

J Clin Oncol. 2018 Jan 25:JCO2017746586

DBCG 99C Protokol
ER+ (≥10%) Postmenopausale / tidlig brystkræft
Endokrin behandling: 5 år - monoterapi

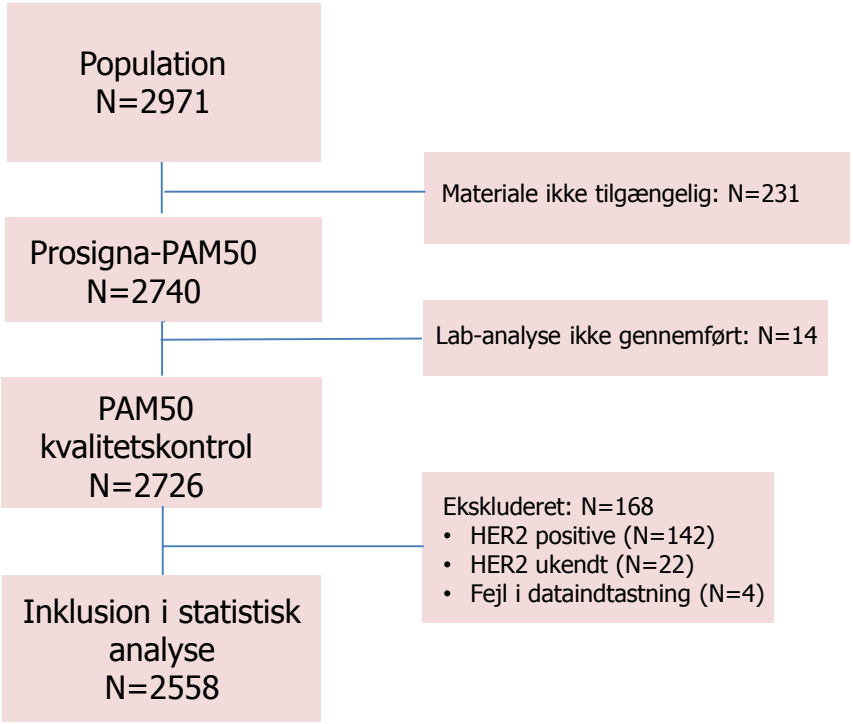
Tumor > 2 cm eller lymfeknudepositiv eller grad 2-3

Inklusion:
Diagnose år 2000-2003
Antal positive lymfeknuder: 0 til 3

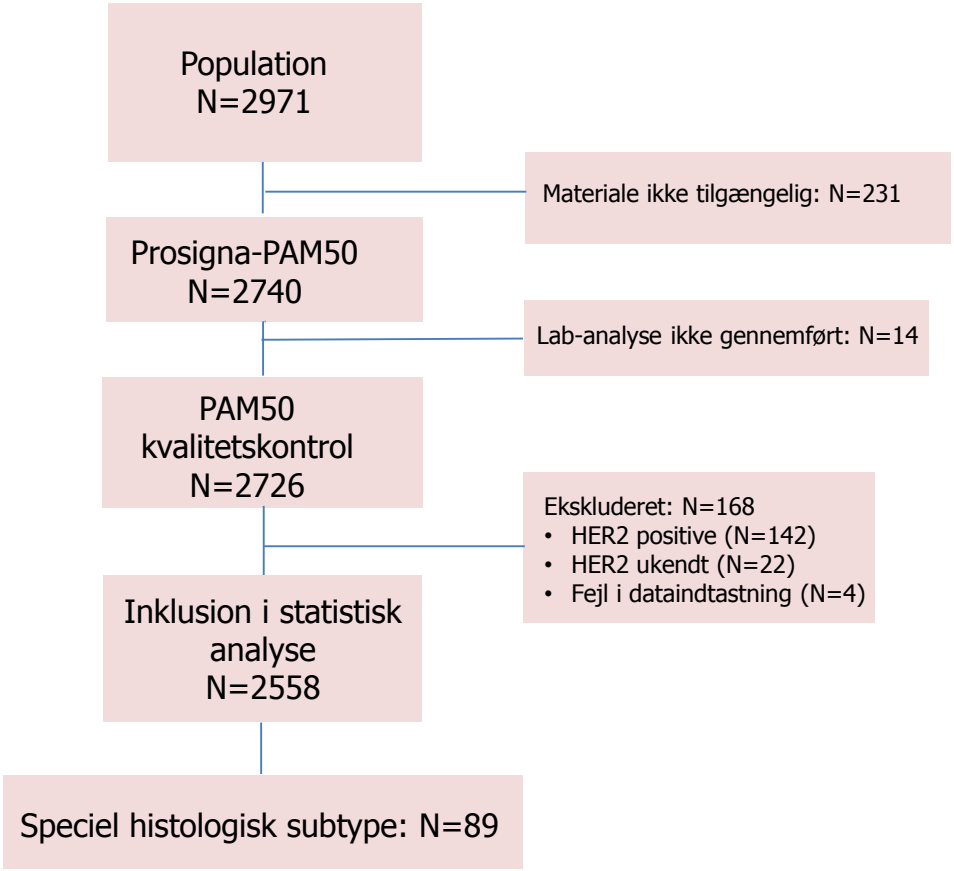
Median F/U: 9.25 år

Ejlertsen B et al. Acta Oncol. 2014 Feb;53(2):174-85.

Consort diagram DBCG99C



Consort diagram DBCG99C



Fordeling molekylær subtype N=2558

Molekylær subtype		Antal Positive lymfeknuder			
	N (%)	0	1	2	3
Luminal A	1474 (58%)	611	499	241	123
Luminal B	947 (37%)	485	242	136	84
HER2enriched	110 (4%)	50	31	14	15
Basallike	27 (1%)	17	7	2	1
ROR gruppe					
Lav	720 (28%)	361	296	63	NA
Intermediær	763 (30%)	374	231	131	26
Høj	1075 (42%)	428	252	199	197

Lænkholm et al. JCO 2018;36

Der ses significant association (P<0.0001) for kontinuerlig ROR score - Distant Recurrence 10 år

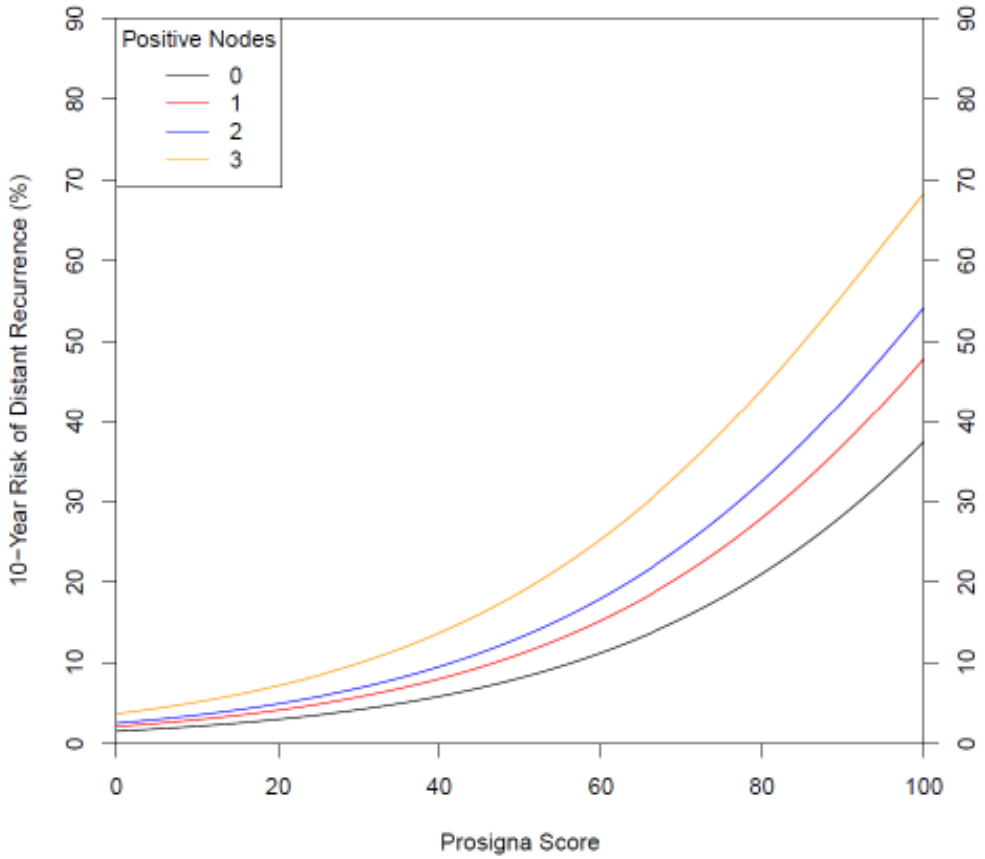


Figure 1. Continuous relationship between the 10-year risk of distant recurrence and the ROR score by number of positive nodes (0, 1, 2, and 3).

Univariate Fine-Gray model

Lænkholm et al. JCO 2018;36

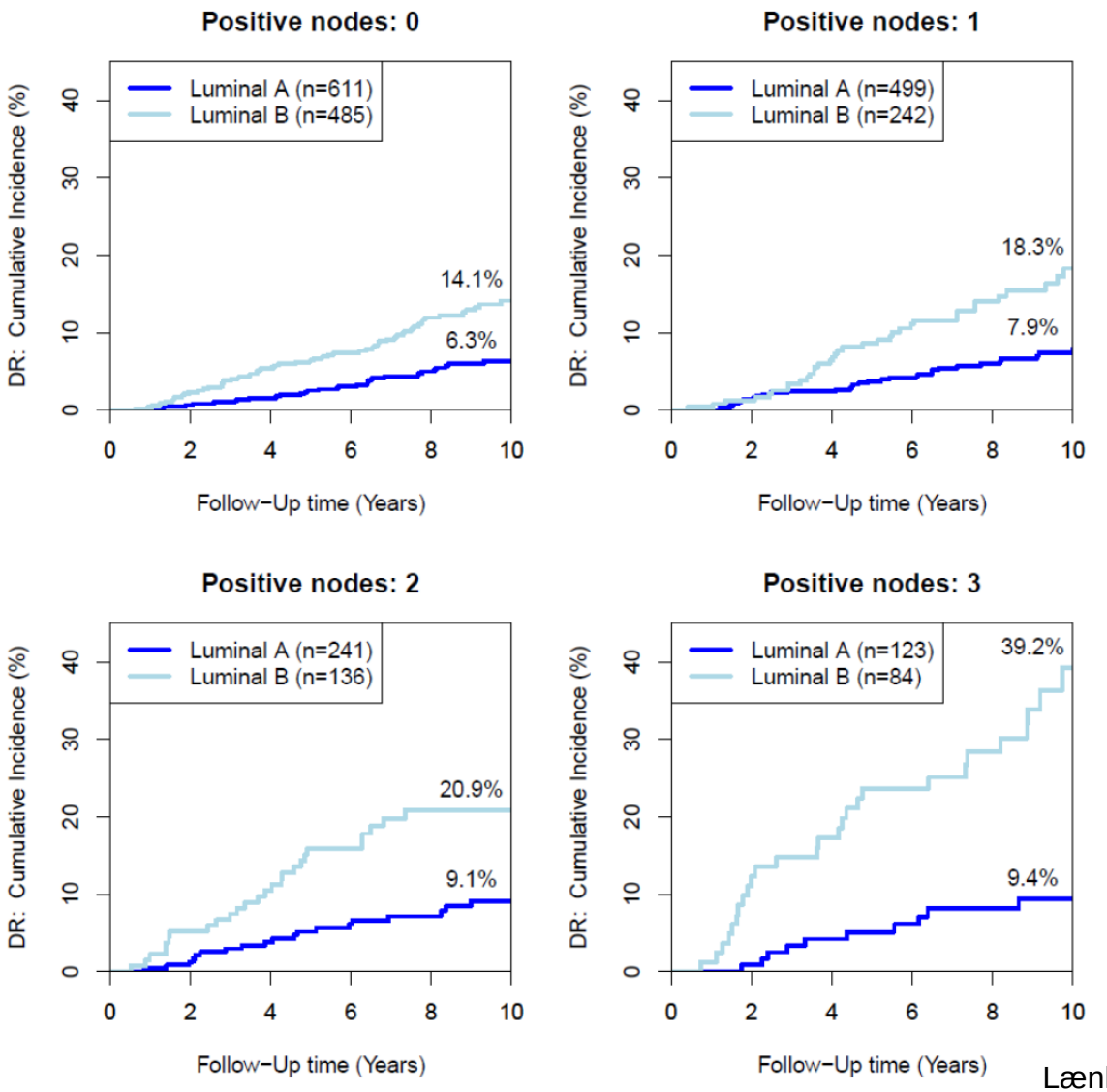
Multivariat analyse Distant Recurrence

		1 to 3 positive nodes		0 to 3 positive nodes	
		HR (95% CI)	P	HR (95% CI)	P
ROR	Cont	1.68 (1.42;1.99)	<.0001	1.67 (1.46;1.92)	<.0001
	Low vs Intermediate	0.39 (0.20;0.77)	0.0001	0.53 (0.33;0.85)	<0.0001
	High vs Intermediate	1.54 (1.04;2.26)		1.81 (1.33;2.44)	
Subtype	Luminal B vs Luminal A	1.97 (1.38;2.82)	0.0002	1.93 (1.45;2.56)	<.0001

Table 2. Multivariate analyses for distant recurrence. HR-estimates from Fine-Gray multivariate modelling of DR for 1-3 and 0-3 positive nodes.

Lænkholm et al. JCO 2018;36

Kumulativ incidens rate for Molekylær Subtype ved 0, 1, 2 og 3 positive lymfeknuder (10 år DR)



Lænkholm et al. JCO 2018;36

Konklusion

- Identifikation af patienter der kan skånes for kemoterapi
- Molekylær subtypeklassifikation implementeret i DBCG
  - Postmenopausale kvinder med ER+, HER2- brystkræft og 0-3 positive lymfeknuder (PSI – Q2 score) får udført PAM50 analyse

PAM50 analyser udført i 2017

	2017		PAM50	
Q		Protokol		Protokol
1	1268	C		
2	**300** (17%)	B	**55 Lum A (74%)**	C
			19 Lum B	B
3	136	B		
4	33	B		
		Q2 med PAM50 test	Juli-sep: 26/65 = 40% Okt-dec: 44/71 = 62%	

Acta Oncologica, 2017;doi.org/10.1080/0284186X.2017.1403044

The ability of PAM50 risk of recurrence score to predict 10-year distant recurrence in hormone receptor-positive postmenopausal women with special histological subtypes.

Anne-Vibeke Lænkholm, Maj-Britt Jensen, Jens Ole Eriksen, Wesley Buckingham, Sean Ferree, Torsten O. Nielsen & Bent Ejlertsen

ABSTRACT

Introduction: The Prosigna-PAM50 risk of recurrence (ROR) score has been validated in randomized clinical trials to predict 10-year distant recurrence (DR) in hormone receptor-positive breast cancer. Here, we examine the ability of Prosigna for predicting DR at 10 years in a subgroup of postmenopausal breast cancer patients with special histological subtypes.

Methods: Using the population based Danish Breast Cancer Group database, follow-up data were collected on all patients diagnosed from 2000 to 2003 with estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2) normal breast cancer who by nationwide guidelines were treated with 5 year of endocrine therapy ($N = 2558$). Among patients with 1 to 3 positive lymph nodes or a tumor size >20 mm, we identified 1570 with invasive ductal carcinoma (IDC) and 89 with special histological subtypes (apocrine, medullary, mucinous, papillary, secretory, tubular, neuroendocrine) who were tested with Prosigna. Fine and Gray models were applied to determine the prognostic value of the Prosigna-PAM50 ROR score for DR special subtypes as compared to IDC.

Results: Median follow-up for DR was 9.2 year and for OS 15.2 year. The 10-year DR rate for the special subtypes was 9.2% (95% CI: 4.0% to 17.2%) as compared to 13.7% (95% CI: 11.9% to 15.7%) for IDC. The 10-year OS was 74.2% (95% CI: 63.7% to 82.0%) for the special subtypes and 75.4% (95% CI: 73.2% to 77.4%) for IDC. Prosigna showed a statistical significant association of the continuous ROR score with risk of DR for both IDC and the special subtypes (IDC: $p < .0001$; special subtypes: $p = .01$).

Conclusion: In the present study, we demonstrated that Prosigna-PAM50 continuous ROR score added significant prognostic information for 10-year DR in postmenopausal patients with special subtypes (tumor size >20 mm or 1 to 3 positive lymph nodes) and ER-positive, HER2-normal early breast cancer.

Kvalitetsindikatorrapport for brystkræft 2016

	Alle		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
Histologisk type										
Duktal	12228	(79.7)	3118	(79.6)	3056	(78.8)	3099	(81.2)	2955	(79.3)
Lobulær	1769	(11.5)	441	(11.3)	458	(11.8)	406	(10.6)	464	(12.5)
Mucinøs	325	(2.1)	69	(1.8)	90	(2.3)	87	(2.3)	79	(2.1)
Medullær	35	(0.2)	10	(0.3)	18	(0.5)	3	(0.1)	4	(0.1)
Papillær	109	(0.7)	26	(0.7)	34	(0.9)	15	(0.4)	34	(0.9)
Tubulær	210	(1.4)	65	(1.7)	58	(1.5)	46	(1.2)	41	(1.1)
Andre invasiv	662	(4.3)	187	(4.8)	165	(4.3)	161	(4.2)	149	(4.0)
Total	15338	(100.0)	3916	(100.0)	3879	(100.0)	3817	(100.0)	3726	(100.0)

Patient materiale

Table 2. Patient characteristics. Special subtypes (except for invasive lobular carcinoma) are not graded according to national guidelines [www.dbcg.dk].

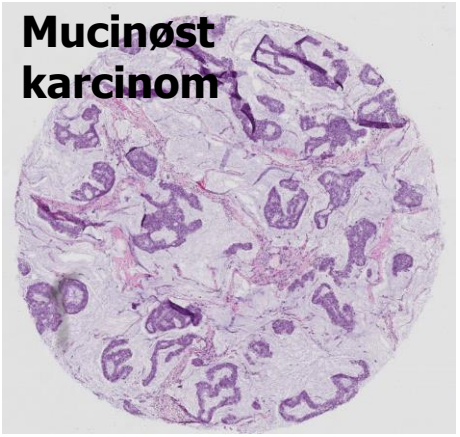
	IDC ($N = 1570$)	(%)	Special subtypes ($N = 89$)	(%)	p
Number of positive lymph nodes					.0005
0	425	(27%)	42	(47%)	
1	636	(40%)	30	(34%)	
2	324	(21%)	11	(12%)	
3	185	(12%)	6	(7%)	
Tumor size (mm)					.0002
≤10	100	(6%)	6	(7%)	
11–20	560	(36%)	16	(18%)	
21–30	680	(43%)	41	(46%)	
>30	230	(15%)	26	(29%)	
Grade					
1	562	(36%)	6	(7%)	
2	790	(50%)	4	(4%)	
3	218	(14%)	0	(0%)	
Not done	0	(0%)	79	(89%)	
Lymphovascular invasion					.10
Present	221	(14%)	7	(8%)	
Absent	1349	(86%)	82	(92%)	
ER expression level					.54
10–59%	161	(10%)	6	(7%)	
60–89%	335	(21%)	17	(19%)	
90–99%	415	(27%)	27	(30%)	
100%	638	(41%)	39	(44%)	
Positive[a]	21	(1%)	0	(0%)	
Molecular subtype					[b].052
Luminal A	863	(55%)	42	(47%)	
Luminal B	620	(39%)	37	(42%)	
HER2Enriched	73	(5%)	7	(8%)	
Basallike	14	(1%)	3	(3%)	
ROR group					
Low/intermediate (≤40)	532	(34%)	29	(33%)	
High (>40)	1038	(66%)	60	(67%)	

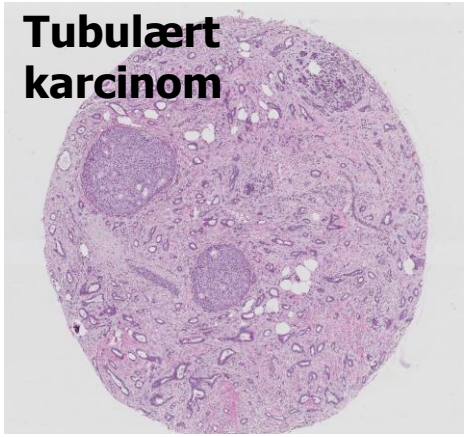
[a]ER ≥10% the exact percentage unknown;
[b]Fisher's Exact Test.

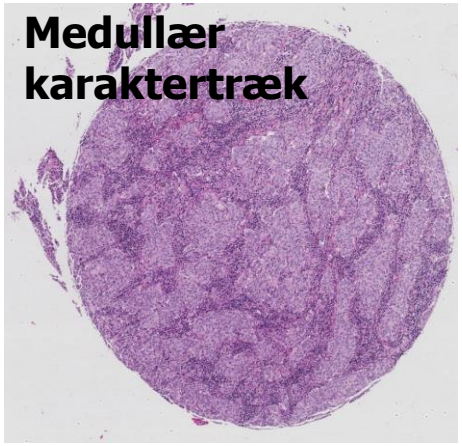
Histologisk subtype / Molekylær subtype

Table 1. Histological special subtypes and distribution of molecular intrinsic subtype including DR events and Deaths (any cause) ($N = 89$).

Histological subtypes	$N = 89$	Luminal A	Luminal B	HER2Enriched	Basallike	DR events	Deaths any cause
Apocrine	3	0	1	2	0	1	1
Medullary	5	0	1	1	3	1	2
Mucinous	51	23	26	2	0	4	28
Papillary	12	2	8	2	0	1	5
Secretory	1	1	0	0	0	0	0
Tubular	16	16	0	0	0	0	5
Neuroendocrine	1	0	1	0	0	0	0







Supplerende immunhistokemiske farvninger kan bidrage yderligere til den histopatologiske klassifikation

Der ses en signifikant association med kontinuerlig ROR score

IDC: p<.0001
Speciel subtype: p=0.01

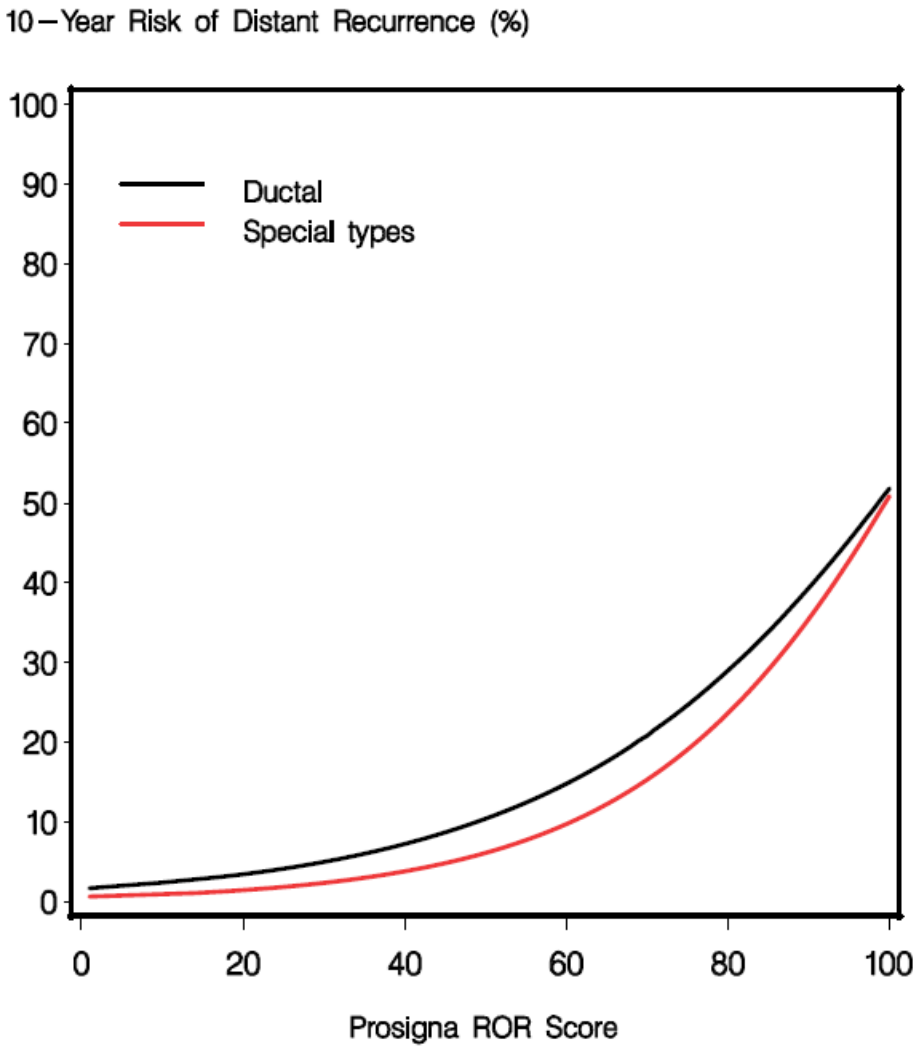


Figure 1. Continuous relationship between 10-year risk of distant recurrence and the continuous PAM50-Prosigna ROR score by IDC and special subtypes.

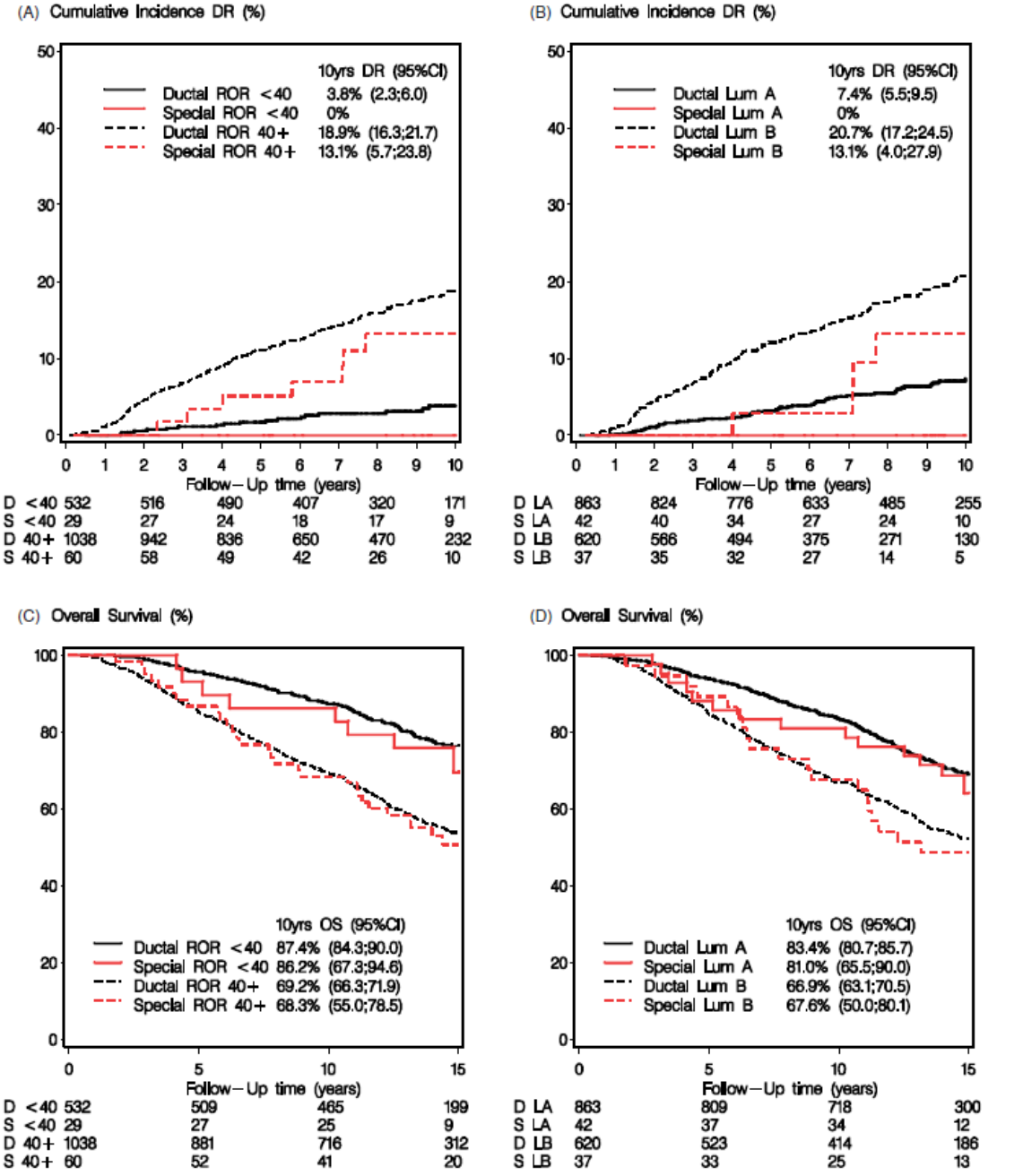


Figure 2. Cumulative incidence and overall survival according to ROR score low/intermediate versus high (A + C) and molecular subtype (B + D) for IDC and special types (black = ductal, red = special types).

Konklusion

Prosigna PAM50 bidrager med prognostisk information i gruppen af brystkræfttumorer med speciel histologisk subtype

Fremtidsperspektiv: histopatologi og molekylære subtyper

- Synergieffekt ved kombination af histopatologi herunder immunhistokemi og molekylær subtypeklassifikation

  ⇒ optimering af behandlingsallokering

- (Molekylær-)Patologi Procedurer
  - implementering af analyser (IHC, GEP, NGS)
  - fokus på analytisk validitet
  - Automatiseret Digital Billedanalyse
  - Artificiel Intelligens
    - https://doi.org/10.1016/j.trsl.2017.10.010

- Duktalt Karcinom in Situ
  - Stratificering af patienter med duktalt karcinom in situ til +/- strålebehandling?


DBCG
40