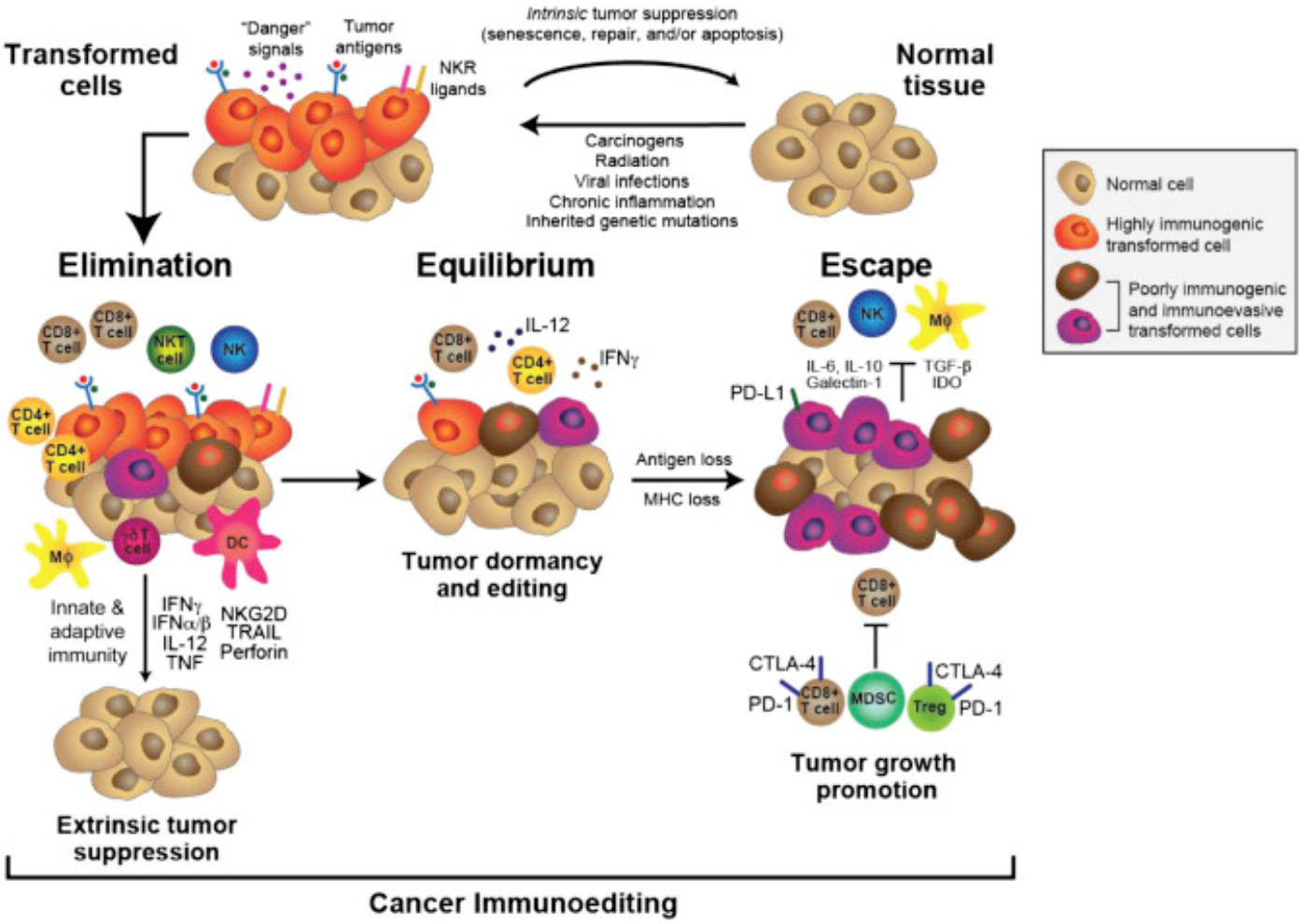
Tumor-infiltrerende lymfocytter (TILs)

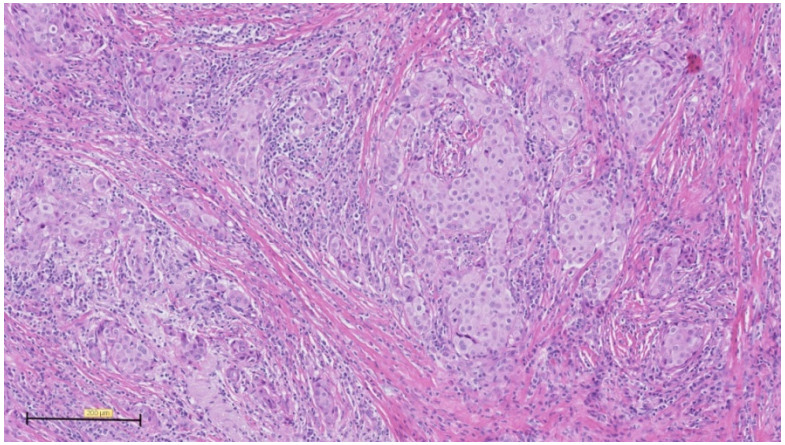
Overlæge, Ph.d.
Trine Tramm
Patologi
Aarhus Universitetshospital

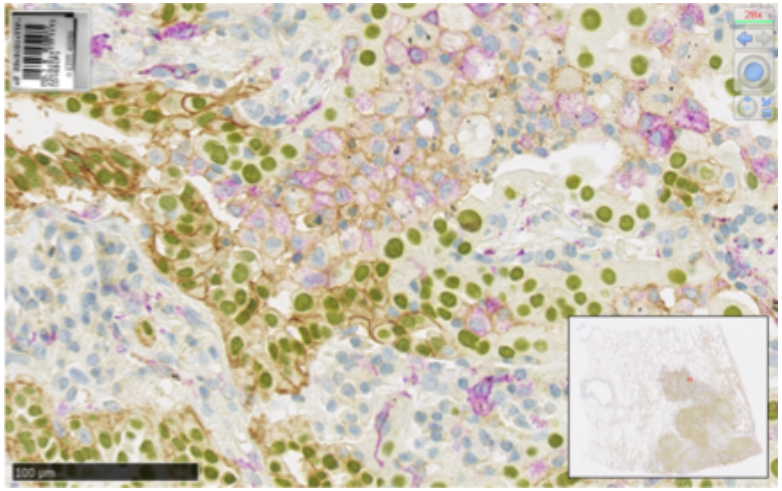
Immuno-editing



Detektion og estimering af TILs

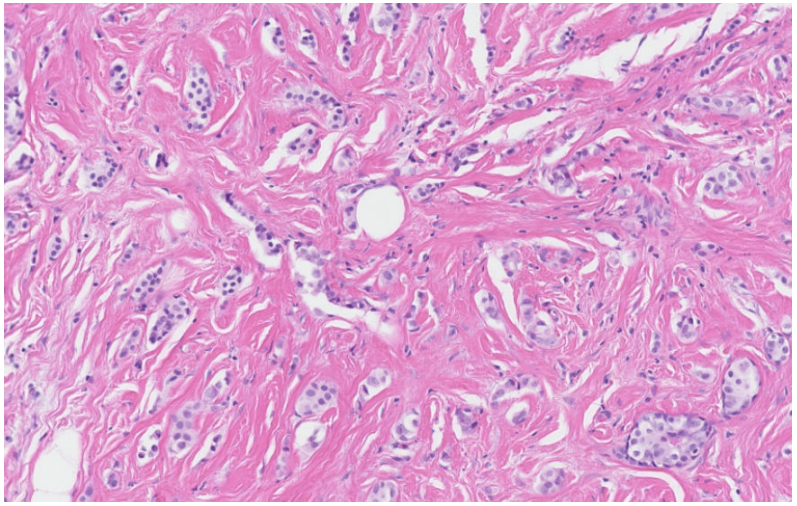
- Surrogat markør for adaptive immunsystem (især T-celle respons)
- TILs er en blanding af celler (T/B-lymf., plasmaceller)
- Immunhistokemiske markører kan differentiere mellem lymfocyttyper
- Kan vurderes stromalt eller intratumoralt

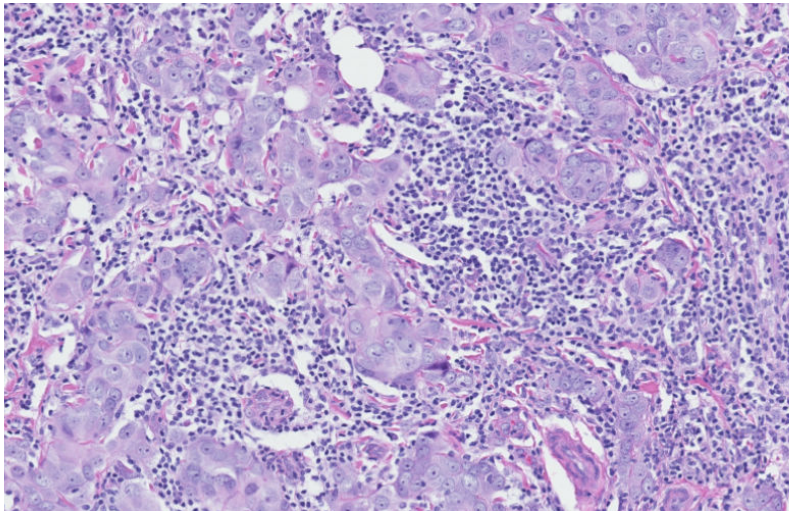




Niveau af TILs er afhængig af subtype

- Generelt få TILs i brystkræft (non-immunogen)
- Triple negative, HER2 pos.:
  - højere niveau af TILs
  - højere mutational load
  - højere proliferation
- Alle subtyper viser low, intermediære, høje TILs niveauer





Betydning af lymfocytært respons

1922

LIFE EXPECTANCY FOLLOWING RADICAL AMPUTATION FOR CARCINOMA OF THE BREAST: A CLINICAL AND PATHOLOGIC STUDY OF 218 CASES*

By Walter E. Sistrunk, M.D.
of the Section on Surgery
and
William C. MacCarty, M.D.
of the Section on Surgical Pathology, of the Mayo Clinic,
Rochester, Minn.

10. The average length of postoperative life of patients without local lymphocytic infiltration was 15 per cent. less than the average length of post-operative life of patients with local lymphocytic infiltration.

1949

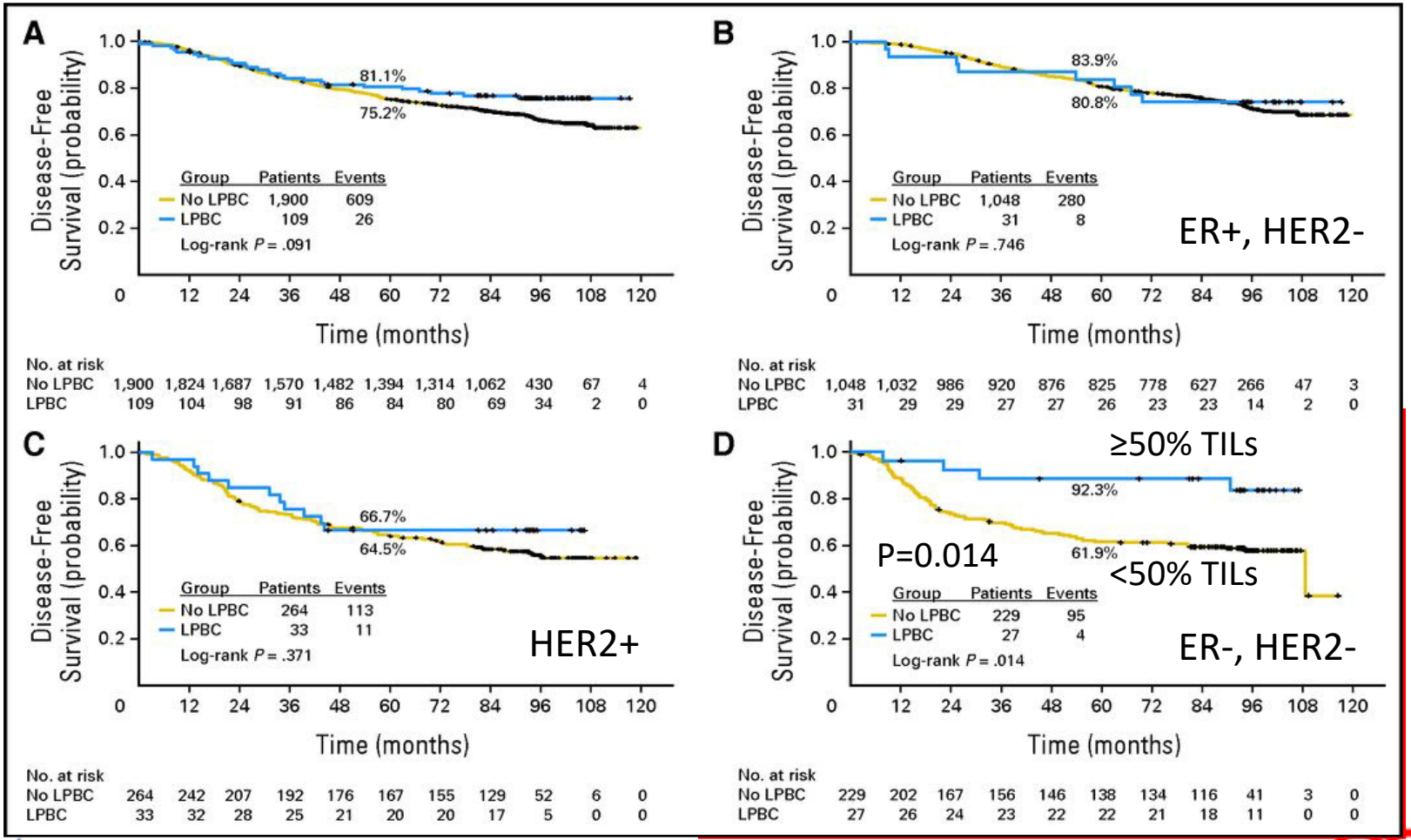
THE RELATIVELY FAVORABLE PROGNOSIS OF MEDULLARY CARCINOMA OF THE BREAST

Oliver S. Moore, Jr., M.D.,* and Frank W. Foote, Jr., M.D.

Sistrunk et al. Ann Surg. 1922 Jan;75(1):61-9
Moore et al. Cancer. 1949 Jul;2(4):635-42.

TILs er en prognostisk markør i triple negative

BIG02-98: Adjuverende, fase III, 2009 N+ BC pts., Median FU: 8 år



Loi et al. J Clin Oncol. 2013 Mar 1;31(7):860-7.

Prognostisk værdi af TILs i triple negative

Linær sammenhæng mellem TILs og prognose:

- For hver 10% stigning i stromale TILs:
  - hhv. 15-17% reduktion i risiko for recidiv og død

Valideret i ECOG2197 og ECOG1199

og FinHER studiet (level 1 evidens)

Metaanalyse (8 studier; 2987 TNBC pts.)
For hver 10% stigning i TILs
→ ca. 15-20% reduktion i recidiv, DM og død

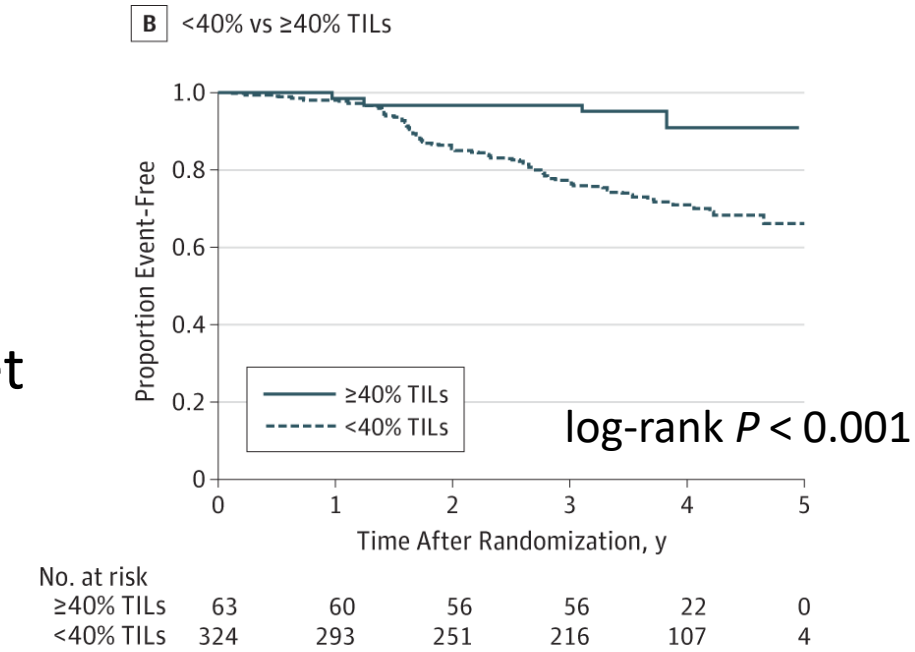
Loi et al. J Clin Oncol. 2013;31(7):860-7
Adams et al. J Clin Oncol. 2014;32:2959-67
Loi et al. Ann Oncol 2014;25:1544-50
Ibrahim et al. Breast Cancer ResTreat2014;148:467-476

Tilsvarende prognostisk værdi i HER2 +

NeoALLTO:
455 HER2+ BC pts.,
Median FU: 3,77 år

Hver 1% stigning i TILs associeret med 3% reduktion i recidiv rate

Effekt afh. af Herceptin, som inducerer type 1 immunitet



Salgado et al. JAMA Oncol. 2015 Jul;1(4):448-54

TILs som prædiktiv markør

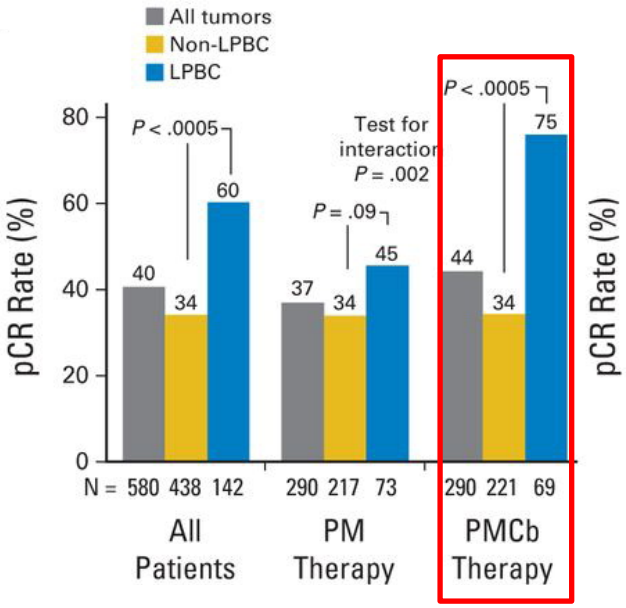
TILS er ass. med forbedrede pCR rater ved neoadj. KT

- I GeparDuo og GeparTrio (1058 pts):

40% vs. 7% pCR (”høj” /ingen TILs)

- I GeparSixto (580 pts):

70% pCR (”høj” TILs) ved tillæg af Carboplatin



Anvendelig prædiktivt for PDL-1 inhibitorer?

- PDL-1 expr. ass med ”høj” TILs
- Ikke veldefineret som prædiktiv markør

Denkert et al. J Clin Oncol. 2010;28(1):105-13
Denkert at al. J Clin Oncol. 2015;33(9):983-91

Analytisk validitet af TILs

Reproducerbarhedsstudie i DBCGs patologiudvalg

Standardized assessment of tumor-infiltrating lymphocytes in breast cancer: an evaluation of inter-observer agreement between pathologists

Trine Tramm[a], Tina Di Caterino[b], Anne-Marie B. Jylling[b], Giedrius Lelkaitis[c], Anne-Vibeke Lænkholm[d], Péter Ragó[e], Tomasz P. Tabor[f], Maj-Lis M. Talman[c] and Emmanouela Vouza[g]; On behalf of the Scientific Committee of Pathology, Danish Breast Cancer Group (DBCG)

Formål:

- Vurdering af inter-observer variabiliteten for aflæsning af TILs

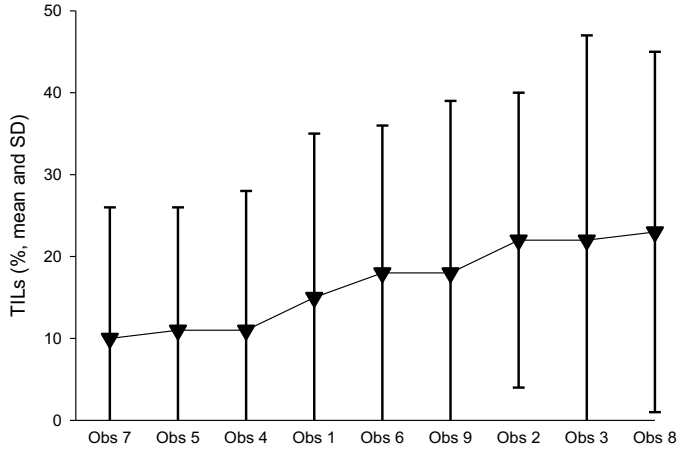
Materiale og metoder:

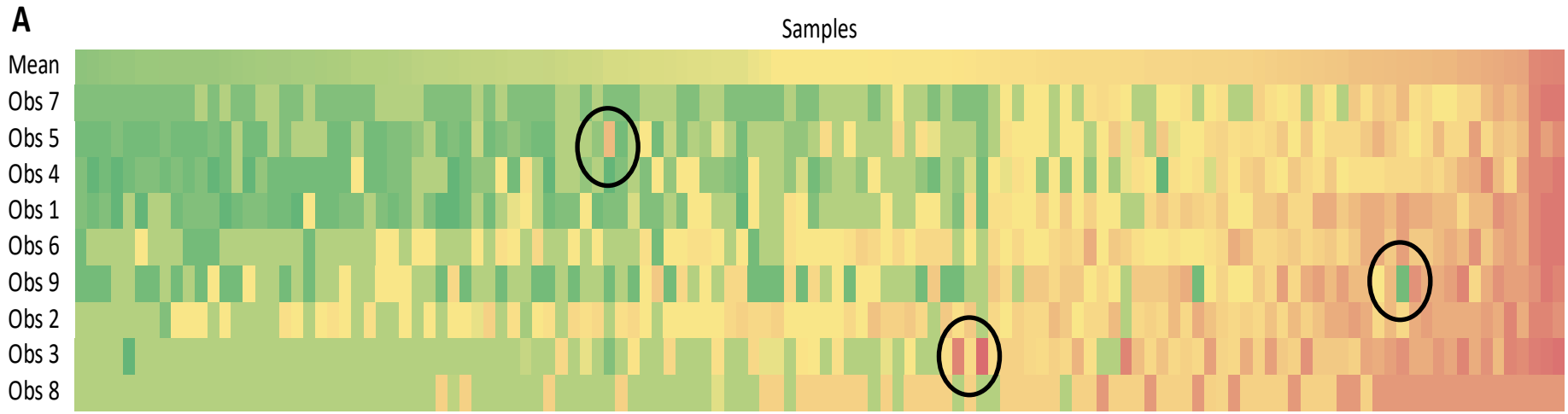
- 124 indscannede tumorer (varierende histologiske typer, ER/HER2 status)
- 9 patologer
- Internationale guidelines for aflæsning af TILs (HE-snit)

Salgado et al., Ann Oncol 2015;26:259-271
Tramm et al. Acta Oncol. 2018 Jan;57:90-94

Reproducerbarhedstudie Resultater

- Individuel ”tærskel”
- Outliers
  - Fejlindtastning
  - Fejlvurdering





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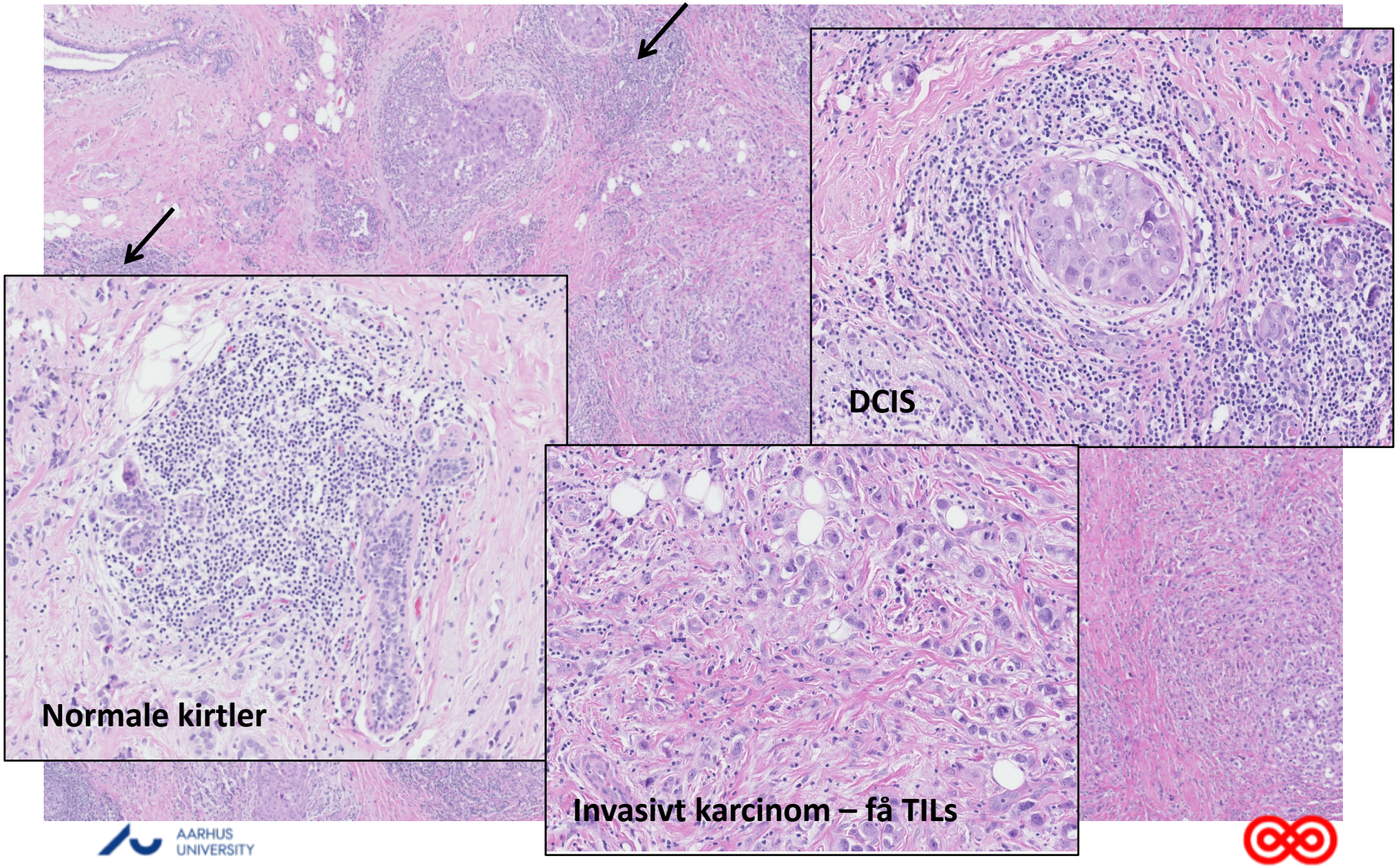
Tramm et al. Acta Oncol. 2018 Jan;57:90-94

Fejlkilder



Reproducerbarhedstudie Resultater

Table 2 Interobserver agreement in assessment of tumour-infiltrating lymphocytes (TILs)		
Intraclass coefficient (ICC)		0.71 (95% CI: 0.65-0.77)
Fleiss´ kappa values		
	TILs 0-10%, 11-39%, ≥40%	0.41
	TILs 0-20%, 21-49%, ≥50%	0.36
	TILs <50% *vs* ≥50%	0.48
	TILs <60% *vs* ≥60%	0.44
Concordance rates		
	TILs 0-10%, 11-39%, ≥40%	0.79 (range: 0.60-0.94)
	TILs 0-20%, 21-49%, ≥50%	0.82 (range: 0.54-0.92)
	TILs <50% *vs* ≥50%	0.93 (range: 0.81-0.99)
	TILs <60% *vs* ≥60%	0.95 (range: 0.77-0.99)

Fair-moderate

Konklusion:

- Bedst overenstemmelse ved dichotomisering i ”lav”/”høj”
- Ikke anvendelig endnu i rutine diagnostik

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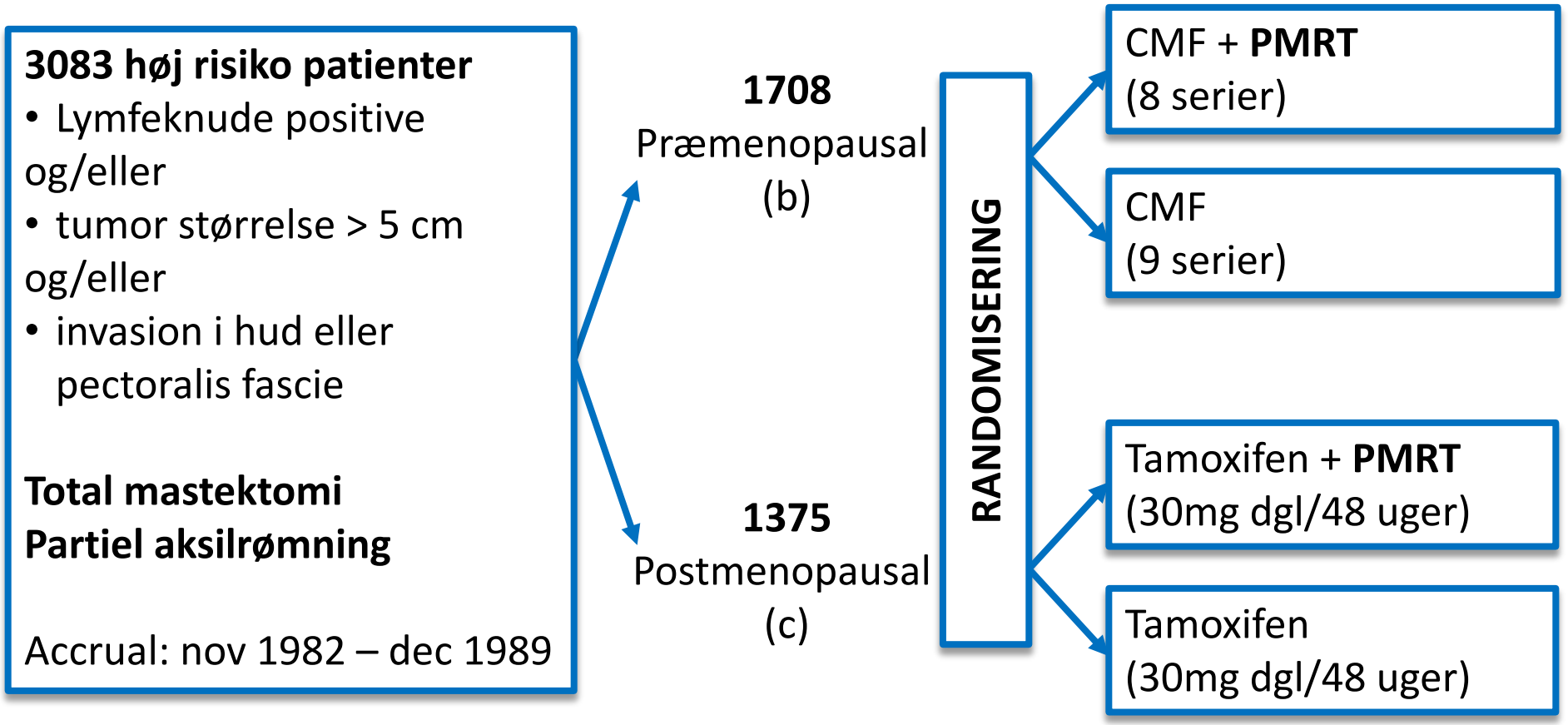
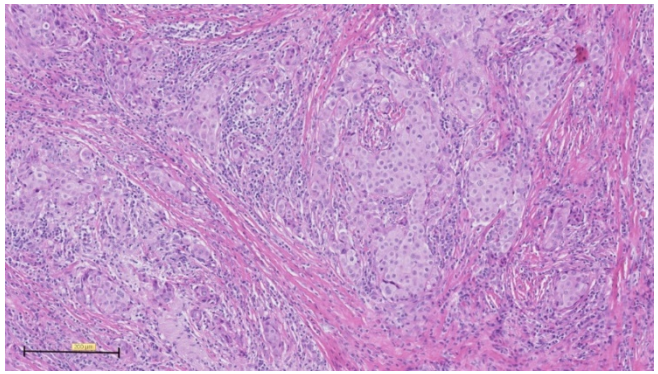
Tramm et al. Acta Oncol. 2018 Jan;57:90-94

TILs og stråleterapi: ”DBCG82bc revisited”



TILs i DBCG82bc

- 999 DBCG82bc patienter
- 2 observatører
- ER, PR, HER2, Ki67 (IHC4)

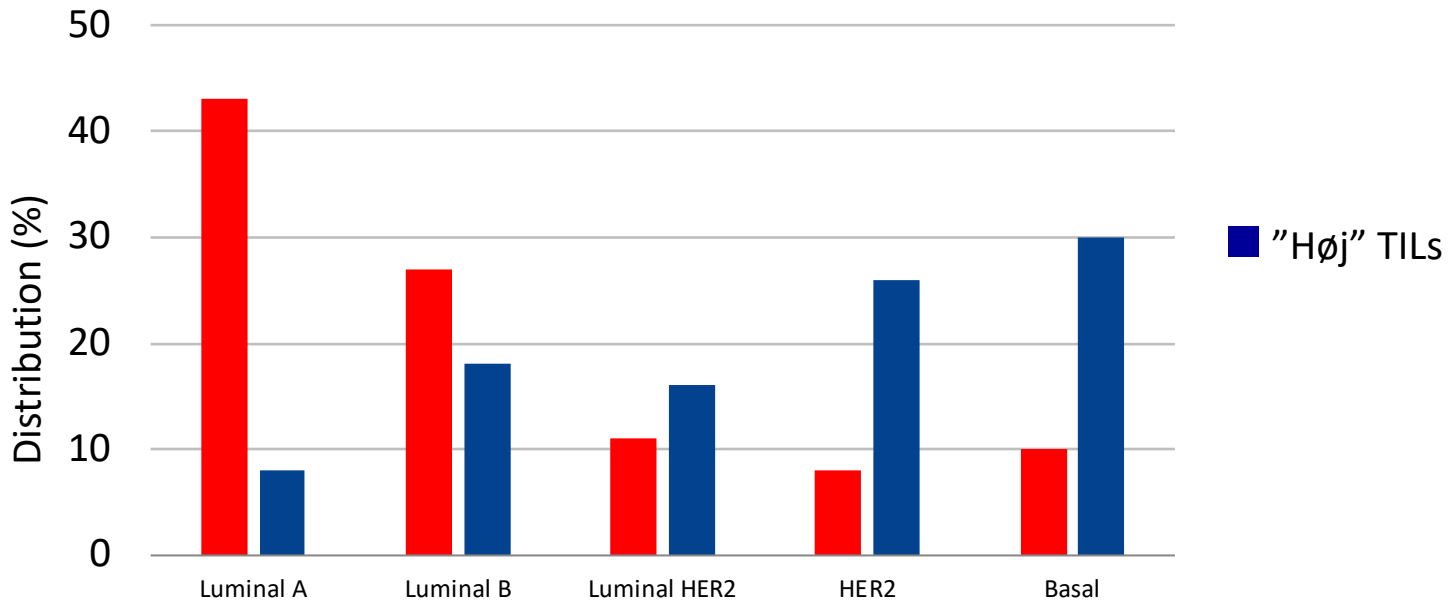


Interobserver agreement in assessment of tumour-infiltrating lymphocytes (TILs)	
Intraclass coefficient (ICC)	0.74 (95% CI: 0.72-0.77)
Fleiss´ kappa values	
TILs 0-10%, 11-39%, ≥40%	0.61
TILs 0-20%, 21-49%, ≥50%	0.61
TILs <30% *vs* ≥30%	0.69
TILs <50% *vs* ≥50%	0.65
TILs <60% *vs* ≥60%	0.66
Agreement rates (genereret ud fra udregning af Kappa)	
TILs 0-10%, 11-39%, ≥40%	0.83
TILs 0-20%, 21-49%, ≥50%	0.88
TILs <30% *vs* ≥30%	0.92
TILs <50% *vs* ≥50%	0.93
TILs <60% *vs* ≥60%	0.94

Good

Fordelingen af TILs i DBCG82bc

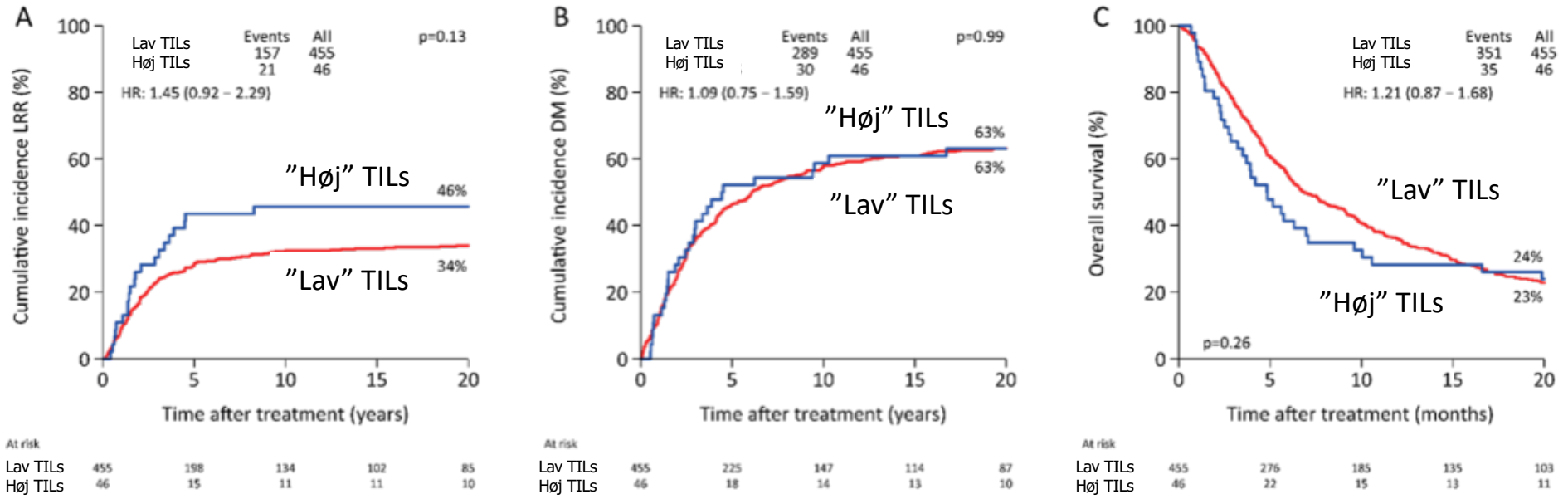
105/999 pts med ”høj” TILs = 10,5%



ER+ HER2- Ki67< 14%	ER+ HER2- Ki67≥ 14%	ER+ HER2+	ER- HER2+	ER- HER2-

Prognostisk værdi af TILs i DBCG82bc

No PMRT gruppe (501 pts)



Ingen påvist prognostisk effekt på LRR, DM, OS
For lille antal til subgruppe analyse (subtyper)

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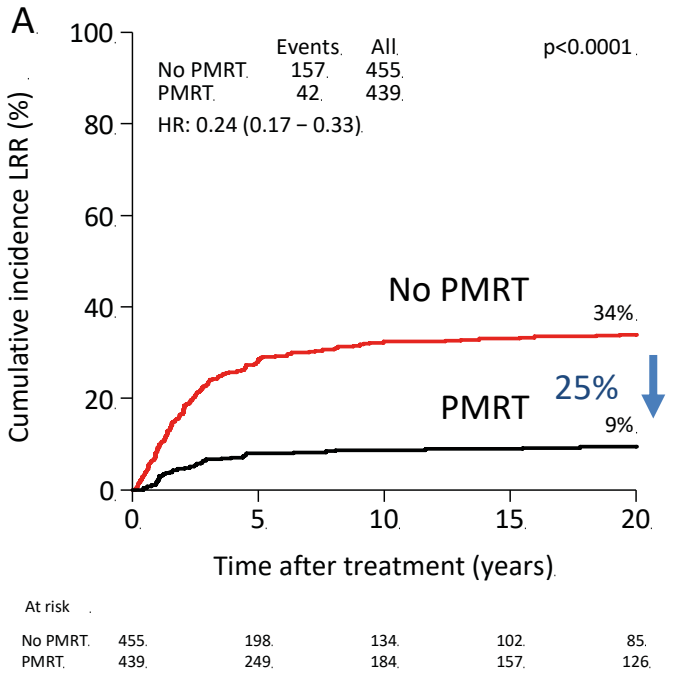
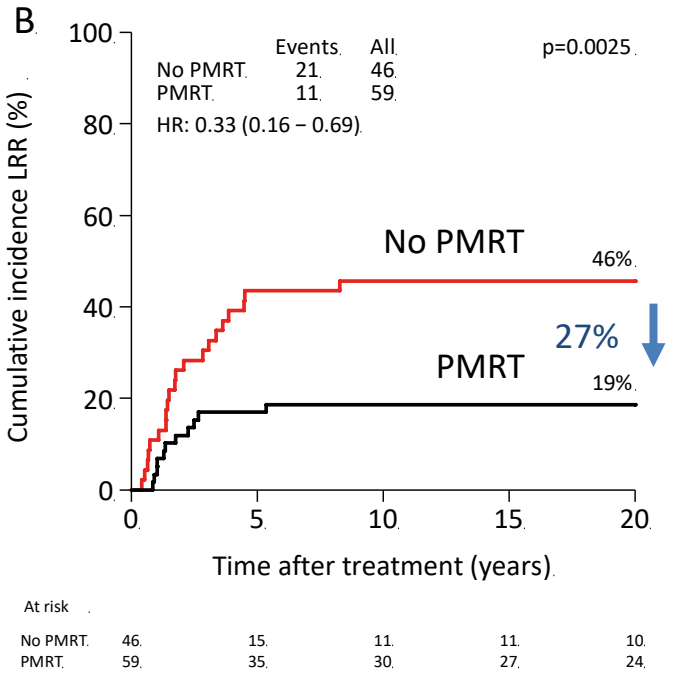
Prædiktiv værdi af TILs
Loco-regional kontrol

"Lav" TILs



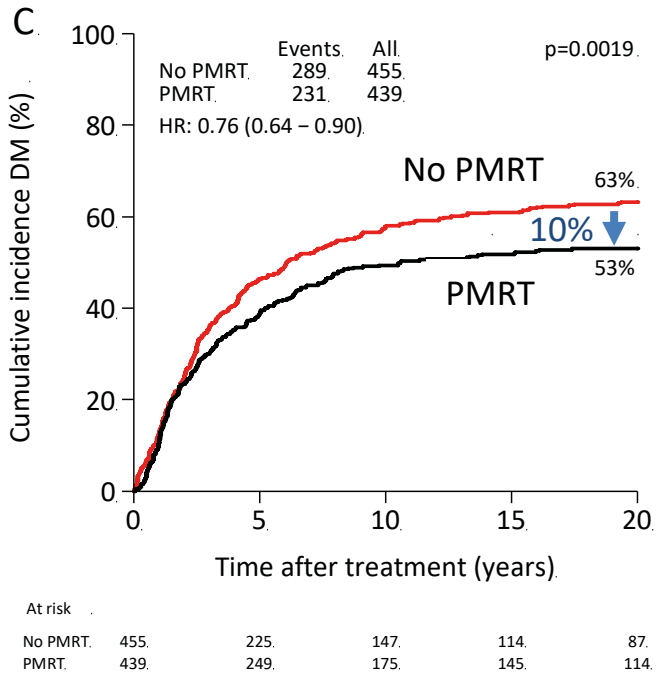
"Høj" TILs



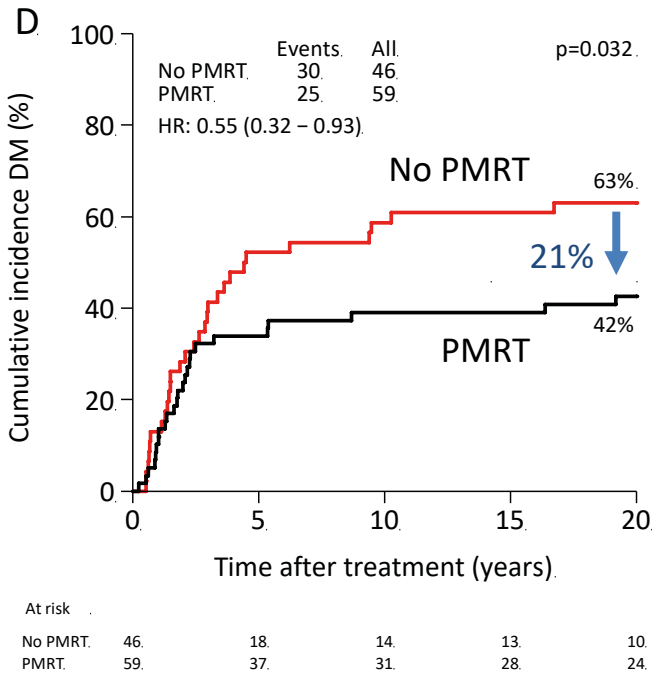
Samme gavn af PMRT uanset niveau af TILs

Prædiktiv værdi af TILs
Fjernmetastaser

"Lav" TILs



"Høj" TILs

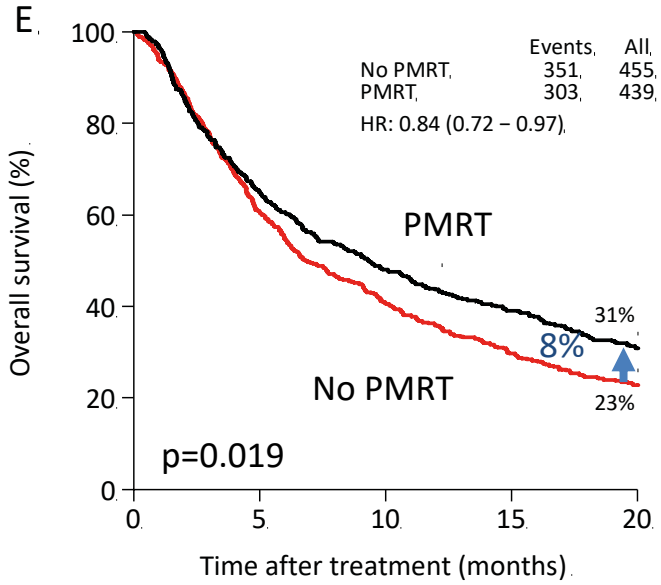


Forskellen i gavn af PMRT ikke signifikant (interaktionstest)

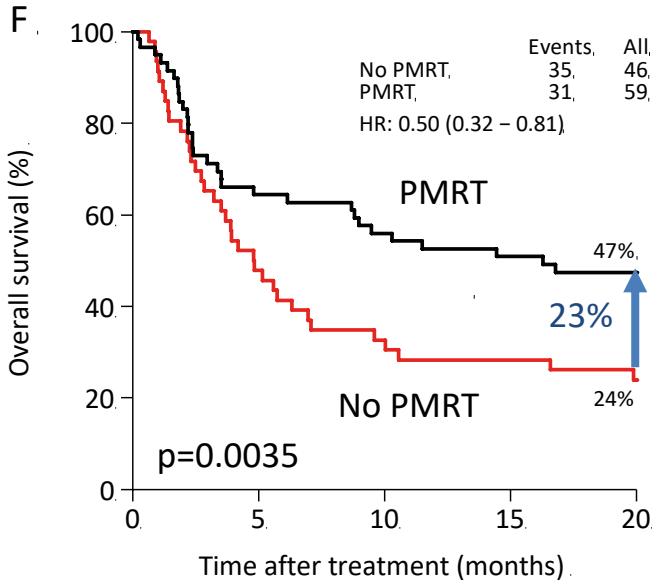
Prædiktiv værdi af TILs
Overall survival

Interaktionstest, p=0.033

"Lav" TILs



"Høj" TILs



Patienter med "høj" TILS har signifikant mere gavn af PMRT i fht. OS
- også ved justering for diverse faktorer i MVA (incl. ER/HER2)

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Værtsimmunitet og strålebehandling

THE LANCET, NOVEMBER 30, 1974

DECREASED SURVIVAL RELATED TO IRRADIATION POSTOPERATIVELY IN EARLY OPERABLE BREAST CANCER

JAN STJERNSWÄRD

Department of Clinical Oncology, Swiss Institute for Experimental Cancer Research, Ludwig Cancer Institute (Lausanne Branch), and Department of Radiotherapy, University Hospital of Lausanne, Switzerland

A possible explanation for the increased mortality in the irradiated groups may be the effect of irradiation on host immunity. In a situation where we have minimal residual tumour cells, later expressing themselves as metastases, local irradiation leads to a long-lasting lymphopenia (see figure). Tumour-associated immune reactions against human breast cancer have been found in vivo and in vitro, and it is possible that breast-cancer cells possess tumour-associated antigens that may induce rejection reactions of importance for the clinical outcome. The irradiation-induced decrease of host immunity in a situation where the patients have minimal residual tumour [1] may be related to the slight but constant earlier appearance or increase of distant metastasis.[12] This may give an indication of the importance, if any, of host anti-tumour immunity in a cancer patient where, by definition, early immune surveillance has already failed.

Opsummering

- Få brystkræft tumorer har ”højt” niveau af TILs
  - oftest i triple negative (TNBC) og HER2+
- ”Højt” niveau af TILS er udtryk for god prognose
  - lineær ass. mellem TILs og RFS/OS for TNBC/HER2+
- TILs er associeret med pCR rate
  - navnligt i TNBC/HER2+
- ”Højt” TILs niveau er ass. med PDL-1 ekspression
  - repræsenterer muligt subgruppe med potentiale for immunmodulerende behandling
  - endnu ikke fastlagt ass. mellem TILs og gavn af PDL-1 inhibitorer
- TILs kan ikke aktuelt anvendes til behandlingsselektion

Tak for opmærksomheden