DBCG

Betydning af systemisk behandling

Maj-Britt Jensen

1977
40
2017
DBCG

16th ACTA ONCOLOGICA SYMPOSIUM

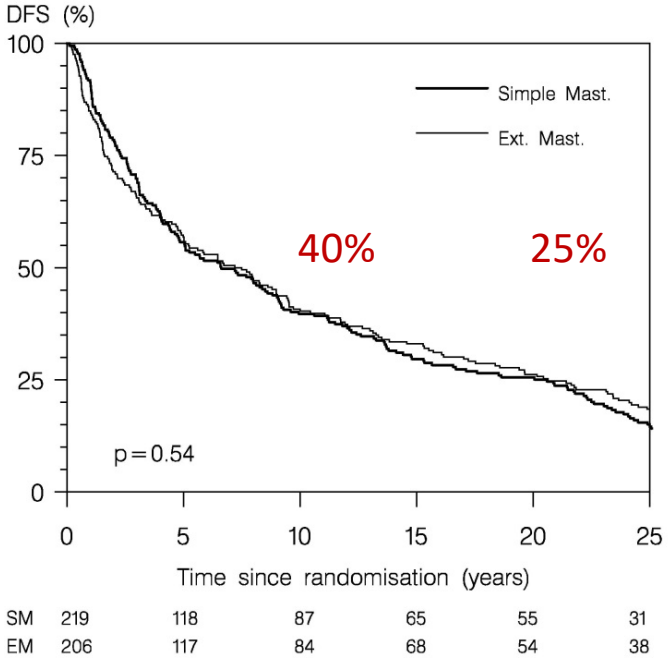
Long time ago

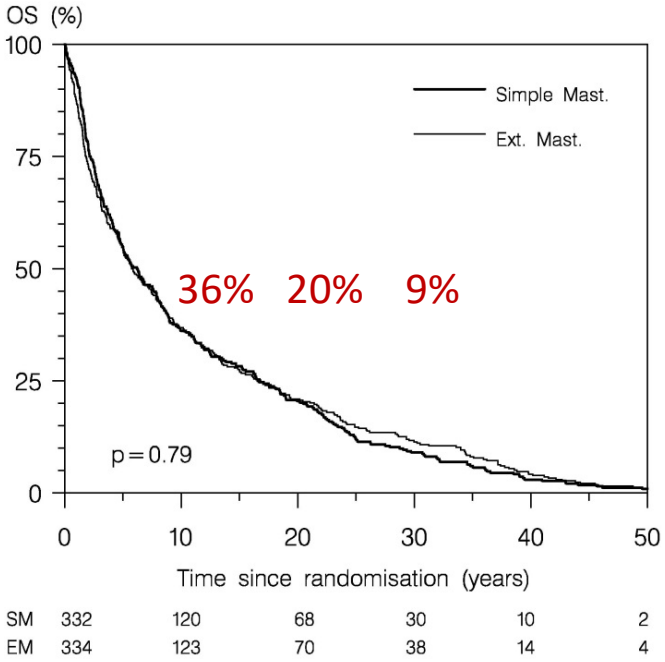
Acta Oncologica, 2008; 47: 633-638

Extended radical mastectomy versus simple mastectomy followed by radiotherapy in primary breast cancer. A fifty-year follow-up to the Copenhagen Breast Cancer randomised study

HELGE JOHANSEN, SIGVARD KAAE, MAJ-BRITT JENSEN & HENNING T. MOURIDSEN

Indgået 1951-1957
Alder: median 58





DBCG 77

Nodal status og tumorstørrelse allokerede patienter til

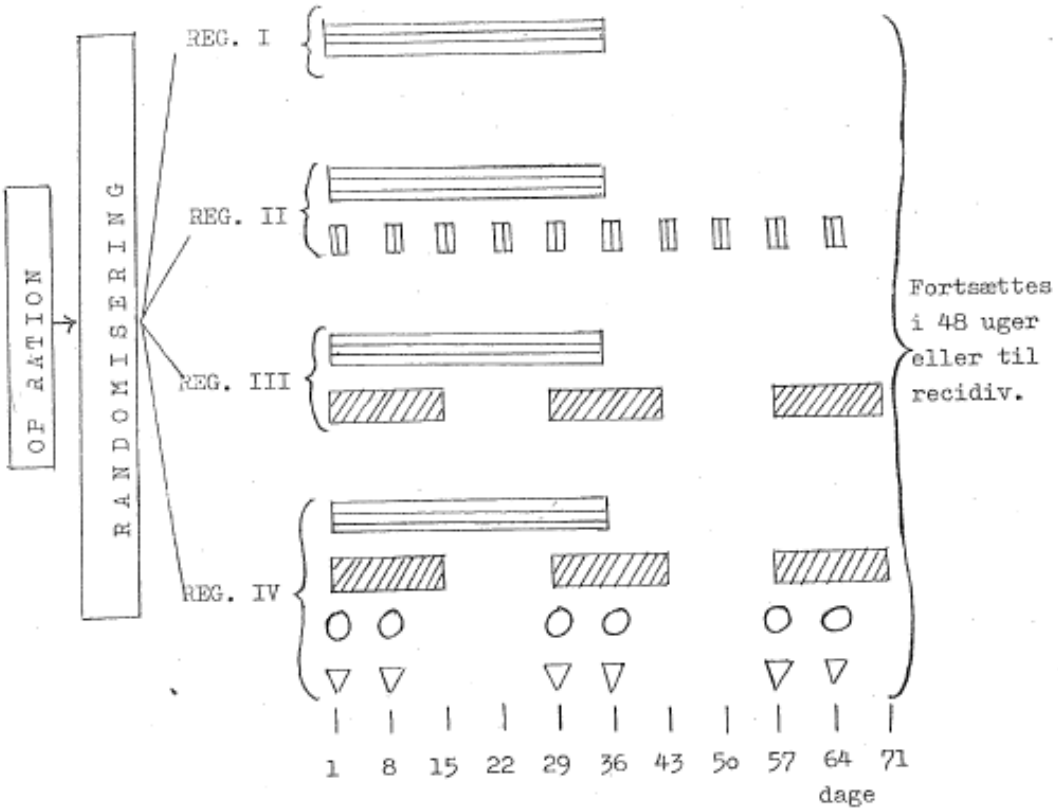
- lav-risiko gruppen (node-negative, tumor < 5cm),
  ingen adjuverende lokal eller systemisk behandling

- høj-risiko gruppen
  strålebehandling +/- systemisk behandling

DBCG 77B

DBCG 77-1b

SKITSE OVER BEHANDLINGSPLAN.



= strålebehandling

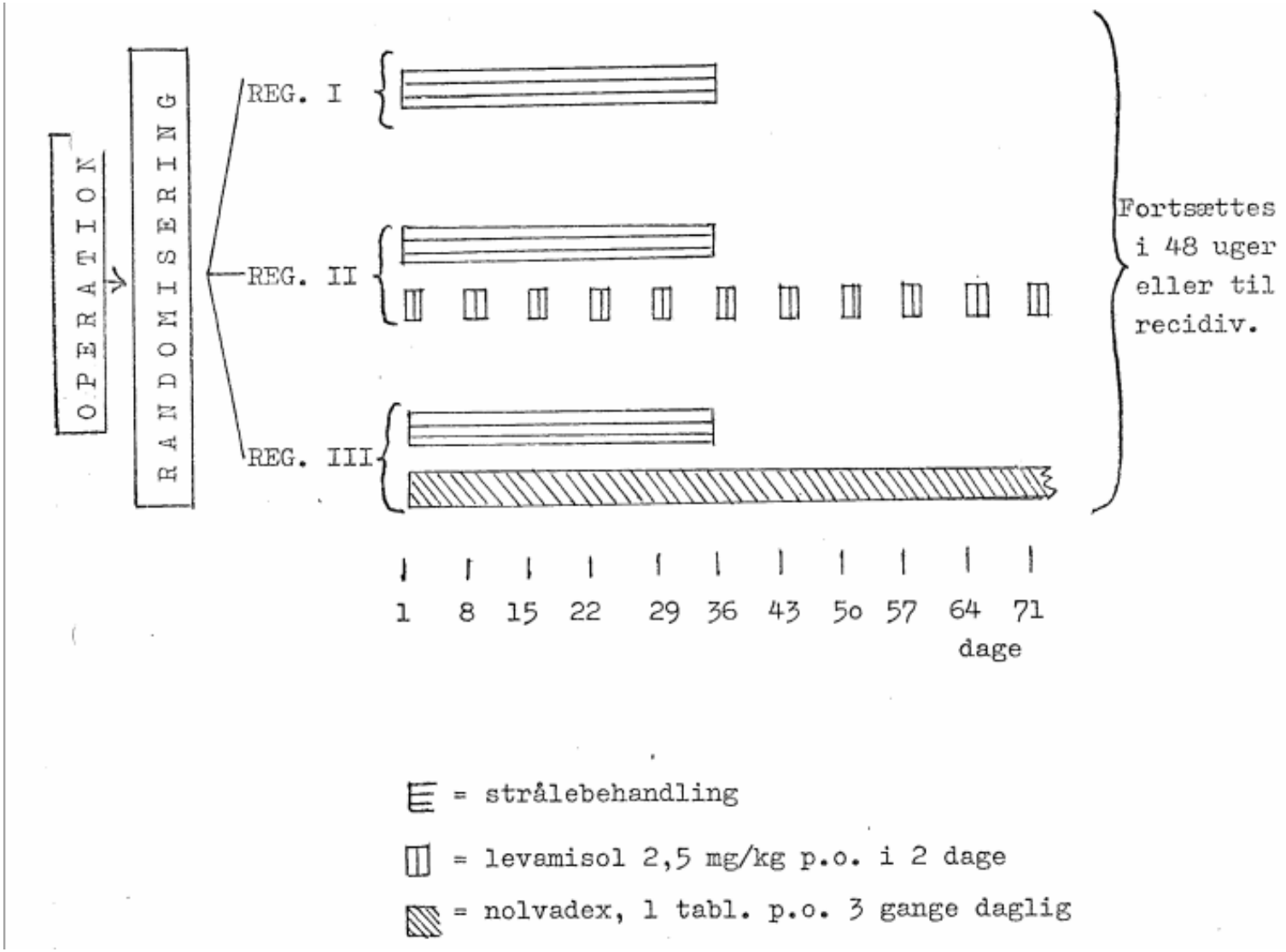
= levamisol 2,5 mg/kg p.o. i 2 dage

= 5-fluorouracil 500 mg/m^2 i.v.

= metotrexat 30 mg/m^2 i.v.

= cyclophosphamid, REG. III 130 mg/m^2 p.o. i 14 dg.
REG. IV 80 mg/m^2 p.o. i 14 dg.

DBCG 77C

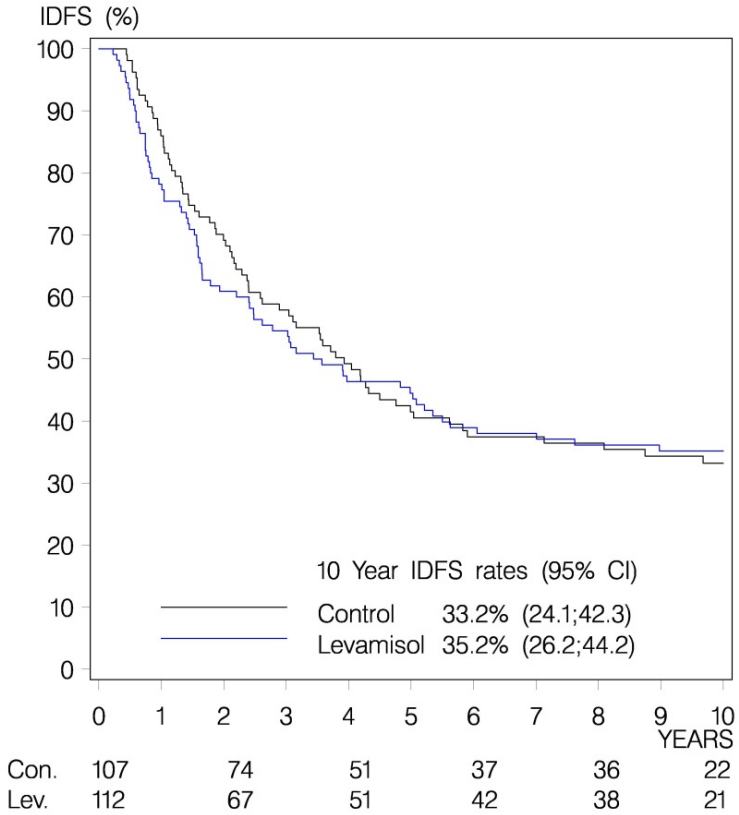

OPERATION
RANDOMISERING
REG. I
REG. II
REG. III
Fortsættes i 48 uger eller til recidiv.
1 8 15 22 29 36 43 5o 57 64 71
dage
= strålebehandling
= levamisol 2,5 mg/kg p.o. i 2 dage
= nolvadex, 1 tabl. p.o. 3 gange daglig

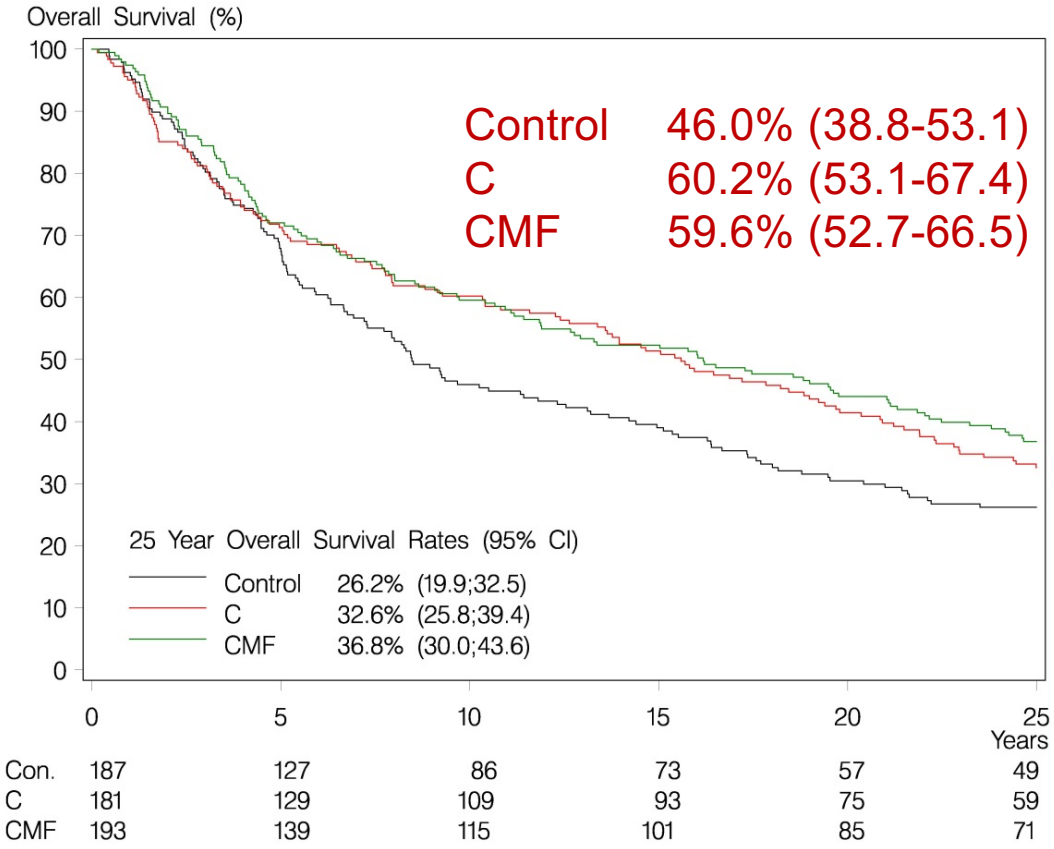
DBCG 77B

Cancer 2010

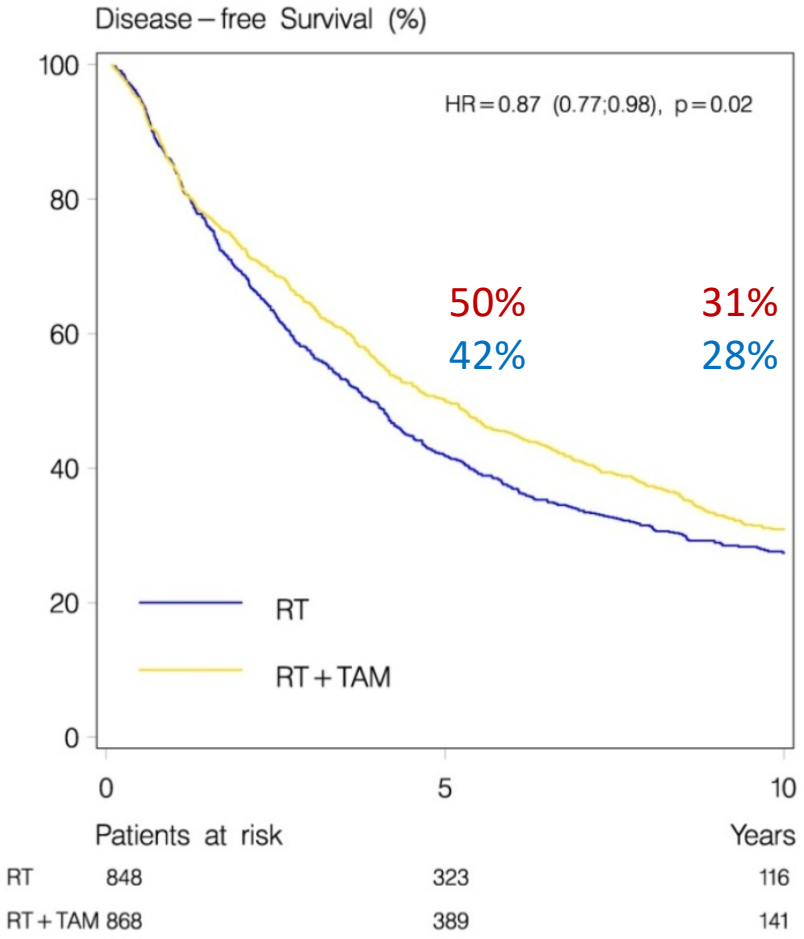
Cyclophosphamide, Methotrexate, and Fluorouracil; Oral Cyclophosphamide; Levamisole; or No Adjuvant Therapy for Patients With High-Risk, Premenopausal Breast Cancer

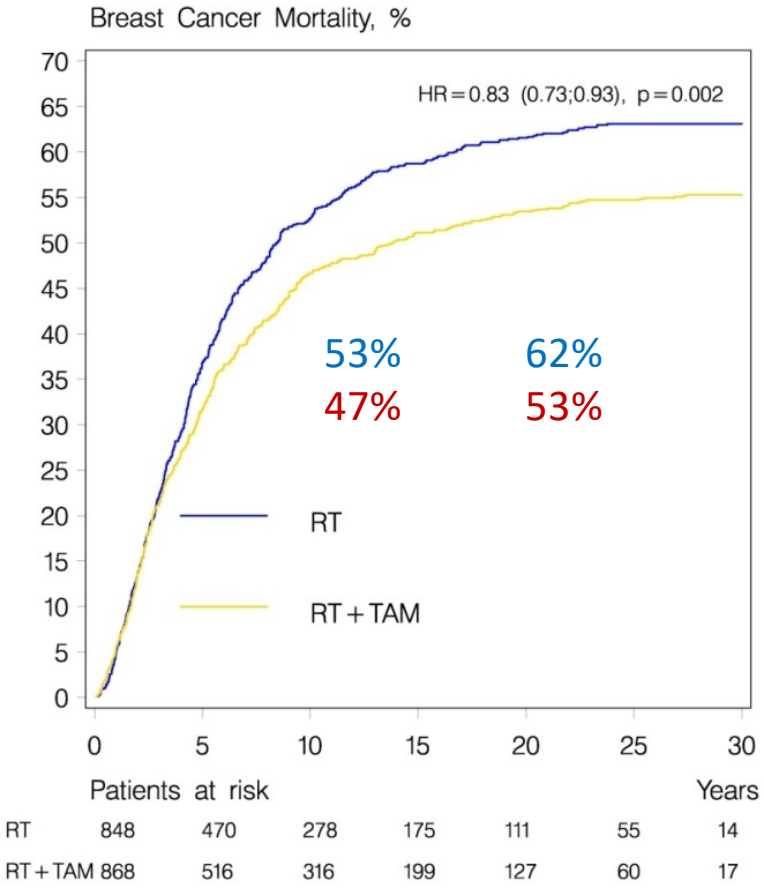
Bent Ejlertsen, Henning T. Mouridsen, Maj-Britt Jensen, Jørn Andersen, Michael Andersson, Claus Kamby, Ann S. Knoop





DBCG 77C


Disease – free Survival (%)
HR = 0.87 (0.77;0.98), p = 0.02
50%
42%
31%
28%
RT
RT + TAM
100
80
60
40
20
0
0
5
10
Patients at risk
Years
RT 848 323 116
RT + TAM 868 389 141


Breast Cancer Mortality, %
HR = 0.83 (0.73;0.93), p = 0.002
53%
47%
62%
53%
RT
RT + TAM
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Patients at risk
Years
RT 848 470 278 175 111 55 14
RT + TAM 868 516 316 199 127 60 17

DBCG 77 B&C

Høj-risiko patienter:
Mastektomi + AD, Strålebehandling
Receptor-ukendte

Bedre markører til at prognosticere patienter:

Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747–52.

Molekylære subtyper: Luminal A, Lum B, HER2-enriched og basal-like
- kan bestemmes med rimelig nøjagtighed vha IHC

ER
PR
HER2
Ki67,EGFR

}

	R	HER2		Ki67	EGFR
Lum A	+	-	&	Lav	
Lum B	+	+	v	Høj	
HER2+	-	+			
Basal-Like	-	-			+

European Journal of Cancer (2014) 50, 1412–1421

Available at www.sciencedirect.com

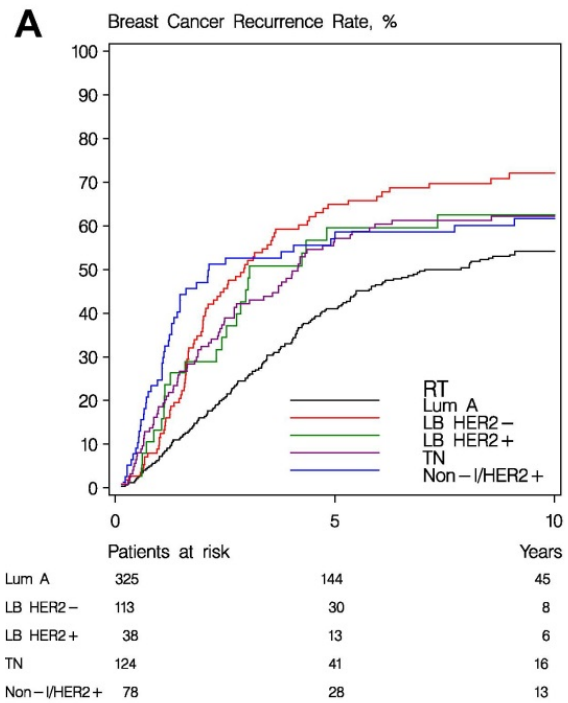
ScienceDirect

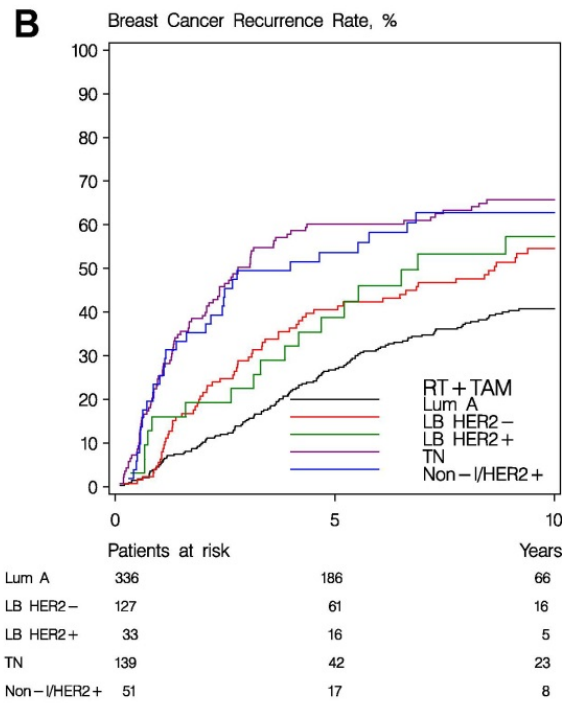
journal homepage: www.ejcancer.com

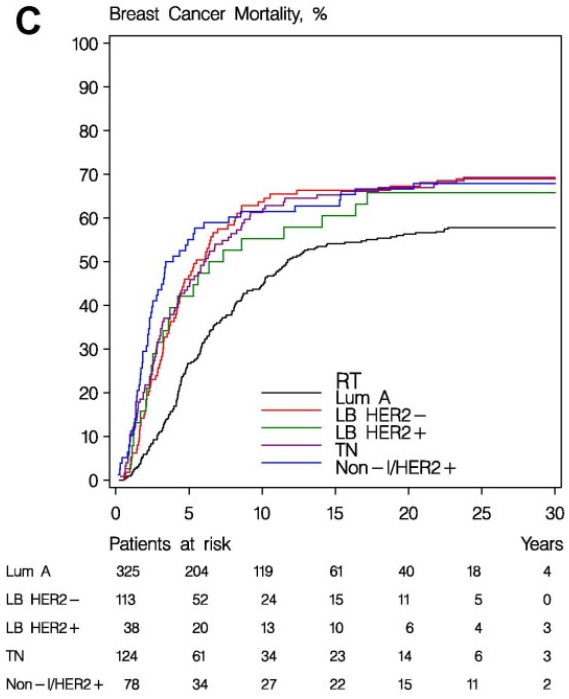
Estrogen receptor, Progesterone receptor, HER2 status and Ki67 index and responsiveness to adjuvant tamoxifen in postmenopausal high-risk breast cancer patients enrolled in the DBCG 77C trial

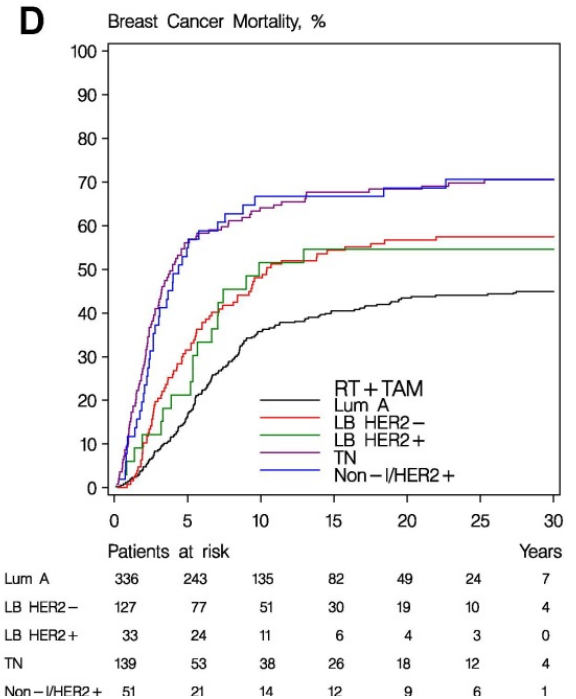
Ann S. Knoop [a,b,*], Anne-Vibeke Lænkholm [g], Maj-Britt Jensen [c], Kirsten V. Nielsen [d], Jørn Andersen [e], Dorte Nielsen [f], Bent Ejlertsen [b,c], for the Danish Breast Cancer Cooperative Group

N=678 RT
N=686 RT+TAM









DBCG 77B

Personalized Medicine and Imaging

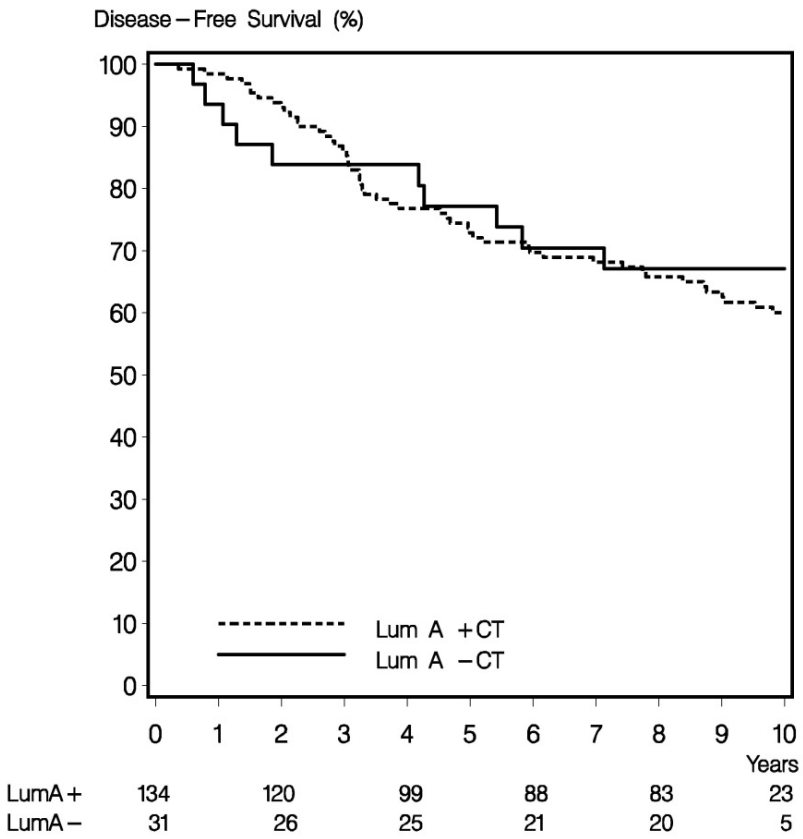
Clinical Cancer Research

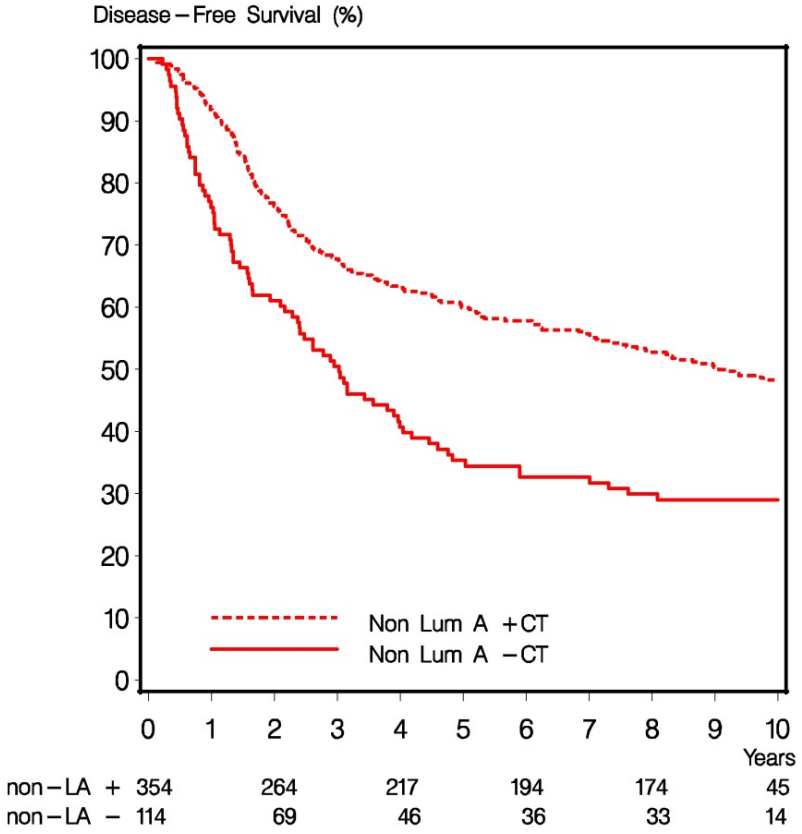
High-Risk Premenopausal Luminal A Breast Cancer Patients Derive no Benefit from Adjuvant Cyclophosphamide-based Chemotherapy: Results from the DBCG77B Clinical Trial

Torsten O. Nielsen[1], Maj-Brit Jensen[2], Samantha Burugu[1], Dongxia Gao[1], Charlotte L. Tykjaer Jørgensen[2], Eva Balslev[2], and Bent Ejlertsen[2]

Clinical Cancer Research. 2016; 22(17).

Subtypebestemmelse på 709 patienter vha. IHC.


Disease – Free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Lum A +CT
Lum A –CT
0 1 2 3 4 5 6 7 8 9 10
Years
LumA + 134 120 99 88 83 23
LumA – 31 26 25 21 20 5


Disease – Free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Non Lum A +CT
Non Lum A –CT
0 1 2 3 4 5 6 7 8 9 10
Years
non – LA + 354 264 217 194 174 45
non – LA – 114 69 46 36 33 14

ORIGINAL ARTICLE

Mortality and recurrence rates among systemically untreated high risk breast cancer patients included in the DBCG 77 trials

Maj-Britt Jensen, Torsten O. Nielsen, Ann S. Knoop, Anne-Vibeke Lænkholm, Eva Balslev and Bent Ejlertsen

Background:
Following loco-regional treatment for early breast cancer accurate prognostication is essential for communicating benefits of systemic treatment. The aim of this study was to determine time to recurrence and long-term mortality rates in high risk patients according to patient characteristics and subtypes as assigned by immunohistochemistry panels.

Patients and methods:
In November 1977 through January 1983, 2862 patients with tumors larger than 5 cm or positive axillary nodes were included in the DBCG 77 trials. Archival tumor tissue from patients randomly assigned to no systemic treatment was analyzed for ER, PR, Ki67, EGFR and HER2. Intrinsic subtypes were defined as follows: Luminal A, ER or PR >0%, HER2-negative, PR >10% and Ki67<14%; Luminal B, ER or PR >0%, (PR 10% or HER2-positive or Ki6714%); HER2E, ER 0%, PR 0%, HER2 positive; Core basal, ER 0%, PR 0%, HER2 negative and EGFR positive. Multivariate categorical and fractional polynomials (MFP) models were used to construct prognostic subsets by clinicopathologic characteristics.

Results:
In a multivariate model, mortality rate was significantly associated with age, tumor size, nodal status, invasion, histological type and grade, as well as subtype classification.

Conclusions:
With 35 years of follow-up, in this population of high-risk patients with no systemic therapy, no subgroup based on a composite prognostic score and/or molecular subtypes could be identified without excess mortality as compared to the background population.

Mortality and recurrence rates among systemically untreated high risk breast cancer patients included in the DBCG 77 trials

- Alle patienter i DBCG 77B og 77C modtog strålebehandling.
- I DBCG 77B blev patienter randomiseret til 1 af 4 arme: ingen systemisk behandling, levamisol, oral cyclophosphamide, eller oral cyclophosphamide plus methotrexate og fluorouracil.
- Patienter i DBCG 77C blev randomiseret til ingen systemisk behandling eller tamoxifen.
- Ingen af patienterne indgået i denne kohorte modtog adjuverende systemisk behandling. Kun patienter randomiseret til RT alene er inkluderet.
- Primære endepunkt i studiet er standardized mortality ratio (SMR).
- Sekundære endepunkter er tid til recidiv og overall survival (OS).

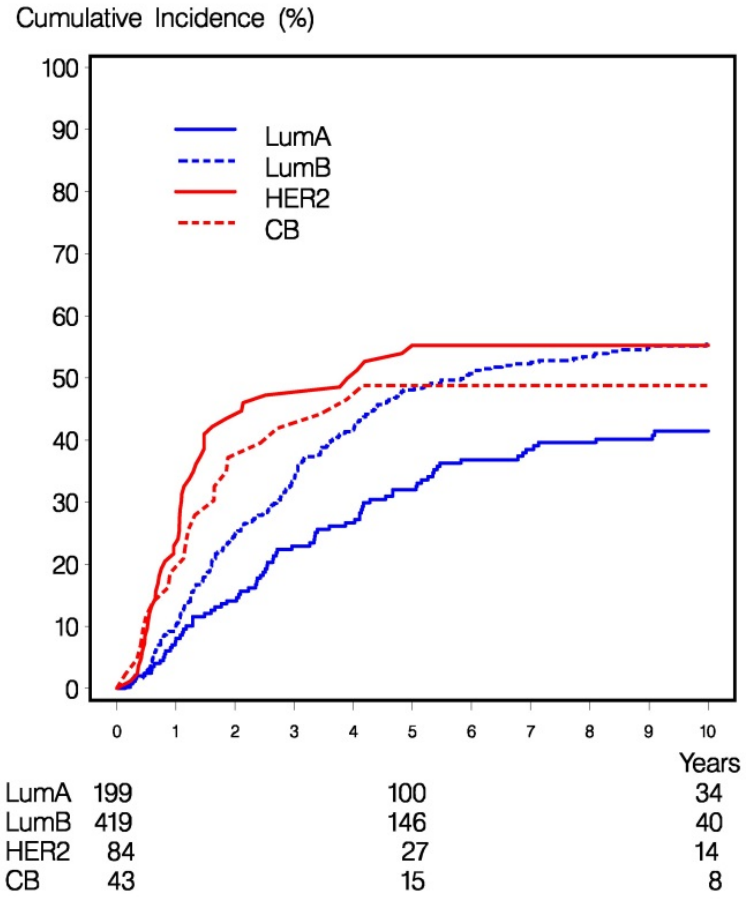
Mortality and recurrence rates among systemically untreated high risk breast cancer patients included in the DBCG 77 trials

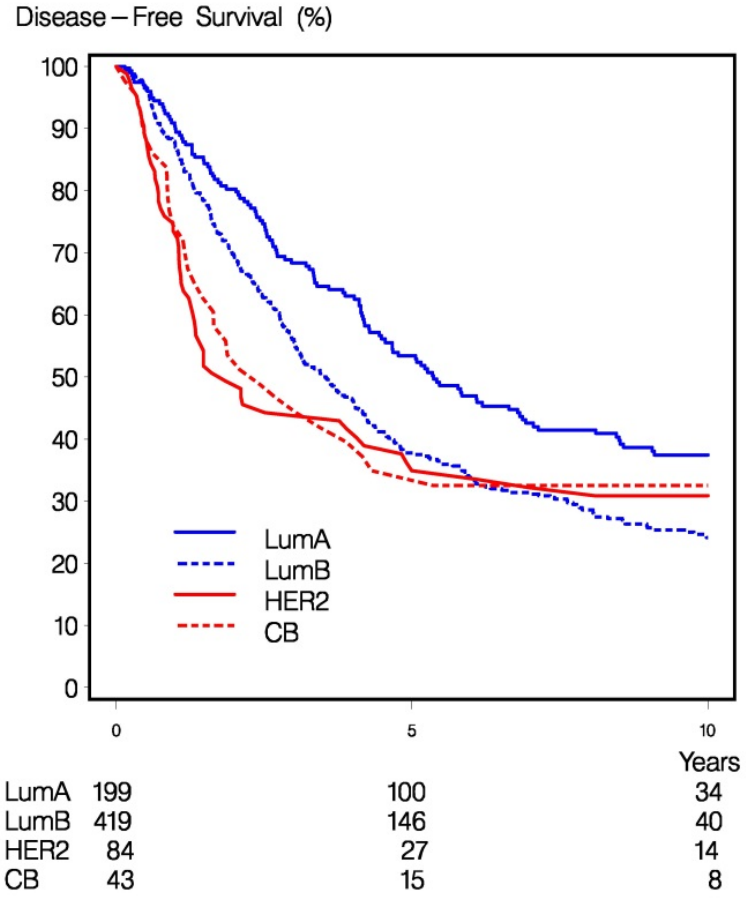
Total	<60 år	Node-positive	2-5cm	>5cm	Invasion fascien	G II	G III
1100	*42%*	*86%*	*53%*	*19%*	*25%*	*55%*	*17%*

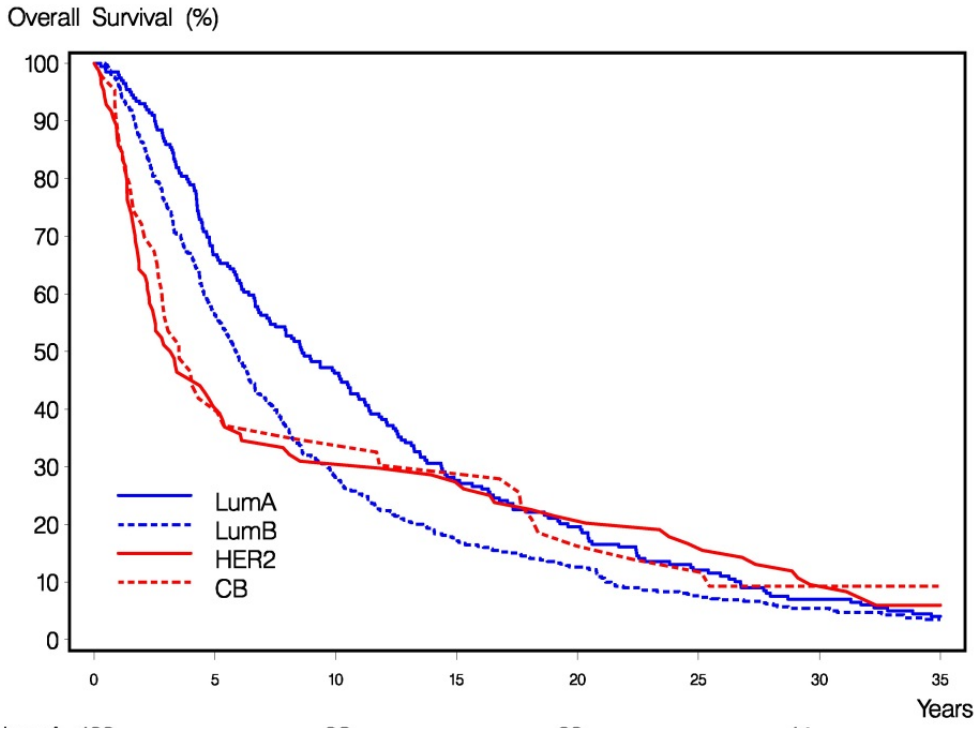
Subtype	Luminal A		Luminal B		HER2E		Core Basal		NA	
N	N	%	N	%	N	%	N	%	N	%
745	199	*27*	419	*56*	84	*11*	43	*6*	355	*32*

Med en opfølgning på 10 år har 526 patienter (48%) recidiv, heraf 450 fjernrecidiv. 203 patienter (19%) har en hændelse med konkurrerende årsag.

Indenfor de første 2½ år har 20% af Luminal A patienter et recidiv, for Luminal B er tallet 30%, og 40% eller mere for HER2E og Core-basal.







Observeret antal døde er 1050, forventet 372

SMR 2.82 (2.65; 2.99)

SMR		Years after surgery				Overall	
Subtype		0-5		5-10	>10		
	Lum A	**3.20**	(2.52;4.08)	2.14	1.76	**2.18**	(1.89;2.51)
	Lum B	**5.13**	(4.43;5.92)	4.46	1.65	**3.23**	(2.93;3.55)
	HER2E	**13.0**	(9.87;17.2)	2.53	0.88	**2.50**	(2.01;3.11)
	Core Basal	**10.1**	(6.81;14.9)	1.35	1.07	**2.60**	(1.90;3.56)

På basis af multivariat model for SMR:
clinical prognostic score index (cPSI) ud fra β koefficienter.

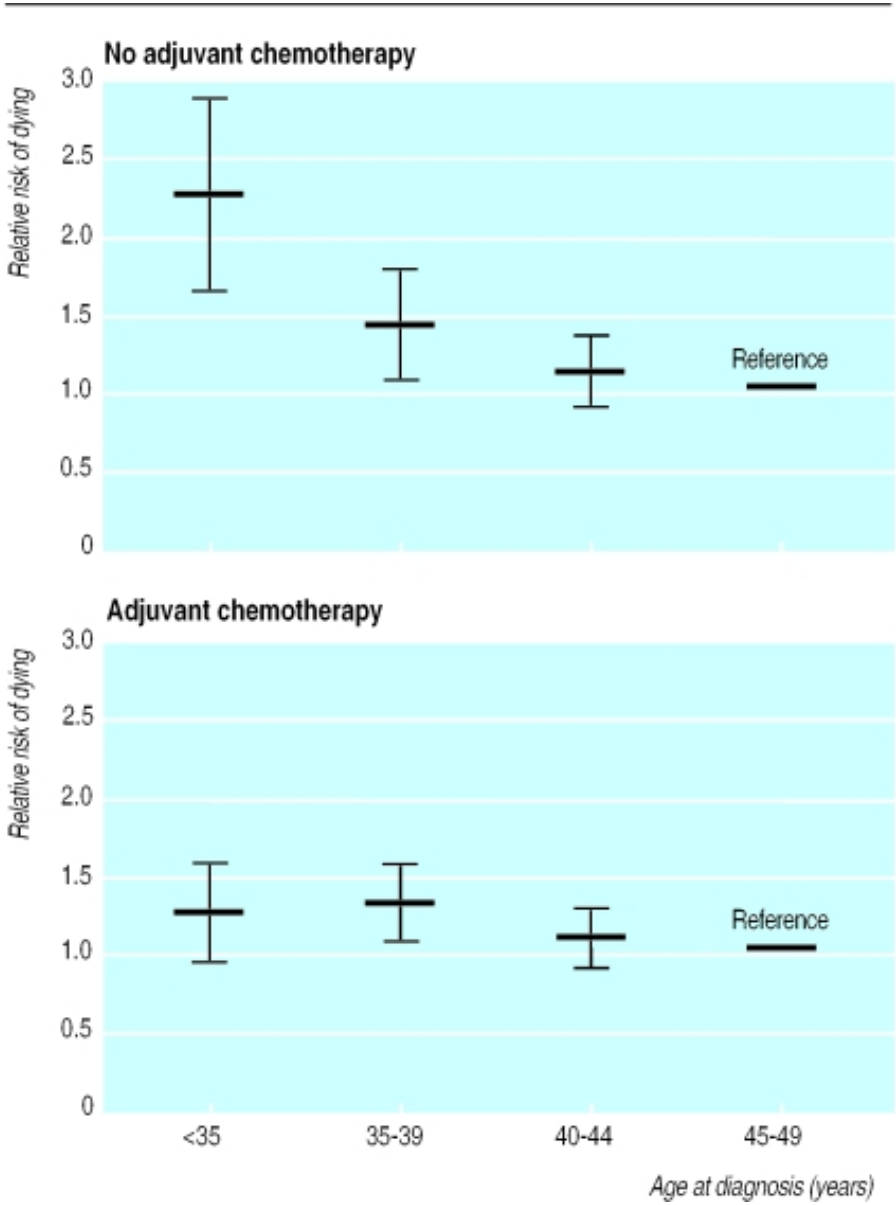
Patienter i 0,1 fraktilen i kombination med Luminal A
har ”excess mortality”, dvs SMR >1.

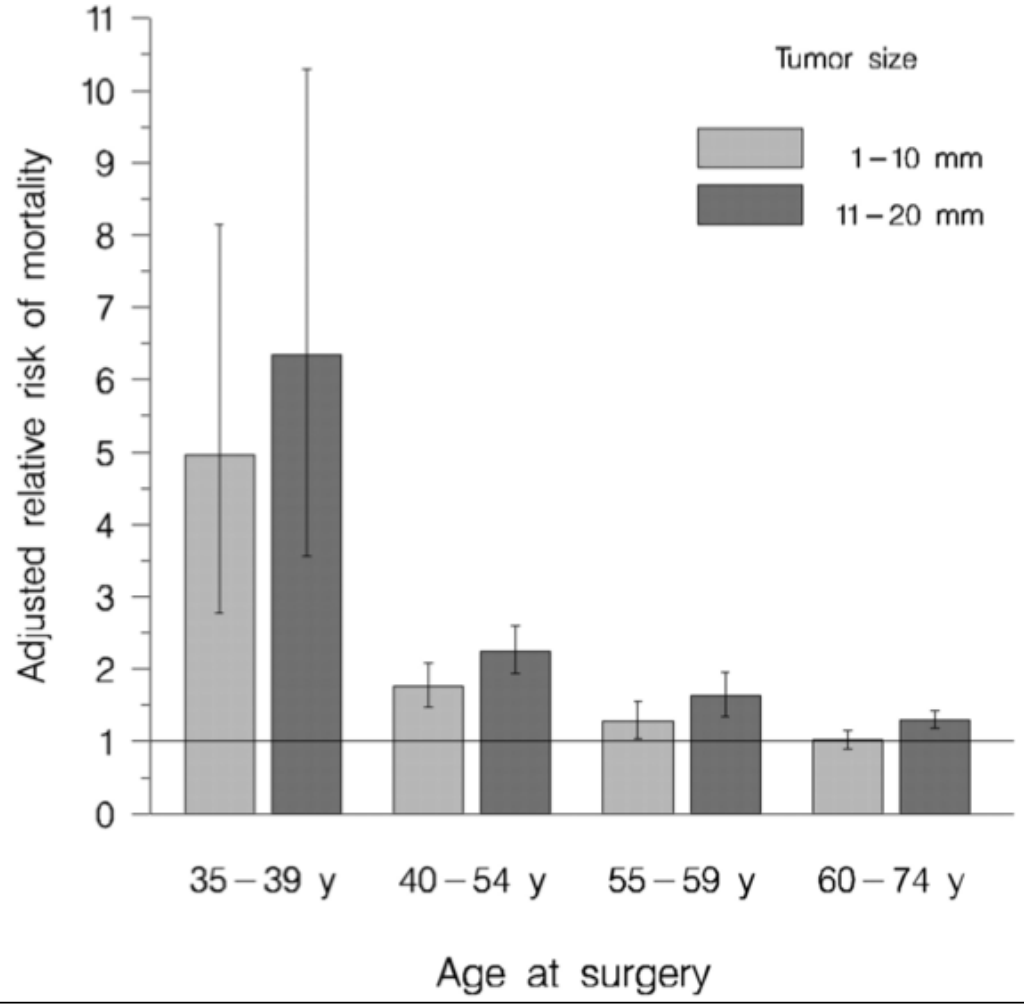
Results:
In a multivariate model mortality rate was significantly associated with age, tumor size, nodal status, invasion, histological type and grade, as well as subtype classification.
Conclusion:
With 35 years of follow-up, in this population of high-risk patients with no systemic therapy, no subgroup based on a composite prognostic score and/or molecular subtypes could be identified without excess mortality as compared to the background population.

BMJ 2000;320:474–9

Factors influencing the effect of age on prognosis in breast cancer: population based study

Niels Kroman, Maj-Britt Jensen, Jan Wohlfahrt, Henning T Mouridsen, Per Kragh Andersen, Mads Melbye

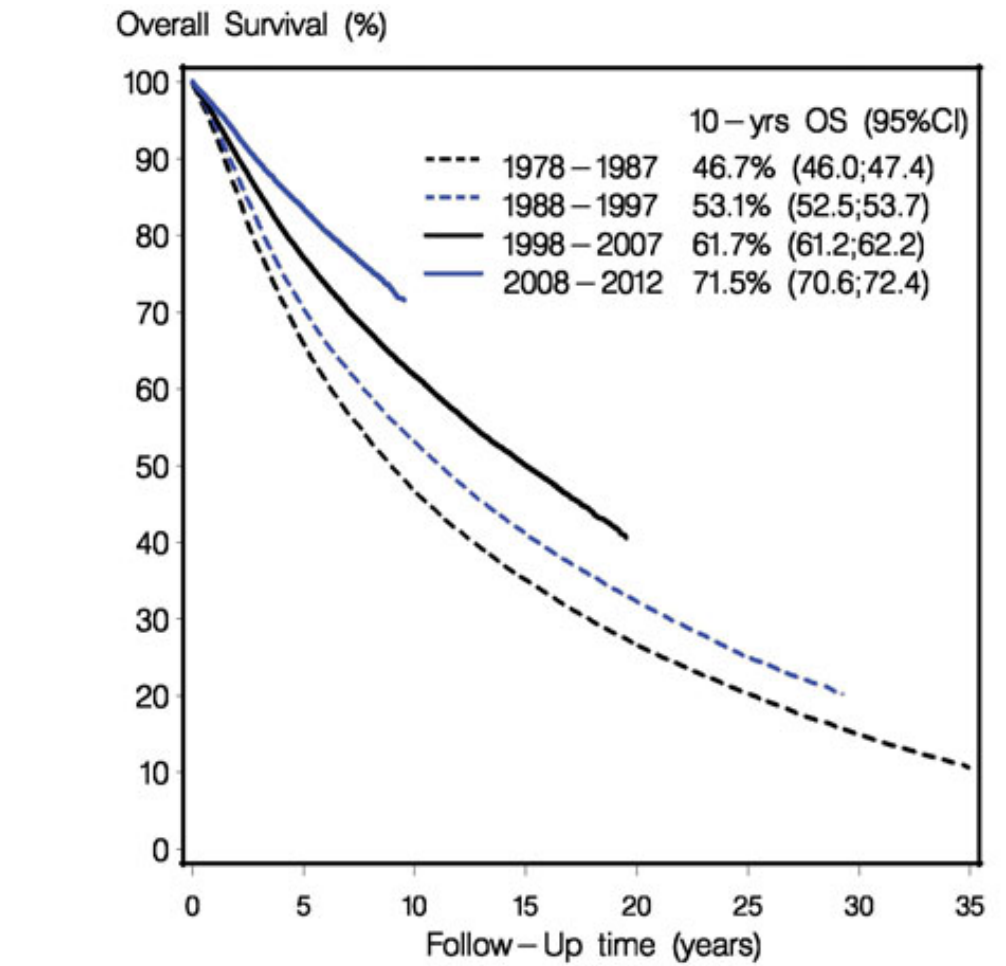




Mortality Rates Among Early-Stage Hormone Receptor–Positive Breast Cancer Patients: A Population-Based Cohort Study in Denmark

Christiansen P, Bjerre K, Ejlertsen B, Jensen MB, Rasmussen BB, Lænkholm AV, Kroman N, Ewertz M, Offersen B, Toftdahl DB, Møller S, Mouridsen HT; Danish Breast Cancer Cooperative Group.

J Natl Cancer Inst. 2011;103(18):1363-1372.


Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
10 – yrs OS (95%CI)
1978 – 1987 46.7% (46.0;47.4)
1988 – 1997 53.1% (52.5;53.7)
1998 – 2007 61.7% (61.2;62.2)
2008 – 2012 71.5% (70.6;72.4)
0 5 10 15 20 25 30 35
Follow – Up time (years)
1978 – 1987 20794 13699 9696 7289 5522 4212 2989 916
1988 – 1997 28537 20084 15107 11669 18847 2973
1998 – 2007 35990 27674 21455 7921
2008 – 2012 23427 18540

ACTA ONCOLOGICA, 2016
http://dx.doi.org/10.3109/0284186X.2015.1128119

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Improvements in breast cancer survival between 1995 and 2012 in Denmark: The importance of earlier diagnosis and adjuvant treatment

Maj-Britt Jensen[a], Bent Ejlertsen[a], Henning T. Mouridsen[a] and Peer Christiansen[b]; for the Danish Breast Cancer Cooperative Group

Table 1. Patient characteristics.

Year of inclusion			1995–1999		2000–2004		2005–2009		2010–2012		1995–2012	
Number of patients			15753		18039		21308		13742		68842	
Median age			60		61		62		63		62	
			N	%	*N*	%	*N*	%	*N*	%	*N*	%
Age												
15–44			1688	11	1818	10	1890	9	1201	9	6597	10
45–54			3813	24	3936	22	3926	18	2688	20	14363	21
55–64			3960	25	5017	28	6669	31	3743	27	19389	28
65–74			3444	22	3739	21	5045	24	3611	26	15839	23
≥75			2848	18	3529	20	3778	18	2499	18	12654	18
Cancer extension												
Localized	Nodal status	Negative	7708	49	8214	46	9871	46	6958	51	32751	48
		Positive	6343	40	7970	44	9139	43	5054	37	28506	41
		Unknown	1298	8	1337	7	1500	7	1231	9	5366	8
Advanced	LABC		140	1	193	1	375	2	230	2	938	1
	DM		264	2	325	2	423	2	269	2	1281	2
CCI												
0			13207	84	14204	79	16259	76	10316	75	53986	78
1			1467	9	2159	12	2821	13	1969	14	8416	12
2			735	5	1063	6	1293	6	863	6	3954	6
≥3			344	2	613	3	935	4	594	4	2486	4

CCI, Charlson Comorbidity Index; DM, distant metastatic; LABC, locally advanced breast cancer.

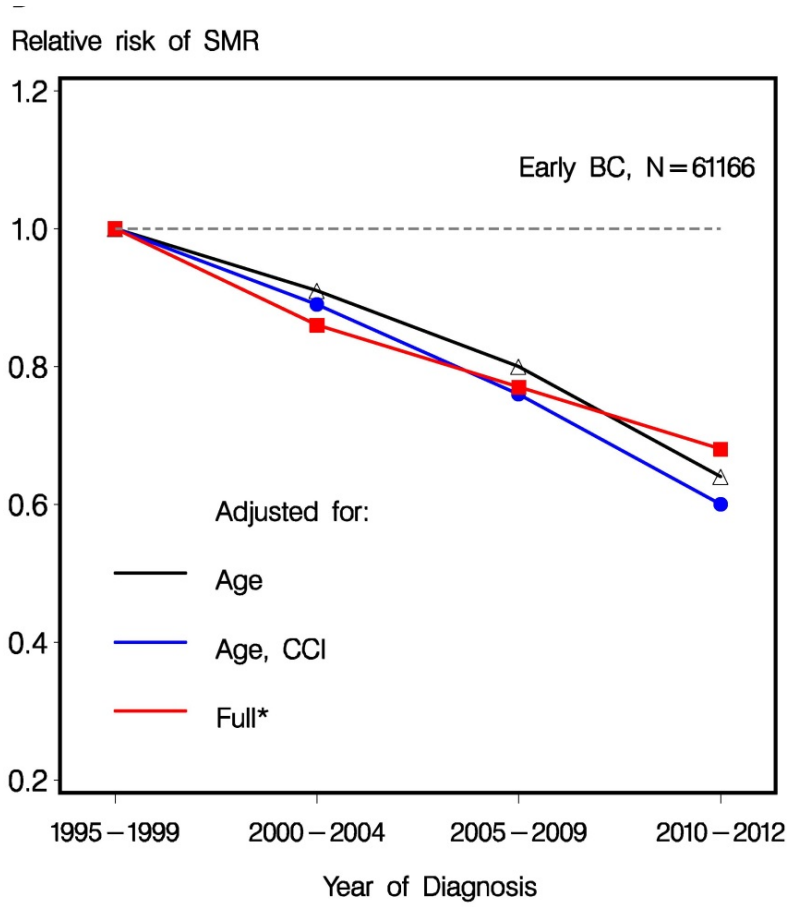
EBC, kendt nodal-status, n=61.166

Year	1995–1999		2000–2004		2005–2009		2010–2012		Total
Size, mm									
0–10	2105	15	2432	15	3378	18	2792	23	**10 707**
11–20	5569	40	6579	41	7872	42	5118	43	**25 138**
21–30	3515	25	4190	26	4686	25	2471	21	**14 861**
31–50	1935	14	2135	13	2232	12	1171	10	**7473**
51+	645	5	672	4	638	3	366	3	**2321**
?	574	2	169	1	150	1	73	1	**666**
ER									
Negative (0–9%)	3267	23	3238	20	3221	17	1869	16	**11 594**
Positive (10+%)	9310	66	12 744	79	15 614	82	10 018	84	**47 686**
?	1465	10	195	1	121	1	104	1	**1885**

Relative risk of SMR

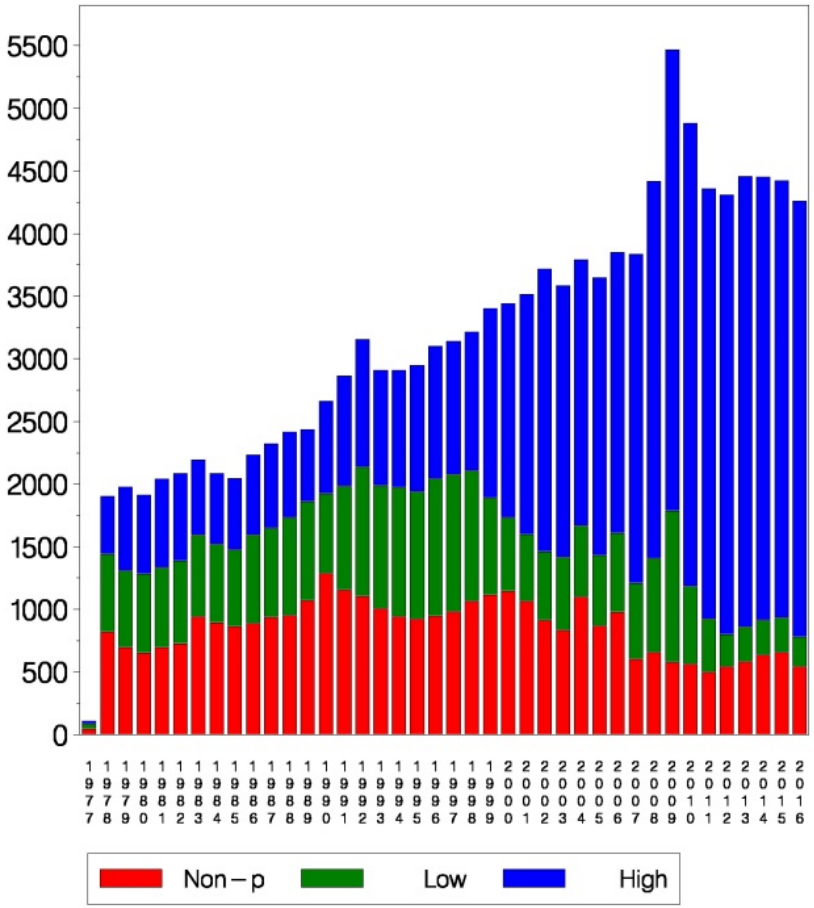
*Justeret for

- Alder
- CCI
- Tumorstørrelse
- nodal status
- histological type & grad
- LVI
- ER



Conclusion:
The impact of screening was by nature of limited magnitude. The modified treatment strategies implemented by the use of nationwide guidelines seemed to have a major impact on the substantial survival improvements.

Allokering



N ≈ 130.000

2016:

94% høj-risiko, adjuverende medicinsk behandling (N=3482)

6% lav-risiko (N=240)

13% udenfor protokol (N=539)