OVERVIEW OF DANISH BREAST CANCER TRIALS

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- Introduction
- DBC 82b
- DBC 82c
- Combined Analysis of 82b & c.
- High local recurrence risk & survival analysis.
- Second Primary cancers after RT.
- Estrogen Receptor, Progesterone Receptor, HER-2, and Response to Postmastectomy Radiotherapy in High-Risk Breast Cancer
- Gene profile predicting PMRT.

Introduction

- The Danish Breast Cancer Cooperative Group (DBCG) was established as a nationwide multidisciplinary organization in 1977 on the initiative from the Danish Surgical Society.
- The organization comprises all the departments in Denmark responsible for

  diagnosis,

  treatment,

  follow-up, and

  research in breast cancer .

Includes a central database.

AIM of the Organization

To offer *similar* nationwide diagnostic and therapeutic procedures to all patients with *primary breast cancer* and to improve the prognosis.

Study population

From 1977 through 2014, ~110,000 women with

early unilateral

non metastastic

invasive breast cancer,

have been entered into the database.

In the case of bilateral cancer, a detailed registration is restricted to the most advanced tumor.

Men with breast cancer and women with a second primary breast cancer are not registered.

DBCG database

Civil Registration System

(to obtain vital status)

National Pathology Registry

(to monitor the completeness of the reporting)

Danish Cancer Registry

(monitor the presence of other malignant diseases and second primaries)

Danish National Patient Registry

(monitor comorbidity and late adverse events)

ain variables reported to the DBCG database

Main groups	Variables
tient characteristics	Age, menopausal status, comorbidity
asons not to enter ndard treatment program r primary breast cancer.	Distant metastases, previous malignant disease (except cancer cutis/cancer colli uteri in situ), bilateral breast cancer, technically inoperable or not operated according to guidelines, patient preference .
mour characteristics	Histological diagnosis, tumor size, number of examined nodes, number of positive nodes, grade, ER status, HER-2 status
rgery	Type of preoperative biopsy, sentinel node biopsy, axillary dissection, lumpectomy +/- oncoplastic surgery, mastectomy +/- reconstruction
juvant therapy	Radiotherapy, chemotherapy, endocrine therapy, anti-HER-2 therapy
llow-up	vital status, recurrence, contralateral breast cancer, other malignant disease

Database

- Used to assess the quality of potential prognostic and predictive factors and surgical and oncological procedures to ensure similar quality on a nationwide basis.

- Through numerous national and international studies, DBCG has contributed to an improvement of the evidence-based guidelines for diagnostic aspects and treatment.

- The results achieved by DBCG have been published in 430 peer-reviewed papers, and the data have contributed to several theses and to the meta-analyses conducted by Early Breast Cancer Triallists' Collaborative Group.

ajor achievements in Surgery for Breast Cancer

- Change in treatment strategy : Mastectomy to breast-conserving surgery (
- 2008, (DBCG study): Similar outcomes of local and distant recurrences and survival with BCS compared with mastectomy.
- BCS :~70% of patients with primary breast cancer.
- Danish guidelines defined "no tumor on ink" as sufficient for invasive cancer and 2 mm free margin in case of ductal carcinoma in situ.
- According to international evidence, the sentinel node technique was introduced in Denmark on the initiative by DBCG.
- Sentinel node technique : decreasing proportion of breast cancer patients are exposed to axillary dissection, which is omitted in the case of negative nodal status.
- Risk of late adverse effects in terms of pain, sensations, reduced mobility, and lymphedema is reduced.

Radiotherapy

- When the DBCG 77 program was introduced, the staging procedure was improved, and radiotherapy following mastectomy was restricted to patients with positive axillary nodes or a primary tumor exceeding 5 cm or deep invasion.
- (DBCG 82), DBCG tested the hypothesis of lack of effect by radiotherapy when administered in addition to systemic therapy.
- Two large national studies demonstrated a significant reduction in the rate of local recurrence and improved survival.
- However, a recent very large Danish study demonstrated that additional radiation to the parasternal nodes was associated with a significant gain in terms of breast cancer mortality and overall survival.

DBCG has conducted trials to evaluate the morbidity following reduction of the irradiated breast volume after breast conserving surgery and following hypofractionation (less numbers of fractions with higher dose per fraction) in patients eligible for irradiation of the residual breast only.

Systemic therapy

- Selection of the patients for systemic therapy has been according classical prognostic factors, from the late eighties complemented with predictive Factor for Endocrine therapy (estrogen receptor status) and from 2007 for biological therapy (human epidermal growth factor receptor [HER2]-status).
- The proportion of patients offered adjuvant systemic therapy has beer increasing since the late seventies from ~50% to close to 90%.
- Large proportion of the patients are overtreated and DBCG :heavily involved in the search for valid genomic assays to better identify the patients who are estimated to benefit from a specific treatment.

- The DBCG database provides data to a vast array of both clinical and epidemiological studies.
- The quality of the data is consecutively assessed by the clinical quality indicators, and studies utilizing the data have contributed substantially to the evidence-based guidelines on diagnosis and treatment of breast cancer prepared by DBCG.
- Since the establishment of DBCG, the prognosis in breast cancer has continuously improved with a decrease in 5-year mortality from ~37% to 15%.

The New England Journal of Medicine

Danish 82b Trial

VOLUME 337 OCTOBER 2, 1997 NUMBER 14

POSTOPERATIVE RADIOTHERAPY IN HIGH-RISK PREMENOPAUSAL WOMEN WITH BREAST CANCER WHO RECEIVE ADJUVANT CHEMOTHERAPY

MARIE OVERGAARD, M.D., PER S. HANSEN, M.D., JENS OVERGAARD, M.D., CARSTEN ROSE, M.D.,

Aim : To evaluate whether the addition of radiotherapy to total mastectomy with axillary dissection and adjuvant chemotherapy influenced locoregional control of tumors,

the likelihood of Freedom from distant metastases, &

overall survival in high-risk Premenopausal patients.

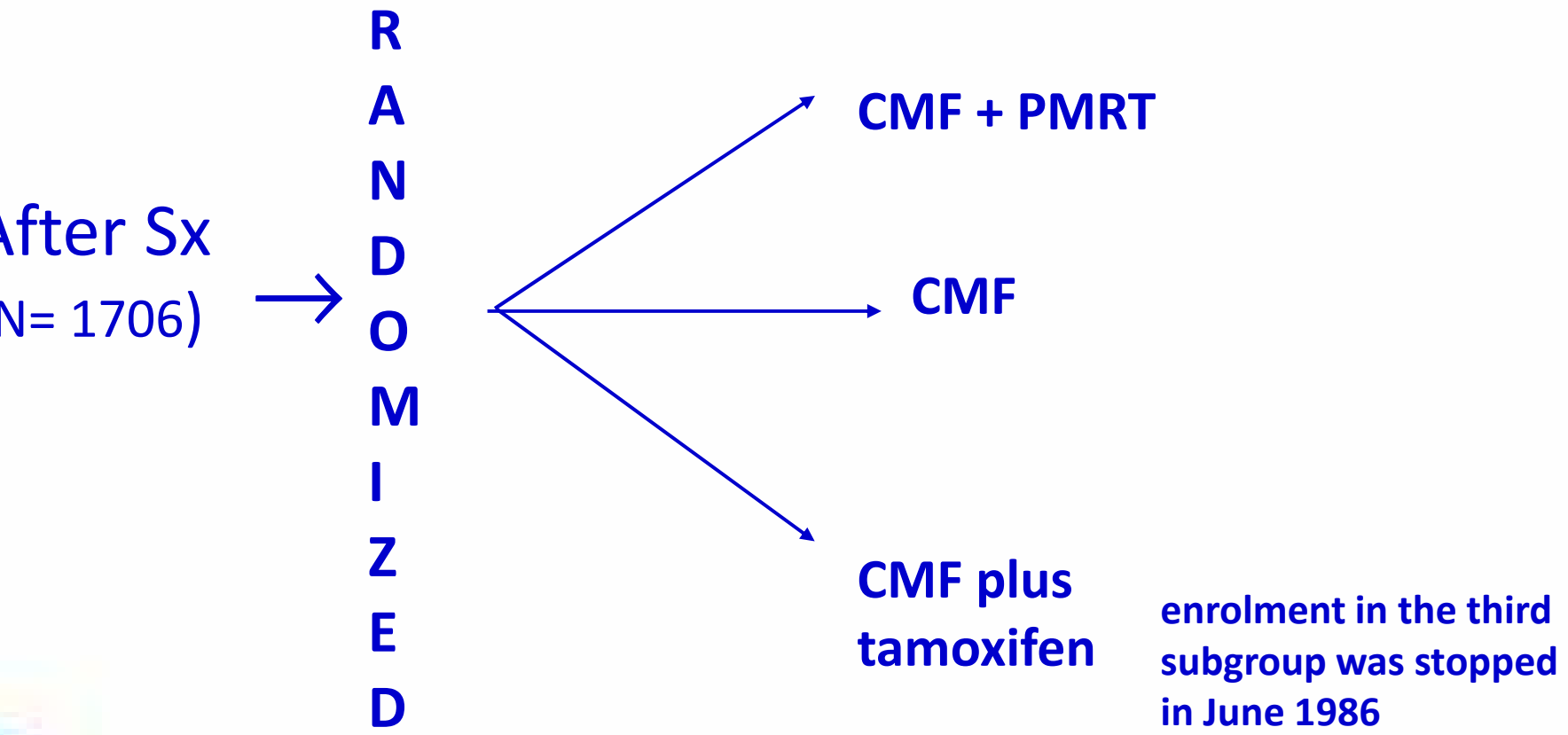
Danish 82b Trial

Protocol Design The Danish Breast Cancer Cooperative Group protoc
82b includes premenopausal high-risk patients with breast cancer.

- High-risk status : involvement of axillary lymph nodes,
  tumor size of more than 5 cm, and
  invasion of the cancer to skin or pectoral fascia
  (pathological stage II or III).
- Premenopausal: if amenorrhric for less than five years or
  had a hysterectomy before the age of 55.
- No evidence of metastatic disease

Danish 82b Trial

November 1982 to December 1989



Radiation therapy :

Delivered to the chest wall, including the surgical scar and regional lymph nodes i.e., supraclavicular,

infraclavicular,

axillary nodes

internal mammary nodes .

Dose : Median absorbed dose

50 Gy/25 fractions over a period of 5 weeks, or 48 Gy, given in 22 fractions over a period of 51⁄2 weeks.

Radiotherapy within one week after the first cycle of chemotherapy.

Adjuvant Systemic Therapy

Cyclophosphamide 600 mg/m
Methotrexate 40 mg / m
Fluorouracil 600 mg /m x every four weeks,

Patients the planned chemotherapy consisted of eight cycles of CMF, whereas the patients who were assigned to CMF without radiotherapy Total of nine cycles of CMF.
Compliance with chemotherapy was the same in both groups, and at least 85 percent.

- **F/U :**

  Clinical examination at regular intervals for up to 10 years
- **Further tested only if they had symptoms or evidence of recurrent disease.**
- **All diagnostic, therapeutic, and follow-up data were validated and processed by the Danish Breast Cancer Cooperative Group's data center.**
- **No interim analysis.**
- **Study monitored regularly by the data center for excess mortality in either treatment group.**

- **Results confirm that tumor size, number of pathologic nodes, and the grade of anaplasia are the major prognostic factors in breast cancer.**
- **Addition of irradiation to chemotherapy reduced the frequency of locoregional recurrence to about one fourth that found in the groups that did not receive radiotherapy.**
- **The fact that 255 patients had fewer than four nodes removed weakens our analysis of the influence of having more than three positive nodes in the study group**

Median potential follow-up was 114 months. (range:78 -167).

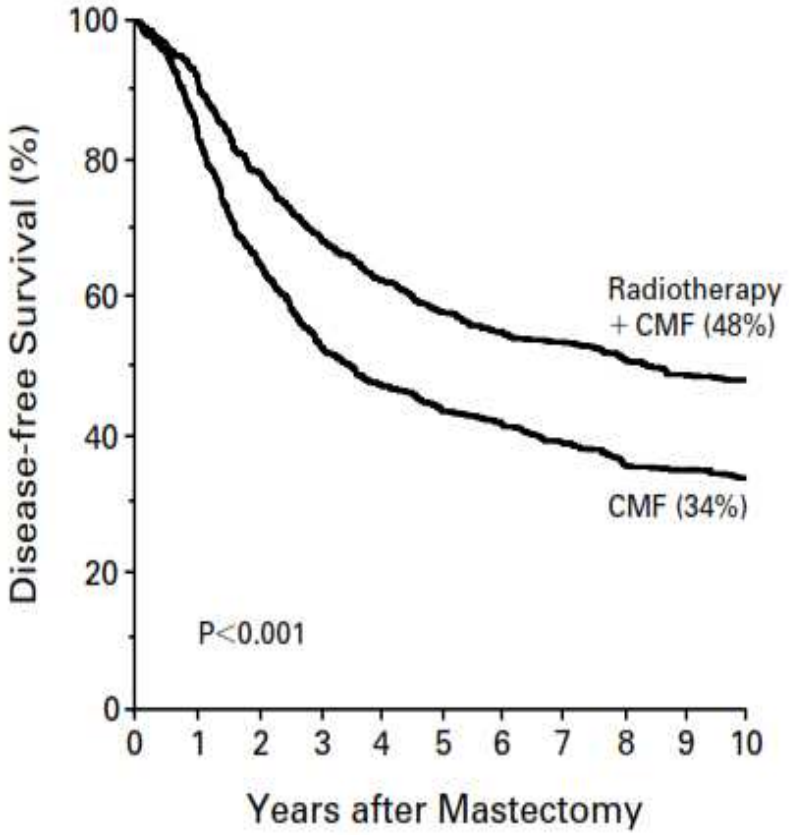
TABLE 1. FREQUENCY OF LOCOREGIONAL RECURRENCES OR DISTANT METASTASES IN WOMEN TREATED WITH RADIOTHERAPY AND CMF OR CMF ALONE AFTER MASTECTOMY.

VARIABLE	NO. OF PATIENTS	RADIOTHERAPY AND CMF				CMF ALONE			
		NO. OF PATIENTS	LOCOREGIONAL RECURRENCES*	DISTANT METASTASES†	OTHER EVENTS‡	NO. OF PATIENTS	LOCOREGIONAL RECURRENCES*	DISTANT METASTASES†	OTHER EVENTS‡
			percent				percent		
All patients	1708	852	9	34	6	856	32	26	4
Age (yr)									
<40	323	156	11	38	4	167	44	26	1
40–49	934	459	8	32	4	475	29	26	4
50–59	451	237	10	35	11	214	30	25	7
Tumor size (mm)									
<21	674	339	6	28	5	335	25	21	5
21–50	772	402	10	37	6	370	35	30	4
>50	234	99	12	38	8	135	42	25	4
Unknown	28	12				16			
No. of nodes removed									
0–3	255	122	10	34	7	133	40	17	5
4–9	1042	531	8	33	5	511	32	26	5
>9	409	198	9	35	6	211	27	30	3
Unknown	2	1				1			
No. of positive nodes									
None	135	58	3	19	2	77	17	17	4
1–3	1061	545	7	30	5	516	30	23	4
>3	510	248	14	46	8	262	42	34	5
Unknown	2	1				1			
Frequency of positive nodes (%)									
<34	715	360	5	24	4	355	21	22	5
34–67	446	217	7	38	7	229	37	25	3
>67	532	269	15	42	8	263	44	31	5
Unknown	15	6				9			
Histopathological classification of tumor§									
Ductal	1461	741	10	33	6	720	34	25	5
Lobular	162	69	4	43	7	93	22	31	1
Medullary	45	21	5	19	10	24	25	21	0
Unknown or other	40	21				19			
Grade of anaplasia (ductal carcinoma only)									
Grade I	363	182	6	23	5	181	29	17	3
Grade II	701	361	7	37	6	340	31	29	7
Grade III	351	176	18	39	5	175	46	28	4
Unknown	46	22				24			

TABLE 2. TYPES OF FIRST RECURRENCES OR EVENTS.

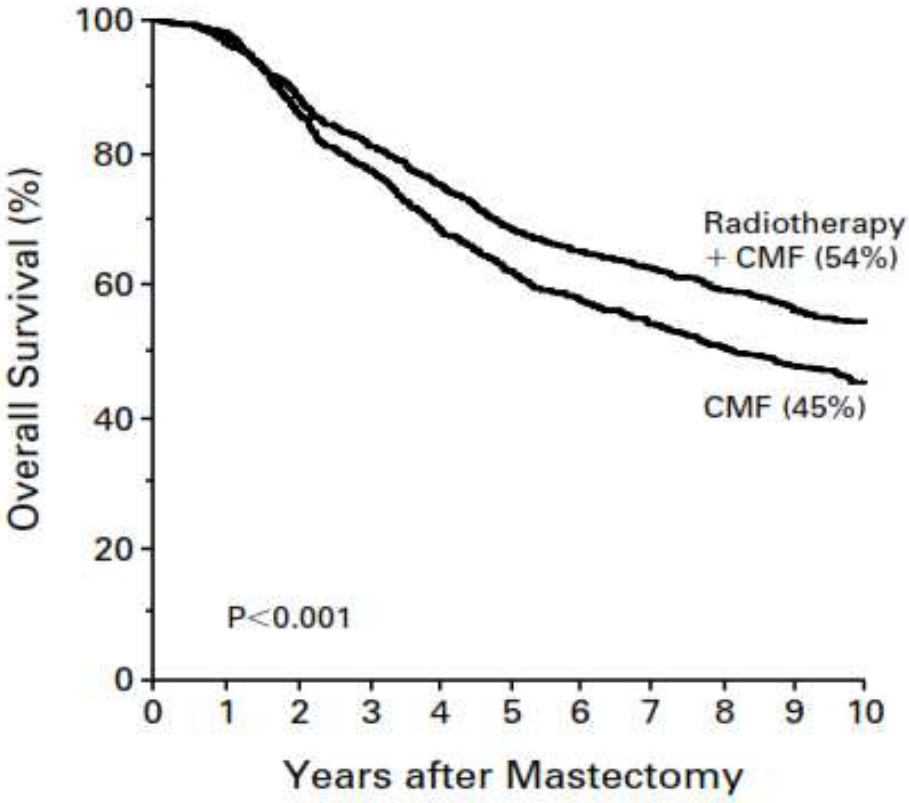
TREATMENT	NO. OF PATIENTS	DISTANT METASTASES ALONE	LOCOREGIONAL RECURRENCE		OTHER EVENTS*	CENSORED OBSERVATIONS†
			ALONE OR WITH DISTANT METASTASES	ALONE		
		number of patients (percent)				
Radiotherapy + CMF	852	287 (34)	75 (9)	44 (5)	50 (6)	440 (52)
CMF alone	856	219 (26)	277 (32)	221 (26)	37 (4)	323 (38)
All patients	1708	506 (30)	352 (21)	265 (16)	87 (5)	763 (45)

Disease free Survival



Radiotherapy + CMF	852	643	505	429	308	102
CMF	856	537	382	327	216	74

Overall Survival



Radiotherapy + CMF	852	755	641	555	392	188
CMF	856	738	587	494	329	163

F (↓23%)
9% vs CMF 32%, $p < 0.001$

-year DFS (↑14%)
MF 34% vs RT 48%, $p < 0.001$

erall survival (↑11%)
MF 45% v. RT 54%, $p < 0.001$

TABLE 4. COX MULTIVARIATE PROPORTIONAL-HAZARDS ANALYSIS OF THE RELATIVE F
OF ANY TYPE OF RECURRENCE OR DEATH OR OF DEATH FROM ANY CAUSE.*

VARIABLE	ANY TYPE OF RECURRENCE OR DEATH		DEATH	
	P VALUE	RR (95% CI)	P VALUE	RR (95% CI)
Tumor size (<21 mm, 21–50 mm, >50 mm)†	<0.001	1.43 (1.30–1.58)	<0.001	1.49 (1.35–1.65)
No. of positive nodes (0, 1–3, >3)†	<0.001	1.57 (1.36–1.81)	<0.001	1.75 (1.50–2.05)
Frequency of positive nodes (<34%, 34–67%, >67%)†	<0.001	1.44 (1.30–1.58)	<0.001	1.38 (1.24–1.53)
Grade of anaplasia (I, II, III)†	<0.001	1.44 (1.31–1.59)	<0.001	1.52 (1.37–1.70)
Age of 40 to 49 yr (vs. <40 yr and 50–59 yr)	<0.001	0.73 (0.64–0.83)	<0.001	0.76 (0.66–0.87)
Radiotherapy + CMF (vs. CMF alone)	<0.001	0.59 (0.51–0.67)	<0.001	0.71 (0.62–0.82)

ostoperative radiotherapy in high-risk postmenopausal breast ncer patients given adjuvant tamoxifen: Danish Breast Canc operative Group DBCG 82c randomised trial

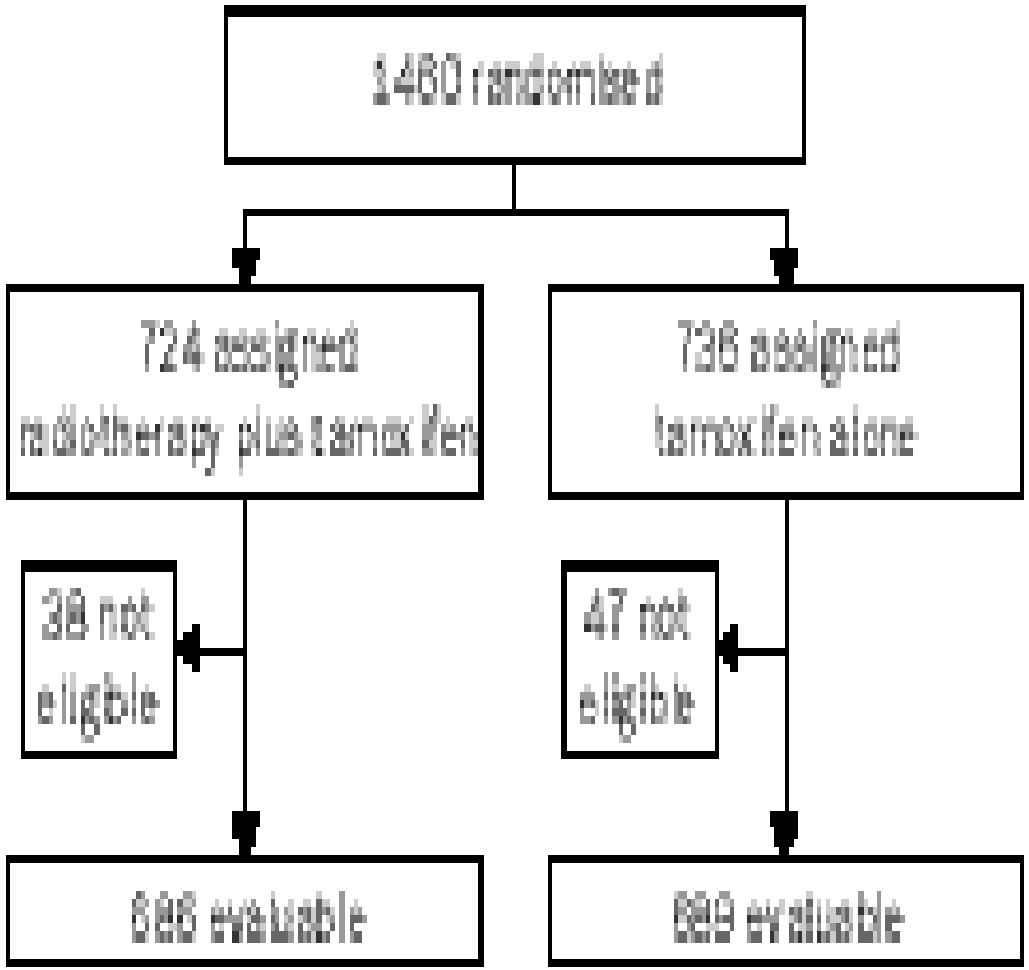
Postmastectomy radiotherapy is associated with a lower locoregional recurrence rate and improved disease-free and overall survival when combined with chemotherapy in postmenopausal women .

M e t h o d s: Between 1982 and 1990, postmenopausal women with high-risk breast cancer (stage II or III) were randomly assigned adjuvant tamoxifen (30 mg daily for 1 year) alone (689) or with postoperative radiotherapy to the chest wall an regional lymph nodes (686). Median followup was 123 months.

The endpoints were first site of recurrence (locoregional recurrence, distant metastases, or both), and disease-free and overall survival.

Lancet 1999; **353:** 1641–

Danish 82c Trial



Included postmenopausal high-risk brea cancer Patients < 70 years of age.

High - risk status : node positive, tumour size greater than5 cm, invasion to skin or pectoral fascia, or an combination of these characteristics.

Postmenopausal status was defined as 5 years or more of amenorrhoea or, for women who had undergone hysterectomy, age over 55 years

f first recurrence	Radiotherapy plus tamoxifen (n=686)	Tamoxifen only (n=689)	All patients (n=1375)
nt metastases only	269 (39%)	169 (25%)	438 (32%)
egional only	30 (4%)	203 (29%)	233 (17%)
nt metastases and locoregional	22 (3%)	39 (6%)	61 (4%)
currences	321 (47%)	411 (60%)	732 (53%)

- Surgical : total mastectomy and axillary-node dissection.
- Included removal of the central axillary lymph nodes involving lev I and part of level II.
- Median of seven lymph nodes we removed.
- Tamoxifen was started 2–4 weeks after surgery, and was given concomitantly with PORT.
- Patients were followed up with clinical examinations regularly for 10 years.

- Radiotherapy was directed towards the chest wall, which included the surgical scar and regional lymph nodes (the supraclavicular, infraclavicular, and axillary nodes, and IMC. The intended dose was either a median absorbed dose in the target mammary nodes in the four upper intercostal spaces).
- Dose: 50·0 Gy / 25 fractions in 35 days,

  48·0 Gy / 22fractions in 38 days.

Anterior photon field :supraclavicular and axillary region, and an

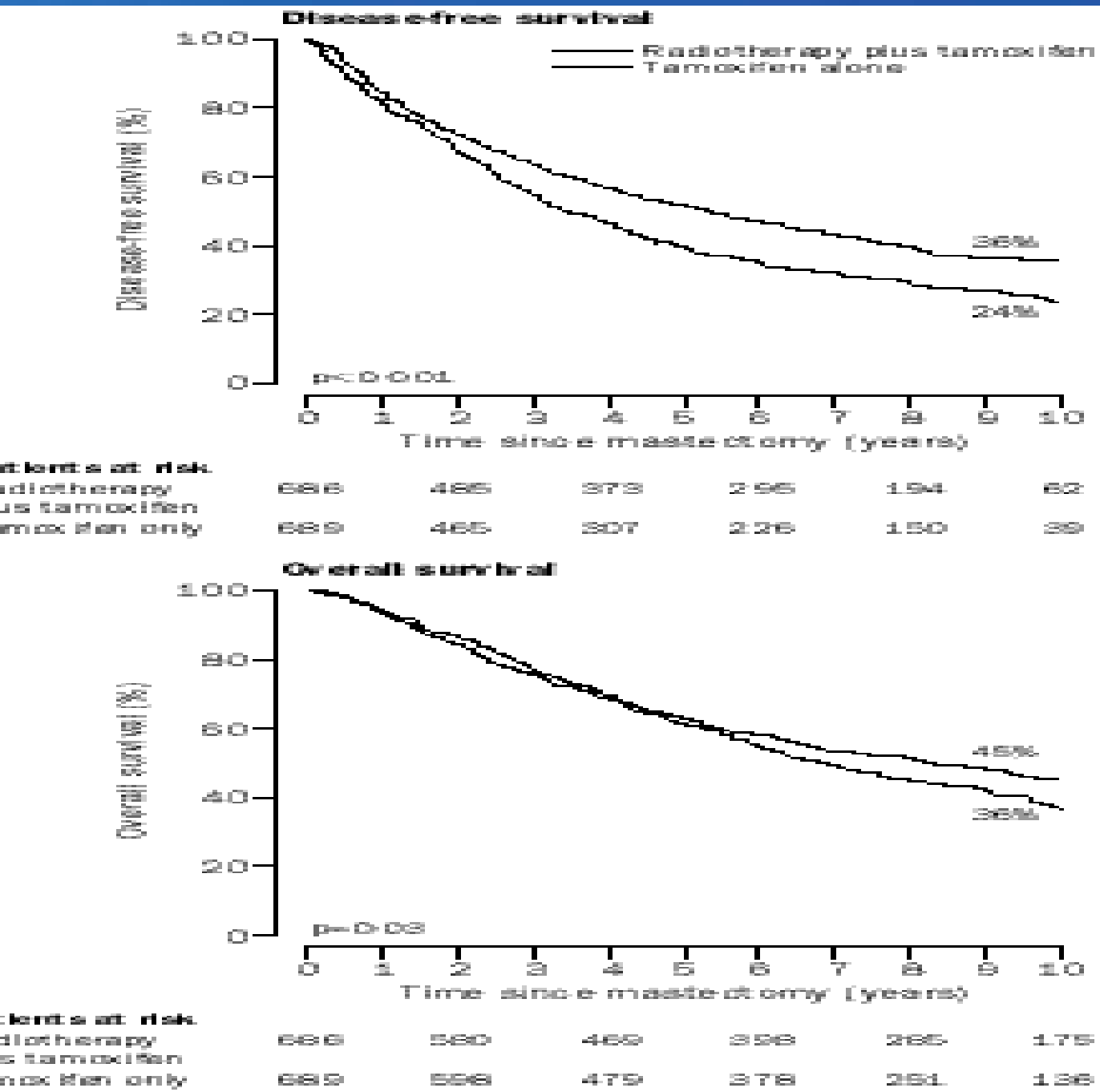
Anterior electron field against the internal mammary nodes and the chest wall

Posterior axillary fields for patients with large anterior to posterior diameter to limit the maximum absorbed dose to 55·0 Gy in 25 fractions, or 52·8 Gy in 22.fractions.

Most patients were treated at six departments with a linear accelerator.

However, 69 patients (10% of the patients)were treated at small departments with 250 kV X-rays, the lowest intended dose was 36·0 Gy in 20 fractions in 4 weeks.

- Compliance to radiotherapy was high, and only 30 (4%) patients did not complete the treatment.
- Patients received adjuvant tamoxifen 30 mg daily for 1 year.
- Tamoxifen was started 2–4 weeks after surgery, and was given concomitantly with postoperative radiotherapy.



The effect of treatmen
was assessed by
intention to treat.
The primary endpoint
was survival (all
deaths from any caus
were included in the
analysis) and
locoregional reurranc

e of first recurrence	Radiotherapy plus tamoxifen	Tamoxifen only	All patients
recurrence	637	444	1081
e*			
est wall	31 (16)	123 (17)	154 (33)
llary nodes	9 (2)	73 (8)	82 (10)
l nodes	7 (2)	29 (8)	36 (10)
lla and chest wall	3 (1)	9 (2)	12 (3)
lla and S/I nodes	0	5 (2)	5 (2)
est wall plus S/I nodes	2 (1)	3 (2)	5 (3)
recurrences	52 (22)	242 (39)	294 (61)

The definition of the endpoint of locoregional recurrence was first site of failure (chest wall, axilla, supra/infraclavicular), alone or together with distant metastases (diagnosed within 1 month).

Danish 82c Trial

- **Results:**

  Tamoxifen ± PMRT , N=1374

  LRF (↓27%)
  35% v 8%, p < 0.001

  DFS (↑12%)
  36% v. 24%, p < 0.001

  Overall survival (↑9%)
  45% vs 36%, p = 0.03

VOLUME 24 · NUMBER 15 · MAY 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Study of Failure Pattern Among High-Risk Breast Cancer Patients With or Without Postmastectomy Radiotherapy i Addition to Adjuvant Systemic Therapy: Long-Term Resu From the Danish Breast Cancer Cooperative Group DBC 82 b and c Randomized Studies

Hanne M. Nielsen, Marie Overgaard, Cai Grau, Anni R. Jensen, and Jens Overgaard

PURPOSE: -

Radiation Decrease

↓

Loco regional recurrences [LRRS]

↓

Disease free Survival

AIM: To examine the overall disease recurrence pattern among patients randomly assigned to receive treatment with or without RT.

atients and Methods

PATIENTS & METHODS:-

3083 patients from DBCCG 82 b & 82 c

END POINTS

↙ ↓ ↘

LRR DM CBC

Follow-up continued until DM, CBC, emigration, or death.

Information was selected from medical records, general practitioners, and the National Causes of Death Registry.

The median potential follow-up time was 18 years.

Only first site of BC events recorded.

PT's PROFILE

- No evidence of DM,
- no prior h/o cancer
- < 70 years .
- unilateral BC ,

↗ Tumour >5

- High Risk → Positive

axillary node

↘ Invasion of sk

/Pectoral faci

Post total mastectomy and partial axillary dissection.

Median of 7 L Nodes removed

Adjuvant Systemic Therapy

C Cyclophosphamide 600 mg/m2

M Methotrexate 40 mg/m2

F Fluorouracil 600 mg/m2

4 weekly X 8 Cycles → RT arm

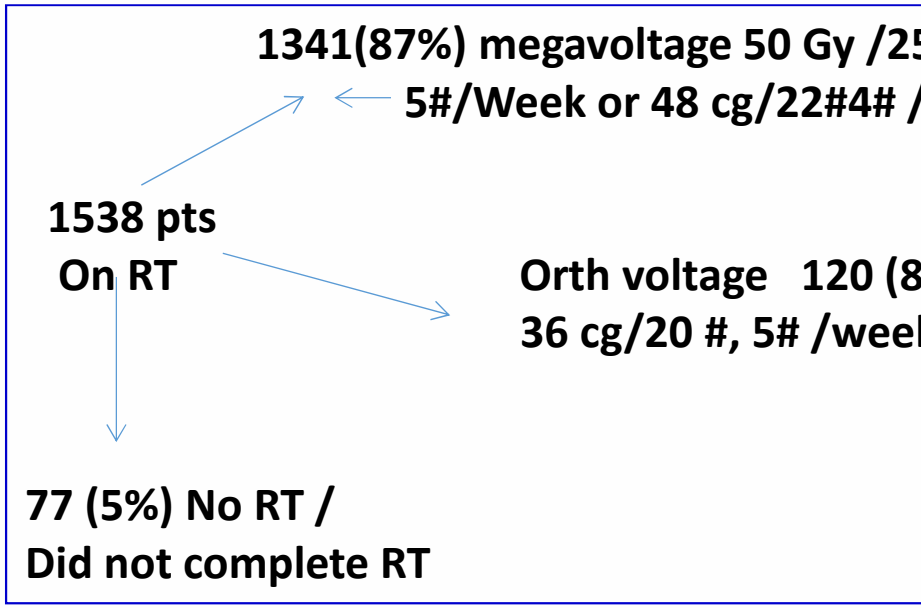
X 9 Cycles → No RT

RT interpolated after 1st Cycle of CMF.

Post-menopausal women received Tamoxifen 30 mg daily for 1 year.

RT → Chest wall + Regional Lymph nodes .

MEDIAN FOLLOW UP TIME - 18 YEARS



Information collected by questionnaire

→ Medical records
→ Death Certificate
→ GP;

Results: STATISTICAL ANALYSIS Kapplan Meir Method;Log rank test for Compassion B/w treatment group

RR → X2 test used for Comparrision of data

Table 1. Site of First LRR Alone and simLRR-DM in the Two Randomization Groups

	No RT (n = 1,545)				RT (n = 1,538)				*P*	
	LRR		SimLRR-DM*		LRR		SimLRR-DM*			
Site of First LRR	No.	%	No.	%	No.	%	No.	%	LRR†	SimLRR-DM‡
Chest wall	209	14	48	3	50	3	39	3	< .001	.34
Axilla	143	9	28	2	10	0.7	11	0.7	< .001	.006
S/I	34	2	28	2	10	0.7	11	0.7	< .001	.006
Axilla and chest wall	41	3	7	0.5	5	0.3	5	0.3	< .001	.57
Axilla and S/I	20	1	12	0.8	3	0.2	1	0.1	< .001	.002
Chest wall and S/I	8	0.5	5	0.3	1	0.1	5	0.3	.02	.99
Chest wall + axilla + S/I	1	0.1	2	0.1	0	0	1	0.1	—	—
All recurrences	456	30	130	8	79	5	73	5	< .001	< .001

Abbreviations: S/I, supra/infraclavicular; LRR, locoregional recurrence alone; simLRR-DM, simultaneous locoregional recurrence and distant metastases; no RT, randomized to no radiotherapy; RT, randomized to radiotherapy.

*For simLRR-DM, the localizations of three LRR are absent (n = 203 instead of 206).

†Comparison of site of first LRR between the two randomization groups using the χ^2 test.

‡Comparison of site of first simLRR-DM between the two randomization groups using the χ^2 test.

3 –Year Acturial Probability of DM in all Pts

Table 2. 18-Year Actuarial Probability of Distant Metastases in All Patients

	No RT (n = 1,545)		RT (n = 1,538)		Log-Rank		
Type of First DM	%	95% CI	%	95% CI	P*	RR†	95% CI
DM following LRR	35	31 to 38	6	4 to 8	< .001	0.15	0.11 to 0.20
DM first failure	37	34 to 40	47	44 to 49	< .001	1.38	1.22 to 1.56
SimLRR-DM	12	11 to 15	6	5 to 8	< .001	0.52	0.39 to 0.70
Any DM	64	61 to 66	53	50 to 56	< .001	0.78	0.71 to 0.86

Abbreviations: DM, distant metastases; LRR, locoregional recurrence alone; simLRR-DM, simultaneous locoregional recurrence and distant metastases; no RT, randomly assigned to no radiotherapy; RT, randomly assigned to radiotherapy; RR, relative risk of failure in the RT v no-RT group.

†RR < 1 shows a decreased risk of DM in the RT group.

*Comparison between the no-RT and RT group.

8-yr Acturial Probability of Different sites of DM events in e two Randomized groups

Table 3. 18-Year Actuarial Probability of Different Sites of DM (only as first DM event) in the Two Randomization Groups

Site of DM	No RT (n = 1,545)		RT (n = 1,538)		Log-Rank P*	RR†	95% CI
	%	95% CI	%	95% CI			
Bone	40	36 to 42	32	29 to 34	.003	0.81	0.71 to 0.93
Lung	17	15 to 20	12	11 to 15	.009	0.75	0.60 to 0.93
Pleura	15	12 to 17	12	10 to 14	.22	0.86	0.67 to 1.10
Liver	16	14 to 18	12	10 to 14	.07	0.82	0.66 to 1.02
CNS	5	4 to 7	3	2 to 4	.03	0.61	0.39 to 0.96
Skin	9	7 to 11	4	3 to 5	.002	0.57	0.39 to 0.82
Any DM	64	61 to 66	53	50 to 56	< .001	0.78	0.71 to 0.86

Abbreviations: DM, distant metastases; no RT, randomly assigned to no radiotherapy; RT, randomly assigned to radiotherapy; RR, relative risk of failure in the RT versus no-RT group.

*Comparison between the no-RT and RT group.

†RR < 1 shows a decreased risk of that DM site in the RT group.

RESULT: -

	No RT		RT
18 year probability of any first Breast Cancer event	73%	Vs (P<0.001)	59%
18 year probability of LRR with/without DM	49%	Vs	14%
18 year probability of DM Subsequent to DM	35%	Vs	6%
Probability of any dist Met	64%	Vs	53%

Conclusion

Post Mastectomy RT Changes the disease recurrence patter in High Risk breast Canc patients fewer patients have LRR as first site of recurrence and overall fewer patien have DM.

orbidity and mortality of ischaemic heart disease in high-risk
east-cancer patients after adjuvant postmastectomy systemic
eatment with or without radiotherapy: analysis of DBCG 82b a
2c randomised trials

THE LANCET • Vol 354 • October 23, 199

- Sx + RT $\rightarrow$ LRR

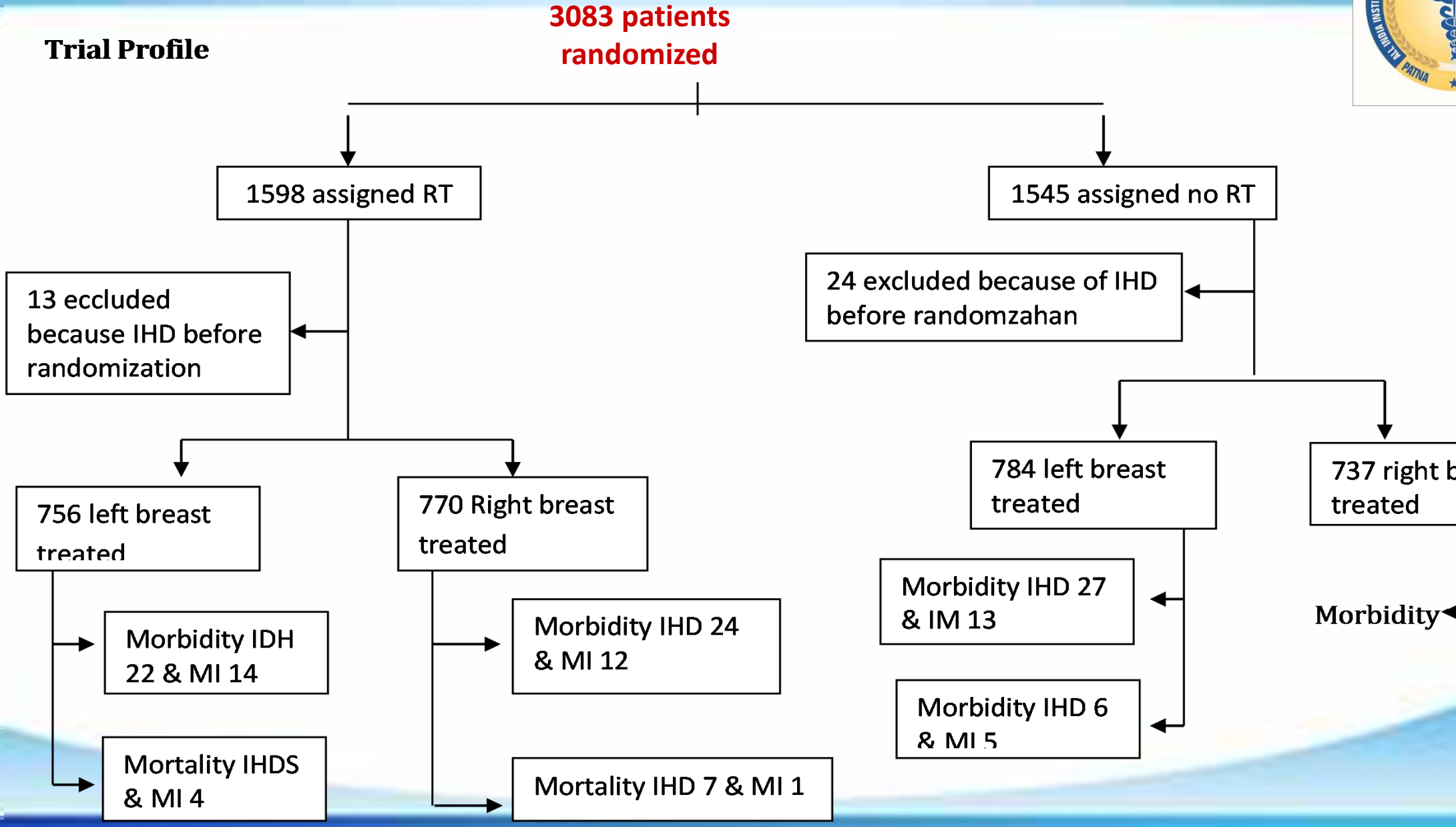
  ? Survival (Benefit less clear).
- Meta analysis of 8 randomised trials
- Increased late deaths in women (Sx + RT) compared to (Sx) alone.
- Meta analysis later : Difference in overall mortality not significant (Large contribution of recent appropriate trials).
- Harmful effect of radiation on the heart had been reported.
- As more & more women with BC become long team survivors.
- ? Morbidity from cardiac disease pertinent

(DBCG) 82b & 82c : Addition of RT lengthens survival in High Risk women.

- ***AIM***:- To investigate morbidity and mortality from ischemic heart disease in High Risk BC give systemic T/+ment ± RT after Sx.
- *Methods*
- ***Patients***:- 1982 to 1990
  Mastectomy + partial axillary clearance.
  No evidence of metastatic disease
  No history of cancer,
  Unilateral breast cancer
  Age younger than <70years.
  Verbal informed consent
  High Risk for recurrence.

Node positive Tumour size >5cm Invasion of skin or pectoral facia.

Trial Profile

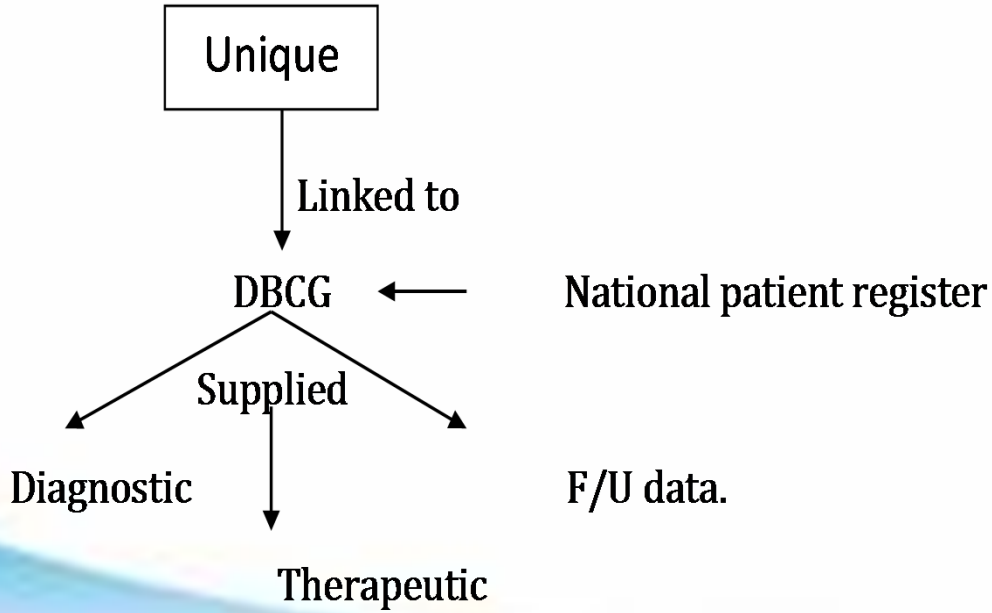


motherapy and or radiotherapy or patient 82b & 82c protocol:

women were followed by clinical assessment at regular visits over 10years.

ry women had a unique national identification no.

ients were linked into the DBCG.



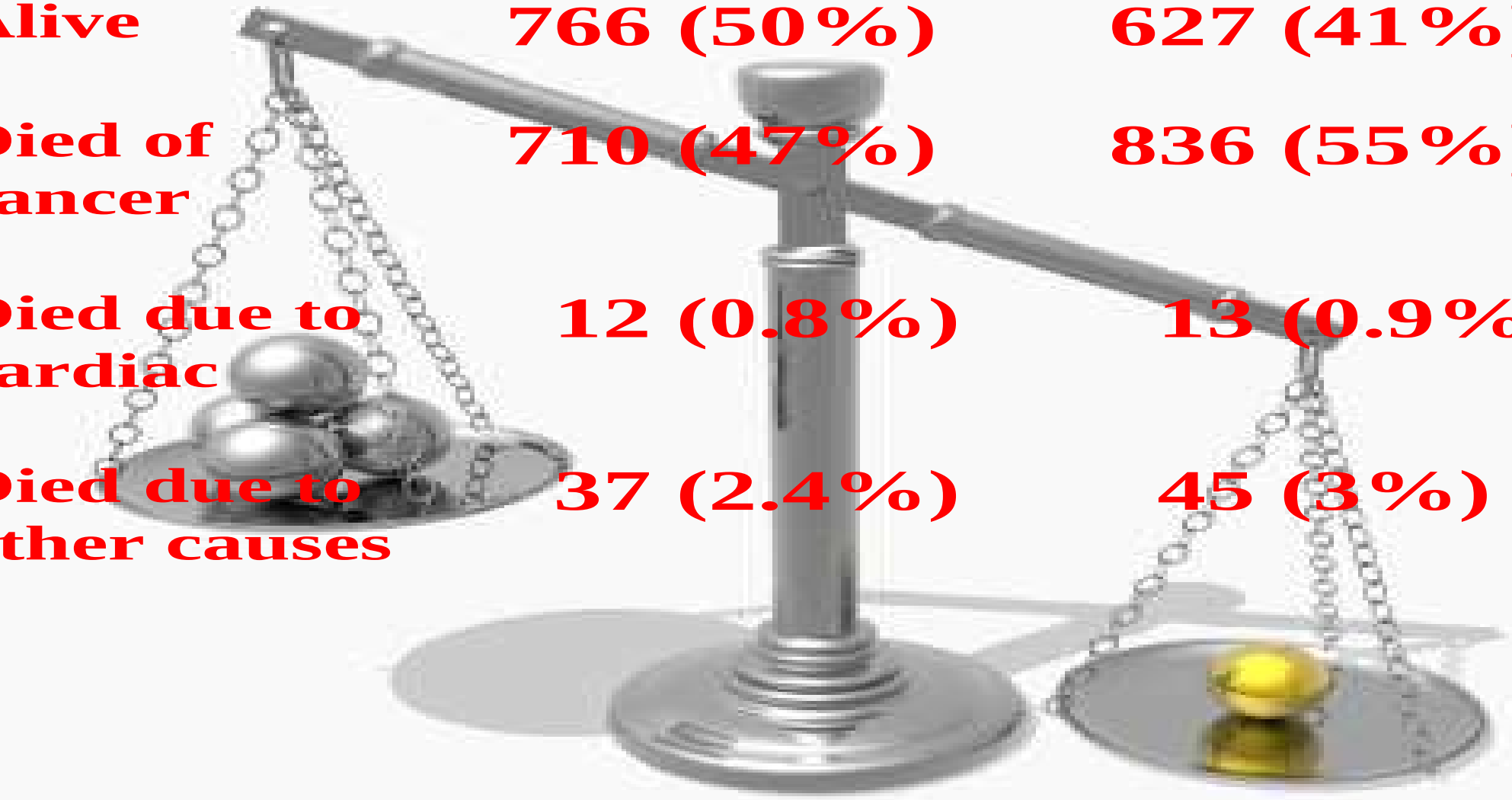
Assessment of Morbidity & Mortality.

Crude survival and cause of death:

	No RT (n>1525)	RT (n>1521)
Alive (41.2%)	766 (50.2%)	627
Causes of death		
Breast Cancer	674(44.2%)	799 (52.5%)
Other Causes	36 (2.4%)	37 (2.4%)
Ischaemic heart disease	12 (0.8%)	13 (0.9%)
Unknown Causes	5 (0.3%)	4 (0.3%)
Other Causes	32 (2.1%)	41 (2.7%)

Danish Trial 82b & 82c (Lancet 1999)

	With RT	Without RT
Alive	766 (50%)	627 (41%)
Died of cancer	710 (47%)	836 (55%)
Died due to cardiac	12 (0.8%)	13 (0.9%)
Died due to other causes	37 (2.4%)	45 (3%)



Statistical Analyses.

- Morbidity & Mortality = Kaplan Meier ethod.
- og Rank test: Compare the treatment oups;
- elative Hazard of Ischaemic Heart sease.
- PSS version 8.0 for window.
- nalyses was on Intention to treat.
- ate of assessment: Dec 31 1996;
- Median potential follow up time: 122 ths. (range 81-171).
- 7 women excluded.
- 046 women analysed.
- 393 women was alive at analyses.
- 393 F/U 117 months (range 81-171)

To covere confounding effect of HD by Subsequent Treatment / RT or Anthracyclines
Data was reanalysed Censoring patients.

Median time to death = 45 mths (1-170mths.)
Cumulative survival at 12 years
RT group no RT group.
46% 36% p<0.001.
More women of no – radiotherapy g
than in radiotherapy group died of B
whereas similar proportions of each
group died from ischemic Heart disea
0.9% vs 0.8%

RH Morbidity =0.86 (95% CI 0.6-1.3)
Relative Hazard Death = 0.84 (0.4-

To assess whether the risk of ischaemic HD increased with time after treatment with RT.

Hazard Ratio was calculated for 2 year periods.

There was no trend for an ⇈ in HR of Morbidity with time

Discussion:

Morbidity and mortality from ischaemic HD was not significantly altered by use of adjuvant RT after mastectomy.

Risk of Ischaemic Heart disease was not planned or analysed.

Further F/U necessary to rule out harmful effects on the heart >12years.

However F/U was long enough to show significant survival benefit from systemic treatment plus RT vs systemic treatment alone.

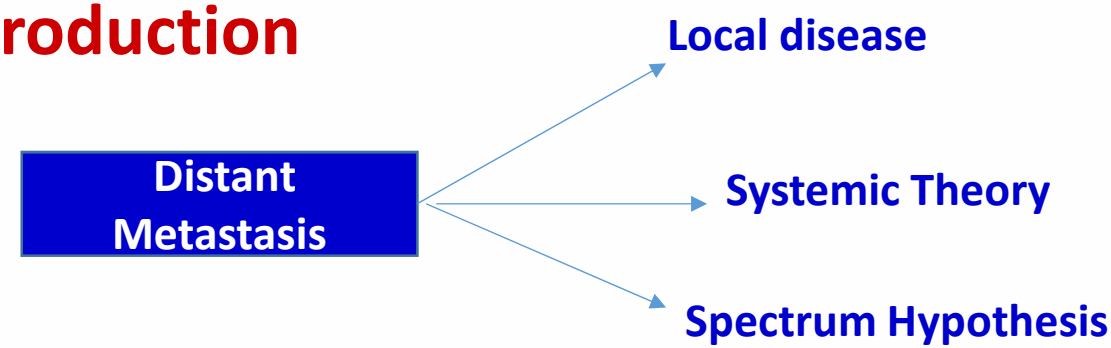
- **Limitation**

Rate of IHD	RT + CT (CMF).
Same	RT + Tamoxifen.

- **Further studies with anthracyclines/taxanes with RT needed.**
- **Only upper 4 inter coastal spaces included in the initial mammary field ; dose received by heart will be small.**
- **Radiotherapy treatment technique :did not use individual three dimensional dose planning.**
- **Many unanswered question.**

igh Local recurrence is not associated with large survival reduction after post
nastectomy RT in High Risk Brest Cancer a Sub group analysis of DBCG 82 B &

- **Introduction**



1000 high – Risk BCP
↓
Systemic Therapy + PMRT
↓
Representative of LR probability
(Clinico pathological Markers)
↓
Subsequently Breast Cancer Speci
& overall Survival probability

included 1000 out of 3083 high-risk breast cancer patients
randomly assigned to postmastectomy radiotherapy in the DBCG82 b&c trials

Materials & methods:-

1982-1990 → 3083 high Risk DBC Pt.
High Risk → Positive Lymph node
Tumour size >5 cm
involvement of skin or pectoral fascia.
Total mastectomy + axillary clearance

Premenopausal ↗ RT + CMF 8 Cycle
↘ CMF Alone 9 Cycle

Postmenopausal ↗ RT + tamoxifen 30 mg daily x 1 Year
↘ Tamoxifen Alone

At least 8 lymph nodes surgically removed & paraffin Blocks available
1078 Patients selected for extended biological update

Paraffin Blocks
↓ Tissue transferred
Tissue Micro arranged
↓
IHC stained for ER, Progesterone accepto and Her 2 neu

- Staging TNM.
- HP Grade – Blood Richardson grade .
- Median potential F/U = 17 years.
- Endpoints → Local Recurrence
  Distant Metastasis
  Breast Cancer Morality
  Overall Mortality

tatistical Analysis: - STATA Version 8.2

2 or exact test → Testing relationship between variables Kaplan – Meier Curves

ox Univariate analyses

Smallest LR Risk
At least 4 out of 5
≤ 3 positive lymph node
Tumour size ≤ 2 cm
Grade 1 Malignant Tumour
Hormonal receptor tumour
Her 2 negative tumour

Intermediate group

Highest LR Risk - 2 out of 3
> 3 Positive lymph node
Tumour size > 5 cm
Grade 3 malignant tumour

5 Year LR Probability of 11%

5 yr LR Probability of 26%

5 Year LR Probability of 50%

Absolute Reduction in LR Probability after PMRT

Poor prognosis = 36%

Intermediate = 21%

Good prognosis = 11%

Highest Mortality was seen for the poor prognosis group matching 81%.

- The very large absolute reduction in LR Probability was not translated into an absolute reduction in 15 year Breast Cancer Mortality

- A continuously improved Breast Cancer specific and overall survival after PMRT was seen throughout the total period of 15 Years for the “Good” and “Intermediate” prognostic Subgroup.

- For poor prognosis neither breast Cancer Specific nor was Overall Survival significantly improved after PMRT throughout 15 years

cancer

nd primary cancers after adjuvant radiotherapy in early breast cancer nts: A national population based study under the Danish Breast Cancer erative Group (DBCG) ☆

Grantzau [a,*], Lene Mellemkjær [b], Jens Overgaard [a]

Advances in treatment → **Long term survivors**

↓

Risk

Radiotherapy Induced second malignancies.

AIM: Evaluate occurrence of second primary solid non-breast cancer among Danish women treated for early breast cancer with postoplative radiotherapy.

Patients & Methods: All women > 20years with primary invasive Loco regional breast cancer.

DBCG database.

- Treatment → Sx
  Systemic treatment
  RT
  } According to DBCA guidelines.

Vital status updated annually ⟷ linkage ⟷ Danish Civil Registration system

All patients treatment on linear Accelerator. (132 treated on ortho voltage excluded)

46 , 176 women:

- Post op RT
- no post op RT

RT changed overtime

Majority of patients : with 3-field anterior electron/photon techniqu

Election field to chest wall ± IMC photon to Lateral thoracic wall + SC

Dose 48-50Gy/24-25 # over 5 weeks.

Breast conserving Sx → PORT → Remaining breast.

Tangential Photons to the conserved breast + BOOST to Tumour bed with Electrons.

Median Dose 48-50Gy/24-25# over 4.5-5weeks + Boost 10-24Gy 5-12

econd primary cancers were identified

Linking Cohort

National Danish Cancer Registry:

Clinical Dept. Pathology Forensic Information from Death Certificates.

High Degree of Completeness and Validity of the Registry.

olid Cancers → Excluding → Non melanoma skin – 11 defined second
Breast cancer.

Women censored if C/L BC was first event dewing clinical F/U

Only 1st, 2nd Primary cancer was counted to avoid influence of other? Treatment.

Second Cancers

Sites potentially associated with RT exposes (RT Associated)*

Sites not associated with RT (non RT – Associated)

Oesophagus
one & Soft tissue sarcomas
ung
leura
leart / Mediastinum

} RT Associated Sites.

/U → 1 Years after BC diagnoses (1983-2008) → till second primary malignancy
Recurrence of BC
Date of Death.
Date of emigration.
End of F/U (Dec 31 2008).

- **Statistical Methods: - Standardised incidence Ratio: No of Cancer Case / Expected no (Computed).**

- **Comparison of Cancer Incidence**

RT group
Non RT group } **Cox regression Analyses with Estimation of HR.**

Interaction between Radiotherapy & Treatment with Chemotherapy Endocrine therapy or Combination

Second Cancers Among women not treated with RT — **Second cancers among irradiated women** → **Observed No. of Cancers**

- Attributable risk = $\frac{\text{No of excess cancers}}{\text{Total No of cancer cases}}$

Excess Absolute Risk (EAR)= $\frac{\text{No of excess cancers Associated to RT x 1000}}{\text{Person – years at risk}}$

- Analysis performed by SAS & strata IC.

RESULTS

tal 46, 176 patients,
% PORT Younger at BC Diagnosis
% No PORT,

58 second primary cancer developed
adiated patients → 928 second primary cancers developed.
784 cancer were expected.
SIR 1.18; 95% CI (1.11-1.26)

n Irradiated women → 1430 second primary cancer observed
→ 1350 cancer were expected.

justed HR 1.10 (95%CI 1.01-1-21).
mary

justed HR for RT associated sites
34 (95%CI 1.11-1.61 P 0.002).

for individual sites
creased for Lung cancer (HR 1.27 95%CI 1.04-1.55)
t increased for oesophageal cancer (HR 2.96; 95%CI 1.17-6.18)

IRRADIATED WOMEN

ARRIBUTABLE RISK RELATED TO RT

9% for solid cancers

Excess Absolute risk .6/10,000 person years.

RT associated sites

ARRIATTRI BUTABLE RISK 25%

Excess absolute risk 4/10,000 person yea

JOURNAL OF CLINICAL ONCOLOGY

Estrogen Receptor, Progesterone Receptor, HER-2, and Response to Postmastectomy Radiotherapy in High-Risk Brea Cancer: The Danish Breast Cancer Cooperative Group

Marianne Kyndi, Flemming B. Sørensen, Helle Knudsen, Marie Overgaard, Hanne Melgaard Nielsen, and Jens Overgaard

- **Purpose :**To examine the importance of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER-2), and constructed subtypes to patients receiving ± PMRT

- **Patients and Methods**

  1,000 of the 3,083 high-risk BCP (DBCG) protocol 82 trials b and c

  Randomly assigned to assigned to ± PMRT

Tissue microarray sections were stained for ER, PgR, and HER-2.

Median follow-up time for patients alive was 17 years.

End points were locoregional recurrence as isolated first event, distant metastases, and overall survival.

- For statistical analyses four subgroups were constructed from hormonal receptors (Rec).

Rec + was defined as ER+ and/or PgR+.

Rec– as both ER– and PgR–.

The four subgroups were Rec+HER-2–,

Rec+/HER-2+,

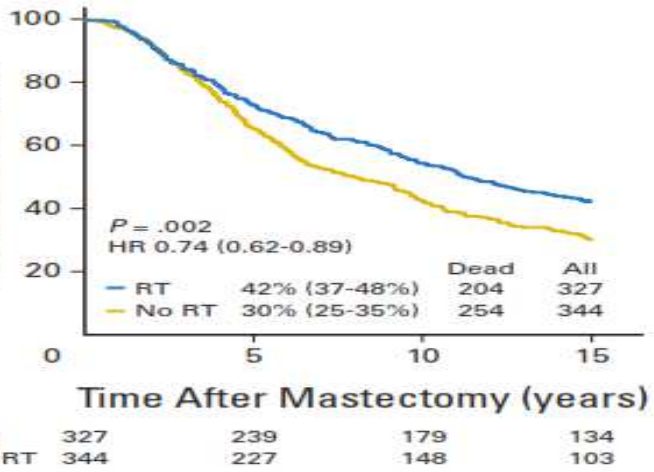
Rec–/HER-2– (triple negative),

Rec–/HER-2+.

Results

- **Improved OS after PMRT : Good prognostic markers : HR+ and HER-2- N OS improvement after PMRT : poor prognosis,**
- **HR –negative and HER-2+ patients, and in particular the Rec–/HER-2+ subtype.**
- **Hazard ratios and 95% CIs ,smaller improvements in LR control after PMRT were found for**

ER– & PgR– tumors vs ER+ & PgR+ tumors (P=.003 and .04, respectively and for the triple-negative (P = .02), and the Rec–/HER-2+ subtypes (P = .003) compared with the Rec+/HER-2– subtype.



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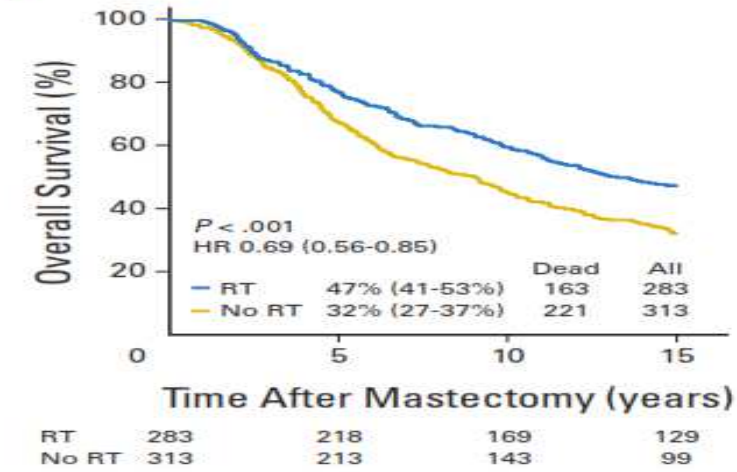
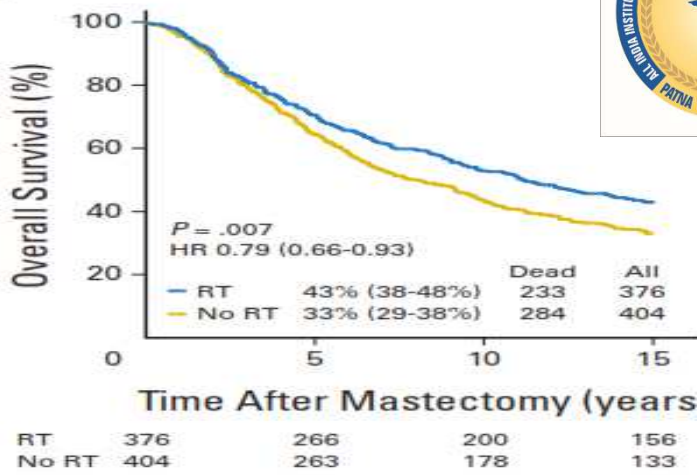
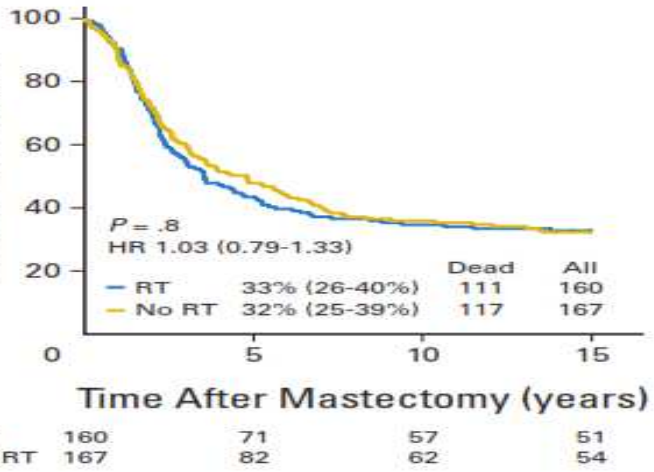
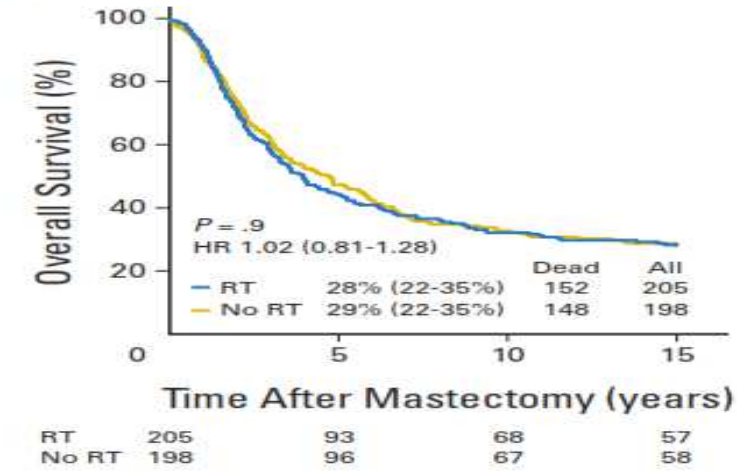


C





E



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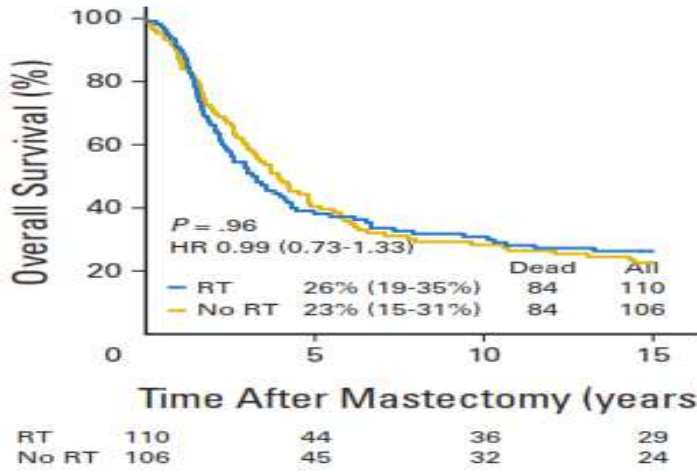


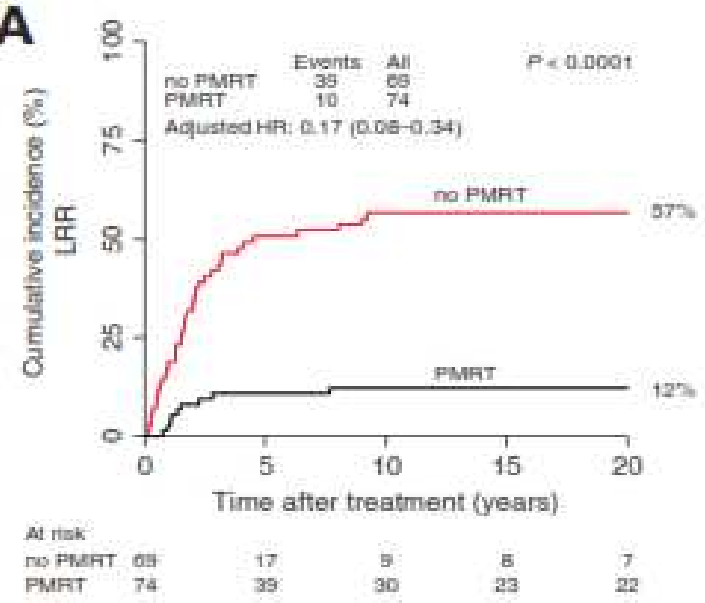
nclusion:

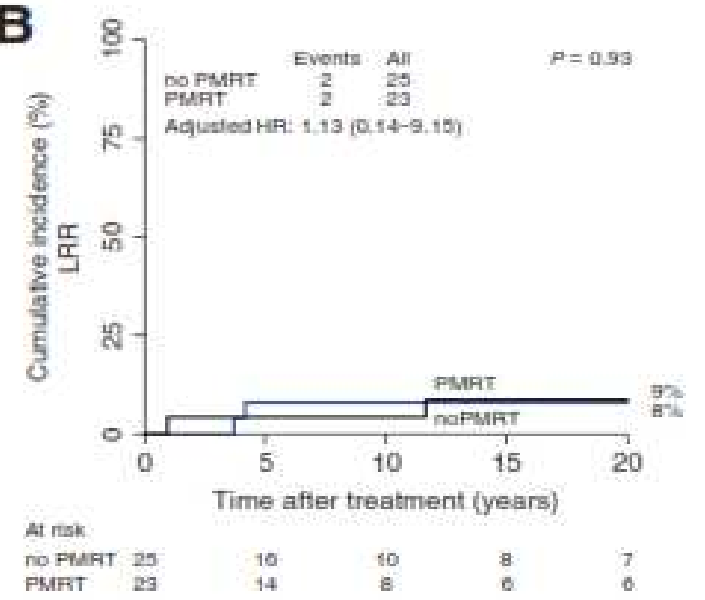
rmonal receptor status, HER-2, and the constructed subtypes may be predictive of coregional recurrence and survival after postmastectomy radiotherapy.

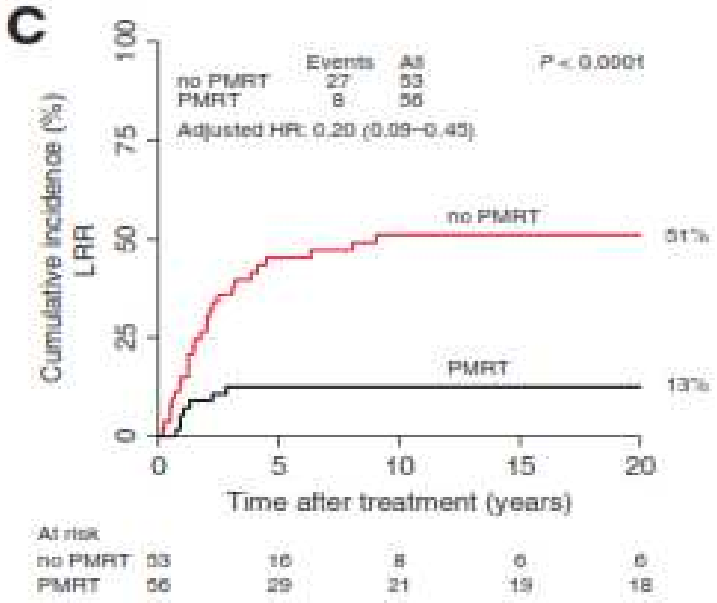
Development and Validation of a Gene Profile Predicting Benefit of Postmastectomy Radiotherapy in Patients with High-Risk Breast Cancer: A Study of Gene Expression in the DBCG82bc Cohort

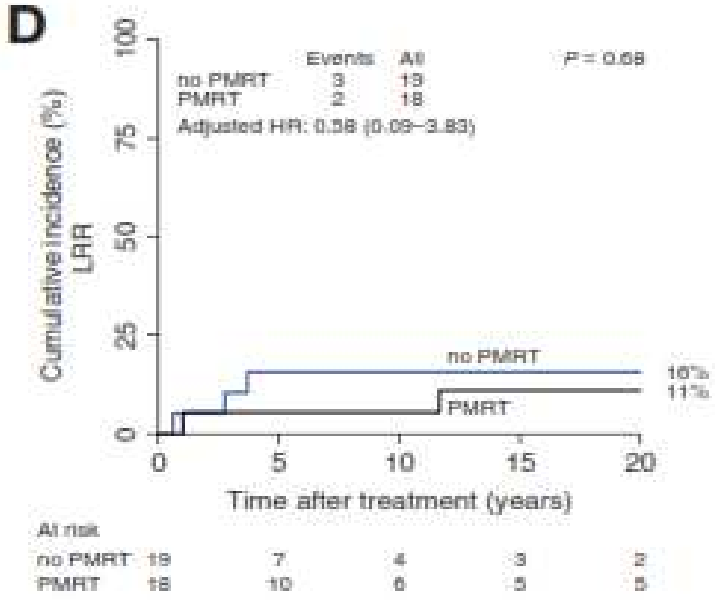
Trine Tramm[1], Hayat Mohammed[2], Simen Myhre[3,4,5], Marianne Kyndi[1], Jan Alsner[1], Anne-Lise Børresen-Dale[3,4], Therese Sørlie[3,4], Arnoldo Frigessi[2], and Jens Overgaard[1]

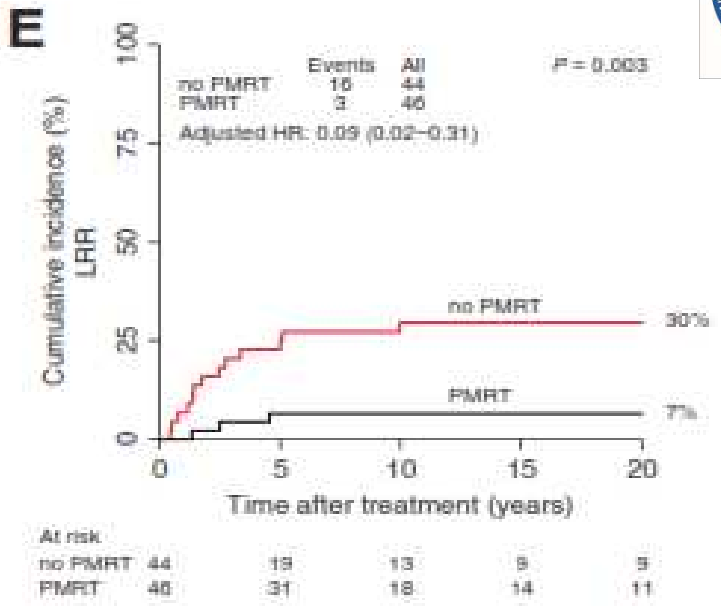
- **Purpose**: To identify genes predicting benefit of radiotherapy in patients with high-ri breast cancer treated with systemic therapy and randomized to receive or not receiv postmastectomy radiotherapy (PMRT).
- Gene-expression analysis was performed in a training set of frozen tumor tissue from 191 patients.
- Genes were identified through the Lasso method with the endpoint being locoregion recurrence (LRR).
- A weighted gene-expression index (DBCG-RT profile) was calculated and transferred quantitative real-time PCR (qRT-PCR) in corresponding formalin-fixed, paraffin-embedded (FFPE) samples, before validation in FFPE from 112 additional patients.

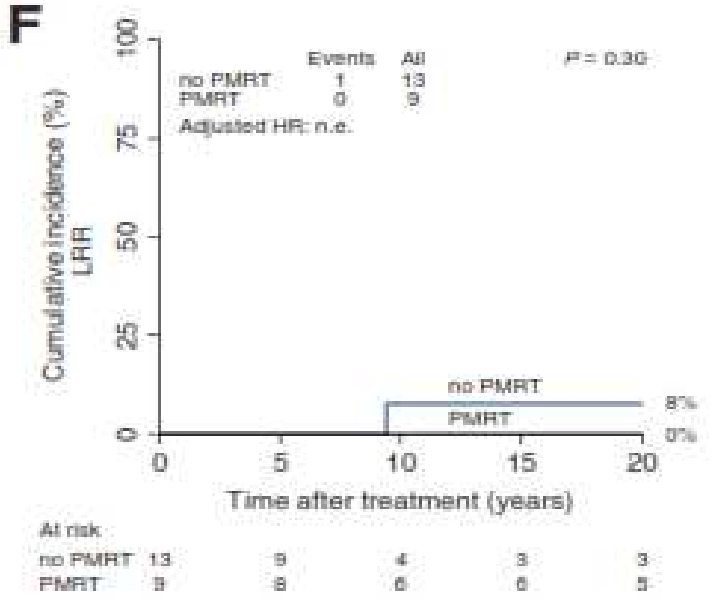

A
Events All
no PMRT 39 69
PMRT 10 74
P < 0.0001
Adjusted HR: 0.17 (0.08–0.34)
no PMRT
PMRT
57%
12%
Cumulative incidence (%) LRR
Time after treatment (years)
At risk
no PMRT 69 17 9 8 7
PMRT 74 39 30 23 22


B
Events All
no PMRT 2 25
PMRT 2 23
P = 0.93
Adjusted HR: 1.13 (0.14–9.15)
PMRT
noPMRT
9%
8%
Cumulative incidence (%) LRR
Time after treatment (years)
At risk
no PMRT 25 16 10 8 7
PMRT 23 14 8 6 6


C
Events All
no PMRT 27 53
PMRT 8 56
P < 0.0001
Adjusted HR: 0.20 (0.09–0.45)
no PMRT
PMRT
51%
13%
Cumulative incidence (%) LRR
Time after treatment (years)
At risk
no PMRT 53 16 8 6 6
PMRT 56 29 21 13 12


D
Events All
no PMRT 3 19
PMRT 2 18
P = 0.69
Adjusted HR: 0.58 (0.09–3.83)
no PMRT
PMRT
16%
11%
Cumulative incidence (%) LRR
Time after treatment (years)
At risk
no PMRT 19 7 4 3 2
PMRT 18 10 6 5 5


E
Events All
no PMRT 16 44
PMRT 3 46
P = 0.003
Adjusted HR: 0.09 (0.02–0.31)
no PMRT
PMRT
30%
7%
Cumulative incidence (%) LRR
Time after treatment (years)
At risk
no PMRT 44 19 13 9 5
PMRT 46 31 18 14 11


F
Events All
no PMRT 1 13
PMRT 0 9
P = 0.30
Adjusted HR: n.e.
no PMRT
PMRT
8%
0%
Cumulative incidence (%) LRR
Time after treatment (years)
At risk
no PMRT 13 9 4 3 3
PMRT 9 8 6 6 5

Results: Seven genes were identified, and the derived DBCG-RT profile divided the 191 patients into"high LRR risk" and "low LRR risk" groups.

- PMRT significantly reduced risk of LRR in "high LRR risk“ patients, whereas "low LRR risk" patients showed no additional reduction in LRR rate.
- Technical transfer of the DBCG-RT profile to FFPE/qRT-PCR was successful, and the predictive impact was successfully validated in another 112 patients.

Conclusions: A DBCG-RT gene profile was identified and validated, identifying patients with very low risk of LRR and no benefit from PMRT

- The profile may provide a method to individualize treatment with PMRT

Clin Cancer Res; 20(20); 5272–80. 2014 AACR

Additional Achievements

- Abnormal expression of TOP2A as predictive marker for therapeutic effect of anthracycline containing regimen.
- Ongoing trials:

1) Moderately hypofractionated loco-regional adjuvant radiation therapy of early breast cancer combined with a simultaneous integrated boost in patients with an indication for boost: DBCG HYPO II, a randomised clinically controlled trial.

- Quality assurance of diagnostic work-up and treatment regimens. Team work has been accomplished.
- Protocolized research activities .
- Novel evidence-based treatment modalities are implemented immediately nation-wide .
- DBCG activities :improved prognosis : 5-year survival ascending from 60% to roughly 80%.
- Indicators for national quality assurance programe and monitoring.
- Promotes transitional research.
- Improves patient care and education.

Conclusion

High-quality DBCG studies of various designs and scope, nationwide or in international collaboration, have contributed to the current updating of the guidelines, and have been an instrumental resource in the improvement of management and prognosis of breast cancer .

Prognosis in breast cancer has continuously improved with a decrease in 5-year mortality from ~37% to 15%.

"The keynote of progress in the 20th century is system and organization in other words, "team-work".

Dr. Charles H Mayo.


Thanks