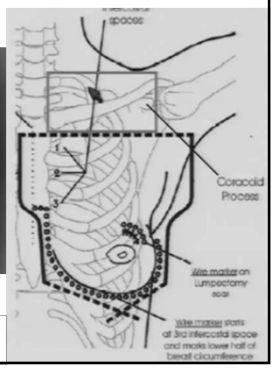
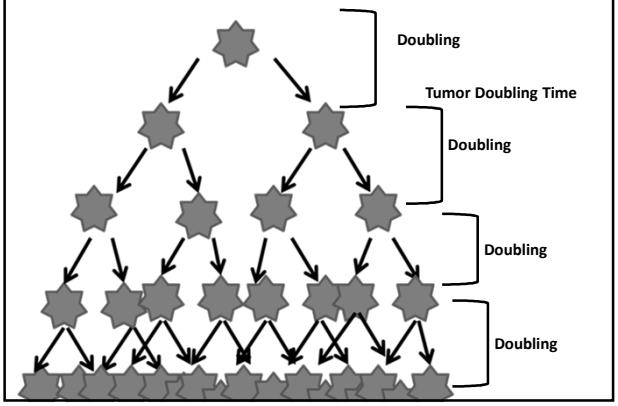
Meta Analysis in Ca Breast
Role of Radiotherapy

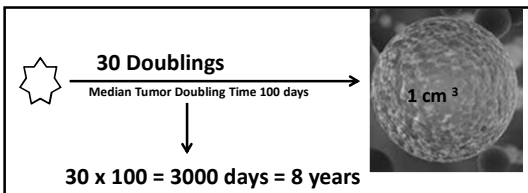


Dr Manoj Gupta,
Prof & Head
AIIMS, Rishikesh.

ICRO Coimbtoor
1st September, 2018

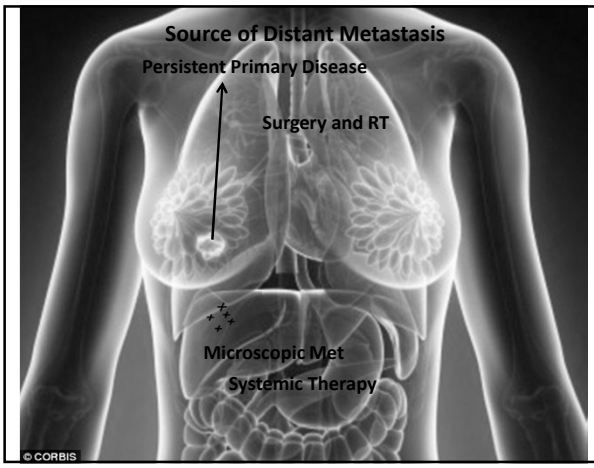
Tumor Biology





30 x 100 = 3000 days = 8 years

1. **Primary Gross**
2. **Microscopic Distant Metastasis**



Meta analysis in Ca Breast Role of Radiotherapy

- Post Mastectomy Radiotherapy (PMRT)
- Post Breast Conservative Surgery (Post BCS)
- Long Term Side Effect

PMRT

Recurrence Risk

- **Positive Axillary Nodes**
  - ↑ with more LN involvement
  - 1-3 LN+: 5-15% at 10yrs
  - ≥4 LN+: 15-50%
  - Ratio of LN+ (>20%) = LRR >20%
- **Tumour Size**
  Increases with Size

Truong IJRBP. 68(1):59-65. 2007

Recurrence Risk

- **High Risk Features**
  - **Grade III Tumors**
  - **LVSI**
  - **TNBC**
  - **ER/PR Negative Tumours**

Where are the recurrences?

- >50% chest wall (mastectomy scar/skin)
- 20-40% supraclav or infraclavicular
- <5% post ALND (I/II)
- Internal mammary LN
  - 1/3 path involvement in high risk
  - Few clinical recurrences

Indication of PMRT

- **Definitive**
  - Tm size >5cm
  - 4 or >4 axillary nodes metastasis
  - Positive Surgical Margins
  - Pectoralis muscle involvement
- **Debatable**
  - 1to 3 axillary nodes metastasis
  - 2 to 5 cm primary tumor

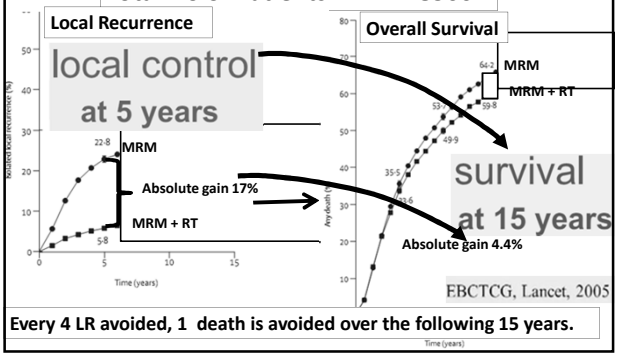
↓

Early Breast Cancer

Oxford 2005 Meta-analysis

LN + patients → +/- Postmastectomy Radiation

Total No of Patients 8500

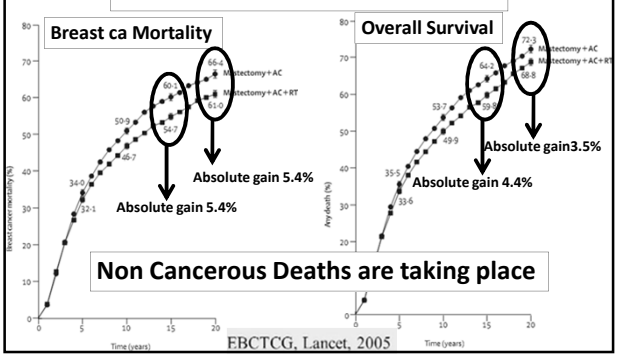


Every 4 LR avoided, 1 death is avoided over the following 15 years.

Oxford 2005 Meta-analysis

LN + patients → +/- Postmastectomy Radiation

Total No of Patients 8500



Non Cancerous Deaths are taking place

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*

www.thelancet.com Published online March 19, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60488-8

Negative Axilla

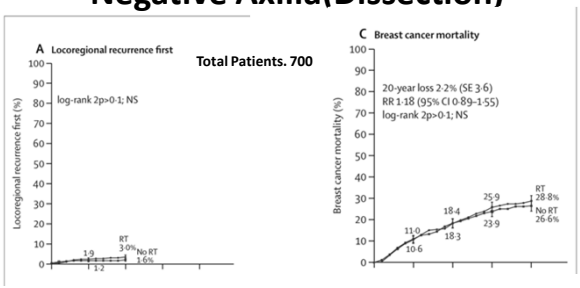
Positive Axilla

1-3 +ve Nodes

→ Axillary Dissection Level I & II or Min 10 nodes

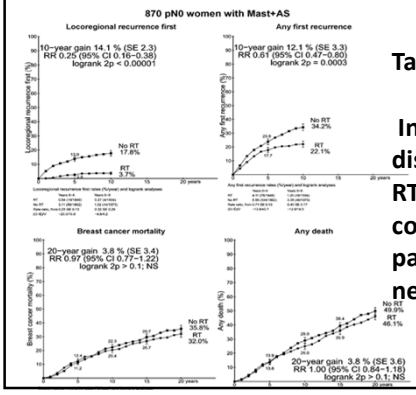
→ Axillary Sampling

Negative Axilla(Dissection)



Take Home In adequately dissected axilla PMRT does not provide any advantage

Negative Axilla(Sampling)



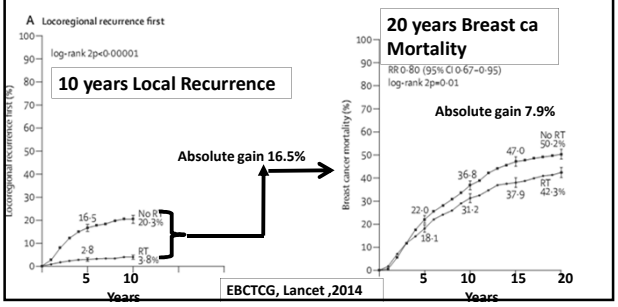
Take Home

In inadequately dissected Axilla, RT may be considered in patients with negative axilla

Patients with 1-3 Positive Nodes

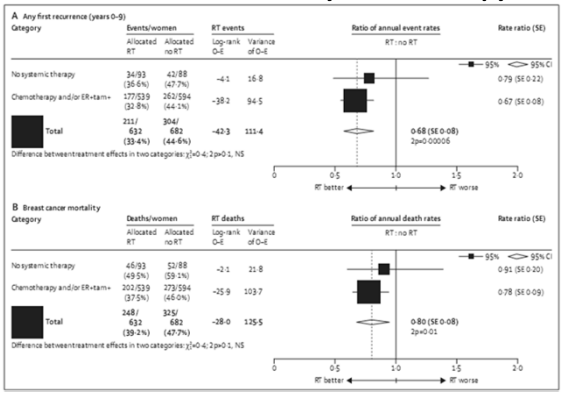
Total No of Patients 1314

Every 2 LR avoided, 1 death is avoided over the following 20 years.



EBCTCG, Lancet ,2014

Effect of PMRT Based on Systemic Therapy



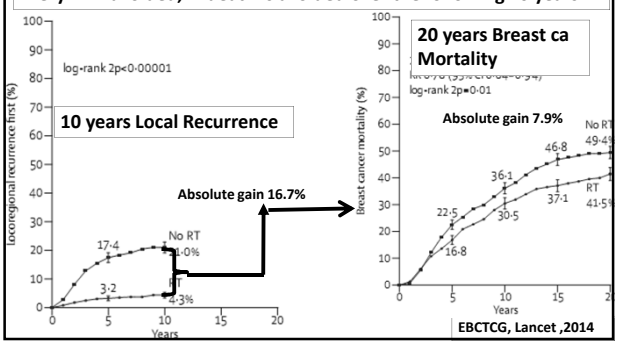
EBCTCG, Lancet ,2014

Oxford 2014 Meta-analysis

PMRT in 1-3 Positive Nodes Who received Systemic Treatment

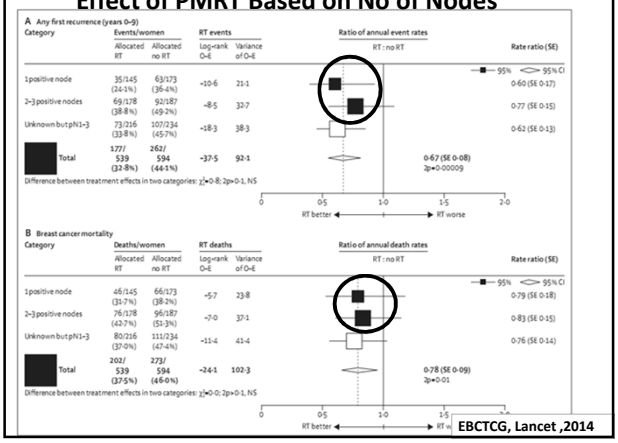
Total No of Patients 1133

Every 2 LR avoided, 1 death is avoided over the following 20 years.



EBCTCG, Lancet ,2014

Effect of PMRT Based on No of Nodes



EBCTCG, Lancet ,2014

Oxford Meta Analysis

- Two Danish Study
  - 82b Premenopausal Women
  - 82c Postmenopausal Women
- British Columbia Study

82 b Premenopausal Women
T1 & T2 (85%)
1-3 +ve Node (62%)

The New England
Journal of Medicine

VOLUME 337 OCTOBER 2, 1997 NUMBER 14

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

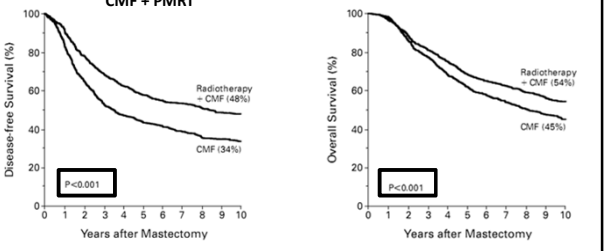
MARIE OVERGAARD, M.D., PER S. HANSEN, M.D., JENS OVERGAARD, M.D., CARSTEN ROSE, M.D., MICHAEL ANDERSSON, M.D., FLEMMING BACH, M.D., MOGENS KJAER, M.D., CARL C. GADEBERG, M.D., HENNING T. MOURIDSEN, M.D., MAJ-BRITT JENSEN, M.Sc., AND KARIN ZEDELER, M.Sc., FOR THE DANISH BREAST CANCER COOPERATIVE GROUP 82b TRIAL

Danish 82b Trial

N=1708

CMF + PMRT

CMF



Disease Free Survival

Overall Survival

Median Follow Up 10Years

The New England Journal of Medicine Volume 337 Number 14 October 2, 1997

82 b Postmenopausal Women
T1 & T2 (87%)
1-3 +ve Node (58%)

Articles

Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial

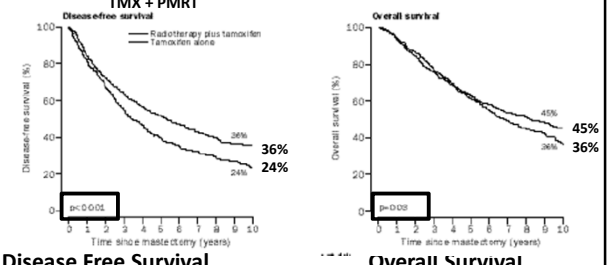
Marie Overgaard, Maj-Britt Jensen, Jens Overgaard, Per S Hansen, Carsten Rose, Michael Andersson, Claus Kamby, Mogens Kjær, Carl C Gadeberg, Birgitte Bruun Rasmussen, Mogens Blichert-Toft, Henning T Mouridsen

Danish 82c Trial

N=1375

TMX + PMRT

TMX



Disease Free Survival

Overall Survival

Median Follow Up 10 Years

THE LANCET • Vol 353 • May 15, 1999

Limitation of these Results

ECOG: 10 Year Cumulative Incidence of Loco-Regional Failure without XRT

Tumor Size, No. of Nodes	No. of Patients	Isolated LRF %	SE
T1, 1-3	407	9.1	1.5
T2, 1-3	576	7.0	1.1
T3, 1-3	35	22.9	7.2
Danish trial 82b[6]		30	
Danish trial 82c[7]		31	

Recht et al, JCO, 1999

Limitation of these Results

NSABP

	1-3 LN+		
	≤ 2	2.1-5	> 5
No. of patients	1,045	1,489	229
Isolated LF, %	4.3	7.2	5.2
Isolated RF, %	2.4	3.5	2.3
Isolated LRF, %	6.0	9.7	7.5
LRF with or without DF, %	10.6	15.3	11.4
DF, %	24.6	35.7	40.5

NOTE. Subcolumn headings indicate tumor size (in centimeters).
Abbreviations: LN+, positive lymph nodes; LF, local failure; RF, regional failu

Taghian et al, JCO, 2004

Limitation of these Results

- **Surgery was not adequate specially the axillary dissection as compare to other trials.**
- **Median no of lymph nodes removed**
  - **Danish Trials 7**

Danish Trial 82b & 82c

Sub-group Analysis

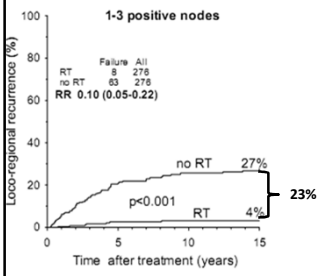
- **Only select patients with no of nodes removed 8 or more.**
- **Further grouped based on 1-3 nodes or ⩾ 4 nodes**
- **N=1152**

M. Overgaard et al. / Radiotherapy and Oncology 82 (2007) 247–253

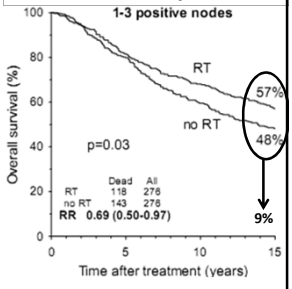
Danish Trial 82b & 82c

Sub-group Analysis

Loco regional Recurrence



Median Follow Up 15 Years

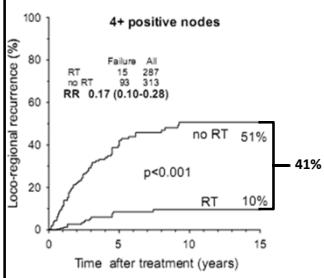


M. Overgaard et al. / Radiotherapy and Oncology 82 (2007) 247–253

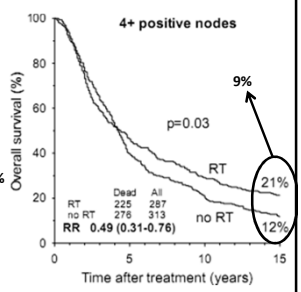
Danish Trial 82b & 82c

Sub-group Analysis

Loco regional Recurrence



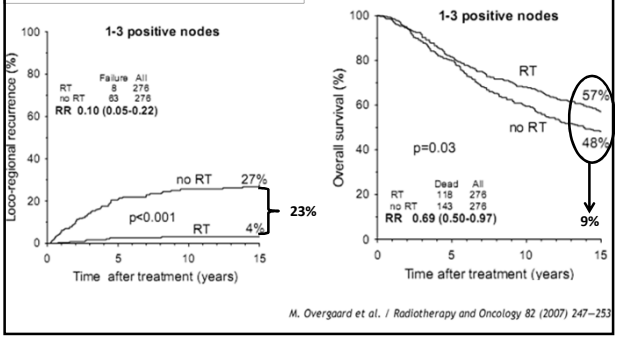
Median Follow Up 15 Years



M. Overgaard et al. / Radiotherapy and Oncology 82 (2007) 247–253

Danish Trial 82b & 82c
Sub-group Analysis

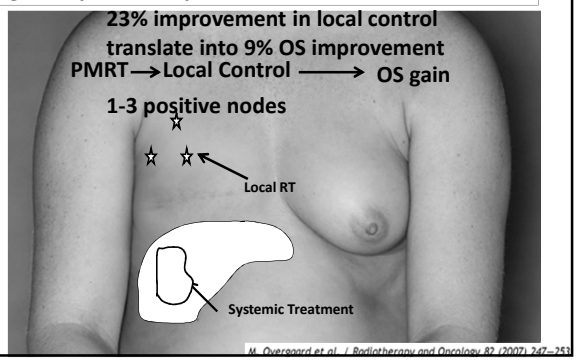
Loco regional Recurrence | **Median Follow Up 15 Years**



M. Overgaard et al. / Radiotherapy and Oncology 82 (2007) 247–253

Danish Trial 82b & 82c
Sub-group Analysis (Hypothesis)

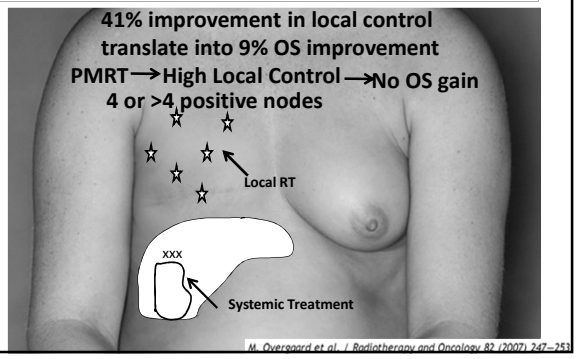
Larger Proportion of patients will have survival benefit



M. Overgaard et al. / Radiotherapy and Oncology 82 (2007) 247–253

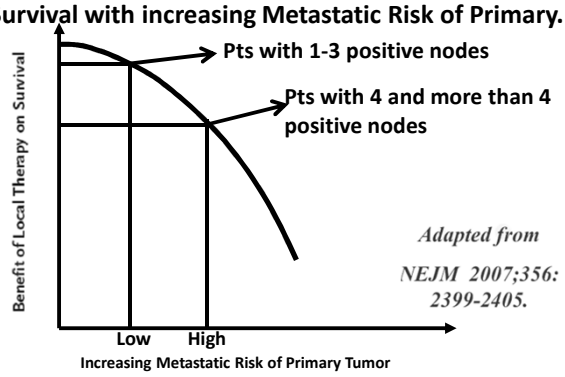
Danish Trial 82b & 82c
Sub-group Analysis

Limited Proportion of patients will have survival benefit



M. Overgaard et al. / Radiotherapy and Oncology 82 (2007) 247–253

Hypothetical benefit of Local Tumor Control on Survival with increasing Metastatic Risk of Primary.



Radiotherapy and Oncology 90 (2009) 74–79

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Postmastectomy irradiation

High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: A subgroup analysis of DBCG 82 b&c ☆

Marianne Kyndi [a,b,*], Marie Overgaard [c], Hanne M. Nielsen [a], Flemming B. Sørensen [b], Helle Knudsen [d], Jens Overgaard [a]

[a] Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark
[b] Department of Pathology, Aarhus University Hospital, Denmark
[c] Department of Oncology, Århus University Hospital, Denmark
[d] Department of Pathology, Herlev Hospital, Denmark

Danish Trial 82b & 82c Sub-group Analysis

- **Among patients in 82b and 82c randomized to no radiation, 3 risk groups were identified**
- **Good: 4 of 5 favorable features**
  - **≤3 nodes**
  - **Size <2 cm**
  - **Grade 1**
  - **ER or PR positive, her2 negative**

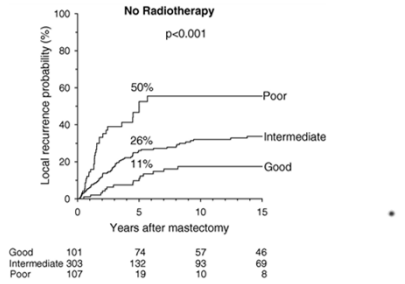
Intermediate risk = all others

- **Poor: 2 of 3**
  - **Grade 3, >3 nodes, size >5 cm**

Radiother Oncol 2009 Jan;90(1):74-9

Danish Trial 82b & 82c
Sub-group Analysis

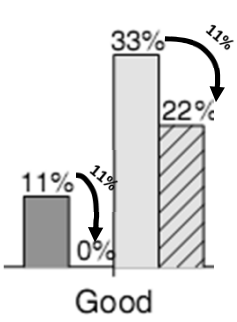
LRR by Risk Group



Radiother Oncol 2009 Jan;90(1):74-9

Danish Trial 82b & 82c
Sub-group Analysis

5 year LRR & 15 year Breast Cancer Mortality by Risk Group



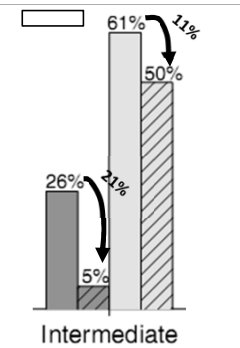
no RT Local rec. (5-year)
+ RT
no RT Breast cancer mortality
+ RT (15-year) 61%

Improvement in local control translate excellently into improvement in cancer specific survival

Radiother Oncol 2009 Jan;90(1):74-9

Danish Trial 82b & 82c
Sub-group Analysis

5 year LRR & 15 year Breast Cancer Mortality by Risk Group



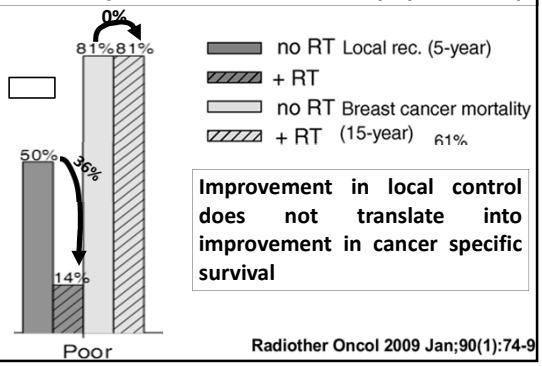
no RT Local rec. (5-year)
+ RT
no RT Breast cancer mortality
+ RT (15-year) 61%

Improvement in local control translate reasonable into improvement in cancer specific survival

Radiother Oncol 2009 Jan;90(1):74-9

Danish Trial 82b & 82c Sub-group Analysis

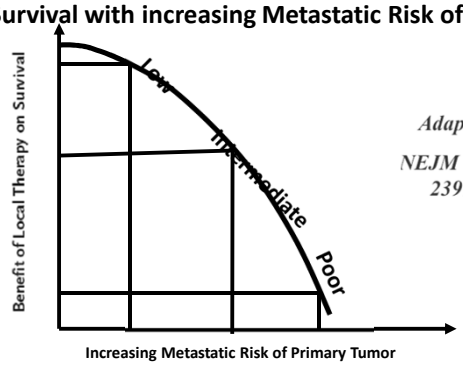
5 year LRR & 15 year Breast Cancer Mortality by Risk Group



Improvement in local control does not translate into improvement in cancer specific survival

Radiother Oncol 2009 Jan;90(1):74-9

Hypothetical benefit of Local Tumor Control on Survival with increasing Metastatic Risk of Primary.



Adapted from NEJM 2007;356: 2399-2405.

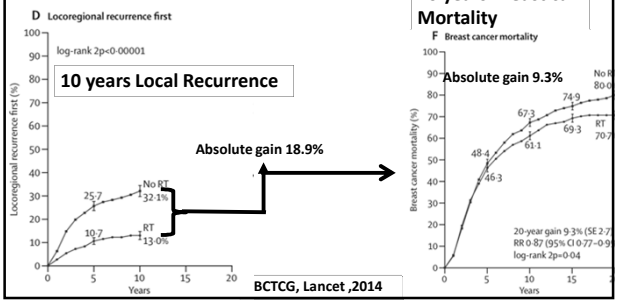
Oxford 2014 Meta-analysis

PMRT in 4 or >4 Positive Nodes

Total No of Patients 1772

Every 2 LR avoided, 1 death is avoided over the following 20 years.

20 years Breast ca Mortality



10 years Local Recurrence

Absolute gain 18.9%

Absolute gain 9.3%

BCTCG, Lancet ,2014

Take Home

All reports related with Danish trial 82b & c make strong case of PMRT in patients with 1-3 positive axillary nodes

Criticisms

- **Local recurrence was still high in sub group analysis of patients with > 8 nodes removed (27%) surgery alone arm**
- **Sub optimal Chemotherapy used (CMF).**
- **Tamoxifan was given for 1 years only.**

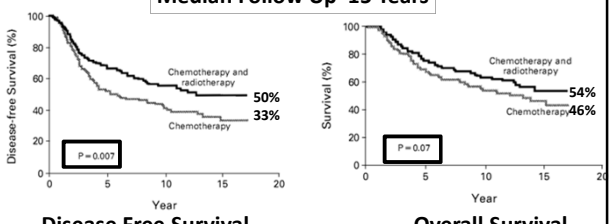
Less Effective Systemic Therapy

British Columbia Trial

Pre menopausal Early Breast Cancer Majority T1 & T2 with pN+ve
N=318 (60% 1-3 nodes +)

CMF + PMRT **CMF**

Median Follow Up 15 Years

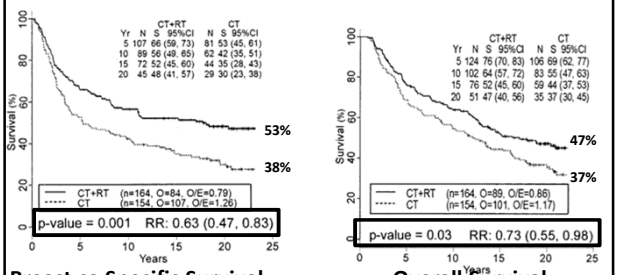


Disease Free Survival **Overall Survival**

The New England Journal of Medicine Volume 337 Number 14 October 2, 1997

Updated Result of British Columbia

Median Follow Up 20 Years



Breast ca Specific Survival

Overall Survival

Journal of the National Cancer Institute, Vol. 97, No. 2, January 19, 2005

Limitation of Oxford Meta-analysis

- **All trials since 1960 onwards.**
- **Radiotherapy technique was old.**
- **Usually radiation was given to all regional lymphatic (Axilla, S/C and IM)**

↓

More Long term side effects

With Modern radiotherapy the impact in improving the outcome may be much higher

Limitation of Oxford Meta-analysis

- **With Modern Systemic Chemotherapy**
- **Much improved Surgical Technique**

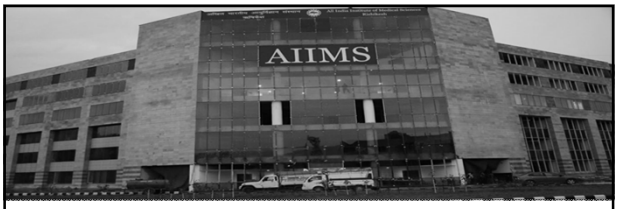
↓

5 years Local Recurrence may be much less than in these trial

The impact of Radiotherapy in improving the outcome likely to be smaller

Oxford Meta-analysis

- **This also support the use of PMRT in patients with early breast ca with 1-3 positive nodes**



Thanks

Greetings From Rishikesh