Meta Analysis in Ca Breast
Role of Radiotherapy

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Tumor Biology

30 Doublings
Median Tumor Doubling Time 100 days

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
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

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Recurrence Risk

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

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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**
  - 1 to 3 axillary nodes metastasis
  - 2 to 5 cm primary tumor

**Early Breast Cancer**

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**Oxford 2005 Meta-analysis**

**LN + patients → +/- Postmastectomy Radiation**

**Total No of Patients** 8500

- **Local Recurrence**
- **Overall Survival**

- **Absolute gain 17%**
- **Absolute gain 4.4%**

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

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**Breast ca Mortality**

- **Absolute gain 5.4%**
- **Absolute gain 5.4%**
- **Absolute gain 3.5%**

Non Cancerous Deaths are taking place
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**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**

- Negative Axilla
- Positive Axilla
- 1-3 +ve Nodes

Axillary Dissection Level I & II or Min 10 nodes

Axillary Sampling

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**Negative Axilla (Dissection)**

- Total Patients: 700

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

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**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.

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.
Oxford Meta Analysis

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

- British Columbia Study

82b Premenopausal Women

T1 & T2 (85%)
1-3 +ve Node (62%)

The New England Journal of Medicine
Danish 82b Trial

N=1708

CMF + PMRT

CMF

Disease Free Survival

Overall Survival

Median Follow Up 10 Years

Danish 82b Trial

Postmenopausal Women

T1 & T2 (87%)

1-3 +ve Node (58%)

82 b Postmenopausal Women

T1 & T2 (87%)

1-3 +ve Node (58%)

Danish 82c Trial

N=1375

TMX + PMRT

TMX

Disease Free Survival

Overall Survival

Median Follow Up 10 Years

29th ICRO, GKNM, Coimbatore

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Limitation of these Results

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

<table>
<thead>
<tr>
<th>Tumor Size, No. of Nodes</th>
<th>No. of Patients</th>
<th>Isolated LRF %</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1, 1-3</td>
<td>407</td>
<td>9.1</td>
<td>1.5</td>
</tr>
<tr>
<td>T2, 1-3</td>
<td>576</td>
<td>7.0</td>
<td>1.1</td>
</tr>
<tr>
<td>T3, 1-3</td>
<td>35</td>
<td>22.9</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Danish trial 62c⁶: 30
Danish trial 62c⁷: 31

Rafii et al, JCO, 1999

Limitation of these Results

NSABP

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Isolated LF, %</th>
<th>Isolated RF, %</th>
<th>Isolated LRF, %</th>
<th>LRF with or without DF, %</th>
<th>DF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2 LN+ ≤ 2</td>
<td>4.3</td>
<td>2.4</td>
<td>8.6</td>
<td>10.6</td>
<td>24.6</td>
</tr>
<tr>
<td></td>
<td>2.16</td>
<td>3.5</td>
<td>9.2</td>
<td>15.3</td>
<td>35.7</td>
</tr>
<tr>
<td></td>
<td>2.15</td>
<td>2.2</td>
<td>7.2</td>
<td>11.4</td>
<td>40.5</td>
</tr>
</tbody>
</table>

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

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

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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

Danish Trial 82b & 82c
Sub-group Analysis
Loco regional Recurrence
1-3 positive nodes
- 23%
- Time after treatment (years)

Median Follow Up 15 Years
1-3 positive nodes
- 9%
- Time after treatment (years)

Danish Trial 82b & 82c
Sub-group Analysis
Loco regional Recurrence
4+ positive nodes
- 41%
- Time after treatment (years)

Median Follow Up 15 Years
4+ positive nodes
- 9%
- Time after treatment (years)
Danish Trial 82b & 82c
Sub-group Analysis

<table>
<thead>
<tr>
<th>Loco regional Recurrence</th>
<th>Median Follow Up 15 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 positive nodes</td>
<td>1-3 positive nodes</td>
</tr>
<tr>
<td>p=0.001</td>
<td>p=0.03</td>
</tr>
<tr>
<td>no RT 27%</td>
<td>RT 9%</td>
</tr>
<tr>
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</tbody>
</table>

Loco regional Recurrence:
- 1-3 positive nodes
- p=0.001
- no RT 27%
- RT 9%
- Median Follow Up 15 Years:
- 1-3 positive nodes
- p=0.03
- no RT 9%
- RT 4%

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

Larger Proportion of patients will have survival benefit

- 23% improvement in local control
- translate into 9% OS improvement
- PMRT → Local Control → OS gain
- 1-3 positive nodes
  - Local RT
  - Systemic Treatment

Limited Proportion of patients will have survival benefit

- 41% improvement in local control
- translate into 9% OS improvement
- PMRT → High Local Control → No OS gain
- 4 or >4 positive nodes
  - Local RT
  - Systemic Treatment

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Increasing Metastatic Risk of Primary Tumor

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

- Pts with 1-3 positive nodes
- Pts with 4 and more than 4 positive nodes

Adapted from NEJM 2007;356:2399-2405.

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

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Danish Trial 82b & 82c
Sub-group Analysis

LRR by Risk Group

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

Danish Trial 82b & 82c
Sub-group Analysis

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

Improvement in local control translate reasonably into improvement in cancer specific survival
**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):49-9"}

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

*Adapted from NEJM 2007;356: 2399-2405.*

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**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.

*Absolute gain 18.9%*

*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 subgroup 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 +)

Disease Free Survival

Overall Survival

Median Follow Up 15 Years

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Updated Result of British Columbia

**Median Follow Up 20 Years**

<table>
<thead>
<tr>
<th></th>
<th>Breast ca Specific Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>47%</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Breast ca Specific Survival*  *Overall Survival*

**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