Evidence based medicine for breast radiation therapy and limitations

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HEGP

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What is « evidence based medicine » in radiotherapy for breast cancer?

Are we all talking about of the same level of evidence?

- IA Evidence from meta-analysis of randomized controlled trials
- IB Evidence from at least one randomized controlled trial
- IIA Evidence from at least one controlled study without randomization
- IIB Evidence from at least one other type of quasi-experimental study
- III Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
Radiation therapy for Breast cancer
What have we learned for 120 years?

Invasive breast tumors

1895 - 1900

The same active ingredient:

beams of photons X

2015

Electrons
Protons
What do we really know?
In conservative treatment, post-operative radiotherapy reduces the 10-year risk of any first recurrence

Meta-analysis of Early Breast Cancer Trialists Collaborative Group (EBCTCG)
- 10,801 women in 17 trials beginning before 2000 and comparing RT vs no RT
- Median follow-up: 9.5 years

- pN0 = 7287 pts (67%)
- pN+ = 1050 pts
- All = 10,801 pts
What do we really know?
In conservative treatment, post-operative radiotherapy reduces the 15-year risk of breast cancer death

Meta-analysis of EBCTCG
- 10,801 women in 17 trials beginning before 2000 and comparing RT vs no RT
- Median follow-up: 9.5 years

Lancet 2011; 378: 107
What limitations for these results?

The example of radiotherapy

<table>
<thead>
<tr>
<th>17 trials</th>
<th>Breast irradiation</th>
<th>Boost irradiation</th>
<th>Regional nodal irradiation</th>
</tr>
</thead>
</table>
| 76B NSABP B-06 | 50 Gy (2 Gy/f) c or m  
54 Gy d (2 Gy/f) m | None | None |
| 82Y St George’s | 40 Gy (2.5 Gy/f) c  
50 Gy (2-2.5 Gy/f) m | 10 Gy (2 Gy/f) o or e | 0-50 Gy (2 Gy/f) m (IMC and SC/AF)† |
| 84P Ontario COG | 40 Gy (2.7 Gy/f) or  
50 Gy (2 Gy/f) d c Various | 12.5 Gy (2.5 Gy/f) c  
10-30 Gy (2-3 Gy/f) o,e or i | None |
| 85B Scottish | 48-54 Gy (1.9-2.2 Gy/f) m | 15 Gy (3 Gy/f) e/c | 50 Gy (2.5 Gy/f) m (IMC),  
0-45 (2.3 Gy/f) m (SC/AF)† |
| 85D West Midlands | 54 Gy (2 Gy/f) c or m  
50 Gy (2 Gy/f) c or m  
50 Gy (2 Gy/f) m | Various | 40 Gy (2.7 Gy/f) or  
50 Gy (2 Gy/f) c (SC/AF)† |
| 86C CRC UK | 50 Gy (2 Gy/f) c or m  
40 Gy (2.5 Gy/f) or  
50 Gy (2 Gy/f) c or m  
45-50 Gy (2-2.3 Gy/f) m | 15 Gy (3 Gy/f) e/c | Various |
| 81L Uppsala-Orebro | 48-54 Gy (1.9-2.2 Gy/f) m | Various | None |
| 87R INT Milan III | 50 Gy (2 Gy/f) c or m  
40 Gy (2.5 Gy/f) m | 10 Gy (2 Gy/f) o or e | None |
| 90M Tampere | 50 Gy (2 Gy/f) m | 10-12 Gy (2.0 Gy/f) e | None |
| 91P SweBCG 91-RT | 48-54 Gy (1.9-2.2 Gy/f) m | 12.5 Gy (2.5 Gy/f) o or e | None |
| 89L NSABP B-21 | 50 Gy (2 Gy/f) c or m  
40 Gy (2.5 Gy/f) or  
50 Gy (2 Gy/f) c or m  
45-50 Gy (2-2.3 Gy/f) m | 10 Gy (2 Gy/f) o | None |
| 91J GBSG V Germany | 45 Gy (1.8 Gy/f) c or m  
50 Gy (2 Gy/f) c or m | 10-15 Gy (2-3 Gy/f) e  
14 Gy (2 Gy/f) e | None |
| 92A PMH Toronto | 50 Gy (2 Gy/f) c or m  
45-50 Gy (2-2.3 Gy/f) m | 10 Gy (0-2 Gy/f) e or l | None |
| 92P BASO II | 45-50 Gy (2-2.3 Gy/f) m | 0-15 Gy (0-2 Gy/f) e | None |
| 94C CALGB 9343†† | 50 Gy (2 Gy/f) c or m  
45-50 Gy (2-2.3 Gy/f) m | 10 Gy (0-2 Gy/f) e | None |
| 96Y ABCSG 8a†† | 50 Gy (2 Gy/f) c or m  
45-50 Gy (2-2.3 Gy/f) m | 10 Gy (0-2 Gy/f) e | None |
| 99W PRIME 1†† | 50 Gy (2 Gy/f) c or m  
45-50 Gy (2-2.3 Gy/f) m | 10 Gy (0-2 Gy/f) e | None |
What do we really know?
After mastectomy, post-operative radiotherapy has no significant effect on the 10-year recurrence for pN0 patients on axillary dissection.

Meta-analysis of EBCTCG
- 8,135 women in 22 trials
- beginning before 2000
- comparing RT vs no RT
- pN status unknown in 720 patients
- 3,887 axillary dissections
- 4,065 samplings
- 183 extent unknown
- Median follow-up : 9.4 years

Lancet 2014 ; 383 : 2127
pN0 = 700 pts (8.6 %, axillary dissection)
What do we really know?

After mastectomy, post-operative radiotherapy has no significant effect on the 20-year cancer breast mortality for pN0 patients on axillary dissection.

Meta-analysis of EBCTCG

- 8,135 women in 22 trials
- beginning before 2000
- comparing RT vs no RT
- pN status unknown in 720 patients
- 3,887 axillary dissections
- 4,065 samplings
- 183 extent unknown
- Median follow-up: 9.4 years

pN0 = 700 pts (8.6%, axillary dissection)

Lancet 2014; 383: 2127
What do we really know?
After mastectomy, post-operative radiotherapy reduces the 10-year risk of any first recurrence for pN+ patients

pN+ = 3 131 pts (38.4%, axillary dissection)

Meta-analysis of EBCTCG
- 8 135 women in 22 trials
- beginning before 2000
- comparing RT vs no RT
- pN status unknown in 720 pts
- 3 887 axillary dissections
- 4 065 samplings
- 183 extent unknown
- Median follow-up: 9.4 years
What do we really know?
After mastectomy in pN+ patient, there is a benefit of post-operative radiotherapy on loco-regional recurrence rate whatever is the number of positive nodes.

Meta-analysis of EBCTCG
- 8,135 women in 22 trials
- beginning before 2000
- comparing RT vs no RT
- pN status unknown in 720 pts
- 3,887 axillary dissections
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- 183 extent unknown
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Chest wall and nodes

Lancet 2011; 378: 107
What do we really know?
After mastectomy, post-operative radiotherapy reduces the 20-year risk of cancer breast mortality for pN+ patients

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- 8,135 women in 22 trials
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- pN status unknown in 720 pts
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Chest wall and nodes

pN+ = 3,131 pts
(38.4%, axillary dissection)
What do we really know?

After mastectomy in pN+ patient, there is a benefit of post-operative radiotherapy on breast-cancer mortality whatever is the number of positive nodes.

Meta-analysis of EBCTCG

- 8,135 women in 22 trials
- beginning before 2000
- comparing RT vs no RT
- pN status unknown in 720 pts
- 3,887 axillary dissections
- 4,065 samplings
- 183 extent unknown
- Median follow-up: 9.4 years
What do we really know?
After mastectomy in pN+ patients, the chest wall has to be irradiated to limit loco-regional recurrence

Regional nodes only : 8 trials
1029 pN+

Meta-analysis of EBCTCG
- 2304 women in 8 trials
- beginning before 2000
- comparing RT vs non RT
- pN status known in 1494 pts
- Median follow-up : 7.2 years

10-year gain: 17.7% (SE 3.0)
RR 0.30 (95% CI 0.20–0.44)
logrank 2p < 0.00001

Locoregional recurrence first

Breast cancer mortality

Breast cancer mortality (%)

Locoregional recurrence first (%)

20-year gain: 2.7% (SE 3.9)
RR 1.00 (95% CI 0.82–1.20)
logrank 2p > 0.1; NS
What limitations for these results?
The example of radiotherapy

<table>
<thead>
<tr>
<th></th>
<th>Chest wall</th>
<th>Supraclavicular Axillary fossa</th>
<th>IMC</th>
<th>Boost on scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose range (Gy)</td>
<td>25 - 60</td>
<td>18 - 60</td>
<td>0 - 60</td>
<td>2 trials</td>
</tr>
</tbody>
</table>

- **Fractionation range**: 1.3 Gy – 4.5 Gy
- **Variation of dose per fraction between chest wall and nodes**: 4 trials
- **Mix of various techniques**: Orthovoltage, Cobalt, Megavoltage, Electrons
Other limitations for both meta-analysis?

Because of an essential long follow-up

Meta-analysis couldn’t take into account

- Tumor size / pT
- Sentinel procedure in nodal assessment
- Type of surgery and margins status
- Advances in anatomopathology: grading, isolated tumor cells …
- Advances in systemic treatment: taxanes, aromatase inhibitors, trastuzumab …
- After mastectomy, isn't there some benefit in pN0 patients?
  - T3-T4
  - young age, multifocal tumors, grade III, vascular invasion, triple negative and HER 2 positive tumors

Moran MS. Lancet Oncol. 2015;16(3):e113 - 22
Floyd SR. Radiother Oncol. 2009; 91(1):33-7
Boost or not boost in conservative treatment?

Boost improved local control at ten years.

**Phase III of EORTC 22 881-10 882**

- 5,318 women
- 31 centers, 9 countries
- From 1989 to 1996
- Comparing boost (16 Gy = 2,661 pts) vs no boost (2,657 pts)
- Microscopically complete resection + axillary dissection
- Whole breast irradiation 50 Gy (5x2Gy)
- Boost = tangential fields, electrons or low dose rate brachytherapy
- Median follow-up: 10.8 years

**Graph**

- Cumulative incidence (%)
- Time (years)
- No boost: 10.2%
- 16 Gy boost: 6.2%
Boost or not boost in conservative treatment?

Boost improved local control at ten years in all age groups.

Phase III of EORTC 22 881-10 882
- 5,318 women
- 31 centers, 9 countries
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- Comparing boost (16 Gy = 2,661 pts) vs no boost (2,657 pts)
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Boost or not boost in conservative treatment?

Boost does not improved disease-free survival at ten years.

- **Phase III of EORTC 22 881-10 882**
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- Comparing boost (16 Gy = 2,661 pts) vs no boost (2,657 pts)
- Microscopically complete resection + axillary dissection
- Whole breast irradiation 50 Gy (5x2Gy)
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IMN or no IMN irradiation? Is the question always discussed?

- Is the issue worth debating?

Local recurrences after mastectomy and systemic treatment without RT (%)

<table>
<thead>
<tr>
<th></th>
<th>N pts</th>
<th>Total</th>
<th>Chest wall</th>
<th>Clavicular</th>
<th>Axillary</th>
<th>IMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP 2004</td>
<td>5758</td>
<td>19.8</td>
<td>56.9</td>
<td>22.6</td>
<td>11.7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>IBCSG 2003</td>
<td>5352</td>
<td>21</td>
<td>53</td>
<td>26</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>MD Anderson Cancer Center 2005</td>
<td>1031</td>
<td>19</td>
<td>67*</td>
<td>43</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

- Numerous retrospective studies with conflicting results
- Pulmonary and cardiac toxicity
- IMN involvement on surgical dissection

Chen RC. JCO 2008. 26 : 4981
**IMN or no IMN irradiation?**

*The clever Danish trial: the natural random!*

3,089 early-stage node-positive breast cancers

- Mastectomy or conservative treatment with axillary dissection + systemic therapy
- **Natural random right breast vs left breast; assessment in intent to treat**
- Chest wall irradiation for both groups; with assurance quality of IMN dose coverage
- Median follow-up: 8.9 years

<table>
<thead>
<tr>
<th></th>
<th>IMNI = right breast 1492 pts</th>
<th>No IMNI = left breast 1597 pts</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8-year overall survival (first endpoint)</strong></td>
<td>75.9%</td>
<td>72.2%</td>
<td>Death 0.8 [0.72 – 0.94] ; <strong>p = 0.005</strong></td>
</tr>
<tr>
<td><strong>8-year breast mortality</strong></td>
<td>20.9%</td>
<td>23.4%</td>
<td>Death 0.85 [0.73 – 0.98] ; <strong>p = 0.03</strong></td>
</tr>
<tr>
<td><strong>Distant recurrences</strong></td>
<td>27.4%</td>
<td>29.7%</td>
<td>0.89 [0.78 – 1.01] ; <strong>p = 0.07</strong></td>
</tr>
</tbody>
</table>

 IB or IIA?  
 Thorsen LB. JCO 2015, in press
## IMN or no IMN irradiation? Three randomized trials

<table>
<thead>
<tr>
<th>N pts</th>
<th>Surgery</th>
<th>Inclusion criteria</th>
<th>RT: control arm</th>
<th>RT: experimental arm</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1334</td>
<td>Mastectomy</td>
<td>pN+</td>
<td>Chest wall</td>
<td>IMN</td>
<td>10-year overall survival: 3.3% ; p = 0.8</td>
</tr>
<tr>
<td>4004</td>
<td>Conservative (76%) Mastectomy</td>
<td>pN+</td>
<td>Chest wall / Breast</td>
<td>IMN</td>
<td>10-year DFS: 3.3% ; p = 0.35</td>
</tr>
<tr>
<td>1832</td>
<td>Conservative</td>
<td>pN+</td>
<td>Breast</td>
<td>IMN</td>
<td>10-year overall survival: 1.6% ; p= 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pN0: internal/central</td>
<td>Supraclav/axillary</td>
<td>Supraclav</td>
<td>1% ; p = 0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pN0: High risk</td>
<td>Supraclav/axillary</td>
<td>IMN</td>
<td>10-year DFS: 3% ; p = 0.04</td>
</tr>
</tbody>
</table>

- **French trial 1991-1997**
- **EORTC 1996-2004**
- **MA-20 (Canadian) 2000-2007**

Hennequin C. Red J2013. 86 : 860
Poortmans P. N Engl 2015. 373 : 317
Whelan TJ. N Engl 2015. 373 : 307
IMN or no IMN irradiation? One meta-analysis

Budach et al. Radiat Oncol 2015. 10:258

Comparison I: (MS+IM)+(WBI/CWl) vs. (WBI/CWl)
MA.20 [10]: n=1832; HR 0.91 (95% CL 0.72 - 1.13)
EORTC [12]: n=4004; HR 0.87 (95% CL 0.76 - 1.00)
Subtotal*: n=5836; HR 0.88 (95% CL 0.78 - 0.99)

Comparison II: IM+(WBI/CWl+MS) vs. (WBI/CWl+MS)
French [13]: n=1334; HR 0.94 (95% CL 0.79 - 1.11)
Subtotal: n=1334; HR 0.94 (95% CL 0.79 - 1.11)

Comparison I+II
Total**: n=7170; HR 0.90 (95% CL 0.82 - 0.99)

*= fixed effect model
** = random effect model

Overall Survival

Hazard Ratio

p=0.034

p=0.80

p=0.031

IA?
IMN or no IMN irradiation?

Where is the IMN?

2D technique

3D technique

Thin chest wall

Thick chest wall

Supra-clavicular field

Internal border of the internal tangential field

IMN and PET

Pectum excavatum
Axillary nodes: Surgery or radiotherapy?

The AMAROS trial

Phase III of EORTC 22 023-10 981

- Non-inferiority trial From 2001 to 2010
- 4,823 women with T1-T2
- 34 centers, 9 countries
- Comparing axillary dissection (2,402 pts) vs RT (2,404 pts)
- 1,425 pts (30%) with positive sentinel nodes:
  - 704 pts = axillary dissection (median: 15 nodes)
  - 681 pts = RT
- Axillary RT = 50 Gy (5x2Gy) on levels I to III
- Axillary RT allowed if ≥ 4 positive nodes (41 pts)
- Median follow-up: 6.1 years

Lancet Oncol 2014. 15 : 1303
Axillary nodes: Surgery or radiotherapy?

The AMAROS trial

<table>
<thead>
<tr>
<th></th>
<th>Axillary dissection 704 pts</th>
<th>Axillary RT 681 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN+</td>
<td>220 (33%)</td>
<td>NA</td>
</tr>
<tr>
<td>Axillary recurrence</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>5-year axillary recurrence rate</td>
<td>0.43 [0.0-0.92]</td>
<td>1.19 [0.31-2.08]</td>
</tr>
</tbody>
</table>

Louis-Sylvestre C. JCO 2004. 22 : 97

Lancet Oncol 2014. 15 : 1303
What about fractionation?
Conservative treatment

- Hypofractionation: daily dose > 2Gy
- Evidence-based guidelines Task force of ASTRO
- Randomized trials of whole breast irradiation comparing CF vs HF
- Clinical eligibility criteria:

1. Patient is 50 years or older at diagnosis.
2. Pathologic stage is T1–2 N0 and patient has been treated with breast-conserving surgery.
3. Patient has not been treated with systemic chemotherapy.
4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (±7%) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).
What about fractionation?  
Conservative treatment

<table>
<thead>
<tr>
<th></th>
<th>Canada 1234 pts</th>
<th>Royal Marsden 1410 pts</th>
<th>START A 2236 pts</th>
<th>START B 2215 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast conserving</td>
<td>100%</td>
<td>100%</td>
<td>85%</td>
<td>92%</td>
</tr>
<tr>
<td>T1-T2</td>
<td>100%</td>
<td>94%</td>
<td>&lt; 2cm = 51%</td>
<td>&lt; 2cm = 64%</td>
</tr>
<tr>
<td>pN0</td>
<td>100%</td>
<td>40%</td>
<td>69%</td>
<td>74%</td>
</tr>
<tr>
<td>No CT</td>
<td>89%</td>
<td>86%</td>
<td>65%</td>
<td>78%</td>
</tr>
<tr>
<td>Boost (Gy)</td>
<td>-</td>
<td>14, 7f</td>
<td>10, 5f</td>
<td>10, 5f</td>
</tr>
<tr>
<td>Nodal RT</td>
<td>0%</td>
<td>21%</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>Doses (Gy)</td>
<td>42.5, 16f</td>
<td>50, 25f</td>
<td>50, 25f</td>
<td>50, 25f</td>
</tr>
<tr>
<td>Days</td>
<td>22</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Median FU (year)</td>
<td>12</td>
<td>39, 13f</td>
<td>39, 13f</td>
<td>39, 13f</td>
</tr>
<tr>
<td>Time point</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Ipsilateral breast rec</td>
<td>6.2%</td>
<td>6.7%</td>
<td>9.6%</td>
<td>6.3%</td>
</tr>
<tr>
<td></td>
<td>14.8%</td>
<td>12.1%</td>
<td>8.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td></td>
<td>p=0.027</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosmetic results good</td>
<td>69.8%</td>
<td>71.3%</td>
<td>74.4%</td>
<td>71.2</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Slide 28
What about fractionation?

START A and B: cosmetic results

### A
- Hazard ratio (95% CI)
- 41.6 Gy vs 50 Gy
  - Breast shrinkage
  - Breast induration
  - Breast oedema
  - Telangiectasia
  - Shoulder stiffness
  - Arm oedema
- 39 Gy vs 50 Gy
  - Breast shrinkage
  - Breast induration
  - Breast oedema
  - Telangiectasia
  - Shoulder stiffness
  - Arm oedema

### B
- Hazard ratio (95% CI)
- 40 Gy vs 50 Gy
  - Breast shrinkage
  - Breast induration
  - Breast oedema
  - Telangiectasia
  - Shoulder stiffness
  - Arm oedema

- Favours 41.6 Gy or 39 Gy
- Favours 50 Gy
Conclusions

- In breast cancer, large part of our routine practice is based on level I of evidence for radiotherapy.
- In breast cancer, the necessity of a long follow-up impacts on the conclusions of the phase III trials because of the constant technological progress.
- The quality of the techniques of irradiation must be assessed by expert committee for every randomized trial to validate the results of the trial.
- Evidence based medicine stays mandatory to compare modern techniques and choose the best one.