Leci n’est pas une pipe.
To treat or not

IMN: Balancing Risks and Benefits
Conflict of interest:

I am a radiation oncologist
To treat or not to treat the IMN

1. Introduction

2. The recent trials

3. Technical improvements

4. Discussion

5. Conclusions
To treat or not to treat the IMN: *Introduction*

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)*

*Lancet 2014; 383: 2127–35*
Interpretation: *RT reduced both recurrence and breast cancer mortality in women with positive lymph nodes.*

Similar effects:

- Irrespective of the number of involved lymph nodes
- Whether systemic therapy was given or not
- More benefit after partial or no AD
- Less benefit if only regional RT
To treat or not to treat the IMN: *Introduction*

Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Darby S et al. NEJM 2013:368:987-998.
To treat or not to treat the IMN: *Introduction*

**Non-anthracycline (CMF) ChT**

Risk of congestive heart failure

- **RT + ChT**
- **RT**
- **No RT**

To treat or not to treat the IMN: *Introduction*

*Reduction of the dose to the cardiac structures with tangential field irradiation (left breast)*

<table>
<thead>
<tr>
<th>Year</th>
<th>Heart</th>
<th>Left anterior descending artery</th>
<th>Right coronary artery</th>
<th>Circumflex coronary artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden 1970s*</td>
<td>13.3</td>
<td>31.8</td>
<td>9.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Sweden 1990s*</td>
<td>4.7</td>
<td>21.9</td>
<td>2.0</td>
<td>2.8</td>
</tr>
<tr>
<td>UK 2006</td>
<td>2.3</td>
<td>7.6</td>
<td>2.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>
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To treat or not to treat the IMN: Recent trials

Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

Regional Nodal Irradiation in Early-Stage Breast Cancer


To treat or not to treat the IMN: Recent trials

Published Ahead of Print on November 23, 2015 as 10.1200/JCO.2015.63.6456
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.63.6456

DBC6-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer


To treat or not to treat the IMN: *Recent trials*

**Disease-free survival at 10 years:**
Improved with regional irradiation

**Distant metastases-free survival at 10 years:**
Improved with regional irradiation

**Overall survival at 10 years:**
Overall trend towards improvement with regional irradiation

**Breast cancer specific survival at 10 years:**
Improved with regional irradiation

**Late side effects at 10 years following regional RT:**
- Pulmonary and skin
- Limited; most often ≤ grade 2; some transient
- No increased lethal toxicity
To treat or not to treat the IMN: *Recent trials*

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To treat or not to treat the IMN: *Recent trials*

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To treat or not to treat the IMN: *Recent trials*
To treat or not to treat the IMN: *Recent trials*

Overall survival + 1.6%
Overall Logrank test: $p=0.056$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (N)</th>
<th>Observed Events (O)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value (Log-Rank)</th>
<th>Median (95% CI) (Years)</th>
<th>% at 10 Year(s) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IM-MS</td>
<td>2002</td>
<td>429</td>
<td>1.00</td>
<td>0.0556</td>
<td>Not reached</td>
<td>80.71 (78.82, 82.45)</td>
</tr>
<tr>
<td>IM-MS</td>
<td>2002</td>
<td>382</td>
<td>0.87 (0.76, 1.00)</td>
<td></td>
<td>Not reached</td>
<td>82.26 (80.43, 83.94)</td>
</tr>
</tbody>
</table>

To treat or not to treat the IMN: Recent trials

Overall survival + 13 months
DFS + 16.5 months

To treat or not to treat the IMN: Recent trials

But whom to select for regional RT?
To treat or not to treat the IMN

1. Introduction

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To treat or not to treat the IMN: *Techniques*

- Breast
- Boost
- PBI
- Thoracic wall
- LN supraclavicular
- LN axilla level III
- LN axilla level II
- LN axilla Rotter
- LN axilla level I
- LN internal mammary

*Heart*

1) Brachiocephalic vein
2+7) Subclavian vessels
3+8) Axillary vessels
4) Internal jugular vein
5) External jugular vein
6) Brachiocephalic trunk
9) Common carotid artery
10) Vertebral artery
To treat or not to treat the IMN: *Techniques*

**Level 1** - **level 2** - Rotter - **level 3** - **level 4**

To treat or not to treat the IMN: Techniques
To treat or not to treat the IMN:

Techniques

This well-received book, now in its fifth edition, is unique in providing a detailed description of the technological basis of radiation therapy. Another novel feature is the collaborative writing of the chapters by North American and European authors. This considerably broadens the book's perspective and increases its applicability in daily practice throughout the world. The book is divided into two sections. The first covers basic concepts in treatment planning, including essential physics and biological principles related to time-dose fractionation, and explains the various technological approaches to radiation therapy, such as intensity-modulated radiation therapy, tomotherapy, stereotactic radiotherapy, and high and low dose rate brachytherapy. Issues relating to quality assurance, technology assessment, and cost-benefit analysis are also reviewed. The second part of the book discusses in depth the practical clinical applications of the different radiation therapy techniques in a wide range of cancer sites. All of the chapters have been written by leaders in the field. This book will serve to instruct and acquaint teachers, students, and practitioners in the various fields of oncology with the basic technological factors and approaches in radiation therapy.
To treat or not to treat the IMN: *Techniques*

*RT of the thoracic wall - with IM-MS: the next steps.*
To treat or not to treat the IMN: *Techniques*

**Free breathing**

**Breath Hold**
To treat or not to treat the IMN: *Techniques*

<table>
<thead>
<tr>
<th></th>
<th>Free breathing</th>
<th>Breath hold</th>
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<tbody>
<tr>
<td></td>
<td>3D-CRT</td>
<td>υIMRT</td>
</tr>
<tr>
<td>Heart $V_{30Gy}$ (%)</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
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<td>7.7</td>
<td></td>
</tr>
<tr>
<td>IL Lung $V_{20Gy}$ (%)</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>IL Lung $V_{10Gy}$ (%)</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td>CL breast $D_{mean}$ (Gy)</td>
<td>0.29</td>
<td></td>
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**To treat or not to treat the IMN: Techniques**

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<td>0.6</td>
</tr>
<tr>
<td>IL Lung $V_{20Gy}$(%)</td>
<td>16.4</td>
<td>5.8</td>
</tr>
<tr>
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<td>26.5</td>
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<td>CL breast $D_{mean}$(Gy)</td>
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<td>3.7</td>
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To treat or not to treat the IMN:

Techniques
To treat or not to treat the IMN: *Techniques*
To treat or not to treat the IMN: *Techniques*

Patients with unfavourable anatomy: *e.g. pectus excavatus*

IMPT  IMRT

But wouldn’t breath hold +/- vIMRT be a better solution?
To treat or not to treat the IMN: Techniques

What are the benefits of proton therapy for breast cancer patients?

Proton therapy is a relatively newer cancer treatment for early stage breast cancer, and it has already shown remarkable promise and advantages over conventional breast cancer treatment. The accuracy and low impact of proton radiation is a non-invasive and low-risk option for breast cancer treatment used to destroy cancerous cells. Proton radiation treatment is extremely precise and therefore more effective at targeting cancerous cells without causing damage to surrounding breast tissue.

Proton therapy is not a substitute for a lumpectomy, but rather an alternative to traditional radiation therapy. After the lumpectomy is complete, a breast cancer patient would receive 10 days of proton treatment instead of five to six weeks of traditional radiation therapy.

Breast cancer patients benefit from non-invasive proton therapy treatment.

- Proton treatment is noninvasive and painless
- Proton therapy is effective for treating early stage breast cancer
- Treatment offers quicker recovery times with minimal side effects
- Causes less cosmetic damage compared with the burn marks caused by regular radiation
- More accurate and precise than other kinds of radiation
- Treatment is provided in an outpatient setting
- Proton radiation has little to no impact on patient energy level
To treat or not to treat the IMN: *Techniques*

Please keep a healthy dose of scepticism!
To treat or not to treat the IMN: Techniques

- **Margins**
- **IGRT**

\[ M = 2.5 \Sigma_{tot} + 1.64 (\sigma_{tot} - \sigma_p) \]
To treat or not to treat the IMN

1. Introduction

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To treat or not to treat the IMN: Discussion

Proof of principle:

Elective regional treatment $\rightarrow$ less DM $\rightarrow$ improved S

It is likely that not the full effect of regional RT has been obtained: see also EORTC IJROBP 2001 paper.

Nowadays CT based target volume delineation and better RT techniques (IMRT):

$\rightarrow$ better target volume coverage $\rightarrow$ higher efficacy

$\rightarrow$ lower doses to organs at risk $\rightarrow$ less toxicity
To treat or not to treat the IMN: *Discussion*

*Lymphoedema rates*

<table>
<thead>
<tr>
<th>Rate (%)</th>
<th>SLNB</th>
<th>ALND</th>
<th>SLNB+RT</th>
<th>ALND+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z0011 (1y):</td>
<td>6</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMAROS (5y):</td>
<td>28.0</td>
<td>13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22922 (10.9y):</td>
<td>9.8</td>
<td></td>
<td></td>
<td>11.1</td>
</tr>
<tr>
<td>MA.20 (9.5y):</td>
<td>4.5</td>
<td></td>
<td></td>
<td>8.4</td>
</tr>
</tbody>
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To treat or not to treat the IMN: *Discussion*

Better local treatment adds to the effects of systemic therapy on local recurrence and on breast cancer mortality.
To treat or not to treat the IMN: *Discussion*

EORTC 22922  NCIC MA.20  DBCG IMN

To treat or not to treat the IMN: Discussion

Systemic therapy

- CMF – ACx4
  - Tam

- Anthr +/- T
  - AI – Tam

- CEF - CMF
  - Tam – AI/Tam

- EORTC 22922
- NCIC MA.20
- DBCG IMN

- 1996 – 2004
- 2000 – 2007
- 2003 - 2007
To treat or not to treat the IMN: Discussion

To treat or not to treat the IMN: Discussion

Early Breast Cancer Trialists Collaboration Group
To treat or not to treat the IMN: *Discussion*

→ *consensus agreements*
To treat or not to treat the IMN: *Discussion*

1. **Mastectomy for cT1-4; cN0 (US); no PST**

- Indien tumor ≤3 cm en graad I-II-> geen okselbehandeling
- RT thoraxwand & level I-II indien tumor graad III of >3 cm
- RT thoraxwand & level I-II bij T4 en/of pN2 (4 of meer macro)
- RT thoraxwand & level I-IV bij tumorgraad III of >3 cm of T4 of pN2 (4 of meer macro)
- V plus parasternaal bij medaial gelegen tumor

Haute couture tailoring of RT: Surgery or RT?

2. BCT for cT1-3; cN0 (US); no PST

- RT mamma +/- boost bij graad I-II en tumor ≤ 3 cm
- RT mamma +/- boost & level I-II bij tumor graad III of >3 cm
- RT mamma & level I-IV (plus parasternaal bij mediaal gelegen tumor) bij pN2 (4 of meer massa's)

- RT mamma +/- boost & level I-II bij geen risicofactoren
- RT mamma +/- boost & level I-IV bij tumor graad III of >3 cm of pN2 (4 of meer massa's)
- RT mamma +/- boost & level I-IV plus parasternaal bij mediaal gelegen tumor
To treat or not to treat the IMN: *Discussion*

3.1. PST; cN0 (US +/- FNA)

- RT thoraxwand/mamma volgens eerder genoemde indicaties
  - geen oksel RT bij eerder cT1-3
  - cT4 RT mamma/thoraxwand en level I-IV

- RT thoraxwand/mamma en oksel
  - level I-II bij mi zonder risicofactoren
  - level I-IV bij mi met risicofactor (graad III, tumor >3 cm pre-PST) en bij macrometastase en bij pN2
  - bij cT3 en cT4 RT thoraxwand/mamma en level I-IV
  - bij mediaal gelegen tumoren: thoraxwand/mamma en level I-IV plus parasternaal

- OKD
  - na OKD RT thoraxwand/mamma en oksel level II/III-IV plus parasternaal bij medially gelegen tumoren
To treat or not to treat the IMN: Discussion

3.2. PST; cN+(1-3) (US +/- FNA); MARI advised

- OKD
- Na OKD RT
- Mammaplasty/thoraxwand en Oksel level II/III-IV (plus parasternaal bij mediaal gelegen tumoren)

- OKD
- Na OKD RT
- Mammaplasty/thoraxwand en Oksel level II/III-IV (plus parasternaal bij mediaal gelegen tumoren)

- OKD
- Na OKD RT
- Mammaplasty/thoraxwand en Oksel level II/III-IV (plus parasternaal bij mediaal gelegen tumoren)

RT mamma/thoraxwand en Oksel level II-IV (plus parasternaal bij mediaal gelegen tumoren)

na PST: US / FNA -
SNB
ypN0/N1 mi
ypN1 (macro)
To treat or not to treat the IMN: Discussion

Precision radiation medicine

Personalised/individualised/stratified approaches:

• Biological optimisation
• Technological optimisation
• Shared decision making
To treat or not to treat the IMN

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To treat or not to treat the IMN: Conclusions

Original article

Over-irradiation

In general, the use of RT compensates for the decreasing extent of surgery to the breast and the axillary lymph nodes, eliminating residual tumour cells while maintaining better aesthetic and functional results. In some occasions, however, the indications for the extent of RT have to be based on limited pathological staging information. Research is ongoing to individualise RT more on the basis of biological factors including gene expression profiles. When considering age, treatment decisions should rather be based on biological instead of formal age.
To treat or not to treat the IMN: Conclusions

• Regional RT improves outcome.

• Interaction with risk factors & other treatments.

• (Very) limited toxicity.

• No treatment related mortality (yet?)

• Selection of pts to be worked out.

• If you do it, do it safe!
“Once again, there is no conclusive evidence of climate change. From Fairbanks, Alaska, this is Joe Matthews reporting.”
Selecting for RT: Acknowledgements

- All the patients participating to the trials.
- All the investigators participating to the trials.
- The research teams of the trials.
- The research fellows involved in the trials.
- Special words of thanks to (alphabetically): Marianne Aznar; Harry Bartelink; Liesbeth Boersma; Laurence & Sandra Collette; Marion Essers; Sandra Hol; Birgitte Offersen; Emiel Rutgers; John Yarnold; Walter Van den Bogaert; Timothy Whelan
- In fact: to many to list here!!!!