New paradigms in regional nodal irradiation - breast cancer

Punita Lal
Department of Radiotherapy
Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow
Breast cancers - Regional Radiotherapy
Aspects to be touched upon

- MRM +/- RT
- BCS → RT
- NACT

- High risk
- Intermediate risk
- CW/W+RNI
- PMRT +RNI
- ?RNI

ICRO, Kolkata, 2019-07-28
Breast radiotherapy planning

2 case scenario
- Post mastectomy
- Post BCS

- RNI integral
Aim of Regional nodal irradiation

• To eradicate micro/macroscopic disease within the lymph nodes
• To reduce the risk of loco-regional recurrences and distant metastasis & confer survival benefit
• Goals to be set balancing the potential toxicity
Regional radiotherapy – until recently

**Axilla** – if axillary dissection omitted/ incomplete
Concern – limb edema/Br plexus

**SCF** -> 4 Level 1 evidence; 1-3 insufficient

**IMC** - debatable; Concern heart
High risk breast cancer

- 5 cm tumors
- 4 or more Axillary Lymph node positive
Modified radical mastectomy - gold standard

Overgaard et al. NEJM 1997 337:949
Ragaz et al. NEJM 1997 337:956
Overgaard et al. 1999, 353:1641

PMRT – Improved DFS and OS
Does Locoregional Radiation Therapy Improve Survival in Breast Cancer? A Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeBoer</td>
<td>50</td>
<td>0.87</td>
<td>0.28, 2.65</td>
</tr>
<tr>
<td>Foroglou</td>
<td>71</td>
<td>0.38</td>
<td>0.14, 1.05</td>
</tr>
<tr>
<td>Klefstrom</td>
<td>79</td>
<td>0.17</td>
<td>0.04, 0.67</td>
</tr>
<tr>
<td>Trampisch</td>
<td>88</td>
<td>1.25</td>
<td>0.53, 2.95</td>
</tr>
<tr>
<td>Blomqvist</td>
<td>99</td>
<td>1.16</td>
<td>0.50, 2.70</td>
</tr>
<tr>
<td>Hayat</td>
<td>112</td>
<td>1.53</td>
<td>0.70, 3.37</td>
</tr>
<tr>
<td>Gervasio</td>
<td>112</td>
<td>1.11</td>
<td>0.51, 2.43</td>
</tr>
<tr>
<td>Muss</td>
<td>159</td>
<td>0.81</td>
<td>0.43, 1.50</td>
</tr>
<tr>
<td>Schmoor</td>
<td>199</td>
<td>0.72</td>
<td>0.32, 1.67</td>
</tr>
<tr>
<td>Griem</td>
<td>218</td>
<td>1.17</td>
<td>0.68, 1.99</td>
</tr>
<tr>
<td>McArdle</td>
<td>219</td>
<td>0.83</td>
<td>0.49, 1.43</td>
</tr>
<tr>
<td>Velez-Garcia</td>
<td>239</td>
<td>0.70</td>
<td>0.42, 1.17</td>
</tr>
<tr>
<td>Martinez</td>
<td>241</td>
<td>1.12</td>
<td>0.67, 1.87</td>
</tr>
<tr>
<td>Olson</td>
<td>312</td>
<td>1.01</td>
<td>0.65, 1.58</td>
</tr>
<tr>
<td>Ragaz</td>
<td>318</td>
<td>0.66</td>
<td>0.42, 1.02</td>
</tr>
<tr>
<td>Tennvall-Nittby</td>
<td>768</td>
<td>0.96</td>
<td>0.71, 1.30</td>
</tr>
<tr>
<td>Overgaard(TAM)</td>
<td>1375</td>
<td>0.75</td>
<td>0.61, 0.93</td>
</tr>
<tr>
<td>Overgaard(CMF)</td>
<td>1708</td>
<td>0.73</td>
<td>0.61, 0.89</td>
</tr>
</tbody>
</table>

Random Effects OR = 0.83  95% CI = 0.74, 0.94
Whole breast RT

- 7 prospective randomized trials have shown no significant difference between
  - BCS+RT vs. Mastectomy in Early Breast cancer
    - No difference in terms of LR/DM
      - Survival (26.3 vs 24.1% death rate)
  Post BCS RT:— RT to whole breast and LN+ Boost to tumor bed

<table>
<thead>
<tr>
<th>Post BCS</th>
<th>End point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>With RT</td>
<td>Ipsilateral recurrence</td>
<td>1/3</td>
</tr>
<tr>
<td></td>
<td>Any recurrence</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Improved OS
Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)*

<table>
<thead>
<tr>
<th></th>
<th>Any rec at 10 yrs</th>
<th>Br ca mortality ↓ at 5 yrs</th>
<th>pN0 rec ↓ 10 yrs</th>
<th>P N+ rec ↓ at 10 yrs</th>
<th>Br ca. mortality ↓ 15 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>19%</td>
<td>21%</td>
<td>16%</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>No RT</td>
<td>35%</td>
<td>25%</td>
<td>31%</td>
<td>64%</td>
<td>51%</td>
</tr>
<tr>
<td>P value</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
<td>s</td>
</tr>
</tbody>
</table>

4 rec (any) avoided at 10 yrs → 1 breast cancer death at 15yrs.
RT – reduces recurrence by ½ and prevents breast cancer death by 1/6
A new paradigm

Non breast cancer related

Recurrence - local/distant

Radiotherapy

Second cancers

Contra lateral breast ca.

Mortality

Radiotherapy

RT kills tumor foci – prevents local & distant rec
Substantial decrease in rec; modest decrease in death
A paradigm shift is due to:

- Adjuvant Systemic therapy
- Chemotherapy
- Hormones
- Targeted therapy

Cardiac toxicity
- Brachial plexus
- Lymph edema
- Second cancers
- Contralateral breast rec

Screen detected
Intermediate risk breast cancer

High risk node negative pT3N0M0/ pT2N0M0 – grade 3/ ER negative/ LVI+
Low risk node positive disease (1-3LN+)
The genesis of 3 trials

- SCF LN – life time risk > 5%
- IMN – Axillary LN (-) - <10%
- IMN – Axillary LN(+) - > 30%

- Older overviews – No survival benefit
- Detriment - Cardiac toxicity

Cuzick et al, Recent Results Ca Res 1988,111;108-29

Better RT techniques
EORTC & MA20 trials

• Research question - Whether more extensive lymphatic radiation treatment benefited patients with higher-risk lymph node-negative, or lower risk lymph node-positive disease.

• Regional nodal irradiation (RNI) to the level III axillary, supraclavicular and upper internal mammary lymph nodes

• End points disease free survival and distant metastasis free survival as well as overall survival advantage.
## EORTC22922-NCIC MA20-French trial

<table>
<thead>
<tr>
<th></th>
<th>Incl</th>
<th>Design</th>
<th>n</th>
<th>BCS</th>
<th>Med FU</th>
<th>OS</th>
<th>DFS</th>
<th>DDFS</th>
<th>BCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC ‘96-’04</td>
<td>Central / med LN+/-</td>
<td>RNI No RNI</td>
<td>4004</td>
<td>75%</td>
<td>10.9</td>
<td>82%</td>
<td>72%</td>
<td>78%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80%</td>
<td>69%</td>
<td>75%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72%</td>
<td>69%</td>
<td>75%</td>
<td>14%</td>
</tr>
<tr>
<td>MA20 00-07</td>
<td>LN+ LN-(H)</td>
<td>RNI No RNI</td>
<td>1832</td>
<td>100%</td>
<td>9.5</td>
<td>83%</td>
<td>82%</td>
<td>82%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>82%</td>
<td>77%</td>
<td>77%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>82%</td>
<td>77%</td>
<td>77%</td>
<td>13%</td>
</tr>
<tr>
<td>French</td>
<td>pN+ C/M N+/-</td>
<td>IMN No IMN</td>
<td>1334</td>
<td>-</td>
<td>11.3</td>
<td>63%</td>
<td>59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59%</td>
<td>59%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICRO, Kolkata, 2019-07-28
### Enrollment characteristics

<table>
<thead>
<tr>
<th></th>
<th>NCIC MA.20</th>
<th>EORTC 22922</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>1832</td>
<td>4004</td>
</tr>
<tr>
<td><strong>% Breast conserving surgery</strong></td>
<td>100%</td>
<td>76.1%</td>
</tr>
<tr>
<td><strong>RNI targets</strong></td>
<td>IMC + SCV + Level III axilla</td>
<td>IMC + medial SCV</td>
</tr>
<tr>
<td><strong>Median age (years)</strong></td>
<td>53–54</td>
<td>54</td>
</tr>
<tr>
<td><strong>% Tumor size ≥ 2 cm, RNI vs. Control</strong></td>
<td>50.1% vs. 54.7%</td>
<td>60.2% vs. 60.1%</td>
</tr>
<tr>
<td><strong>% ALN(+) RNI vs. Control</strong></td>
<td>9.6% vs. 9.7%</td>
<td>44.4% vs. 44.5%</td>
</tr>
<tr>
<td>0 ALN positive</td>
<td>84.9% vs. 85.1%</td>
<td>42.9% vs. 43.3%</td>
</tr>
<tr>
<td>1–3 ALN positive</td>
<td>5.5% vs. 5.1%</td>
<td>12.2% vs. 12.2%</td>
</tr>
<tr>
<td>&gt;3 ALN positive</td>
<td>90.7% vs. 90.5%</td>
<td>54.6% vs. 55.1%</td>
</tr>
<tr>
<td>% Chemotherapy, RNI vs. Control</td>
<td>75.7% vs. 76%</td>
<td>59.2% vs. 60%</td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th></th>
<th>NCIC MA.20</th>
<th>EORTC 22922</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow up (years)</strong></td>
<td>9.5</td>
<td>10.9</td>
</tr>
<tr>
<td><strong>10-yr OS, RNI vs. Control</strong></td>
<td>82.8% vs. 81.8% ($P = 0.38$)</td>
<td>82.3% vs. 80.7% ($P = 0.06$)</td>
</tr>
<tr>
<td><strong>10-yr DFS, RNI vs. Control</strong></td>
<td>82% vs. 77%</td>
<td>72.1% vs. 69.1%</td>
</tr>
<tr>
<td><strong>10-yr Distant DFS, RNI vs. Control</strong></td>
<td>86.3% vs. 82.4%</td>
<td>78% vs. 75%</td>
</tr>
<tr>
<td><strong>10-yr Breast cancer mortality</strong></td>
<td>10.3% vs. 12.3%</td>
<td>12.5% vs. 14.4%</td>
</tr>
<tr>
<td><strong>Toxicities, RNI vs. Control</strong></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Grade 2 acute pneumonitis</td>
<td>1.2% vs. 0.2%</td>
<td>4.4% vs. 1.7%</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>NA</td>
<td>5.6% vs. 6.5%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.9% vs. 0.4%</td>
<td>12% vs. 10.5%</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>8.4% vs. 4.5%</td>
<td></td>
</tr>
</tbody>
</table>
Inference from EORTC & MA20 trials

- Neither showed survival benefit. EORTC – nearly significant!
- MA20 – HR(-) benefits with RNI
- **Exact impact of IMN & SCF can’t be ascertained**
- **Risk – benefit for patient selection**
Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials - an update

Wilfried Budach¹, Edwin Bölke¹, Kai Kammers², Peter Arne Gerber³, Carolin Nestle-Krämling⁴ and Christiane Matuschek¹

RNI – Improved DFS, DMFS, and OS
Preliminary results show addition of both IMN and SCF improve DFS and OS
With IMN – concern heart
**Meta analysis - Budach et al**

**Disease free survival**

**Comparison: (MS+IM)+(WBI/CWI) vs. (WBI/CWI)**

- **MA.20**
  - EORTC: MA.20 [10]: n=183
  - Total: n=5836; HR 0

**Distant metastasis free survival**

**Comparison: (MS-IM)+(WBI/CWI) vs. (WBI/CWI)**

- **EORTC**
  - Total: n=4004

**Overall Survival**

- **Comparison I: (MS+IM)+(WBI/CWI) vs. (WBI/CWI)**
  - 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)
  - p=0.034

- **Comparison II: IM+(WBI/CWI+MS) vs. (WBI/CWI+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)
  - p=0.80

- **Comparison I+II**
  - Total**: n=7170; HR 0.90 (95% CL 0.82 - 0.99)
  - **p=0.031

---

* = fixed effect model
** = random effect model
LN RT better
no LN RT better
The panel clearly agreed that irradiation should be applied to regional nodes in all patients with $\geq 4$ positive nodes (94%), but in cases of 1–3 positive nodes, a majority (56%) indicated that RNI should only be administered if the present features are poor (e.g., TNBC, residual disease after PST), while 29% felt that RNI should be indicated for all patients with 1–3 positive nodes.
Predicting loco-regional recurrence risk in T1, T2 breast cancer with 1–3 positive axillary nodes postmastectomy: Development of a predictive nomogram

Wadasadawala T, Kannan S¹, Gudi S, Rishi A, Budrukkar A, Parmar V², Shet T³, Desai S³, Gupta S⁴, Badwe R², Sarin R

Departments of Radiation Oncology, ¹Medical Statistics, ²Surgical Oncology, ³Pathology and ⁴Medical Oncology, Tata Memorial Centre, Mumbai Maharashtra India

<table>
<thead>
<tr>
<th>Points</th>
<th>LN Ratio</th>
<th>pT Size</th>
<th>Base</th>
<th>Grade</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  0</td>
<td>0  0</td>
<td>0  0</td>
<td>0  0</td>
<td>0  0</td>
</tr>
<tr>
<td></td>
<td>1  1</td>
<td>1  1</td>
<td>1  1</td>
<td>1  1</td>
<td>1  1</td>
</tr>
<tr>
<td></td>
<td>2  2</td>
<td>2  2</td>
<td>2  2</td>
<td>2  2</td>
<td>2  2</td>
</tr>
<tr>
<td></td>
<td>3  3</td>
<td>3  3</td>
<td>3  3</td>
<td>3  3</td>
<td>3  3</td>
</tr>
<tr>
<td></td>
<td>4  4</td>
<td>4  4</td>
<td>4  4</td>
<td>4  4</td>
<td>4  4</td>
</tr>
<tr>
<td></td>
<td>5  5</td>
<td>5  5</td>
<td>5  5</td>
<td>5  5</td>
<td>5  5</td>
</tr>
</tbody>
</table>

**Figure 1:** Nomogram showing predicted risk of loco-regional recurrence at 5 and 7 years. LN Ratio = Number of lymph nodes positive/number of lymph nodes dissected; pT Size = Pathologic tumor size in centimeters; Base = Distance of base from tumor in millimeter; Grade = Grade grouping scored as 1 if Grade I or Grade II and scored as 2 if Grade III; TNBC = Triple negative breast cancer scored as 0 if non-TNBC and 1 if TNBC; OS prob = Overall survival probability. As an example if patient with tumor size of 5 cm (40 points), 7 mm from base (0 points), Grade III tumor (60 points), lymph node ratio of 5 (score 15) and non-TNBC receptor status (0 points) will have total points of 115 and predicted LRC is between 90% and 95%. TNBC = Triple negative breast cancer; LRC = Loco-regional control

<table>
<thead>
<tr>
<th>Linear Predictor</th>
<th>Predicted Loco-regional control (5 years)</th>
<th>Predicted Loco-regional control (7 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0</td>
<td>0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0</td>
</tr>
</tbody>
</table>

**Table 3:** Multivariate analysis for loco-regional control

**Figure 2:** Kaplan-Meier curves for the four groups derived for predictive nomogram. The difference in the survival among these groups was statistically significant as estimated by log rank test
Summary

• Modest benefit – DFS, DMFS, OS
• pN+ benefit
• No difference between N1-3 and N≥ 4
• pN0 central & medial quadrant tumors

Supra clavicular LN + Axillary LN

Internal mammary LN
Regional RT portals
Internal Mammary LN RT – an eternal debate until recently

Clinic Investigation: Breast Cancer

Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy

Christophe Hennequin, MD, PhD,* Nadine Bossard, MD, PhD,†

- 3% benefit in OS (59% to 62%)
- over estimated IMN involvement – overestimated survival diff
- Subgroup – Central/Medial tumors –benefit
- “Cannot recommend IMN RT for or against”
DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer

Lise Bech Jellesmark Thorsen, Birgitte Vrou Offersen, Hella Dane, Martin Berg, Ingelise Jensen, Anders Navrsted Pedersen, Sune Jürg Zimmermann, Hans-Jürgen Brodersen, Marie Overgaard, and Jens Overgaard

<table>
<thead>
<tr>
<th></th>
<th>OS at 8 yrs</th>
<th>BC Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMN RT</td>
<td>76%</td>
<td>21%</td>
</tr>
<tr>
<td>No IMN RT</td>
<td>72%</td>
<td>23%</td>
</tr>
</tbody>
</table>

• Right sided – IMN RT
• Left sided – No IMN RT

Subset analysis – Only subset that doesn’t benefit with IMN RT– lateral lesions with 1-3 LN nodes
Small benefit. IHD deaths similar. Cardiac morbidity?

Points of debate- 1. Added toxicity of IMN RT in left sided lesions not determined
2. OS benefit with IMN RT right side when excess cardiac deaths left side.
There is mounting evidence towards the use of IMN RT

- EBC- Central/Inner quad lesions with +ve axilla
- Role in LOBC/LABC
- Cardiac issue - unresolved
CONCLUSIONS

In patients with early-stage breast cancer, irradiation of the regional nodes had a marginal effect on overall survival. Disease-free survival and distant disease-free survival were improved, and breast-cancer mortality was reduced. (Funded by Fonds Cancer; ClinicalTrials.gov number, NCT00002851.)

There is limited experience of IMN RT with Hypofr RT & its consequences on heart
IMC RT - where do we stand?

End point – OS DFS & DDFS benefit

Exact role of IMN RT - unclear

Debatable – cardiac!

EORTC trial. NEJM, 2015;373:317-27
To conclude

- RNI beneficial
- Every 4 recurrences avoided – 1 death prevented
- Distinction of 1-3 LN artificial
- Cardiac risk

Are we ready to give IMN RT routinely to our patients?
Axillary Surgery and implications for RNI

- Sentinel LN surgery → Stage migration (newer techniques – occult micrometastasis 10-50%) – Will Rogers phenomenon
Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial


Figure 2: Disease-free survival and overall survival

HR=hazard ratio.
Amaros trial

- Underpowered results to show non-inferiority
- RNI an alternative to ALND – potential treatment option in early stage, node-positive breast cancer treated with SLN dissection alone.
- ↓ rates of lymphedema
- Comparable 5-year DFS and OS.

Donker et al, Lancet Oncology, 2014
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)*

<table>
<thead>
<tr>
<th>LN</th>
<th>n</th>
<th>LRR</th>
<th>OR</th>
<th>BCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN0</td>
<td>700</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>LN1-3</td>
<td>1314</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>LN&gt;4</td>
<td>1772</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

N 1-3 (Int risk) even with syst th – abs gains smaller BUT proportional gains large due to effective RT

EBCTCG, Lancet, 2014
CONCLUSIONS AND RELEVANCE  Among women with T1 or T2 invasive primary breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases, 10-year overall survival for patients treated with sentinel lymph node dissection alone was noninferior to overall survival for those treated with axillary lymph node dissection. These findings do not support routine use of axillary lymph node dissection in this patient population based on 10-year outcomes.
Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial

- cN0 disease – SNLB
- Positive axilla needs to be addressed
- Axillary dissection – Gold standard
- Lymphedema & shoulder movement
- Factors – size, grade, VI, ECE

Axillary RT – comparable results; less morbidity
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)*

For 1314 women with axillary dissection and one to three positive nodes, radiotherapy reduced locoregional recurrence (2p<0.00001), overall recurrence (RR 0.68, 95% CI 0.57–0.82, 2p=0.00006), and breast cancer mortality (RR 0.80, 95% CI 0.67–0.95, 2p=0.01). 1133 of these 1314 women were in trials in which systemic therapy (cyclophosphamide, methotrexate, and fluorouracil, or tamoxifen) was given in both trial groups and, for them, radiotherapy again reduced locoregional recurrence (2p<0.00001), overall recurrence (RR 0.67, 95% CI 0.55–0.82, 2p=0.00009), and breast cancer mortality (RR 0.78, 95% CI 0.64–0.94, 2p=0.01).

**Interpretation** After mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality in the women with one to three positive lymph nodes in these trials even when systemic therapy was given. For today’s women, who in many countries are at lower risk of recurrence, absolute gains might be smaller but proportional gains might be larger because of more effective radiotherapy.
Reasons

• Use of endocrine therapy
• High tangents
• Level III in SCF LN
What if Axilla needs to be addressed?

- Unaddressed axilla/ incompletely dissected axilla
- Ontario practice advocates normofractionated RT to axilla in “heavy nodal burden”
- Type of surgery and chemotherapy
- Brachial plexus & lung toxicity

In India where the need for axillary RT may be more – issue unresolved
Meta Analysis

Can axillary radiotherapy replace axillary dissection for patients with positive sentinel nodes? A systematic review and meta-analysis

Min Zhao\textsuperscript{a}, Wei-Guang Liu\textsuperscript{a}, Lei Zhang, Zi-Ning Jin, Zhan Li, Cheng Liu, Dong-Bao Li, Ying Ma, Jing-Wen Zhang, Feng Jin, Bo Chen\textsuperscript{*}

Department of Breast Surgery, The First Hospital of China Medical University, Shenyang, Liaoning 110001, China

Administration of adjuvant systemic therapy.

Conclusions: ART is not inferior to cALND in the patients with clinically node-negative breast cancer who had a positive sentinel lymph node. Information obtained by using cALND after SLNB may have no major impact on the administration of adjuvant systemic therapy.
Fig. 2. Forest plot showing the pooled effect of overall survival with ART compared to that with cALND for the patients with SLN-positive breast cancer. HR: hazard ratio; CI: confidence interval; ART: axillary radiotherapy; cALND: completion axillary lymph node dissection.

Fig. 3. Forest plot showing the pooled effect of disease-free survival with ART compared to that with cALND for the patients with SLN-positive breast cancer. HR: hazard ratio; CI: confidence interval; ART: axillary radiotherapy; cALND: completion axillary lymph node dissection.
Hypo fractionation – another dimension to RNI

Hypofractionated regional nodal irradiation for breast cancer: Examining the data and potential for future studies

Shahed N. Badiyan a, Chirag Shah b, Douglas Arthur c, Atif J. Khan d, Gary Freedman e, Matthew M. Poppe f, Frank A. Vicini g,h

- Hypofractionated RT – safe & efficacious
- Long term data – limited
- Addition of RNI always adds to toxicity irrespective of fr
- Impact of systemic therapy to Hypo fr RT to be studied
The panel indicated that hypofractionated breast irradiation can be used for most patients as a care standard (52% for all patients, 19% following breast conservation only, and 21% abstention). With respect to radiotherapy on the breast and on regional lymph nodes (LNMs), hypofractionated radiotherapy did not find a clear consensus (36% for most patients, age >50 years 30%, and 30% abstention).
Concerns regarding Brachial plexopathy

- <1%
- START – FU 9.9yrs – Insufficient
- May manifest up to 30yrs; At least 25% incidence beyond 10yrs. *Budach et al Breast care, 2015.*

---

**Acta Oncologica, 2006; 45: 280–284**

**ORIGINAL ARTICLE**

**Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer—a review**

**JACEK GALECKI¹, JOANNA HICER-GRZENKOWICZ¹, MAŁGORZATA GRUDZIEN-KOWALSKA¹, TERESA MICHALSKA² & WOJCIECH ZAŁUcki¹**

¹Department of Radiotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, W K. Roentgen 5, 02-781 Warsaw, Poland and ²Neurological Clinic, Second Department, Academy of Medicine, Warsaw, Poland

Regimens increase the risk of damage to the brachial plexus. A review of the published literature shows that the use of doses per fraction in the range from 2.2 Gy to 4.58 Gy with the total doses between 43.5 Gy and 60 Gy causes a significant risk of brachial plexus injury which ranged from 1.7% up to 73%. The risk of radiation induced brachial plexopathy was smaller than 1% using regimens with doses per fraction between 2.2 and 2.5 Gy with the total doses between 34 and 40 Gy. Surgical manipulations in the axilla and chemotherapy have to be taken into account as additional factors which may increase the risk of brachial plexopathy.
RNI - post NACT

Accurately staged Pre NACT stag
Post NACT pathological stage

Un ambiguous role –
Advanced tumor pre NACT
All residual LN positive disease

Grey area –
Moderate burden disease; pCR ypN0 – Clinical trials
Post NACT

NSABP – B 51

Clinically T1–3, N1 Breast Cancer
Documented Positive Axillary Nodes by FNA
or by Core Needle Biopsy

Minimum of 12 Weeks of Standard Neoadjuvant Chemotherapy
Plus Anti-HER2 Therapy for Patients with HER2-Positive Tumors

Definitive Surgery with Histologic Documentation of Negative Axillary Nodes
(Either by Axillary Dissection or by Sentinel Node Biopsy ± Axillary Dissection)

STRATIFICATION
- Type of surgery (mastectomy, lumpectomy)
- Hormone receptor status (ER-positive and/or PgR-positive; ER- and PgR-negative)
- HER2 status (negative, positive)
- Adjuvant chemotherapy (yes, no)
- pCR in breast (yes, no)

RANDOMIZATION

Arm 1
(Groups 1A and 1B)*, **
No Regional Nodal XRT
- Group 1A Lumpectomy: No regional nodal XRT with WBI
- Group 1B Mastectomy: No regional nodal XRT and no chestwall XRT

Arm 2
(Groups 2A and 2B)*, **
Regional Nodal XRT
- Group 2A Lumpectomy: Regional nodal XRT with WBI
- Group 2B Mastectomy: Regional nodal XRT and chestwall XRT
RNI was also decided on as a standard by 44% of the panelists for patients with cN1 → PST situations when post-PST SLNB has retrieved a negative SN, while 23% felt that RNI should only be indicated if risk factors are present, and 17% did not think RNI should be a standard in such situations.
**PMRT - ASCO/ASTRO/SSO guidelines**

**Clinical Question 1**

Is PMRT indicated in patients with T1-2 tumors with one to three positive axillary lymph nodes who undergo ALND?

**Clinical Question 2**

Is PMRT indicated in patients with T1-2 tumors and a positive SNB who do not undergo completion ALND?

**Clinical Question 3**

Is PMRT indicated in patients with clinical stage I cancers who have received NAST?

**Clinical Question 4**

Should RNI include both the IMNs and supraclavicular-axillary apical nodes when PMRT is used in patients with T1-2 tumors with one to three positive axillary nodes?

↓LRF, ↓ Any Rec, ↓ BCM

SLNB +; ALND not done – risk adaptive

Post NACT – pCR Insuff evidence for PMRT

Most will need both RT

Moreno et al, The Breast 2017

Treatment Algorithm for Clinical Stage II Breast Cancer

- cT2-3N0
  - BCS or M + SLND
    - SLN (-)
      - 1-3 LN (+)
      - No RNI
    - SLN (+)
      - ≥4 LN (+)
      - Low Risk
      - High Risk

- cT1-2N1 FNA (+)
  - BCS or M + SLND
  - Neoadjuvant chemotherapy
    - BCS or M + ALND*
      - ypN0
        - NSABP B51
      - ypN1
        - Alliance A011202
      - ypN2-3
        - RNI

Low Risk: Favorable histology, ER(+) HER2(-), low Oncotype Dx score, micrometastatic disease.
High Risk: Triple negative, high Oncotype DX score, large nodal deposits, lymphovascular invasion, gross extracapsular extension.
### 50 years ago and now.....

<table>
<thead>
<tr>
<th>Topic</th>
<th>Then</th>
<th>Now</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring the benefit of RT</td>
<td>Reduced benefit of radiation in “any first event (LRR or DM)”</td>
<td></td>
</tr>
<tr>
<td>Breast-conserving therapy (BCT)</td>
<td>High morbidity and mortality</td>
<td>Higher cure rates with survival and LRR rates similar to mastectomy</td>
</tr>
<tr>
<td>Post-mastectomy RT</td>
<td>The benefit of RT is not well understood.</td>
<td>Improves survival in appropriate patients</td>
</tr>
<tr>
<td>Fractionation</td>
<td>1.8-Gy per fraction</td>
<td>1.8-Gy per fraction is just as effective and safe in BCT shortening 6 to 3-4 wk</td>
</tr>
<tr>
<td>Adjuvant systemic therapy</td>
<td>Not yet developed</td>
<td>Effective and serendipitously makes RT more effective and important</td>
</tr>
<tr>
<td>Delivery of RT</td>
<td>Conventional therapy and energy linear accelerators</td>
<td>6 MV energies and in vivo treatment planning simulation</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>High cardiac doses and no knowledge of the problem</td>
<td>Cardiac doses are minimized by the use of heart blocks, prone technique, and deep inspiration breath hold techniques</td>
</tr>
</tbody>
</table>
Thank you