Radiotherapy in breast cancer – a tailored approach

Dr Lai Cheng Yew

1 July 2019
Tailored approach

• De-escalation / increase dose intensity
  – Patient selection
  – Rationale
    • Reduction in early and late toxicities without affecting efficacy
    • Improving outcomes
    • Improvements in systemic therapies / surgical/RT techniques
    • Risk stratification by molecular subtype

• Early breast cancer
  – Low risk
    • Omission
    • Partial breast irradiation (PBI)
  – Intermediate/high risk (LN+)
    • Mx axilla: ALND vs ART vs no treatment esp in context NACT
    • RNI including IMC
    • PMRT following immediate breast reconstruction (IBR)

• Oligometastatic breast cancer - SABR
WBRT

- **EBCTCG meta-analysis**
  - ~ halves rate 1\textsuperscript{st} recurrence
  - Reduces breast cancer death by ~ 1/6th
  - Reduces 10-yr risk 1\textsuperscript{st} recurrence by 15.7%
  - Reduces 15-yr risk breast cancer death by 3.8% (1 breast Ca death avoided for every 4 recurrences)

Darby et al., Lancet 2011 Nov 12; 378(9804): 1707-1716
Absolute benefit varies substantially between subgroups

Darby et al., Lancet 2011 Nov 12; 378(9804): 1707-1716
Cardiac toxicity

• Breast cancer RT increases rate major coronary events 7.4% per Gray mean heart dose
• Increased risk in pts with pre-existing cardiac risk factors

Darby et al., NEJM 2013;368(11):987-998
Second malignancy

• Meta-analysis >750000 pts: breast RT significant 2\textsuperscript{nd} cancer risk
  – Lung (RR 1.66)
  – Oesophageal (RR 2.17)

• RT vs no RT meta-analysis
  – Lung cancer incidence rate ratio 2.10
  – Cardiac mortality rate ratio 1.30
  – Smoking determined net effect RT on mortality

Grantzau et al., Radioth Oncol. 2015;114(1):56-65
Taylor et al., J Clin Oncol. 2017;35(15):1641-1649
One size fits all?

<table>
<thead>
<tr>
<th>Low</th>
<th>High</th>
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<tbody>
<tr>
<td><strong>Grade</strong></td>
<td></td>
</tr>
<tr>
<td>G1-2</td>
<td>G3</td>
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<tr>
<td><strong>Size</strong></td>
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<tr>
<td>T1</td>
<td>T2</td>
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<td></td>
<td>T3-4</td>
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<tr>
<td><strong>ER status</strong></td>
<td></td>
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<tr>
<td>Pos</td>
<td>Neg</td>
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<td><strong>Her 2 status</strong></td>
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<tr>
<td>Neg</td>
<td>Pos</td>
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<tr>
<td><strong>LN status</strong></td>
<td></td>
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<tr>
<td>0</td>
<td>1-3</td>
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<tr>
<td></td>
<td>≥4</td>
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<tr>
<td><strong>Menopausal status</strong></td>
<td></td>
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<tr>
<td>Post</td>
<td>Pre</td>
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</tbody>
</table>
Low risk early breast cancer

• Omission RT
  – PRIME/PRIMETIME

• Partial breast RT (PBI)
  – IORT (ELIOT/TARGIT)
  – Post-op
    • EBRT
    • Brachytherapy (intracavity and interstitial)
    • Accelerated PBI (ABPI)
Omission RT

Low-risk, elderly

• **PRIME II**
  - 1326 pts
  - ≥ 65 y.o. T1-2 up to 3cm, LN-, ER+ (included G3 or LVSI)
  - Randomised WBRT vs no RT
  - Primary endpoint: IBTR
  - At 5 yrs f/up:
    • IBTR 1.3% WBRT vs 4.1% no RT (p=0.0002)
    • OS 93.9% both groups

• **CALGB 9343**
  - 636 pts
  - ≥70 y.o. T1 N0, ER+
  - Randomised TamRT vs Tam alone
  - At 10 yrs:
    • 98% TamRT vs 90% Tam free from L/R recurrence
    • OS 67% vs 66%

**Conclusion:** although small improvement in local recurrence with RT, considered low enough to consider omission RT in this group of patients

Kunkler et al., Lancet Oncology 2015 Mar; 6(3):266-273
Hughes et al., J Clin Oncol 2013 Jul 1;31(19):2382-7
Biomarker directed treatment

- Low risk pts
- Omission RT based on molecular subtypes
- Trials Canada/US/Australia/NZ/UK
  - LUMINA/IDEA/PRECISION/EXPERT/PRIMETIME
- IHC/multigene expression profiling
  - PAM50
  - Oncotype DX
  - Ki67
  - IHC4+C
PRIMETIME

Eligible Patient Group (n=2400)
- ≥60 years
- T1, N0, G1-2
- ER/PR+ve, HER2-ve

Central testing of Ki67

WLE & SLNB

Confirmation of eligibility - PRIMETIME study registration

IHC4+C score:
- very low
  - No Radiotherapy
    (endocrine therapy as per standard of care)
- Low, intermediate, high
  - Radiotherapy
    (endocrine therapy as per standard of care)
PBI

• Rationale
  – 74% recurrences ≤ 2cm from scar
  – Smaller volume → less toxicity

• Techniques
  – IORT (TARGIT)
  – Post-op
    • External beam RT
    • Brachytherapy (intracavity and interstitial)

Salvadori B et al., BJS,1999, 86, 84-87
TARGIT A

• 3451 patients
• Intraoperative RT (photons) vs WBRT
• 15% pts given supplemental EBRT (if unpredicted adverse features final histology)
• 5 yr IBRT 3.3% TARGIT vs 1.3% WBRT (p=0.04)
• Median f/up: 2yr 5mths

Vaidya et al., Lancet 2014 Nov 15; 383(9917): 603-613
Breast cancer vs non-breast cancer deaths

- WBRT – increased no. non-breast cancer deaths (cardiovascular/2\textsuperscript{nd} malignancy) 3.5% vs 1.4% TARGIT
- No diff OS

\textit{Vaidya et al., Lancet 2014 Nov 15; 383(9917): 603-613}
External beam PBI

- Linac
- Partial breast
- IMPORT LOW
IMPORT LOW

- Intensity Modulated Partial Organ RT
- Phase 3 non-inferiority trial, 2018 pts
- Whole breast vs reduced dose vs partial breast
- Inclusion criteria
  - ≥ 50 y.o.
  - ≤ 3cm, unifocal
  - Any grade
  - N0 or N1
  - Margin ≥ 2mm

Randomisation

Whole breast  
Reduced dose  
Partial breast

- Whole breast: 40 Gy in 15 fractions
- Reduced dose: 36 Gy in 15 fractions
- Partial breast: NO RT, 40 Gy in 15 fractions
Planning

• CT-based volumetric approach
• CTV outlined to include
  – Surgical clips / gold seeds
  – Any change in surrounding tissue architecture
  – 15mm margin: CTV partial breast (edited off pectoral fascia)
  – 10mm margin: PTV
Planning
Results

• Biological features: mostly low risk
  – 95% ER pos
  – >94% Her 2 neg
  – >96% LN-
  – Median tumour size 1.2cm
  – Only ~10% G3
• Median f/up: 72.2 mths
• Non-inferiority confirmed – reduced dose and partial breast
# Events

<table>
<thead>
<tr>
<th></th>
<th>Whole (n=674)</th>
<th>Reduced (n=673)</th>
<th>Partial (n=669)</th>
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<tbody>
<tr>
<td>No. LR events</td>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>5 yr cumulative LR incidence</td>
<td>1.1%</td>
<td>0.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>HR</td>
<td>0.33 (p=0.003)</td>
<td>0.65 (p=0.01)</td>
<td></td>
</tr>
<tr>
<td>Regional relapse</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Distant relapse</td>
<td>13</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Deaths</td>
<td>40 (6%)</td>
<td>39 (6%)</td>
<td>37 (6%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>9 (1%)</td>
<td>7 (1%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>2nd cancer</td>
<td>14 (2%)</td>
<td>16 (2%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>12</td>
<td>11</td>
<td>13</td>
</tr>
</tbody>
</table>
Toxicities

• Similar adverse effects
  – Photographic / **patient** / clinical assessments
• Change in breast appearance and breast harder/firmer domains – lower adverse effects with PBI (both groups)
• Comprehensive PROMS assessment (1,2,5 and 10 years)
Patient selection

<table>
<thead>
<tr>
<th></th>
<th>Low risk (n=1088)</th>
<th>High risk (n=162)</th>
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</thead>
<tbody>
<tr>
<td>No. local relapses</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Grade</td>
<td>1-2</td>
<td>3</td>
</tr>
<tr>
<td>ER status</td>
<td>Pos</td>
<td>Poor</td>
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<tr>
<td>Her 2 status</td>
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<td>Pos</td>
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<tr>
<td>Nodal status</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>LVSI</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

- **IMRT technique**
  - Time
    - Clinician – voluming
    - Physics – planning
  - Training

? Left-sided/UOQ
Accelerated PBI

• 2 trials reported at San Antonio
  – RAPID (38.5Gy/10# bd over 5 days vs WBRT 42.5Gy/16# or 50Gy/25# +/- boost)
    • 2135 patients
    • Non-inferiority demonstrated
    • **Cosmetic outcome** (5 yrs: 32% vs 16%) and **late normal-tissue toxicity worse in APBI** (G2: 32% vs 13%, G3: 4.5% vs 1%)
  – NSABP B39 (APBI 34-38.5Gy/10#bd over 5 days vs WBI 50Gy/25#)
    • 4216 pts
    • Primary endpoint: IBTR
    • 10 yr IBTR-free rate: 95.2% PBI vs 95.9% WBI
    • HR not statistically significant
    • **G3 toxicity higher in PBI group** (9.6% vs 7.1%); G4-5 toxicity slightly higher PBI group (0.5% vs 0.3%)
RCR consensus statements 2016

Partial breast radiotherapy after breast-conserving surgery

- Can be considered for patients ≥50 years, Grade 1–2, ≤3 centimetres (cm), oestrogen receptor positive (ER+), human epidermal growth factor receptor negative (HER2-), N0 with minimum 1 millimetre (mm) radial excision margins for invasive disease, using either (i) external beam radiotherapy with 40 Gray (Gy) in 15 fractions over three weeks or (ii) multicatheter brachytherapy using fractionation schedules as per the Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) trial.

- Classical lobular cancer and/or lymphovascular space invasion should be excluded.

Safe omission of radiotherapy after breast-conserving surgery

Avoidance of radiotherapy should be considered:

- In women deemed to be at very low risk of local recurrence, for example patients ≥70 years out of a research study and ≥60 years in study with T1N0 oestrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor negative (HER2-), Grade 1–2 tumours AND who are willing to take adjuvant endocrine therapy for a minimum of five years AND have regular mammograms for ten years. These criteria are best fulfilled within the UK PRIMETIME bio-marker directed study and participation is recommended.
1.10.4 Consider partial breast radiotherapy (as an alternative to whole-breast radiotherapy) for women who have had breast-conserving surgery for invasive cancer (excluding lobular type) with clear margins and who:

- have a low absolute risk of local recurrence (defined as women aged 50 and over with tumours that are 3 cm or less, N0, ER-positive, HER2-negative and grade 1 to 2) and
- have been advised to have adjuvant endocrine therapy for a minimum of 5 years. [2018]

1.10.5 When considering partial breast radiotherapy (see recommendation 1.10.4), discuss the benefits and risks, and explain that:

- local recurrence with partial breast radiotherapy at 5 years is equivalent to that with whole-breast radiotherapy
- the risk of local recurrence beyond 5 years is not yet known
- there is a potential reduction in late adverse effects. [2018]

1.10.6 When delivering partial breast radiotherapy, use external beam radiotherapy. [2018]
NICE guidance 2018: omission RT

1.10.7 Consider omitting radiotherapy for women who:

- have had breast-conserving surgery for invasive breast cancer with clear margins and
- have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours that are T1N0, ER-positive, HER2-negative and grade 1 to 2) and
- are willing to take adjuvant endocrine therapy for a minimum of 5 years. [2018]

1.10.8 When considering omitting radiotherapy for the population in recommendation 1.10.7, discuss the benefits and risks, including those in table 5, and explain that:

- without radiotherapy, local recurrence occurs in about 50 women per 1,000 at 5 years, and with radiotherapy, occurs in about 10 women per 1,000 at 5 years
- overall survival at 10 years is the same with or without radiotherapy
- there is no increase in serious late effects if radiotherapy is given (for example, congestive cardiac failure, myocardial infarction or secondary cancer). [2018]
Summary mx low risk breast Ca

Low risk features
- Node neg
- G1/2
- T1
- Post-menopausal
- ER +/-Her 2 -

≥70
Consider omission RT
Or PRIMETIME if ≥60

<70
Consider PBI (esp if left-sided)
EBRT – standard tangential fields
Axillary mx node positive

<table>
<thead>
<tr>
<th></th>
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<th>High</th>
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<tbody>
<tr>
<td>Grade</td>
<td>G1</td>
<td>G2</td>
</tr>
<tr>
<td>Size</td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>ER status</td>
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<tr>
<td>Her 2 status</td>
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<td>LN status</td>
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<td>1-3</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Post</td>
<td>≥4</td>
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<tr>
<td></td>
<td></td>
<td>Pre</td>
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</table>
Further local treatment for the malignant sentinel lymph node (SLN) in individuals with early invasive breast cancer

- **Isolated tumour cells and micrometastases** – if the sentinel node(s) shows isolated tumour cells and/or micrometastases, no further axillary treatment is required in addition to breast-conserving surgery or mastectomy.

- **1–2 sentinel nodes with macrometastases** – further axillary treatment is no longer mandatory in breast conservation with whole-breast radiotherapy, in patients who are postmenopausal and have T1, Grade 1 or 2, oestrogen receptor positive (ER+) and human epidermal growth factor receptor negative (HER2-) tumours. *These patients could also be entered into the POSNOC or equivalent clinical trial.*

- **3 or more sentinel nodes with macrometastases** – patients should usually be recommended to have further axillary treatment.

- **Further axillary treatment should usually be recommended for patients undergoing mastectomy or with tumours with one or more of the following features:** T3, Grade 3, ER- or HER2+. *These patients could also be entered into the POSNOC or equivalent clinical trial.*

- **No consensus was reached** on the management of patients with one or more of the following features: premenopausal status, T2 tumours, lymphovascular invasion or extranodal spread.
Node positive
Axillary RT – adjuvant setting

- **AMAROS**
  - Phase 3 non-inferiority trial
  - T1-2, non-palpable LN
  - 4806 pts enrolled
  - 1425 pts SNB pos: randomised ALND or ART (40% ITC/micromets)
  - 5 yr axillary recurrence 0.43% ALND vs 1.19% ART
  - Planned non-inferiority test underpowered as low no. events
  - Lymphoedema rate higher in ALND group
  - 10 yr rates (SABCS 2018): 0.93% vs 1.82%
  - Second primaries including contralateral breast Ca higher in ART group 75/681 vs 57/744 (p=0.035)

- **POSNOC (1 or 2 LN+ on SNB)**
Post-NACT radiotherapy

• Considerations
  – Higher risk patients/biology
  – Usually node positive
  – Timing of SNB
  – Response to chemo
  – De-escalation for higher risk patients
    • Uncertain long-term consequences
    • ANC vs axillary RT vs no treatment to axilla
    • Patient selection ?biology
Timing SNB

• cN0 at presentation
  – Identification and false negative rates comparable if SNB pre-/post-NACT
  – SNB pre-NACT
    • if positive → ALND or ART post-NACT or POSNOC
    • Repeat SNB not recommended (low identification rate and 50% false neg rate)
    • Disadvantage upfront SNB: 2 surgical procedures, if pos, committed to ALND +/- ART regardless response to NACT
  – SNB post-NACT
    • 96% detection rate, false negative rate 6%
    • If positive (includes ITC, micro/macromets) → ALND
    • Advantages: likely 1 procedure, prognostic value SNB post-NACT may be higher than pre-NACT
cN1 at presentation

• Positive on LN bx pre-NACT
• Considerations
  – No. axillary nodes/ENS on pre-NACT imaging
  – MDT discussion
  – Response to NACT axilla may correlate with breast esp. if TND or Her2+ (trast/pertuz)
  – Some patients may safely be considered for SNB post-NACT even if cN1
    • 90% identification rate, 14% false neg rate
  – If extensive axillary nodal disease on imaging, may still require ALND
SENTINA

- 4 arm trial
- Primary endpoint: accuracy SNB cN1→ cN0 post-NACT (Arm C)
- Arm C
  - 80.1% detection rate
  - 14.2% false neg rate

Kuehn et al., Lancet Oncology 2013 June 14(7): 609-618
Post-NACT SNB

• SNB false neg rate inversely correlated with no. nodes removed (SENTINA, meta-analysis)
  – 1 node: 20-24%
  – 2 nodes: 12-18%
  – ≥ 3 nodes: 4%
• Dual mapping with radioactive colloid and blue dye: lower false neg rates
Targeted axillary dissection

- Surgical technique developed by MD Anderson
- Positive nodes clipped pre-chemo
- Removal sentinel nodes + clipped node + palpable nodes: FNR 2.4%
- Reduced axillary surgery
- Effect on recurrence rates?

Candle et al., J Clin Oncol. 2016 Apr;34(10):1072-1078
cN1 $\rightarrow$ ypN0 in SNB post-NACT

- Consider this group for de-escalation
- Lack of evidence
- Further axillary treatment (ART/ALND) should be offered
- NSABP B-51/RTOG 1304/ATNEC trials
ATNEC

T1-3,N1,M0 breast cancer
FNA/core biopsy documented axillary metastasis

Marking the positive node
- Clip placed
- SPOT dye tattoo – anterior surface, perinodal tissue and tract

NEOADJUVANT CHEMOTHERAPY (NACT)

Axillary ultrasound and FNA or core biopsy of abnormal nodes

Not malignant

Breast conserving surgery or mastectomy + Targeted (dual agent) sampling + at least 3 nodes removed + removal of clipped/tattooed node

No nodal metastasis

RANDOMISATION 1:1

Axillary treatment ALND or ART

No Axillary treatment

nodes positive (micro or macrometastases)

malignant

Failed localisation of clipped/tattooed node

Axillary lymph node dissection (ALND)
cN1 $\rightarrow$ ypN1

- Risks of de-escalation
- Worse prognosis
- Increased probability non-sentinel node mets
- ALND or ART?
  - Cannot extrapolate results AMAROS trial as different pt groups (NACT higher risk)
  - Alliance Trial – randomises ALND vs ART post-NACT
- Completion ALND remains standard of care
Guidelines
Axillary Surgery Following Neoadjuvant Chemotherapy – Multidisciplinary Guidance From the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology∗
A. Gandhi††, C. Coles‡, A. Makris§, E. Provenzano¶, A. Goyal||, A.J. Maxwell***, J. Doughty††

• cN0
  – SNB may be carried out pre or post-NACT
  – If SNB+, post-NACT may be of increased prognostic value

• cN1
  – Can be safely considered for post-NACT SNB
  – 4 nodes should be removed
  – Dual mapping
  – If pCR in nodes → offer axillary RT
  – If SNB+ (ITC, micro or macromets) → offer ALND
  – If extensive axillary disease at presentation, consider ALND post-NACT
RNI – IMC radiotherapy

- Increased use RNI following EORTC 2292 trial
- RCR consensus: high risk pts

Internal mammary chain radiotherapy

- Internal mammary chain (IMC) radiotherapy should be considered in patients at high risk of recurrence (that is, T4 and/or N2–3 disease).
- IMC radiotherapy should be considered in patients at intermediate risk of recurrence (that is, 1–3 axillary macrometastases and central/medial disease, who have been recommended locoregional irradiation).
- IMC radiotherapy should be given using techniques which minimise doses to organs-at-risk. Every centre should have a breath-hold technique available for patients undergoing IMC radiotherapy.
- The following dose constraints are recommended for IMC radiotherapy: heart $V_{17\text{Gray}}$ (Gy) <10%, ipsilateral lung $V_{17\text{Gy}}$ <35%, mean contralateral breast dose <3.5 Gy; in patients at intermediate risk of recurrence, a mean heart dose <6 Gy is considered a reasonable objective.

Poortmans et al., NEJM 2015;373:317-327
IMC RT challenges

- Increased toxicities
- Complex techniques
- Patient selection
- Benefit vs long-term toxicities
- EORTC 2292: 15 yr f/up
  - OS 73.2% RNI vs 70.8% no RNI (p=0.358)
  - 10 yr 1.6% OS benefit no longer demonstrated
  - Breast Ca mortality 15.8% vs 19.7% (p=0.005)
- EBCTCG meta-analysis of RNI in EBC
  - RNI reduces breast Ca recurrence/mortality and OS with no increase in non-breast cancer deaths (only trials after 1989)
    - N2 34.4% vs 42.3%
IMC planning

• Novel field-placement algorithm developed by RMH
• Reduce resource impact of IMC RT
• Uses 6 points to represent CTV border

<table>
<thead>
<tr>
<th>Field border</th>
<th>Point position</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Superior border of anterior field</td>
<td>Superior aspect of subclavian artery</td>
</tr>
<tr>
<td>2 Medial border of anterior field</td>
<td>Medial aspect of internal jugular vein</td>
</tr>
<tr>
<td>3 Lateral border of anterior field</td>
<td>Dependent on nodal level requiring treatment, e.g. level 3 – medial border of pectoralis minor muscle</td>
</tr>
<tr>
<td>4 Posterior border of wide tangents</td>
<td>Most superior part of internal mammary vessels in wide tangential field</td>
</tr>
<tr>
<td>5 Lateral border of wide tangents</td>
<td>Mid-point of anterior surface of latissimus dorsi muscle at the level of the fourth rib</td>
</tr>
<tr>
<td>6 Heart and lung multileaf collimator shielding</td>
<td>Internal mammary vein at the insertion of fourth rib to sternum</td>
</tr>
</tbody>
</table>
6 point algorithm
ESTRO updates

• Consensus guidelines on target volume definition post-immediate breast reconstruction
  – Complete/partial inclusion volume dorsal to implant in CTV chest wall
  – Depends if implant pre- or post-pectoral
  – Presence of adverse factors (T3/non-pCR to NACT/muscle or CW invasion)
RT for oligometastases

• Rationale
  – Evidence prolonged disease control in pts when treated with aggressive MDT management
  – Oligometastatic phenotype consistent with cells of LOW malignant potential
  – ? Accumulation sequential genetic changes gives rise to Mets
  – ?Oligometastatic disease has a less evolved metastatic repertoire
  – Consider treating with curative intent
SABR

– Highly conformal, steep dose fall-off
– High dose, hypofractionated dose schedules – usually >10Gy/#
– SABR-COMET trial: RCT
  • OS benefit 41 mths vs 28 mths
  • PFS doubled 12 mths vs 6 mths
  • Increased toxicities: >G2 30% vs 9%
Summary

• Tailored approach aims to improve long-term outcomes
• Reduced late toxicities
• Complex techniques
• Patient selection/risk stratification
• Intrinsic subtypes
• Biomarker-directed strategies