Belgian Thank You Merry Xmas
Philip Poortmans, MD, PhD
Haute couture tailoring of radiation therapy in breast cancer
I have no conflicts of interest
Haute couture tailoring of RT

1. Introduction
   • General
     • The role of radiation therapy in BCT
     • The role of PMRT

2. Interaction with other treatments
   • Surgery or radiation therapy?
   • Competition with systemic therapy?
   • The case of primary systemic therapy

3. Discussion & Conclusions
Haute couture tailoring of RT: Introduction

Record female life expectancy from 1840 to the present – Oeppen and Vaupel (2002)

Shown is the record female life expectancy and the country with the highest female life expectancy at each point in time.
- The linear-regression trend is depicted by a bold black line (slope = 0.243) and the extrapolated trend by a dashed gray line.
- The horizontal black lines show asserted ceilings on life expectancy, with a shorter vertical line indicating the year of publication.

Haute couture tailoring of RT: Introduction

To fully inform the patient
Haute couture tailoring of RT: Introduction

Early Breast Cancer Trialists Collaboration Group

by acronymsandslang.com
Technique serve the goal — not the other way around!
Haute couture tailoring of RT: *Introduction*

*Contemporary radiation therapy*
Haute couture tailoring of RT: Introduction

- 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
Haute couture tailoring of RT: *Introduction*

Free respiration

Breath hold
Haute couture tailoring of RT: *Introduction*

The role of radiation therapy in BCT

Haute couture tailoring of RT: Introduction

Wound Response Signature

In vitro Wound Model – 516 genes

Prognostic Significance in

• Breast
• Lung
• Gastric cancer

Haute couture tailoring of RT: *Introduction*

*Predict of Local Recurrence in Early Breast Cancer*

*Training*

*Validation*

Still much to learn before adaptation in the clinics

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Haute couture tailoring of RT

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Haute couture tailoring of RT: \textit{RT \& BCT}

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

\textit{Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)*}

\textit{Lancet} 2011; 378: 1707–16
Haute couture tailoring of RT: RT & BCT

Effect of RT after BCS on recurrence and breast cancer mortality in pN+ women.

1050 pN+ women

Any first recurrence

Breast cancer mortality

Any first recurrence

Breast cancer mortality

10-y gain 21.2% (SE 3.4)
Logrank 2p < 0.00001

-21.2%

2.5:1

15-y gain 8.5% (SE 3.4)
Logrank 2p = 0.01

-8.5%
Haute couture tailoring of RT: *RT & BCT*

Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.

- **Any first recurrence**
  - 0 Gy: 31.0%
  - BCS + RT ± 50 Gy: 15.6%
  - 10-y gain: 15.4% (SE 1.1)
  - Logrank 2p < 0.00001
  - **Ratio**: 5:1

- **Breast cancer mortality**
  - 0 Gy: 20.5%
  - BCS + RT ± 50 Gy: 17.2%
  - 15-y gain: 3.3% (SE 1.3)
  - Logrank 2p = 0.005
  - **Ratio**: 5:1

EBCTCG Lancet 2011; 378: 1707–1716
Haute couture tailoring of RT

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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

*EBCTCG (Early Breast Cancer Trialists’ Collaborative Group)*

*Lancet 2014; 383: 2127–35*
Haute couture tailoring of RT: \textit{PMRT}
Haute couture tailoring of RT: \textit{PMRT}

\textbf{Interpretation:} \textit{RT reduced both recurrence and breast cancer mortality in women with positive lymph nodes.}
Haute couture tailoring of RT: *PMRT*

**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
Haute couture tailoring of RT: PMRT

Are the internal mammary lymph nodes a target?

Harris JR, Hellman S.

Put the "hockey stick" on ice.

To treat or not

**IMN: Balancing Risks and Benefits**
Haute couture tailoring of RT

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Haute couture tailoring of RT: *Surgery or RT?*

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Haute couture tailoring of RT: Surgery or RT?

Dutch population based cancer registry

2000-2004 cohort: 37,207 patients

- 58.4% BCT
- 41.6% MRM
Haute couture tailoring of RT: Surgery or RT?

Dutch population based cancer registry

2000-2004 cohort: 37,207 patients

- 58.4% BCT
- 41.6% MRM
Haute couture tailoring of RT: *Surgery or RT?*

*BCT = standard for the majority of the pts*

*BCT = surgery + RT*
Haute couture tailoring of RT: Surgery or RT?

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**PRE-SLN ERA:**

*Impact of ALN on overall survival*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAM</td>
<td>5.6 – 10.9%</td>
</tr>
<tr>
<td>CHT (&lt;50J)</td>
<td>7.0 – 11.0%</td>
</tr>
<tr>
<td>CHT (&gt;50J)</td>
<td>2.0 – 3.0%</td>
</tr>
</tbody>
</table>

5.4% (95% CI = 2.7 – 8.0%)

Haute couture tailoring of RT: *Surgery or RT?*

**EORTC 10981-22023 “AMAROS”**

Stratification: institution

Adjuvant systemic therapy by choice
Haute couture tailoring of RT: Surgery or RT?

*EORTC 10981-22023 “AMAROS”*

RT-fields: inappropriate (too large)!!!
Haute couture tailoring of RT: Surgery or RT?

**EORTC 10981-22023 “AMAROS”**

### Lymphedema

<table>
<thead>
<tr>
<th>Years after randomization</th>
<th>ALND</th>
<th>AxRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.0%</td>
<td>21.7%</td>
</tr>
<tr>
<td>3</td>
<td>29.8%</td>
<td>16.7%</td>
</tr>
<tr>
<td>5</td>
<td>28.0%</td>
<td>13.6%</td>
</tr>
</tbody>
</table>

P < 0.0001

Clinical observation and/or treatment:

- N0 -> no axillary treatment: ???

Haute couture tailoring of RT: Surgery or RT?

ACOSOG Z0011

T1/T2 cN0 Breast Cancer

- pN0
  - No ALD

- BCT + SLNB
  - pN1
    - RANDOM
      - ALD
      - No ALD

All patients received tangential field irradiation without a third field

Giuliano AE et al. JAMA 2011;305:569-75.
Haute couture tailoring of RT: Surgery or RT?

ACOSOG Z0011

Z0011 – Can We Really Abolish Axillary Dissection?

Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M: Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA;305:569–573

Commentary Thorsten Kühn, Esslingen and Philip M.P. Poortmans, Tilburg
Haute couture tailoring of RT: Surgery or RT?

ACOSOG Z0011

- 165 investigators from 177 departments
  ➔ median accrual = 1 patient/year/investigator

- Fields for breast irradiation not clearly defined

Haute couture tailoring of RT: Surgery or RT?

ACOSOG Z0011: QART: 228 replies (= the best 29%?)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>ALND</th>
<th>SLNB</th>
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<tbody>
<tr>
<td>Percentage</td>
<td>39.4%</td>
<td>21.2%</td>
</tr>
<tr>
<td>Percentage</td>
<td>43.7%</td>
<td>16.9%</td>
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Haute couture tailoring of RT: Surgery or RT?

ACOSOG Z0011: QART: 228 replies (= the best 29%?)

ALND: 0.56cm = part L1-2-3-Rotter

SLNB: 0.69cm = part L1-2-3-Rotter
Haute couture tailoring of RT: Surgery or RT?

Conclusions — surgery:

Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients

Significantly less lymphedema after AxRT

AxRT can be considered standard
Haute couture tailoring of RT: Surgery or RT?

Conclusions — radiation therapy:

Proof of principle:

Elective regional treatment $\Rightarrow$ less DM $\Rightarrow$ improved S
Haute couture tailoring of RT: Surgery or RT?

Conclusions – *surgery & radiation therapy*:

- Axillary surgery can be omitted
- Regional RT improves outcome
- No surgery ≠ no radiation therapy!

<table>
<thead>
<tr>
<th>Median FU</th>
<th>+/- 6 years</th>
<th>+/- 10 years</th>
</tr>
</thead>
<tbody>
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<td></td>
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</tr>
</tbody>
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Haute couture tailoring of RT: *Surgery or RT?*

*Should we treat the axilla – and who does it?*
Haute couture tailoring of RT: Surgery or RT?

Consensus agreements
Haute couture tailoring of RT: *Surgery or RT?*

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-IV bij T4 en/of pN2 (4 of meer mi)
- RT thoraxwand & level I-IV plus parasternaal bij mediaal gelegen tumor MET graad III of >3 cm of T4 of pN2

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

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*Protocol Radboud umc, March 2016.*
Haute couture tailoring of RT: Surgery or RT?

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

SNB

pN1mi
- 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 mi)

pN1 macro
- 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 macro)
- RT mamma +/- boost & level I-IV plus parasternaal bij mediaal gelegen tumor
Haute couture tailoring of RT: *Surgery or RT?*

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

- PST cN0
  - na PST: US / FNA -
    - SNB
      - ypN0
        - RT thoraxwand/mamma volgens eerder genoemde indicaties
          - geen oksel RT bij eerder cT1-3
          - cT4 RT mamma/thoraxwand en level I-IV
      - ypN1 mi & macro
        - 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
  - na PST: US / FNA +
    - OKD
      - na OKD RT mamma/thoraxwand en oksel level II/III-IV (plus parasternaal bij mediaal gelegen tumoren)
Haute couture tailoring of RT: Surgery or RT?

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

Diagram:
- PST cN+
  - na PST: US / FNA -
    - SNB
      - ypN0/N1 mi
        - RT mamma/thoraxwand en oksel level I-IV (plus parasternaal bij mediaal gelegen tumoren)
      - ypN1 (macro)
        - CKD
          - Na OKD RT mamma/thoraxwand en oksel level II/III-IV (plus parasternaal bij mediaal gelegen tumoren)
        - OKD
          - Na OKD RT mamma/thoraxwand en oksel level II/III-IV (plus parasternaal bij mediaal gelegen tumoren)
  - na PST: US / FNA +
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Haute couture tailoring of RT: $RT \& ST$

What is the size of a cancer cell

$= 0.01 \text{ mm}^3$
Haute couture tailoring of RT: \( RT \& ST \)

1.000.000.000 = 1 cc = 1 grams
Haute couture tailoring of RT: RT & ST

Duplication time

= 3 months

Detectable with special techniques

Physically detectable.

Not detectable at all

tumoren te klein om te kunnen worden waargenomen

256 cm³

16 cm³

1 cm³

tijd (jaar)

0 1 2 3 4 5 6 7 8 9 10 11 12 13
So what is a “complete pathological remission"?

• Resection specimen = 100 grams ➔ 100.000.000.000 cells

• Do you know a pathologist who can perform a complete evaluation?

• It will rather be around 1 to 5% of the material...
Haute couture tailoring of RT: *RT & ST*

- **Duplication time**
  - = 3 months

- **Detectable with special techniques**

- **Physically detectable**

- **Not detectable at all**

- **tumoren te klein om te kunnen worden waargenomen**

- **PR**
  - 256 cm$^3$
  - 16 cm$^3$
  - 1 cm$^3$

- **CR**

- **tijd (jaar)**
  - 0 1 2 3 4 5 6 7 8 9 10 11 12 13
Systemic treatment cures breast cancer

Contributes to cure
Figure: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour.

Haute couture tailoring of RT: RT & ST

Interaction systemic and locoregional treatments

...requires less systemic treatment OR less systemic treatment...
Haute couture tailoring of RT: \( RT \& ST \)

**RT & survival:**

- \( \rightarrow \quad \times \quad \) interaction with surgery and systemic treatment

  - \( \downarrow \) risk for death < M+ \( \rightarrow \quad \uparrow \) importance of LC
    - \( \rightarrow \) earlier stage BC
    - \( \rightarrow \) improved systemic therapy
Haute couture tailoring of RT: \textit{RT} \& \textit{ST}

Original article

Over-irradiation

Philip M.P. Poortmans \textsuperscript{a, *}, Meritxell Arenas \textsuperscript{b}, Lorenzo Livi \textsuperscript{c}
Haute couture tailoring of RT: *RT & ST*

**RT after tumourectomy: not always required?**

### Overview of prospective clinical trials evaluating postoperative radiation therapy omission.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patients</th>
<th>Study design</th>
<th>Local relapse</th>
<th>DFS</th>
<th>OS</th>
<th>Median FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al., 2002 [11]</td>
<td>1009</td>
<td>TAM vs. placebo + RT vs. TAM + RT</td>
<td>16.5% vs. 9.3% vs. 2.8% (p = 0.008; p &lt; 0.0001; p = 0.001)</td>
<td>—</td>
<td>93% vs. 94% vs. 93% (p = 0.93)</td>
<td>87.5 months</td>
</tr>
<tr>
<td>Fyles et al., 2004 [7]</td>
<td>769</td>
<td>TAM vs. TAM + RT</td>
<td>7.7% vs. 0.6% at 5 years (p &lt; 0.001)</td>
<td>84% vs. 91% at 5 years (p = 0.004) HR 3.48 (p = 0.0021)</td>
<td>92.8% vs. 93.2% (p = 0.83)</td>
<td>67.2 months</td>
</tr>
<tr>
<td>Pötter et al., 2007 [9]</td>
<td>869</td>
<td>TAM/Al vs. TAM/Al + RT</td>
<td>5.1% vs. 0.4% (p = 0.0001)</td>
<td>—</td>
<td>94.5% vs. 97.9% (p = 0.18)</td>
<td>53.8 months</td>
</tr>
<tr>
<td>Hughes et al., 2013 [10]</td>
<td>636</td>
<td>TAM vs. TAM + RT</td>
<td>9% vs. 2% (p &lt; 0.001)</td>
<td>—</td>
<td>66% vs. 67% at 10 years (p = 0.64)</td>
<td>151.2 months</td>
</tr>
<tr>
<td>Blamey et al., 2013 [12]</td>
<td>1135</td>
<td>- without or with TAM - without or with RT 2 × 2 factorial design</td>
<td>- 13% vs. 4% - 11% vs. 3% Both treatments 0% (p &lt; 0.001)</td>
<td>—</td>
<td>96% at 10 years</td>
<td>167 months</td>
</tr>
<tr>
<td>Kunkler et al, 2013 [13]</td>
<td>1326</td>
<td>TAM/Al vs. TAM/Al + RT</td>
<td>4.1% vs. 1.3% (p = 0.0002)</td>
<td>—</td>
<td>93.9% vs. 93.9% (p = 0.34)</td>
<td>60 months</td>
</tr>
</tbody>
</table>

**Abbreviations:** DFS, disease-free survival; OS, overall survival; FU, follow up; TAM, tamoxifen; AI, aromatase inhibitors; RT, radiation therapy; HR, Hazard Ratio.
Haute couture tailoring of RT: \textit{RT & ST}

Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial

Haute couture tailoring of RT: RT & ST

Fig. 2. Survival to first local recurrence by treatment actually received.
Haute couture tailoring of RT: RT & ST

Even in these patients with tumours of excellent prognosis, LR after conservative surgery without adjuvant therapy was still very high. This was reduced to a similar extent by either radiotherapy or tamoxifen but to a greater extent by the receipt of both treatments.
Haute couture tailoring of RT: $RT \& ST$

..., **LR after conservative surgery without adjuvant therapy was still very high**...

**Personal note:**

Virtually none of those pts would get adjuvant systemic treatment according to the Dutch guidelines
### Haute couture tailoring of RT: *RT & ST*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Benefit HT DFS (%)</th>
<th>Benefit HT OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a-bG1-3</td>
<td>4.9-9.5</td>
<td>0.3-1.4</td>
</tr>
<tr>
<td>T1cG1</td>
<td>5.7-8.2</td>
<td>0.9</td>
</tr>
<tr>
<td>T1cG2</td>
<td>7.8-11.1</td>
<td>2.0</td>
</tr>
<tr>
<td>T1cG3</td>
<td>9.6-13.9</td>
<td>3.3</td>
</tr>
<tr>
<td>T2&lt;3cmG1</td>
<td>8.1-11.6</td>
<td>2.4</td>
</tr>
<tr>
<td>T2&lt;3cmG2</td>
<td>10.8-15.7</td>
<td>4.3</td>
</tr>
<tr>
<td>T2&lt;3cmG3</td>
<td>12.7-18.7</td>
<td>5.9</td>
</tr>
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(all 65y;N0;ER+;Her-)

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**Adjuvant!Online**

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**67 |**
## Haute couture tailoring of RT: RT & ST

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Haute couture tailoring of RT: *RT & ST*

Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.

7287 pN0 women

Any first recurrence

10-y gain 15.4% (SE 1.1)
Logrank 2p < 0.00001

0 Gy
BCS 31.0%

15.6% ± 50 Gy

Breast cancer mortality

15-y gain 3.3% (SE 1.3)
Logrank 2p = 0.005

0 Gy
BCS 20.5%

17.2% ± 50 Gy

-15.4% - 3.3%
### Haute couture tailoring of RT: \textit{RT & ST}

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\textbf{-15.4%} \quad \textbf{-3.3%}
Haute couture tailoring of RT: \(RT \& ST\)
Haute couture tailoring of RT: *RT & ST*

The eternal quest

“Studies seeking to identify a subgroup of patients who could undergo breast conserving surgery without radiotherapy, based upon clinicopathologic characteristics alone have largely proved unsuccessful”
Haute couture tailoring of RT

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Haute couture tailoring of RT: *PST*

**Figure:** Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour.
Haute couture tailoring of RT: \( PST \)

**Figure:** Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour.

- **Lum A; minor R**
- **NC/PD Triple -/Her2 type**
- **PR Lum B type**
- **CR Lum A type**

| High risk  |
| No effective ST |
| Most patients |
| Current ST |
| Low risk   |
| Highly effective ST |
Haute couture tailoring of RT: PST

Figure: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour.
Haute couture tailoring of RT: *PST*

**Figure:** Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour.
Haute couture tailoring of RT: PST
Primary or adjuvant systemic therapy?

<table>
<thead>
<tr>
<th>Study</th>
<th>n (stage and size)</th>
<th>Chemotherapy regimen</th>
<th>cRR (%)</th>
<th>pCR (%)</th>
<th>DFS benefit</th>
<th>OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al. [3, 4], Wolmark et al. [5], NSABPB-18</td>
<td>1,523 (operable)</td>
<td>AC</td>
<td>80</td>
<td>13</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Van der Hage et al. [6], EORTC 10902</td>
<td>698 (T1c–4bN0–1)</td>
<td>FEC</td>
<td>49</td>
<td>4</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Gianni et al. [7, 8], ECTO</td>
<td>1,355</td>
<td>AT → CMF</td>
<td>78</td>
<td>23</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mauriac et al. [9]</td>
<td>272 (&gt;3 cm)</td>
<td>EMV/MTV</td>
<td>81</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Scholl et al. [10], Broet et al. [11]</td>
<td>414 (T2–3N0–1)</td>
<td>FAC</td>
<td>85</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Makris et al. [12]</td>
<td>309 (operable)</td>
<td>MM(M)+Tam</td>
<td>84</td>
<td>10</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Haute couture tailoring of RT: \textit{PST}

6 studies (713 pts) PST + surgery ± RT
Haute couture tailoring of RT: PST

226 pts PST $\Rightarrow$ pCR + surgery $\pm$ RT

POSTMASTECTOMY RADIATION IMPROVES THE OUTCOME OF PATIENTS WITH LOCALLY ADVANCED BREAST CANCER WHO ACHIEVE A PATHOLOGIC COMPLETE RESPONSE TO NEOADJUVANT CHEMOTHERAPY

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Haute couture tailoring of RT: PST

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 2.2017 — April 6, 2017
NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients
Haute couture tailoring of RT: PST

NCCN Guidelines Version 2.2017
Invasive Breast Cancer

PREOPERATIVE SYSTEMIC THERAPY: ADJUVANT THERAPY

SURGICAL TREATMENT

Mastectomy and surgical axillary staging\textsuperscript{1,mm} ± reconstruction.\textsuperscript{P}
If SLNB performed prechemotherapy and negative findings, omit axillary lymph node staging. See BINV-11

ADJUVANT TREATMENT

- Complete planned chemotherapy regimen course if not completed preoperatively.

- Adjuvant radiation therapy\textsuperscript{7} post-mastectomy is based on maximal disease stage from pre-chemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results. Adjuvant radiation therapy is recommended:
  - As indicated on BINV-3
  - For cT3-4, cN2-3, stage III, residual disease \( \geq 2 \) cm any ypN+

- Endocrine therapy if ER-positive and/or PR-positive\textsuperscript{2} (category 1)
- Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrently with radiation therapy\textsuperscript{7} and with endocrine therapy if indicated.

Lumpectomy with surgical axillary staging.\textsuperscript{1,mm}
If SLNB performed prechemotherapy and negative findings, omit axillary lymph node staging. See BINV-11

- Complete planned chemotherapy regimen course if not completed preoperatively

- Adjuvant radiation therapy\textsuperscript{7} post-lumpectomy is based on maximal disease stage from pre-chemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results. Adjuvant radiation therapy is recommended:
  - As indicated on BINV-2
  - For cT3-4, cN2-3, stage III, residual disease \( \geq 2 \) cm any ypN+

- Endocrine therapy if ER-positive and/or PR-positive\textsuperscript{2} (category 1)
- Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrently with radiation therapy\textsuperscript{7} and with endocrine therapy if indicated.
Haute couture tailoring of RT: \textit{PST}

Other tools to individualise:

- Response to PST (\textit{= predictor of RLR risk})

- Pre-PST stage incl histology; VI; molecular profile; ...

- Age
Haute couture tailoring of RT: \textit{PST}

A technical radiation oncology note
Haute couture tailoring of RT: PST

Planning-CT-scan before and after PST

March 2013: patient age 49

- Tumour central in left breast:
- Biopsy (histology): IDA G3; triple –
- FNA axillary LN: +
- FNA supraclavicular LN: +
- Conclusion after staging: cT3N3M0

Treatment: PST

- Referred for evaluation by RO
- TAC x 6
Haute couture tailoring of RT: PST

Planning-CT-scan before and after PST

May 2013:
• Major tumour regression on MRI

Treatment:
• Continue TAC ➔ July 2013
• MRM: ypT0ypN0
• PMRT + boost on non-removed nodes
Haute couture tailoring of RT: \textit{PST}

\textit{Planning-CT-scan before and after PST}

\textbf{March 2013} \hspace{0.5cm} \textbf{September 2013}
Haute couture tailoring of RT: \textit{PST}

Planning-CT-scan before and after PST

\textbf{March 2013} \hspace{5cm} \textbf{September 2013}
Haute couture tailoring of RT: \textit{PST}

Planning-CT-scan before and after PST

\textbf{March 2013} \hspace{2cm} \textbf{September 2013}
Haute couture tailoring of RT: \textit{PST}

Planning-CT-scan before and after \textit{PST}

\textbf{March 2013} \hspace{2cm} \textbf{September 2013}
Haute couture tailoring of RT: PST

Planning-CT-scan before and after PST

March 2013

September 2013

OK + ?!?!
Haute couture tailoring of RT: \textit{PST}

\textit{Planning-CT-scan before and after PST}

\textbf{March 2013} \hspace{1cm} \textbf{September 2013}
Haute couture tailoring of RT: PST

Or even a PET-CT?

Courtesy of MC Valli and A Fozza
Haute couture tailoring of RT

1. Introduction
   • General
   • The role of radiation therapy in BCT
   • The role of PMRT

2. Interaction with other treatments
   • Surgery or radiation therapy?
   • Competition with systemic therapy?
   • The case of primary systemic therapy

3. Discussion & Conclusions
Regional treatment improves outcome!

Current & future trials are superfluous; results will be outdated before they are known!

Evidence tells us to reserve surgery for macroscopic resectable disease and radiation therapy for all others!

Use treatment protocols, register data and continue finetuning!
Haute couture tailoring of RT: \( D \& C \)

Precision radiation medicine

Biological + technological optimisation \( \rightarrow \) personalised/individualised/stratified approaches.

Management of women with early stage & low-risk breast cancer: PROMs & PREMs.

Management of women with advanced stage & high-risk breast cancer: individualised intensification.
Haute couture tailoring of RT: $D \& C$

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Management of women with advanced stage & high-risk breast cancer: individualised intensification.
Haute couture tailoring of RT: $D \& C$

**Early stage, low risk**

Long life expectancy: - Surgery + RT

Short life expectancy: - Surgery alone
- Endocrine alone
- RT alone?
- Nothing?
Haute couture tailoring of RT: D & C

GEC-ESTRO Recommendations


Csaba Polgár*, Erik Van Limbergen, Richard Pötter, György Kovács, Alfredo Polo, Jaroslaw Lyczek, Guido Hildebrandt, Peter Niehoff, Jose Luis Guinot, Ferran Guédeà, Bengt Johansson, Oliver J. Ott, Tibor Major, Vratislav Strnad, On behalf of the GEC-ESTRO breast cancer working group

doi:10.1016/j.ijrobp.2009.02.031

CONSENSUS STATEMENT

ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Benjamin D. Smith, M.D.,Douglas W. Arthur, M.D., Thomas A. Buchholz, M.D., Bruce G. Haffty, M.D., Carol A. Hahn, M.D., Patricia H. Hardenbergh, M.D., Thomas B. Julian, M.D., Lawrence B. Marks, M.D., Dorin A. Todor, Ph.D., Frank A. Vicini, M.D., Timothy J. Whelan, M.D., Julia White, M.D., Jennifer Y. Wo, M.D., and Jay R. Harris, M.D.
Haute couture tailoring of RT: \(D \& C\)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Local relapse</th>
<th>DFS</th>
<th>OS</th>
<th>Median FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dodwell et al., 2005</td>
<td>Phase II</td>
<td>174</td>
<td>4% vs. 12% ((p = 0.05))</td>
<td>–</td>
<td>27% vs. 30% ((p = 0.75))</td>
<td>96 months</td>
</tr>
<tr>
<td>Chen et al., 2010</td>
<td>Phase II</td>
<td>94</td>
<td>1.1% at 4 years</td>
<td>95% at 4 years</td>
<td>97% at 4 years</td>
<td>50.4 months</td>
</tr>
<tr>
<td>Vicini et al., 2010</td>
<td>Phase II</td>
<td>52</td>
<td>6% at 4 years</td>
<td>84% at 4 years</td>
<td>96% at 4 years</td>
<td>54 months</td>
</tr>
<tr>
<td>Lei et al., 2013</td>
<td>Phase II</td>
<td>136</td>
<td>0.7% at 4 years</td>
<td>–</td>
<td>96.8% at 4 years</td>
<td>53.1 months</td>
</tr>
<tr>
<td>Veronesi et al., 2013</td>
<td>Phase III</td>
<td>1305 (654 IORT vs. 651 EBRT)</td>
<td>0.4% vs. 4.4% at 5 years ((p &lt; 0.0001))</td>
<td>–</td>
<td>96.8% vs. 96.9% at 5 years ((p = 0.59))</td>
<td>69.6 months</td>
</tr>
<tr>
<td>Vaidya et al., 2014</td>
<td>Phase III</td>
<td>3451 (1730 EBRT vs. 1721 IORT)</td>
<td>1.3% vs. 3.3% at 5 years p = 0.042</td>
<td>–</td>
<td>96.1% vs. 94.7% at 5 years (p = 0.099)</td>
<td>29 months</td>
</tr>
<tr>
<td>Livi et al., 2015</td>
<td>Phase III</td>
<td>520 (260 WBI vs. 260 APBI)</td>
<td>1.4% vs. 1.5% (p = 0.86)</td>
<td>–</td>
<td>96.6% vs. 99.4% at 5 years (p = 0.057)</td>
<td>60 months</td>
</tr>
<tr>
<td>Strnad et al., 2016</td>
<td>Phase III</td>
<td>1184 (551 WBI vs. 633 APBI)</td>
<td>0.92% vs. 1.44% (p = 0.42)</td>
<td>94.45% vs. 95.03% at 5 years (p = 0.79)</td>
<td>79.2 months</td>
<td></td>
</tr>
</tbody>
</table>
Haute couture tailoring of RT: \textit{D \& C}

\textbf{Early stage, low risk}

\begin{center}
\includegraphics[width=0.2\textwidth]{EORTC_logo}
\end{center}

<table>
<thead>
<tr>
<th>Study information</th>
<th>Outline form</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Partial Breast Irradiation versus Endocrine Therapy for women age $\geq 70$ years with Luminal-A early stage breast cancer: a randomized phase III trial comparing Quality of Life by Patient Reported Outcome Measures</td>
</tr>
<tr>
<td><strong>Short title (max 50 characters)</strong></td>
<td>APBI or ET for elderly with early breast cancer</td>
</tr>
<tr>
<td><strong>Study Number</strong></td>
<td>EORTC-1625 QoL-ROG-ETF-BCG</td>
</tr>
<tr>
<td></td>
<td>EORTC ROG</td>
</tr>
</tbody>
</table>
Haute couture tailoring of RT: D & C

Eligible patients group
Females ≥ 70 years of age
cT1-2, N0 breast cancer

BCS with or without SNB

pT1 (<2cm) invasive BC
cN0 or pN0(+)  
- Luminal-A on basis of IHC: ER+ and/or PgR+ (PgR at least >20%), HER2-, Ki67<20%

Signed informed consent

Randomization

Exclusive APBI

Exclusive ET

Follow-up according to protocol
Haute couture tailoring of RT: $D & C$

*Early stage, low risk*

**Tailored treatment in Older Patients**

TOP-1: Omission of radiotherapy in elderly patients with low risk breast cancer
Haute couture tailoring of RT: D & C

INCLUSION CRITERIA:
- ≥70 years
- after breast-conserving surgery
- tumor < 1 cm grade 1-2, tumor ≥ 1-2 cm grade 1
- tumor ER >50% positive, HER2 negative
- sNO or sNO+ (etc)
- surgical resection margins free of tumor

TOP-1 STUDY

GERIATRIC ASSESSMENT & NO ADJUVANT RT AFTER BSC

Directly

At 1 year Questionnaire

At 2 years Questionnaire

At 3 years Questionnaire

At 4 years Questionnaire

At 5 years Questionnaire

LOCAL RECURRENCE RATE AT 5 YEARS

NO-INFORMED CONSENT TOP-1

GUIDELINES CWO 2010: ADJUVANT RT AFTER BSC

THE GOOD
Haute couture tailoring of RT: \( D \& C \)

*Early stage, with risk factors*

Long life expectancy:
- Surgery with
- Systemic T
- RT

Short life expectancy:
- Surgery with
- Systemic T?
- RT?
Haute couture tailoring of RT: $D \& C$

We did improve BCT rates!

So boost only when needed!

Update 2016: 1.8% LRR at 9 years !!!
Haute couture tailoring of RT: D & C

Invasief radicale excisie

Ja
Marge ≥ 15 mm

Neen
> 70 jaar oud

Ja
geen boost

Neen
≤ 50 jaar oud

Ja
standaard boost

Ja
Geen boost

Ja
standaard boost

Neen
G3 en/of tumor >3 cm

Neen
re-excisie

Neen (focaal DCIS of inv.)

Ja
≤ 70 jaar oud hoge boost

Ja
> 70 jaar oud standaard boost

Neen (> focaal DCIS of inv.)
Haute couture tailoring of RT: D & C

Advanced stage, with risk factors

Long life expectancy:
- Surgery with
- Systemic T
- RT

Short life expectancy:
- Surgery with
- Systemic T
- RT
Haute couture tailoring of RT: $D \& C$

Source: Globocan, 2008. Rates shown are age-standardised rate per 100,000 using the standard world population.
Haute couture tailoring of RT: \( D \& C \)

Trust comes on foot and leaves on horseback!
Haute couture tailoring of RT: Conclusions

Still a lot of work to be done!

Predictive molecular and genetic testing of normal tissue and tumour responsiveness.

The role of the immune system and host response.

Test general hypotheses relating to radiation genomics and normal tissue responses.

Large databases incl radionomics

Nanoparticles as radiosensitisers.

Sequential/serial biopsies.

Overall treatment time.
Haute couture tailoring of RT: Acknowledgements

- Harry Bartelink
- Laurence Collette
- Sarah Darby
- Birgitte Offersen
- Roberto Orecchia
- Oliver Ott
- John Yarnold
- Icra Meattini
- Meritxell Arenas
- Lorenzo Livi
- And many others!